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Effects of aerobic exercise on blood pressure in patients with hypertension: a systematic review and dose-response meta-analysis of randomized trials

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Abstract

We aimed to evaluate the dose-dependent effects of aerobic exercise on systolic (SBP) and diastolic blood pressure (DBP) and haemodynamic factors in adults with hypertension. PubMed, Scopus, and Web of Science were searched to April 2022 for randomized trials of aerobic exercise in adults with hypertension. We conducted a random-effects meta-analysis to estimate mean differences (MDs) and 95%CIs for each 30 min/week increase in aerobic exercise. The certainty of evidence was rated using the GRADE approach. The analysis of 34 trials with 1787 participants indicated that each 30 min/week aerobic exercise reduced SBP by 1.78 mmHg (95%CI: -2.22 to -1.33; n=34, GRADE=low), DBP by 1.23 mmHg (95%CI: -1.53 to -0.93; n=34, GRADE=moderate), resting heart rate (MD= -1.08 bpm, 95%CI: -1.46 to -0.71; n=23, GRADE=low), and mean arterial pressure (MD= -1.37 mmHg, 95%CI: -1.80 to -0.93; n=9, GRADE=low). A nonlinear dose-dependent decrement was seen on SBP and DBP, with the greatest decrement at 150 min/week ($MD_{150\ min/week}$ = -7.23 mmHg, 95%CI: -9.08 to -5.39 for SBP and -5.58 mmHg, 95%CI: -6.90 to -4.27 for DBP). Aerobic exercise can lead to a large and clinically important reduction in blood pressure in a dose-dependent manner, with the greatest reduction at 150 min/week.

Keywords: Aerobic training, Hypertensive population, Randomized controlled trial, Dose-response.

Introduction

Based on the American College of Cardiology/American Heart Association, hypertension is defined as having systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg or undertaking medication for high blood pressure [1]. Globally, in the last thirty years, the number of adults aged 30–79 years with hypertension has increased from 650 million to 1.28 billion [2], which affects nearly 40% of adults, leading to 9.4 million deaths each year primarily due to stroke and cardiovascular events [3]. Hence, to prevent upcoming cardiovascular mortality, there is a need to find optimum treatments for high blood pressure. Currently, both pharmacological and non-pharmacological approaches are used for treating hypertension [4,5].

Non-pharmacological treatments such as physical activity are currently recommended as the cornerstone of therapy for either primary or secondary hypertension [4-6]. An appropriate exercise program has been demonstrated not only to reduce blood pressure in individuals with hypertension but also to be as effective as the majority of antihypertensive medications [7,8]. Moreover, exercise has trivial side effects in comparison to medications [9,10]. It is indicated that aerobic exercise with moderate intensity is able to reduce SBP and DBP in hypertensive men and women [11]. Current recommendations from the American College of Sports Medicine suggest that most individuals with hypertension should perform 30-60 min/day moderate-intensity aerobic exercise [12].

Accumulating evidence from randomized control trials (RCTs) suggested that aerobic exercise is an effective non-pharmacological therapy for reducing blood pressure in patients with hypertension [13,14]. However, previous meta-analyses only conducted pairwise comparisons between intervention and control groups, and thus, the optimum dose of aerobic exercise in reducing blood pressure has not been ascertained. Similarly, advanced

network meta-analyses are not able to determine the optimum dose of aerobic exercise for implementing the most effective interventions for blood pressure treatment. To address this gap, we conducted the present systematic review and dose-response meta-analysis of RCTs to investigate the dose-dependent effects of aerobic exercise in reducing ambulatory and resting blood pressure and haemodynamic factors in adults with hypertension.

Methods

We considered instructions in the Cochrane Handbook for Systematic Reviews of Interventions [15] and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Handbook [16] to carry out our systematic review. We registered the protocol for our systematic review with PROSPERO (CRD42022329092) [17].

Data sources and searches

We did a systematic search in three databases including PubMed/Medline, Scopus, and Web of Science from inception up to April 2022. Two investigators (BJG and ZG) independently performed the literature search and screened the titles and abstracts and then full-text articles. Any disagreements were resolved by discussion with a third reviewer (SS-B). We also checked out the reference lists of published meta-analyses of RCTs on the effect of aerobic exercise training in patients with hypertension. The systematic search was restricted to articles published in English. We represented the full search strategy in **Supplementary Table 1**.

Study selection

The following items were used as inclusion criteria for original controlled trials: 1) RCTs (parallel or crossover design) in adult populations (aged≥18 years) who have been diagnosed with hypertension; 2) trials with an intervention period of 4 weeks or longer; 3) trials in which intervention group implemented an aerobic exercise program, regardless of intensity, modality, frequency and session duration, and the other group did not receive any type of exercise; 4) assessed the changes in ambulatory and resting blood pressure and haemodynamic factors as an outcome.

Exclusion criteria

We excluded the trials that included one of these items: 1) intervention period of shorter than 4 weeks; 2) the intervention group received a combined exercise program (aerobic exercise combined with any other type of exercise); 3) the control group performed any exercises (active control); 4) conducted in adolescents (under 18 years of age), pregnant and lactating women; and 5) did not report the duration or frequency of aerobic exercise sessions in the intervention arm. Because we aimed to perform dose-response meta-analyses, we need this information (both duration and frequency of aerobic exercise sessions in the intervention arm) for the analyses.

Outcomes

Our main outcomes were changes in SBP and DBP (mm Hg), while our secondary outcomes included 24 hours, daily, and nightly ambulatory blood pressure (ABP) (mm Hg), maximum (HR_{max}) and resting heart rate (RHR) (bpm), mean arterial pressure (MAP) (mm Hg), cardiac output (CO) (min/L), pulse pressure (PP) (mm Hg), peripheral resistance (dynes.s.cm^{-5}), quality of life (QoL), and adverse events. We extracted all 8 subsets of QoL, including physical functioning, role function/physical, bodily pain, general health, vitality, social functioning, role function/emotional, and mental health [18].

Data extraction

After the screening of the full texts, 2 investigators (BJG and SZM) independently and in duplicate extracted the following characteristics from each trial: author's last name, publication year, population location, sex, age range, baseline body mass index (BMI), total sample size, type, intensity and modality of aerobic exercise, description of the comparison group, taking of antihypertensive medications during the study (yes/no), behavioral support (yes/no), duration of intervention, drop-outs (n) and means and standard deviations (SDs) of changes from baseline for outcomes in every arm. Differences were resolved by discussion with a third investigator (SS-B).

We classified the intensity of aerobic exercise training as the following criteria [19-21]: 1) light: 1.6 to <3 metabolic equivalents (METs), or 40 to <65% HR_{max}, or 20 to <40% maximal oxygen consumption (Volume Oxygen Maximum [Vo_{2max}]), or <40% Vo_2 reserve (Vo_2R) or HR reserve; 2) moderate: 3 to <6 METs, or 65 to <75% HR_{max}, or 40 to <60% Vo_{2max}, or 40%–59% Vo_2R or HR reserve; and 3) vigorous: 6 to <9 METs, or 77 to <93% HR_{max}, or 60 to <85% Vo_2max, or 60%–84% Vo_2R or HR reserve. Aerobic exercise programs that covered more than one category of exercise intensity were defined as light to moderate or moderate to vigorous aerobic exercise programs.

Risk of bias assessment

We assessed the risk of bias (RoB) of the trials using the Cochrane tool for risk of bias assessment [22]. Two authors (BJG and SZM) independently evaluated RoB with disagreements resolved by the third author (SS-B). For RoB assessment, those trials which just had none or 1 item as unclear were rated as low risk of bias. The trials

with 1 high risk of bias criteria or 2 criteria with unclear were judged as having some concerns. Trials were rated as high risk of bias if 2 or more criteria were listed as high or unclear risk of bias.

Data synthesis and analysis

We considered the mean difference or standardized mean difference and its 95% confidence interval (CI) of changes in continuous outcomes in the intervention group compared to the control group as the effect size for reporting the results of the present systematic review.

First, we extracted the mean and standard deviation [23] of changes from baseline till the end of the intervention in each study arm in each trial. For those trials that did not report these changes, we calculated these values using the reported means and SDs of outcomes before and after the intervention using the Cochrane Handbook guidelines [24]. In the case of trials that reported standard errors instead of SDs, we converted them to SDs [25]. If neither SDs nor standard errors were reported in the trials, we used the average SDs obtained from other trials for the analyses [26].

Second, we computed the mean difference and standard error of change in continuous outcomes per each 30 min/week increment in aerobic exercise in the intervention group relative to the control group in each trial according to the method introduced by Crippa and Orsini [27]. Trial-specific mean and standard error of changes in outcomes per each 30 min/week aerobic exercise were pooled using a random-effects model [28].

The following items were needed for using this method: the dose (min/week) of aerobic exercise in the intervention arm, the mean and its corresponding SD of change in outcomes in each study arm (intervention and control), and the number of participants in each arm. The dose (duration) of exercise sessions (min/week) only included the main part of aerobic exercise programs and thus, warm-up and cooling times were not included when calculating the dose (time) of exercise [19]. Some of the trials implemented a progressive aerobic exercise program, in which the frequency (sessions per week) or duration (minutes per session) of aerobic exercise increased during the intervention period. In such cases, for calculating the dose (min/week) of intervention, we first computed the duration of aerobic exercise in each week and then averaged them over the intervention period. Then we performed pre-specified subgroup analyses based on the type, modality and intensity of aerobic exercise, taking the antihypertensive drugs during the study (yes/no), supervised exercise (yes/no), weight status (overweight/obese versus mixed), and intervention duration (≤12 weeks versus >12 weeks). According to 8 criteria suggested by the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN), we examined the credibility of subgroup differences [29]. We used meta-regression analysis for computing the P-value for subgroup differences. We tested the potential impact of each trial on the main results using influence analysis removing each trial at a time. For publication bias, we applied Egger's test [30] and Begg's test [31] and evaluated the funnel plots for asymmetry. For evaluating the heterogeneity across trials, we used the I^2 statistic and performed a $\chi 2$ test ($P_{heterogeneity} > 0.10$) [32].

Finally, we conducted a dose-response meta-analysis to find out the dose-dependent effects of duration (min/week) of aerobic exercise on blood pressure and other haemodynamic outcomes [27]. We used STATA software version 16.0 for our analyses (StataCorp LLC, TX, USA). A two-tailed P-value less than 0.05 was considered statistically significant.

Grading the evidence

We applied the GRADE approach to judge the certainty of the evidence [33]. According to the GRADE, evidence obtained from RCTs starts at high certainty that can be downgraded or upgraded based on pre-specified criteria. Detailed criteria that were used to apply the GRADE approach are described in **Supplementary Table 2**. To rate for the imprecision domain, we downgraded the certainty of evidence when 1) optimum information size was not met (n=400 participants per study arm); 2) the 95%CI was wide; 3) the point estimate did not surpass the threshold set as a minimal clinically important difference (MCID) for resting and ambulatory blood pressure and haemodynamic factors [33,34]. The thresholds set as MCID for all different forms of resting and ambulatory blood pressure were defined as 2 mm Hg [35]. Moreover, the MCID for MAP and PP was defined as 2 mm Hg [36]. If the MCID could not be identified in the literature, it was estimated as a 0.5 SD of each outcome before the intervention [36]. Values of MCID that were used for each outcome are presented in **Supplementary Table 3.**

Results

Literature search and study selection process

As illustrated in **Supplementary Fig. 1**, the initial database and reference lists search identified 29,456 records. After excluding 5,494 duplicates and 23,854 irrelevant articles based on screening of the title and abstract, 108 full texts were reviewed in detail for eligibility. Overall, 39 trials with 3,245 participants were eligible for inclusion in this dose-response meta-analysis [18,37-74]. The list of studies excluded via full-text assessment with reasons for exclusions is provided in **Supplementary Table 4**.

Characteristics of primary trials included in the dose-response meta-analysis

The general characteristics of the trials included in this dose-response meta-analysis are described in **Supplementary Table 5**. Eligible trials were published between 1985 and 2021. Of the 39 studies, 37 trials were carried out in the general hypertension populations [18,37,39-62,64-70,72-74], and the other 2 trials were carried out in patients with hypertension and other chronic diseases including osteoporosis, type 2 diabetes mellitus, cardiovascular disease, depression, anxiety, and dyslipidemia [38,63]. Of 39 RCTs, 26 were conducted in adults with overweight and obesity (BMI $\geq$ 25 kg/m^2) [37-39,41,43-45,48,49,52-56,58,60-64,67-70,72,73]. while the other 13 trials were conducted in a mixed population (normal weight, overweight, and obese) [18,40,42,46,47,50,51,57,59,65,66,72,74].

Seven trials were performed on women [37,39,41,45,55,68,69], 6 on men [53,54,56,57,59,72], and the others on either sex [18,38,40,42-44,46-52,58,60,62-67,70,72-74]. The intervention duration ranged from four to 52 weeks, of which 25 trials lasted ≤12 weeks [18,37,40-42,44,48,51,53,56,57,59,60,62-70,72,74], five trials between 12-24 weeks [43,47,58,61,73], and nine trials more than 24 weeks [38,39,45,46,49,50,52,54,55]. Of 39 trials, 33 trials had no exercise as their control arm [18,37,39,43-48,50,51,53-70,72-74], and the other 6 trials had standard clinical care [38], educational sessions [40], normal daily physical activity [41], or wait-list group [42,49,52], as a control arm. In 18 trials, participants continued their antihypertension drugs during intervention [36,37,39,41,43,45,47,51-53,55,56,59,60,62-64,73] while in the other trials they discontinued antihypertensive medications [18,39,41,43,45,47,49-51,55,58,59,62,66-70,72,73]. Four trials implemented a low-intensity aerobic exercise [40,62,65,73], twenty eight trials implemented moderate-intensity aerobic exercise or at least started with moderate-intensity [18,37,39,41,42,45,46,48,50-52,54-57,59-61,63,64,66-70,72,74], and the rest of the 7 trials implemented a vigorous-intensity program [38,43,44,47,49,53,58]. Nineteen trials implemented a supervised aerobic exercise program [37-39,41-45,49,50,52,55,58,62,63,65,72-74], while in the other 20 trials exercise programs were done without supervision [18,40,46-48,51,53,54,56,57,59-61,64,66-70,72]. Among the included studies, three did not mention the methods of BP measurement [39,48,50], one with the modified Borg scale [74], and the rest used indirect non-invasive BP measurement in a sitting position after at least 5 minutes of rest, whether automatic [56,59,62,72], digital [18,41-45,49,52,53,60,61,63,65,66,73], or manual [37,38,40,46,47,51,54,55,57,58,64,67-71]. Based on Cochran tool for RoB assessment, twenty trials were rated to have some concerns [37-39,41,43-45,47,50-53,57,60-64,69,74], and the other 19 trials had a high risk of bias [18,40,42,46,48,49,54-56,58,59,65-68,70,72,73] (**Supplementary Table 6**).

The effect of aerobic exercise on ambulatory and resting SBP

Thirty-four trials with 1787 participants in the intervention group and 1119 in the control group reported data about the effect of aerobic exercise (per 30 minutes per week) on SBP in patients with hypertension [18,37-41,43-55,57-60,62,64-70,72,73]. Each 30 min/week aerobic exercise reduced SBP by 1.78 mmHg (95%CI: -2.22 to -1.33; I^2 = 87%, $P_{heterogeneity}$ < 0.001, GEADE = low) (**Supplementary Fig. 2**). The main result remained significant and stable after the exclusion of every single trial from the analysis, ranging from -1.66 mmHg (95%CI: -2.09 to -1.22) to -1.85 mmHg (95%CI: -2.35 to -1.35).

In **Table 1**, we did the subgroup analysis of the effect of aerobic exercise (per 30 min/week) on SBP based on exercise intensity, modality, duration, and type, as well as baseline weight, supervised exercise, and using the antihypertension drug during the study. The effect of aerobic exercise on SBP remained significant in all subgroups, and there was not any credible subgroup difference based on 8 criteria introduced by the ICEMAN tool (**Supplementary Table 7**) [29]. We found evidence of publication bias with Egger's test (P = 0.009), Begg's test (P = 0.026), or with the inspection of the funnel plot (**Supplementary Fig. 3**).

Dose-dependent effects of aerobic exercise on levels of SBP are indicated in **Fig. 1** and **Table 2**. The analysis showed the levels of SBP decreased proportionally with the increment of the duration of aerobic exercise up to 150 min/week ($MD_{150\ min/week}$ = -7.23 mmHg, 95%CI: -9.08 to -5.39), with a trivial increase in effect estimate at a higher duration of aerobic exercise ($P_{dose\text{-}response}$ < 0.001, $P_{nonlinearity}$ = 0.006; n = 34) (**Fig. 1A** and **Table 2**). We did a sensitivity analysis to observe the effect of moderate-intensity aerobic exercises on SBP. Levels of SBP decreased with the increase in the duration of moderate-intensity aerobic exercise up to 150 min/week ($MD_{150\ min/week}$ = -7.32 mmHg, 95%CI: -9.72 to -4.91), with a slight increase at a higher duration ($P_{dose\text{-}response}$ < 0.001, $P_{nonlinearity}$ = 0.034; n = 18) (**Fig. 1B** and **Table 2**).

Six trials with 253 participants [42-44,56,62,63], five trials with 192 participants,[42,44,56,62,63] and six trials with 344 participants [42,44,56,59,61,72] reported information on daily, nightly, and 24hrs ambulatory SBP, respectively. Each 30 min/week aerobic exercise did not significantly change daily and nightly ambulatory SBP (**Supplementary Figs. 4-5** and **Table 3**), but reduced 24hrs ambulatory SBP by 1.55 mmHg (95%CI: -2.48 to -0.61; I^2 = 76%, $P_{heterogeneity}$ < 0.001, GRADE = low) (**Supplementary Fig. 6** and **Table 3**).

The effect of aerobic exercise on ambulatory and resting DBP

Thirty-four trials with 1787 participants in the intervention group and 1119 in the control group reported data about the effect of aerobic exercise on DBP in the hypertensive population [18,37-41,43-55,57-60,62,64-70,72,73]. Each 30 min/week aerobic exercise reduced DBP by 1.23 mmHg (95%CI: -1.53 to -0.93; I^2 = 88%, $P_{heterogeneity}$ < 0.001, GRADE = moderate) (**Supplementary Fig. 7**). The main result remained significant and ranged from -1.14 mm Hg (95%CI: -1.43 to -0.85) to -1.28 mmHg (95%CI: -1.58 to -0.98) with the step-by-step exclusion of each trial from the main analysis. In the subgroup analyses, the effect of aerobic exercise on DBP remained significant in all subgroups (**Supplementary Table 8**), and there was not any credible subgroup difference based on 8 criteria introduced by the ICEMAN tool (**Supplementary Table 9**) [29]. There were some indications of publication bias with Egger's test (P = 0.01), Begg's test (P = 0.02), or by the inspection of the funnel plot (**Supplementary Fig. 8**).

Dose-dependent effects of aerobic exercise on levels of DBP are indicated in **Fig. 2** and **Table 2**. The analysis showed that levels of DBP decreased proportionally with the increment of the duration of aerobic exercise up to 150 min/week ($MD_{150\ min/week}$ = -5.58 mmHg, 95%CI: -6.90 to -4.27), with a trivial increase in effect estimate at a higher duration of aerobic exercise ($P_{dose\text{-}response}$ < 0.001, $P_{nonlinearity}$ < 0.001) (**Fig. 2A** and **Table 2**). In a sensitivity analysis restricting to trials with moderate-intensity aerobic exercise (n = 18), levels of DBP decreased with the increase in the duration of moderate-intensity aerobic exercise up to 150 min/week ($MD_{150\ min/week}$ = -6.53 mmHg, 95%CI: -8.63 to -4.43), with a slight increase at higher duration ($P_{dose\text{-}response}$ < 0.001, $P_{nonlinearity}$ = 0.003) (**Fig. 2B** and **Table 2**).

Six trials with 253 participants [42-44,56,62,63], five trials with 192 participants [42,44,56,62,63] and six trials with 344 participants [42,44,56,59,61,72] reported information on daily, nightly, and 24hrs ambulatory DBP, respectively. Each 30 min/week aerobic exercise significantly reduced daily (MD = -0.78 mmHg, 95%CI: -1.44 to -0.11; I^2 = 43%, $P_{heterogeneity}$ = 0.12) (**Supplementary Fig. 9**), and 24hrs ambulatory DBP (MD = -0.72 mmHg, 95%CI: -1.24 to -0.21; I^2 = 50%, $P_{heterogeneity}$ = 0.08) (**Supplementary Fig. 11**), but did not significantly reduce nightly DBP (**Supplementary Fig. 12** and **Table 3**).

The effect of aerobic exercise on haemodynamic factors

Twenty-three trials with 632 participants in the intervention group and 594 in the control group reported data about the effect of aerobic exercise on RHR in the hypertensive population [18,40,41,43,46,47,50,51,53-55,57-59,62,64-66,70,72-74]. Each 30 min/week aerobic exercise reduced RHR by 1.08 bpm (95%CI: -1.46 to -0.71; I^2 = 80%, $P_{heterogeneity}$ < 0.001, GRADE = low) (**Supplementary Fig. 12**). After the exclusion of each trial from the main analysis, the main result remained significant and ranged from -1.00 bpm (95%CI: -1.39 to -0.61) to -1.13 bpm (95%CI: -1.51 to -0.76).

In the subgroup analyses, the effect of aerobic exercise program on RHR remained significant in all subgroups (**Supplementary Table 10**). We did not find any credible subgroup difference (**Supplementary Table 11**) [29]. There was some evidence of publication bias based on the inspection of the funnel plot and Egger's test (Egger's test P = 0.014) and Begg's test (P = 0.712) (**Supplementary Fig. 13**).

Dose-dependent effects of aerobic exercise on RHR are indicated in **Fig. 3** and **Table 2**. The analysis showed a proportional decrease in RHR with the increase in the duration of aerobic exercise ($P_{dose\text{-}response}$ < 0.001, $P_{nonlinearity}$ = 0.058) (**Fig. 3A**). In a sensitivity analysis, levels of RHR decreased with the increase in the duration of moderate-intensity aerobic exercise up to 100 min/week ($MD_{100\ min/week}$ = -5.77 bpm, 95%CI: -7.79 to -3.75), with a modest increase at a higher duration ($P_{dose\text{-}response}$ < 0.001, $P_{nonlinearity}$ = 0.003) (**Fig. 3B**).

The effect of aerobic exercise on other haemodynamic factors is presented in **Table 3** and **Supplementary Figs. 14-18**. Aerobic exercise did not significantly change HR_{max}, peripheral resistance, CO, and PP, but reduced MAP by 1.37 mmHg (95%CI: -1.80 to -0.93; I^2 = 44%, $P_{heterogeneity}$ = 0.07, GRADE = low).

Health-related quality of life

We found 2 trials that reported the effect of aerobic exercise on different aspects of QoL (**Supplementary Figs. 19-S29** and **Table 3**) [18,74]. Aerobic exercise improved bodily pain, physical functioning, role-emotion, and vitality in patients with hypertension (GRADE = very low) but had no significant effects on other aspects of QoL (**Table 3**).

Adverse events

As planned in our prior protocol, we aimed to evaluate the potential adverse events following aerobic exercise programs. However, none of the trials included in the present review reported adverse events following aerobic exercise.

Grading the evidence

The certainty of the evidence was rated by using the GRADE approach. The certainty of the evidence was rated moderate for DBP due to a downgrade for serious inconsistency. For SBP, ambulatory SBP nightly, ambulatory SBP 24hrs, ambulatory DBP nightly, ambulatory DBP daily, ambulatory DBP 24hrs, CO, MAP, and RHR, the certainty of the evidence was rated low and for ambulatory SBP daily, PP, peripheral resistance, and HR_{max}, it was rated very low due to downgrades for serious risk of bias, imprecision, and inconsistency (**Supplementary Tables 12-13**).

Discussion

In the present dose-response meta-analysis of RCTs, we gathered available evidence on the effect of aerobic exercise on blood pressure and hemodynamic factors in patients with hypertension. Based on moderate certainty evidence, aerobic exercise exerted a significant and important reduction, larger than the MCID threshold, on DBP in patients with hypertension. Aerobic exercise also reduced SBP and RHR larger than the MCID threshold, but the certainty of evidence was rated low. The greatest decline in SBP and DBP was seen at 150 min/week in the main analysis and in trials that carried on moderate-intensity aerobic exercise. The greatest decline in RHR was seen at 300 min/week in the main analysis, and at 100 min/week in trials that implemented moderate-intensity aerobic exercise.

The effect of aerobic exercise on ambulatory and resting SBP & DBP

Our dose-response meta-analysis confirmed the findings presented in the previous pairwise meta-analyses of randomized trials about the favorable effects of aerobic exercise on blood pressure [75-78]. A pairwise meta-analysis of 37 trials indicated that aerobic exercise can lead to a significant and clinically important reduction in SBP (MD = -8.29 mm Hg, 95%CI: - 10.12 to - 6.46) and DBP (MD = - 5.19 mm Hg, 95%CI: - 6.24 to - 4.14) in patients with hypertension [77]. Another meta-analysis of 24 trials presented similar findings and indicated that aerobic exercise could reduce SBP and DBP [78]. A meta-analysis of 13 observational studies conducted on an adult with hypertension showed the beneficial effects of aerobic exercise on blood pressure as well [13]. The neuroendocrinological factors rolled in this reduction, for instance, reductions in circulating noradrenaline and its receptors and in angiotensin II; increases in nitric oxide bioavailability, antioxidant capacity, insulin sensitivity; and expression of cardioprotective factors such as apelin [79]. Researchers suggested the apelin/apelin receptor system has a role in regulating blood pressure through a β-arrestin-dependent signaling pathway. Also, Apelin may maintain body fluid homeostasis with arginine vasopressin by inhibiting the release of it, increasing renal blood flow and urine volume, and causing a significant reduction in blood pressure [80]. However, previous meta-analyses only performed a pairwise comparison between intervention and control groups and did not ascertain the optimum dose of aerobic exercise for implementing the most effective interventions.

In the dose-response meta-analyses, we observed a large effect size, about 3 to 4 times larger than the MCID threshold on SBP and about 2 to 3 times larger than the MCID threshold on DBP at 150 min/week aerobic exercise. In the subgroup analyses of SBP and DBP, the summary results were the same across different subgroups defined by exercise modality, indicating that there were not any significant or credible effects by exercise intensity, modality, or type. However, most of the trials implemented running, walking, or jogging in their aerobic exercise program and thus, we had limited evidence about the effects of other types of aerobic exercise such as cycling or dancing on blood pressure. Three previous meta-analyses of RCTs investigated the effects of walking or running trainings on SBP in patients with hypertension and indicated that walking or running training can lead a significant and clinically important reduction in SBP [77,78,81].

Furthermore, our findings on the effects of each 30 min/week aerobic exercise on BP and ABP showed a significant but trivial reduction in SBP (MD = -1.78 mm Hg), DBP (MD = -1.23 mm Hg), 24hrs SBP (MD = -1.55 mm Hg), 24hrs DBP (MD = -0.72 mm Hg), and daily DBP (MD = -0.78 mm Hg). MCID for BP and ABP were 2; therefore, these results would not consider clinically significant. In other words, the significance of the 30-minute unit itself is not obvious in the content. On the other hand, the quality of evidence for all types of ABP was rated low to very low. We failed to observe significant effects on other outcomes including daily and nightly ambulatory SBP and nightly ambulatory DBP. Due to a few studies that assessed the ABP, we did not analyze the nonlinear dose-response. Cao's et al. meta-analysis found a significant reduction in 24hrs SBP and DBP. However, these reductions could account clinically significant (MD = -8.77 mm Hg for 24hrs SBP, MD = -4.90 mm Hg for 24hrs DBP), but it contained two studies [76]. A pairwise meta-analysis of 15 trials showed exercise could lead to a significant and clinically important reduction in 24hrs, daily, and nightly ambulatory systolic and diastolic BP in medicated hypertensive patients, but not for untreated. It should mention among all types of exercise, only aerobic exercise had effects on ABP [82]. Another review study confirmed too that aerobic exercise could reduce ABP, while resistance training only could be a complementary approach [83]. Notably, the trials which contained ABP as an outcome did not mention whether the exercise time has been done day or night.

The effect of aerobic exercise on haemodynamic factors

We found conflicting evidence about the effects of aerobic exercise on HR. Pooling 31 RCTs, Lee et al. showed that aerobic exercise significantly reduced HR (MD = -4.22 bpm) compared to the control group [77]. Another pairwise meta-analysis of RCTs in hypertensive patients aged 30-85 years suggested that HR significantly decreased (MD = −4.94 bpm) in the aerobic exercise programs compared to the control groups. Regular physical activity might reduce norepinephrine levels by about 30% [84]. So, it could cause HR reductions [85]. Whereas another meta-analysis did not show a significant effect of aerobic exercise on RHR [86]. The inconsistent results might be due to the different populations in which this study was performed on stroke patients, and the number of included studies was lesser.

We found that an increase in aerobic exercise up to 300 min/week reduced RHR ($MD_{300min/week}$ = -5.77 bpm; n = 23), exceeding the MCID threshold for RHR (-4.78 bpm). The subgroup analyses based on exercise modality, intensity, type, taking the antihypertensive drug, supervised exercise, weight status and intervention duration did not show a credible or significant subgroup effect. Furthermore, the results of our study suggested evidence of low certainty that every 30 min/week of aerobic exercise slightly reduced MAP, which was far smaller than the MCID threshold. We failed to observe significant effects on other hemodynamic factors such as HR_{max}, CO, PP, and peripheral resistance.

The effect of aerobic exercise on health-related quality of life

In our meta-analysis, aerobic exercise improved two components of each physical and mental assessment which are clinically significant. However, the quality of evidence for all components of QoL was rated very low. Another meta-analysis by Morris et al. represented that supervised exercise-based rehabilitation programs increased the Physical Component Score by 3.98 points and the Mental Component Score by 3.60 among people with pulmonary hypertension [87]. Physical activity affects releasing dopamine, serotonin, or noradrenaline. These neurotransmitter pathways cause well-being feelings and pain inhibiting. Worth mentioning also is the studies showed that supervised exercises and group activities have a higher advantage within the QoL score through social support [38].

Public and clinical implications

Our study showed that aerobic exercise can lead to a significant and clinically important reduction in SBP, DBP, and RHR in the main analyses and in the trials with moderate-intensity exercise programs. Based on the World Health Organization guideline, patients with hypertension should perform at least 150–300 min/week of moderate-intensity aerobic exercise to receive its beneficial effects [88]. Our findings suggest that the optimum duration of moderate-intensity aerobic exercise for reducing blood pressure is 150 min/week, and longer duration of aerobic exercise seems ineffective for further reductions. However, most of the trials performed running, walking, or jogging at moderate intensity in their intervention programs. In addition, only 4 trials were available with an intervention duration ≥6 months [39,45,52,55], and the quality of evidence was low and very low for most outcomes. Thus, more long-term RCTs would be needed to test the long-term effects of aerobic exercise programs in reducing blood pressure. We did not see a significant reduction in taking antihypertensive drugs with aerobic exercise that could be due to small number of trials that reported such outcome.

Strengths and limitations of the study

Our study was the first dose-response meta-analysis that assessed the dose-dependent effects of aerobic exercise on reducing blood pressure in the hypertensive population. We rated the certainty of evidence using the GRADE approach, and used the MCID thresholds to determine whether the results were clinically important. On the other hand, we had few trials with low intensity aerobic exercise, as well as for some types of aerobic exercise such as dancing or cycling. We also had limited evidence about the long-term efficacy of aerobic exercise in reducing blood pressure. In addition, most of the trials failed to report the effects of aerobic exercise on QoL and adverse events.

Conclusions

Based on low to moderate certainty evidence, our study showed that aerobic exercise can lead to a large and clinically important reduction in SBP, DBP, and RHR. The greatest reduction was seen at 150 min/week, suggesting that longer duration of aerobic exercise per week may be ineffective for further reduction in blood pressure. More trials are needed to assess the long-term efficacy of aerobic exercise programs on blood pressure in patients with hypertension.

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Author contributions SS-B designed the study. BJG, SZM, and ZGD: conducted the systematic search and data extraction; SZM and AJ: analyzed the data; BJG, SZM, MD, and RN: wrote the first draft; SZM, SS-B, MSG,

NM, RK, and AJ: entirely revised the manuscript; SSB, had main responsibility for the final manuscript; and all authors: read and affirmed the final manuscript.

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Supplementary Material Supplementary material including Supplementary Tables 1-13 and Supplementary Figures 1-28. Supplementary information is available at Hypertension Research's website.

References

1. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;**71**(6):1269-324.

2. O'Hare ABaR. More than 700 million people with untreated hypertension. https://www.who.int/news/item/25-08-2021-more-than-700-million-people-with-untreated-hypertension.

3. World Health Organization—A Global Brief on Hypertension | The International Society of Hypertension 2017. http://ish-world.com/news/a/World-Health-Organization-A-Global-Brief-onHypertension/.

4. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol.* 2015;**31**(5):549-68.

5. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press.* 2014;**23**(1):3-16.

6. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;**42**(6):1206-52.

7. Naci H, Salcher-Konrad M, Dias S, Blum MR, Sahoo SA, Nunan D, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. *Br J Sports Med.* 2019;**53**(14):859-69.

8. Pescatello LS, Buchner DM, Jakicic JM, Powell KE, Kraus WE, Bloodgood B, et al. Physical Activity to Prevent and Treat Hypertension: A Systematic Review. *Med Sci Sports Exerc.* 2019;**51**(6):1314-23.

9. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology (Bethesda).* 2013;**28**(5):330-58.

10. Valenzuela PL, Carrera-Bastos P, Gálvez BG, Ruiz-Hurtado G, Ordovas JM, Ruilope LM, et al. Lifestyle interventions for the prevention and treatment of hypertension. *Nat Rev Cardiol.* 2021;**18**(4):251-75.

11. Collier SR, Kanaley JA, Carhart R, Jr., Frechette V, Tobin MM, Hall AK, et al. Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre- and stage-1 hypertensives. *J Hum Hypertens.* 2008;**22**(10):678-86.

12. Medicine ACoS, Riebe D, Ehrman JK, Liguori G, Magal M. *ACSM's Guidelines for Exercise Testing and Prescription.* https://books.google.com/books?id=m_L-jwEACAAJ.). Wolters Kluwer2018.

13. Wen H, Wang L. Reducing effect of aerobic exercise on blood pressure of essential hypertensive patients: A meta-analysis. *Medicine (Baltimore).* 2017;**96**(11):e6150.

14. Sharman JE, La Gerche A, Coombes JS. Exercise and cardiovascular risk in patients with hypertension. *Am J Hypertens.* 2015;**28**(2):147-58.

15. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions.* https://books.google.com/books?id=pItOzQEACAAJ.). John Wiley & Sons, Incorporated2019.

16. Schunemann H. *GRADE handbook for grading quality of evidence and strength of recommendation.* http://www cc-ims net/gradepro.)2008.

17. Jabbarzadeh Ganjeh B, Zeraattalab-Motlagh S, Jayedi A, Daneshvar M, Gohari Z, Noorozi R, et al. The effectiveness of aerobic exercise for hypertensive population: a systematic review and dose-response meta analysis of randomized controlled trials. PROSPERO 2022 CRD42022329092 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022329092. 2022.).

18. Tsai JC, Yang HY, Wang WH, Hsieh MH, Chen PT, Kao CC, et al. The beneficial effect of regular endurance exercise training on blood pressure and quality of life in patients with hypertension. *Clin Exp Hypertens.* 2004;**26**(3):255-65.
19. Jayedi A, Emadi A, Shab-Bidar S. Dose-Dependent Effect of Supervised Aerobic Exercise on HbA(1c) in Patients with Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials. *Sports Med.* 2022(e-pub ahead of print 2022/04/02;doi:10.1007/s40279-022-01673-4).
20. Swain DP. Moderate or vigorous intensity exercise: which is better for improving aerobic fitness? *Prev Cardiol.* 2005;**8**(1):55-8.
21. Staying Active. https://www.hsph.harvard.edu/nutritionsource/staying-active/.
22. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;**343**:d5928.
23. Puchau B, Zulet MA, de Echávarri AG, Hermsdorff HH, Martínez JA. Dietary total antioxidant capacity: a novel indicator of diet quality in healthy young adults. *J Am Coll Nutr.* 2009;**28**(6):648-56.
24. Chandler J CM, Li T, Page M, Welch V. *Cochrane handbook for systematic reviews of interventions.*). Wiley: Hoboken, 2019.
25. Higgins JP DJ. Selecting studies and collecting data. In: *Cochrane handbook for systematic reviews of interventions: Cochrane book series.*)2008, 151-85.
26. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol.* 2006;**59**(1):7-10.
27. Crippa A, Orsini N. Dose-response meta-analysis of differences in means. *BMC Med Res Methodol.* 2016;**16**:91.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;**7**(3):177-88.
29. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *Cmaj.* 2020;**192**(32):E901-e6.
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* 1997;**315**(7109):629-34.
31. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;**50**(4):1088-101.
32. Higgins JP SJ, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: *Cochrane handbook for systematic reviews of interventions.*)2019, 205-28.
33. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *J Clin Epidemiol.* 2011;**64**(12):1283-93.
34. Guyatt G, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. Corrigendum to GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol 2011;64:1283-1293. *J Clin Epidemiol.* 2021;**137**:265.
35. Goldenberg JZ, Day A, Brinkworth GD, Sato J, Yamada S, Jönsson T, et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *Bmj.* 2021;**372**:m4743.
36. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care.* 2003;**41**(5):582-92.
37. Ammar T. Effects of aerobic exercise on blood pressure and lipids in overweight hypertensive postmenopausal women. *J Exerc Rehabil.* 2015;**11**(3):145-50.
38. Arija V, Villalobos F, Pedret R, Vinuesa A, Jovani D, Pascual G, et al. Physical activity, cardiovascular health, quality of life and blood pressure control in hypertensive subjects: randomized clinical trial. *Health Qual Life Outcomes.* 2018;**16**(1):184.
39. Arsenault BJ, Côté M, Cartier A, Lemieux I, Després JP, Ross R, et al. Effect of exercise training on cardiometabolic risk markers among sedentary, but metabolically healthy overweight or obese post-menopausal women with elevated blood pressure. *Atherosclerosis.* 2009;**207**(2):530-3.
40. Aweto HA, Owoeye OB, Akinbo SR, Onabajo AA. Effects of dance movement therapy on selected cardiovascular parameters and estimated maximum oxygen consumption in hypertensive patients. *Nig Q J Hosp Med.* 2012;**22**(2):125-9.
41. Azadpour N, Tartibian B, Kosar SN. Effects of aerobic exercise training on ACE and ADRB2 gene expression, plasma angiotensin II level, and flow-mediated dilation: a study on obese postmenopausal women with prehypertension. *Menopause-the Journal of the North American Menopause Society.* 2017;**24**(3):269-77.

42. Bertani RF, Campos GO, Perseguin DM, Bonardi JMT, Ferriolli E, Moriguti JC, et al. Resistance Exercise Training Is More Effective than Interval Aerobic Training in Reducing Blood Pressure During Sleep in Hypertensive Elderly Patients. *J Strength Cond Res.* 2018;**32**(7):2085-90.
43. Blumenthal JA, Siegel WC, Appelbaum M. Failure of Exercise to Reduce Blood Pressure in Patients With Mild Hypertension: Results of a Randomized Controlled Trial. *JAMA.* 1991;**266**(15):2098-104.
44. Boeno FP, Ramis TR, Munhoz SV, Farinha JB, Moritz CEJ, Leal-Menezes R, et al. Effect of aerobic and resistance exercise training on inflammation, endothelial function and ambulatory blood pressure in middle-aged hypertensive patients. *J Hypertens.* 2020;**38**(12):2501-9.
45. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure - A randomized controlled trial. *Jama-Journal of the American Medical Association.* 2007;**297**(19):2081-91.
46. Cononie CC, Graves JE, Pollock ML, Phillips MI, Sumners C, Hagberg JM. Effect of exercise training on blood pressure in 70- to 79-yr-old men and women. *Med Sci Sports Exerc.* 1991;**23**(4):505-11.
47. Duncan JJ, Farr JE, Upton SJ, Hagan RD, Oglesby ME, Blair SN. The Effects of Aerobic Exercise on Plasma Catecholamines and Blood Pressure in Patients With Mild Essential Hypertension. *JAMA.* 1985;**254**(18):2609-13.
48. Galdino G, Silva AM, Bogão JA, Jr., Braz de Oliveira MP, Araújo HA, Oliveira MS, et al. Association between respiratory muscle strength and reduction of arterial blood pressure levels after aerobic training in hypertensive subjects. *J Phys Ther Sci.* 2016;**28**(12):3421-6.
49. Georgiades A, Sherwood A, Gullette ECD, Babyak MA, Hinderliter A, Waugh R, et al. Effects of Exercise and Weight Loss on Mental Stress–Induced Cardiovascular Responses in Individuals With High Blood Pressure. *Hypertension.* 2000;**36**(2):171-6.
50. Hagberg JM, Montain SJ, Martin WH, 3rd, Ehsani AA. Effect of exercise training in 60- to 69-year-old persons with essential hypertension. *Am J Cardiol.* 1989;**64**(5):348-53.
51. Higashi Y, Sasaki S, Kurisu S, Yoshimizu A, Sasaki N, Matsuura H, et al. Regular Aerobic Exercise Augments Endothelium-Dependent Vascular Relaxation in Normotensive As Well As Hypertensive Subjects. *Circulation.* 1999;**100**(11):1194-202.
52. Kaholokula JK, Look M, Mabellos T, Ahn HJ, Choi SY, Sinclair KA, et al. A Cultural Dance Program Improves Hypertension Control and Cardiovascular Disease Risk in Native Hawaiians: A Randomized Controlled Trial. *Ann Behav Med.* 2021(e-pub ahead of print 2021/03/08;doi:10.1093/abm/kaaa127).
53. Knoepfli-Lenzin C, Sennhauser C, Toigo M, Boutellier U, Bangsbo J, Krustrup P, et al. Effects of a 12-week intervention period with football and running for habitually active men with mild hypertension. *Scand J Med Sci Sports.* 2010;**20 Suppl 1**:72-9.
54. Kokkinos PF, Narayan P, Colleran JA, Pittaras A, Notargiacomo A, Reda D, et al. Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. *N Engl J Med.* 1995;**333**(22):1462-7.
55. Krustrup P, Skoradal MB, Randers MB, Weihe P, Uth J, Mortensen J, et al. Broad-spectrum health improvements with one year of soccer training in inactive mildly hypertensive middle-aged women. *Scand J Med Sci Sports.* 2017;**27**(12):1893-901.
56. Kucio C, Narloch D, Kucio E, Kurek J. The application of Nordic walking in the treatment hypertension and obesity. *Family Medicine and Primary Care Review.* 2017;**19**(2):144-8.
57. Lamina S. Effects of continuous and interval training programs in the management of hypertension: a randomized controlled trial. *J Clin Hypertens (Greenwich).* 2010;**12**(11):841-9.
58. Laterza MC, de Matos L, Trombetta IC, Braga AMW, Roveda F, Alves M, et al. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension.* 2007;**49**(6):1298-306.
59. Liang JW, Zhang XY, Xia WH, Tong XZ, Qiu YX, Qiu YM, et al. Promotion of Aerobic Exercise Induced Angiogenesis Is Associated With Decline in Blood Pressure in Hypertension Result of EXCAVATION-CHN1. *Hypertension.* 2021;**77**(4):1141-53.
60. Maruf FA, Akinpelu AO, Salako BL, Akinyemi JO. Effects of aerobic dance training on blood pressure in individuals with uncontrolled hypertension on two antihypertensive drugs: a randomized clinical trial. *J Am Soc Hypertens.* 2016;**10**(4):336-45.
61. Motlagh Z, Hidarnia A, Kaveh MH, Kojuri J. Effect of Theory-Based Training Intervention on Physical Activity and Blood Pressure in Hypertensive Patients: A Randomized Control Trial. *Iranian Red Crescent Medical Journal.* 2017;**19**(7).

62. Nualnim N, Parkhurst K, Dhindsa M, Tarumi T, Vavrek J, Tanaka H. Effects of swimming training on blood pressure and vascular function in adults >50 years of age. *Am J Cardiol.* 2012;**109**(7):1005-10.
63. Pagonas N, Dimeo F, Bauer F, Seibert F, Kiziler F, Zidek W, et al. The impact of aerobic exercise on blood pressure variability. *J Hum Hypertens.* 2014;**28**(6):367-71.
64. Ramos RM, Coelho-Júnior HJ, do Prado RCR, da Silva RS, Asano RY, Prestes J, et al. Moderate Aerobic Training Decreases Blood Pressure but No Other Cardiovascular Risk Factors in Hypertensive Overweight/Obese Elderly Patients. *Gerontol Geriatr Med.* 2018;**4**:2333721418808645.
65. Ruangthai R, Phoemsapthawee J. Combined exercise training improves blood pressure and antioxidant capacity in elderly individuals with hypertension. *J Exerc Sci Fit.* 2019;**17**(2):67-76.
66. Sakai T, Ideishi M, Miura S, Maeda H, Tashiro E, Koga M, et al. Mild exercise activates renal dopamine system in mild hypertensives. *Journal of Human Hypertension.* 1998;**12**(6):355-62.
67. Saptharishi L, Soudarssanane M, Thiruselvakumar D, Navasakthi D, Mathanraj S, Karthigeyan M, et al. Community-based Randomized Controlled Trial of Non-pharmacological Interventions in Prevention and Control of Hypertension among Young Adults. *Indian J Community Med.* 2009;**34**(4):329-34.
68. Staffileno BA, Braun LT, Rosenson RS. The accumulative effects of physical activity in hypertensive post-menopausal women. *J Cardiovasc Risk.* 2001;**8**(5):283-90.
69. Staffileno BA, Minnick A, Coke LA, Hollenberg SM. Blood pressure responses to lifestyle physical activity among young, hypertension-prone African-American women. *J Cardiovasc Nurs.* 2007;**22**(2):107-17.
70. Tanabe Y, Urata H, Kiyonaga A, Ikeda M, Tanaka H, Shindo M, et al. Changes in serum concentrations of taurine and other amino acids in clinical antihypertensive exercise therapy. *Clin Exp Hypertens A.* 1989;**11**(1):149-65.
71. Tsai JC, Chang WY, Kao CC, Lu MS, Chen YJ, Chan P. Beneficial effect on blood pressure and lipid profile by programmed exercise training in Taiwanese patients with mild hypertension. *Clin Exp Hypertens.* 2002;**24**(4):315-24.
72. Tsai JC, Liu JC, Kao CC, Tomlinson B, Kao PF, Chen JW, et al. Beneficial effects on blood pressure and lipid profile of programmed exercise training in subjects with white coat hypertension. *Am J Hypertens.* 2002;**15**(6):571-6.
73. Wong A, Kwak YS, Scott SD, Pekas EJ, Son WM, Kim JS, et al. The effects of swimming training on arterial function, muscular strength, and cardiorespiratory capacity in postmenopausal women with stage 2 hypertension. *Menopause-the Journal of the North American Menopause Society.* 2019;**26**(6):653-8.
74. Yilmaz BC, Guclu MB, Keles MN, Tacoy GA, Cengel A. Effects of upper extremity aerobic exercise training on oxygen consumption, exercise capacity, dyspnea and quality of life in patients with pulmonary arterial hypertension. *Heart & Lung.* 2020;**49**(5):564-71.
75. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2002;**136**(7):493-503.
76. Cao L, Li X, Yan P, Wang X, Li M, Li R, et al. The effectiveness of aerobic exercise for hypertensive population: A systematic review and meta-analysis. *J Clin Hypertens (Greenwich).* 2019;**21**(7):868-76.
77. Lee SH, Chae YR. Characteristics of Aerobic Exercise as Determinants of Blood Pressure Control in Hypertensive Patients: A Systematic Review and Meta-Analysis. *J Korean Acad Nurs.* 2020;**50**(6):740-56.
78. Barcelos G, Heberle I, Coneglian J, Vieira B, Delevatti R, Gerage A. *Effects of Aerobic Training Progression on Blood Pressure in Individuals With Hypertension: A Systematic Review With Meta-Analysis and Meta-Regression.*doi:10.21203/rs.3.rs-156120/v1)2021.
79. Ruivo JA, Alcântara P. [Hypertension and exercise]. *Rev Port Cardiol.* 2012;**31**(2):151-8.
80. Hu G, Wang Z, Zhang R, Sun W, Chen X. The Role of Apelin/Apelin Receptor in Energy Metabolism and Water Homeostasis: A Comprehensive Narrative Review. *Frontiers in Physiology.* 2021;**12**.
81. Igarashi Y, Akazawa N, Maeda S. Regular aerobic exercise and blood pressure in East Asians: A meta-analysis of randomized controlled trials. *Clin Exp Hypertens.* 2018;**40**(4):378-89.
82. Saco-Ledo G, Valenzuela PL, Ruiz-Hurtado G, Ruilope LM, Lucia A. Exercise Reduces Ambulatory Blood Pressure in Patients With Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2020;**9**(24):e018487.
83. Cardoso CG, Jr., Gomides RS, Queiroz AC, Pinto LG, da Silveira Lobo F, Tinucci T, et al. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics (Sao Paulo).* 2010;**65**(3):317-25.
84. Börjesson M, Onerup A, Lundqvist S, Dahlöf B. Physical activity and exercise lower blood pressure in individuals with hypertension: narrative review of 27 RCTs. *Br J Sports Med.* 2016;**50**(6):356-61.

85. Aldred EM, Buck C, Vall K. Chapter 31 - The nervous system. In: Aldred EM, Buck C, Vall K (eds). *Pharmacology*.doi:https://doi.org/10.1016/B978-0-443-06898-0.00031-1) Churchill Livingstone: Edinburgh, 2009, 235-46.
86. Pang MY, Charlesworth SA, Lau RW, Chung RC. Using aerobic exercise to improve health outcomes and quality of life in stroke: evidence-based exercise prescription recommendations. *Cerebrovasc Dis.* 2013;**35**(1):7-22.
87. Morris NR, Kermeen FD, Jones AW, Lee JY, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev.* 2023;**3**(3):Cd011285.
88. Physical activity. https://www.who.int/news-room/fact-sheets/detail/physical-activity.

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Examining the Effect of Exercise and Physical Activity in Reducing the Desire for Social Sexual Deviations

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Abstract

Exercise and physical activity lead to short-term fatigue in the muscles and body, which will be different according to the intensity of the exercise. Sports activities that are carried out continuously help to reduce nervous disorders and reduce emotional problems and prevent the occurrence of many sexual disorders. Physical activity, especially aerobic exercise, which is performed continuously and continuously, helps to reduce nervous disorders, emotional problems and sexual coldness, and prevents the occurrence of many mental disorders and diseases and treats or reduces their complications. . The present study was conducted with the aim of investigating the effect of exercise and physical activity in reducing the desire for sexual and social deviations. Documentary and library methods were used in this research and they were further analyzed. The results showed that in recent years, the trend of spreading depression and anxiety and other mental disorders and especially sexual deviations (homosexuality) has increased significantly. By adjusting the body's hormonal status, exercise and physical activity reduce anxiety and depression, adjust and adjust the amount of stress, and even change personality in the form of a more positive outlook on life. After analyzing the documents, it was found that people who exercise have less anxiety, nervous tension, depression and fatigue and have more strength than other people. Also, the findings showed that nervous tension, depression, anger, fatigue and confusion and desire and tendency to sexual deviations all decrease after physical activities. While mental strength increases. Inactivity and not having a specific program for exercise and physical activity not among teenage and young boys and girls, but also among adults, causes a lack of concentration and a greater desire to use virtual space, followed by the occurrence of sexual deviations that occur with the advancement of technology and the vulgarity of space. Virtualization leads to this. Experts, researchers and experts in exercise physiology believe that exercise and physical activity control and adjust the body's hormones so that the sex hormones testosterone and estrogen reach a balance with physical activity and exercise. Traditionally, exercise is considered a strategic tool to encourage and develop healthy behaviors and a protective and preventive factor against high-risk behaviors, especially sexual risk-taking. Physiology experts believe that negative mental emotions are the main cause of diseases. This also applies to sexual deviations and homosexuality. By strengthening the body's organs and systems, and most importantly, the body's immune system, exercise copes with the occurrence of such emotions and moderates them if they exist. Also, by strengthening the nervous system and relieving nervous spasms, it deals with neurological and physiological diseases. Various stress and anxieties among young people and adults also cause the desire for sexual deviance, so that people who face a lot of stress often want to remove this anxiety from themselves in a new, different and fresh way that leads to deviations. It ends in sex. In response to mental and emotional pressures and stress, all body systems, including the nervous and automatic systems, the endocrine hormonal system, the cardiovascular system, prepare for the appropriate reaction, and as a result, stress hormones such as adrenaline, noradrenaline and Cortisol is released in the blood and the blood pressure increases, the speed of the blood flow increases, and the cardiovascular and respiratory systems perform their tasks faster. In this situation, if exercise and physical activity are done, all body systems, including the immune system, become resistant, and the process of their reaction and confrontation with the stressful factor is facilitated and corrected, and the person relaxes mentally. In relation to this issue, it should be acknowledged that stress hormones make the body hypervigilant and it is difficult to return them to their original state. Exercising can restore the nervous system to a normal state and improve blood circulation, and after that, stress hormones are cleared from the body system and the body returns to a normal state and balance. Therefore, it is suggested that the institutions in charge of this issue consider the unique impact of sports and physical activity in reducing sexual deviations and have their planning and organization aligned with this social issue.

Key words: exercise, physical activity, sexual desire

Reference

Behavior, Miller, E. M. (2000). Homosexuality, birth order, and evolution: Toward an equilibrium reproductive economics of homosexuality. Archives of Sexual Behavior, 29, 1-34.

Bokharayi, A.(2007), "the study of social abnormalities in Iran" . pezhvak publications, Tehran.223.224

Kooshafar, A.(2018), "principles and fundamentals of physical training". 1st edition, Azad university of Tabriz, 20.

Rieger, G., & Sanders, A. R. (2010). Biodemographic and physical correlates of sexual orientation in men. Archives of Sexual.129.

Suitable exercise protocol for people with fatty liver

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Abstract
Non-alcoholic fatty liver disease (NAFLD) is closely associated with other metabolic disease and cardiovascular disease. Regular exercise reduces hepatic fat content and could be the first-line treatment in the management of NAFLD. This review aims to summarize the current evidence of the beneficial effects of exercise training and identify the molecular pathways involved in the response to exercise to define their role in the resolution of NAFLD both in animal and human studies. According to the inclusion criteria, 43 animal studies and 14 RCTs were included in this systematic review. Several exercise modalities were demonstrated to have a positive effect on liver function. Physical activity showed a strong association with improvement in inflammation, and reduction in steatohepatitis and fibrosis in experimental models. Furthermore, both aerobic and resistance exercise in human studies were demonstrated to reduce liver fat, and to improve insulin resistance and blood lipids, regardless of weight loss, although aerobic exercises may be more effective. Resistance exercise is more feasible for patients with NAFLD with poor cardiorespiratory fitness. More effort and awareness should be dedicated to encouraging NAFLD patients to adopt an active lifestyle and benefit from it its effects in order to reduce this growing public health problem.
Keywords: physical activity, exercise training, liver diseases, fatty liver

What is steatotic (fatty) liver disease?
Steatotic liver disease (SLD) includes several conditions associated with steatosis in your liver. “Steatosis” is a term healthcare providers use to describe fat buildup in an organ (usually your liver). A healthy, high-functioning liver contains a small amount of fat. Fat buildup becomes a problem when it reaches over 5% of your liver’s weight.(2)

Why was fatty liver disease renamed steatotic liver disease?
Previously, steatotic liver disease was known as “fatty liver disease.” In 2023, experts renamed the condition and its subcategories to reflect its causes more accurately. For example, while some conditions associated with fat composition in your body (like obesity) can increase your risk of steatosis, there are several risk factors unrelated to weight or body mass index (BMI).(1)
The renaming also avoids language that’s potentially stigmatizing toward people with SLD.(5)

What are the types of steatotic (fatty) liver disease?
Healthcare providers classify SLD based on its causes and the conditions associated with it.(2)

Alcohol-related liver disease (ALD)
With ALD, steatosis occurs because of excessive alcohol consumption. Each time your liver filters alcohol, some of its cells die. Usually, your liver can make new cells to replace the old ones, so there isn’t a problem. But if you drink too much alcohol, your liver may not be able to keep up. Instead, steatosis may set in.(4)

Metabolic dysfunction-associated steatotic liver disease (MASLD)
Previously, healthcare providers referred to MASLD as non-alcohol related fatty liver disease (NASLD) because the steatosis isn’t associated with heavy alcohol consumption. Experts renamed the condition to reflect what the fat buildup in your liver is associated with. With MASLD, the culprit is cardiometabolic risk.(6)
factors.These factors include conditions and characteristics that pose risks to your heart health.
Risk factors associated with MASLD include:
Obesity.
Type 2 diabetes.
High blood pressure.
Lipid abnormalities (lipids are fatty compounds found in cells).

MASLD also applies if you consume small amounts of alcohol weekly. "Small amounts" means less than 140 grams per week for people assigned female at birth (AFAB) and less than 210 grams per week for people assigned male at birth (AMAB). For reference, in the U.S., one standard, 12-oz. beer contains about 14 grams of alcohol.(7)

Metabolic-associated steatohepatitis (MASH)

Metabolic-associated steatohepatitis (MASH) is a serious form of MASLD. With MASH, fat buildup progresses to inflammation, then tissue damage and scarring (fibrosis). Previously, healthcare providers referred to MASH as non-alcohol related steatohepatitis (NASH).

MASLD and increased alcohol intake (MetALD)

If you have MetALD, both metabolic risk factors and alcohol consumption play a role in fat buildup in your liver. With MetALD, you have a cardiometabolic risk factor and consume more than 140 grams per week (AFAB) or more than 210 grams per week (AMAB).

What contributes most to the fat buildup in your liver (alcohol consumption or metabolic risk factors) varies from person to person.(8)

Other forms of SLD

SLD can result from causes other than alcohol use or cardiometabolic risk factors. For example, various medications and diseases can cause steatosis. Sometimes, healthcare providers can't identify a specific cause. SLD without a clear cause is called cryptogenic SLD.(10)

Is steatotic (fatty) liver disease a serious problem?

In most cases, the fat buildup doesn't cause serious problems or prevent your liver from functioning normally.(11)

In some cases, the condition progresses to liver disease. It usually progresses in stages:

Hepatitis: Your liver goes from fatty to inflamed (swollen). The inflammation damages tissue. This stage is called steatohepatitis. For example, this is what happens when MASLD becomes MASH.

Fibrosis: Bands of scar tissue form where the inflammation damages your liver, causing it to stiffen. This process is called fibrosis.

Cirrhosis: Extensive scar tissue replaces healthy tissue. At this point, you have cirrhosis of the liver. Without treatment, cirrhosis can lead to potentially fatal conditions like liver failure and liver cancer. About 90% of people who develop hepatocellular carcinoma (HCC) — a type of liver cancer — have cirrhosis.

This is why it's so important to learn what's causing fat buildup in your liver and get treated. Even if you have early-stage cirrhosis, there are steps you can take to protect your liver from further damage. In some instances, you can even reverse some damage by following your provider's treatment plan for you.(13)

Symptoms and Causes

What are the signs and symptoms of steatotic (fatty) liver disease?

SLD doesn't always cause symptoms. When they're present, symptoms include:

Abdominal pain or a feeling of fullness in the upper right side of your abdomen (belly).

Extreme exhaustion or weakness (fatigue).

More commonly, people notice symptoms once SLD has progressed to cirrhosis of the liver. When cirrhosis develops, you may experience:

Nausea.

Loss of appetite.

Unexplained weight loss.

Yellowish skin and whites of the eyes (jaundice).

Swelling in your abdomen (ascites)

Swelling in your legs, feet or hands (edema).

Bleeding (that your provider finds in your esophagus, stomach or rectum).

What causes steatotic (fatty) liver disease?

SLD has multiple causes. Still, you're more likely to develop SLD if you have a cardiometabolic risk factor, if you consume unhealthy amounts of alcohol or both.

You have a greater chance of developing SLD if you:

Have alcohol use disorder (frequent or heavy alcohol use).

Have metabolic syndrome (insulin resistance, high blood pressure, high cholesterol and high triglyceride levels).

Have Type 2 diabetes.

Have overweight (BMI 25 to 29.9 kilograms kg/m2).

Have obesity (BMI 30 kg/m2 and above).

Have polycystic ovary syndrome (PCOS).

Have obstructive sleep apnea.

Have hypothyroidism (low thyroid hormones).

Have hypopituitarism (low pituitary gland hormones).

Have hypogonadism (low sex hormones).

Take certain prescription medications, such as amiodarone (Cordarone®), diltiazem (Cardizem®), tamoxifen (Nolvadex®) or steroids. (Fat buildup in your liver can be a medication side effect.)

What are the complications of SLD?

Without treatment, a steatotic liver can progress to cirrhosis of the liver, which can lead to liver failure, liver cancer and cancers outside your liver. People with MASLD are also at increased risk of heart disease. Heart disease — not liver disease — is the leading cause of death in people with MASLD.(12)

Diagnosis and Tests

How is steatotic (fatty) liver disease diagnosed?

Because SLD doesn't usually cause symptoms, your healthcare provider may be the first to notice an issue. High levels of liver enzymes that turn up on a blood test for other conditions may raise a red flag. Elevated liver enzymes are a sign your liver is injured.

To make a diagnosis, your provider may perform:

A medical history that includes questions about your conditions, how much alcohol you drink and which medicines you're taking.

A physical exam to check for signs of inflammation, like an enlarged liver, or signs of cirrhosis, like jaundice.

Imaging procedures, including an ultrasound, CT scan (computed tomography scan) or MRI (magnetic resonance imaging), to check your liver for signs of inflammation and scarring. They may order a specialized ultrasound called FibroScan® to learn the amount of fat and scar tissue in your liver.

A liver biopsy (tissue sample) to determine how far the liver disease has progressed. A liver biopsy is the only way to distinguish MASLD from MASH.

. Exercise Items

The exercise prescription items included the following: aerobic exercises aimed at improving overall physical strength and endurance, such as brisk walking, jogging, badminton, cycling, Taichi boxing, and eight-section brocade.

2.1. Basic Exercises: Brisk Walking and Jogging

Brisk walking and jogging are currently the most popular exercises and have the advantages of easily controlled exercise intensity and volume, fewer sports injuries, and simple and easy realization, which is suitable for various populations. Brisk walking is a type of low-intensity aerobic exercise, the essentials of which are as follows: first, breathe naturally and relax the body; second, keep the head up, chest out, and abdomen in; and third, swing the arms naturally and place the center of gravity on the feet. Jogging, also known as slow-paced running, is a type of medium-intensity aerobic exercise, the essentials of which are as follows: first, breathe naturally, relax the upper limbs, and keep the muscles of the lower limbs elastic to avoid injuries; second, lean forward, relax the shoulders, and swing the arms naturally (the range should be natural and comfortable); third, land gently on the forefeet.

References have revealed that brisk walking and jogging promote fat consumption to realize fast weight loss. Brisk walking and jogging can help maintain cardiac function in the middle-aged and elderly, slow the decline in lung elasticity, and exert positive effects in preventing diseases, such as coronary heart disease, hypertension, and arteriosclerosis (12)

2.2. Sports: Swimming, Badminton, and Cycling

Because fatty liver currently has a younger age of onset than in the past, young people can achieve quick therapeutic efficacy through sports, such as swimming, badminton, and cycling, which have the advantages of high exercise intensity and fast benefits. Experimental research has confirmed that [5, 6] sports, by regulating the

lipid metabolism, antioxidation, and inflammation suppression, may ameliorate the level of blood lipids in hyperlipidemic rats. The possible mechanisms underlying swimming in treating fatty liver have been reported as follows: first, sports can repress lipid synthesis in the liver by downregulating the levels of lipid synthesis-related gene expression, such as SREBP-1c and SCD1 [7–9]; second, sports can facilitate the phosphorylation of Akt in the liver and raise the sensitivity to insulin [10–12]; third, sports can upregulate the expression of PPARα, thus enhancing the oxidation of fatty acids in the liver [13–15]. There are many references involving the treatment of fatty liver by swimming, but few studies on other sports are available. Nevertheless, badminton, cycling, and other aerobic exercises can also achieve good therapeutic efficacy on fatty liver.

3. Exercise Intensity, Duration, and Frequency

3.1. Exercise Intensity

Long-term medium and low-intensity general aerobic exercises are most suitable for fatty liver patients. Because the majority of fatty liver patients are accompanied by different degrees of hypertension, overload exercise may induce cardiovascular and cerebrovascular diseases, so it is of vital importance to control the exercise intensity. Fatty liver patients should adopt different exercise intensities according to age and constitution, and the following criteria can be used for evaluation: first, the suggested heart rate variation range is 45–60 beats/min before and after exercise; second, the heart rate in the quiet state is taken as the standard, and it is suggested that the heart rate should revert to the standard level 3–5 min after exercise.

3.2. Exercise Duration and Frequency

The recommended frequency of brisk walking and jogging is 3–6 times per week for 40–90 min (or 3–6 km) each time. Attention should be paid to speed control, and it is best to sweat slightly. When the patients are out of breath, they are engaged in anaerobic exercise. In addition, the patients are suggested to do one of the sports, such as swimming, badminton, and cycling (2-3 times per week for 30–60 min each time) without feeling obvious fatigue after the sports. It is also recommended to practice one of the TCM exercises, such as Taichi boxing and eight-section brocade, 30–6 times per week for 30–45 min (2-3 repeats) each time.

Summary

As an essential organ of the human lipid metabolism, the liver is mainly responsible for excretion of lipids into blood in the form of very low-density lipoprotein and synthesis of triglycerides by absorbing free fatty acids from blood [24]. At present, people are prone to overeating due to improved living standards. As a result, excessive calories are converted into fatty acids, which enter the liver beyond the processing capacity of the liver, thus accumulating in the liver and inducing fatty liver [25]. Thus far, no specific drug for fatty liver has been developed, and exercise training plays a positive and critical role in the treatment of fatty liver. In this study, therefore, the efficacy of different exercise trainings on fatty liver patients was investigated, and suggestions were proposed regarding exercise intensity, duration, frequency, and precautions. In addition, exercise prescriptions were advanced for patients of different ages. It is expected that with the help of more standardized exercise prescription suggestions, more scientific and reasonable exercise schemes can be provided for patients.

References

١- Antunes C, Azadfard M, Hoilat GJ, et al. Fatty Liver (https://www.ncbi.nlm.nih.gov/books/NBK441992/). 2023 Jan 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Accessed 9/27/2023.

٢-National Institute of Diabetes and Digestive and Kidney Diseases (U.S.). Definition and Facts of NAFLD and NASH (https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts). Last reviewed 4/2021. Accessed 9/27/2023.

٣-National Library of Medicine (U.S.). Non-alcoholic Fatty Liver Disease (https://ghr.nlm.nih.gov/condition/non-alcoholic-fatty-liver-disease#inheritance). Last updated 11/1/2016. Accessed 9/27/2023.

۴-Patel R, Mueller M. Alcoholic Liver Disease (https://www.ncbi.nlm.nih.gov/books/NBK546632/). 2022 Oct 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Accessed 9/27/2023.

۵-Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease (https://pubmed.ncbi.nlm.nih.gov/33894145/). Lancet. 2021;397(10290):2212-2224. Accessed 9/27/2023.

۶-Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature [published online ahead of print, 2023 Jun 24]. Hepatology. 2023;10.1097/HEP.0000000000000520. Accessed 9/27/2023.

۷-Wong T, Dang K, Ladhani S, Singal AK, Wong RJ. Prevalence of Alcoholic Fatty Liver Disease Among Adults in the United States, 2001-2016 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6506872/#:~:text=Among%2034%20423%20respondents%20included,%25%2D5.1%25)%20(P%20%3D%20.). JAMA. 2019;321(17):1723-1725. Accessed 9/27/2023.

8. Wong K. K., Chen S., Wu Y., Bufi R., Pescatello L. S. Exercise as A treatment for non-alcoholic fatty liver disease: a meta-review. Medicine and Science in Sports and Exercise . 2021;53:p. 455. doi: 10.1249/01.mss.0000764536.12942.8d. [PubMed] [CrossRef] [Google Scholar]

9. Kim H. S., Ike A., Mathew J. Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver. Journal of Hepatology . 2016;66(3):664–665. [PubMed] [Google Scholar]

10. Thorp A., Stine J. G. Exercise as medicine: the impact of exercise training on nonalcoholic fatty liver disease. Current hepatology reports . 2020;19(4):402–411. doi: 10.1007/s11901-020-00543-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

11. Zhang H.-J., Pan L.-L., Ma Z.-M., et al. Long-term effect of exercise on improving fatty liver and cardiovascular risk factors in obese adults: a 1-year follow-up study. Diabetes, Obesity and Metabolism . 2017;19(2):284–289. doi: 10.1111/dom.12809. [PubMed] [CrossRef] [Google Scholar]

12. Zhao L., Xu X. Effect of aerobic and resistance exercise on fatty liver in mice model: 2578 board #242 may 31 11:00 am-12:30 pm. Medicine and Science in Sports and Exercise . 2019;51:p. 718. doi: 10.1249/01.mss.0000562639.68532.15. [CrossRef] [Google Scholar]

13. Zheng F., Ying C. GW29-e0215 Long-term exercise alleviates non-alcoholic fatty liver disease and insulin resistance via regulating lipid metabolism in ApoE-null mice. Journal of the American College of Cardiology . 2018;72(16):C7–C8. doi: 1016/j.jacc.2018.08.032. [CrossRef] [Google Scholar]

The effect of exercise for patients with sarcopenia

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Abstract

Background

Many clinical practice guidelines strongly recommend exercise as an intervention for patients with sarcopenia. However, the significance of exercise on patient-important outcomes in older adults with sarcopenia is inconsistent when considering available minimal important differences. To synthesize current systematic review and meta-analyses evidence on the efficacy of exercise on patient-important outcomes in the treatment of sarcopenia in older adults.

Results

This umbrella review provided a broad overview of the existing evidence and evaluated the systematic reviews' methodological quality and evidence for all these associations. In older patients with sarcopenia, moderate- to high-quality evidence showed that exercise intervention probably increases walking speed and improved physical performance (measured by TUG test); exercise may increase the muscle strength (grip strength, keen extension strength); but the effect size for grip strength probably too small to achieve patients important changes. Evidence for older people with sarcopenic obesity is limited, and we found the consistent effect of exercise interventions on grip strength and usual walking speed.

Conclusion

Exercise has a positive and important effect on physical performance for older adults with sarcopenia, which supports leaving the current recommendations unchanged. New systematic reviews to summarize the effect of exercise on the quality of life are warranted to fill the current evidence gap.

Keywords: exercise, sarcopenia, meta-analyses, umbrella review, randomized controlled trials

Introduction

Sarcopenia is a generalized and progressive skeletal muscle disorder that involves the accelerated loss of muscle mass and muscle function (1) and has been recognized as an independent disease with an International Classification of Diseases-10 code (M62.84) by the World Health Organization (WHO) in 2016 (2). Recognition of sarcopenia as a disease has led to major research efforts into the best screening, diagnosis, treatment, and management practices.

People with malnutrition are at a high risk of sarcopenia and these two common geriatric syndromes are closely related to each other (3). However, there is another state that co-exisit of sarcopenia and obesity, which refers to sarcopenic obesity (4). Sarcopenia synergistically worsens the adverse effects of obesity in older adults. Obesity also impairs muscle quality and decreases physical function (5, 6). Sarcopenic obesity combines the negative effects of sarcopenia and obesity in older adults and can result in metabolic problems, poor quality of life, disability, hospitalization, and death (7). By translating current, comprehensive evidence into clinical practice, it may be possible to reduce the risk for functional decline, falls, fractures, hospitalization, and mortality associated with sarcopenia or sarcopenic obesity (8, 9).

The most widely cited definition is proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) (10) and updated as EWGSOP2 (11) in January 2019. In clinical practice, a person with low muscle strength and low muscle mass or quality will be diagnosed with sarcopenia by EWGSOP2. The WHO has shifted the focus of providing comprehensive care for older adults from a disease-centred model to a function-centred model. Emphasis on muscle strength and physical function can merit lifelong monitoring. According to the evidence-based clinical practice guidelines published in 2018, grip strength, keen extension strength, walking speed are regarded as critically important (12). Therefore, we defined the patient important outcome as muscle function, physical function, all-cause mortality and quality of life.

The current non-pharmacological interventions for sarcopenia are mainly exercise and nutritional interventions. Because of the lack of high-quality evidence for nutrition, in this paper, we focus on evidence examining exercise interventions compared to background therapy (with or without nutritional intervention). In detail, we included the following comparisons: exercise alone vs. usual care, exercise plus nutrition vs. nutrition alone. Based on previous systematic reviews, most guidelines provided strong recommendations for exercise/physical activity as the primary treatment for older adults with sarcopenia (12–15). A previous systematic umbrella review supports that resistance training or multimodal exercise therapy (includes a combination of resistance training, aerobic training, balance training, walking, and other types of training) can improve muscle mass, muscle strength, and physical performance in patients with sarcopenia (16). However, another umbrella review demonstrated limited quality evidence of the positive effects of mixed and resistance training in treating sarcopenia (17). Although previous systematic reviews reported that exercise had a statistically significant impact on related measurement, they did not assess if these changes exceed patients' minimal important difference (MID). Due to the inconsistency of the evidence described above and lack of considering MID among previous systematic reviews, we performed an umbrella meta-analysis based on all the current evidence already studied to understand better the role of exercise in the treatment for sarcopenia.

Methods

Search Strategy

We searched MEDLINE, EMBASE, Cochrane Library (Cochrane database of systematic review, CDSR) via OvidSP and Web of science until April 2021 using a comprehensive search strategy (Supplementary Table 1) to find meta-analyses or systematic review. Search terms constructed coverage for umbrella reviews according to the PICOS framework. The searches will be developed and combined using broad search terms, keywords and MeSH terms: Participants (P): sarcopenia (e.g., sarcopeni* or myopeni* or dynaponi*); Study design (S): Review, Systematic review, meta-analysis, meta-regression, meta-synthesis, realist review, realist synthesis, rapid review, pragmatic review, umbrella review. In addition, we manually searched references that were finally included in the study. This meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (18).

Selection Criteria

Two reviewers independently selected the titles, abstracts and full texts according to the inclusion and exclusion criteria. Any disagreements were solved by consensus and, if disagreement persisted, by a third reviewer. We included meta-analyses of RCTs that compared any category of exercise intervention with a control group of older patients (≥60 years) with sarcopenia. Sarcopenia diagnosed in any way was included. Also, research must be published in English. We only included the articles that have done meta-analysis, and systematic reviews without meta-analysis and animal studies were excluded.

Data Extraction

Data were extracted by one investigator, then checked by a second investigator. We first extracted data from eligible meta-analyses on the first author, year of publication, search date, number of trials, sample size, age, gender, interventions, diagnostic criteria of sarcopenia, duration of intervention and follow-up time, metric of effect size, effect size with 95% CI and value of I2. Second, meta-analyses investigating multiple outcomes were recorded separately. Third, if there are several meta-analyses on the same intervention and the same outcome, data were extracted from the largest meta-analysis (that is, we chose the effect size of the meta-analysis with the highest number of RCTs). Among them, we included a meta-analysis of the study with the largest number of RCTs (19), in which controlled clinical trial (CCT) was also included. We excluded CCT and re-extracted and merged the data of RCTs.

The Outcomes

The outcomes of interest were muscle or physical function, including but not limited to muscle strength, gait speed. Although sarcopenic obesity is a form of sarcopenia, it has its specific characteristics. We report the results of the study of patients with sarcopenic obesity separately. We are also concerned about the impact of exercise on mortality and quality of life in sarcopenia, as these are patient-important outcomes. We did not consider muscle mass because most people would not put much attention only on the outcome.

Quality Assessment

We used A MeaSurement Tool to Assess systematic Reviews 2(AMSTAR2) (20) to assess the methodological quality of meta-analysis. It retains 10 of the original domains, has 16 items in total (compared with 11 in the original), has simpler response categories than the original AMSTAR (21), includes a more comprehensive user

guide, and has an overall rating based on weaknesses in critical domains (20). Seven domains (item 2,4,7,9,11,13,15) can critically affect the validity of a review and its conclusions be regarded as weaknesses. AMSTAR 2 does not have an overall score. In AMSTAR 2, the methodological quality was usually categorized as high (No or one non-critical weakness), moderate (More than one non-critical weakness), low (One critical flaw with or without non-critical weaknesses), and critically low (More than one critical flaw with or without non-critical weaknesses) (20). Two authors independently assessed the AMSTAR 2; any disagreements were solved by consensus and by a third reviewer if disagreement persisted.

Quality of Overall Evidence

We conducted quality of evidence assessment through the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) framework, which evaluated the quality of evidence as high, moderate, low, and very low for each outcome in the pooled analyses (22) (see Supplementary Table 2). Two reviewers performed these assessments under the supervision of a third reviewer.

Discussion

Principal Findings

In this umbrella review, we provided a broad overview of the existing evidence and evaluated the methodological quality of the meta-analyses and quality of evidence for all these associations. In older patients with sarcopenia, moderate to high-quality evidence showed that exercise intervention probably increases usual walking speed (max) and improved physical performance (measured by TUG test); exercise may increase the muscle strength (grip strength, keen extension strength); but the effect size for grip strength probably too small to achieve patients important changes. Evidence for older people with sarcopenic obesity is limited, and we found the consistent effect of exercise interventions on grip strength and usual walking speed.

Comparison With Other Studies

Our research supports the recommendations from the clinical guideline by Dent et al. (12) and the umbrella systematic review (16) published in 2019 (exercise therapy can improve muscle strength and physical performance in patients with sarcopenia).

We found a statistically significant effect of exercise on grip strength, but the effect may not important to patients. It may be that the type of exercise in the studies we included was not divided into subgroups according to resistance exercise, aerobic exercise and combined exercise; if it had been resistance exercise, this value would probably have reached the MID. In addition, the MIDs were not generated from sarcopenic population as there is no MID for the sarcopenic population. The MID for grip strength in the sarcopenic population may be smaller than the MID for the people we select (American adults with recent stroke), the MID is an individualized thing, the MID only reflects the mean value of the population, which may be important for some individuals to change.

Strengths and Limitations

Our umbrella review had several strengths. (1) It provided a systematic, comprehensive overview of the evidence from all published meta-analyses regarding the role of exercise in the prevention of sarcopenia. (2) Another advantage of our literature study is that it provides a higher level of evidence than narrative reviews, and our umbrella review considers for inclusion the highest level of evidence (meta-analyses). (3) We also evaluated the methodological quality and quality of evidence by using the AMSTAR 2-criteria. Based on these scientific quality assessments, we concluded that the quality of our articles could be supported. (4) In the study, we also applied the minimally important difference (MID) for outcomes to assess if the effects matter to patients.

Our study also had several limitations. (1) Our umbrella review is dependent on the quality of the included systematic reviews/meta-analyses. We were unable to perform further subgroup analyses of exercise. Due to the lack of available evidence, we could not determine the most appropriate type (e.g., resistance exercise, aerobic exercise) or dose (e.g., duration, frequency, number of repetitions) of exercise to treat older adults with sarcopenia. (2) We did not assess the quality of individual randomized clinical trials and only combined the part of original data from selected clinical trials for analysis. (3) We ended up with a small number of included studies. This is also reflected by the fact that none of the included studies reported on the effect of exercise on mortality, quality of life, falls, fractures, etc., in patients with sarcopenia. There were also few included studies focused on obesity sarcopenia, evidence for older people with sarcopenic obesity is limited and needs further investigation. (4) Although several working groups have recommended definitions of “sarcopenia” (10, 38, 39), there are no universally accepted diagnostic criteria for sarcopenia, and these definitions vary slightly. The studies we included did not distinguish between these diagnostic criteria and included all studies that diagnosed sarcopenia, which

may lead to a high degree of heterogeneity in our study. (5) Results should be viewed with caution due to the small sample size and the critically low methodology of meta-analysis.

Future Directions

To better guide clinicians in intervening with exercise in sarcopenia, the authors recommend that researchers apply the new operational definition of sarcopenia, using the recommended cut-points for identifying participants and measuring outcomes. Although exercise appears to improve sarcopenia in the short term, studies on long-term outcomes such as quality of life, and death are still needed. Large-scale RCT studies are needed to determine which types (e.g., resistance training, mixed training) and doses (e.g., frequency, repetitions, time) of exercise are more beneficial for older patients with sarcopenia. Exercise is a relatively low-cost and potentially low-risk treatment for sarcopenia. With the growing interest in sarcopenia, we need more and better research in this area to guide clinical practice.

Conclusion

Exercise has a positive and important effect on physical performance (walking speed and TUG test) for older adults with sarcopenia. The effect of exercise on muscle strength may not be important for older people with sarcopenia. Our results support leaving the current recommendations about exercise for older people with sarcopenia unchanged. New systematic reviews to summarize the effect of exercise on the quality of life or new clinical trials focus on all patients-important outcomes are warranted to fill the current evidence gap.

Sources in the text are referred to as century numbers

References

1. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet.* (2019) 393:2636–46. 10.1016/S0140-6736(19)31138-9

2. Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia Muscle.* (2016) 7:512–4. 10.1002/jcsm.12147

3. Sieber CC. Malnutrition and sarcopenia. *Aging Clin Exp Res.* (2019) 31:793–8. 10.1007/s40520-019-01170-1

4. Goisser S, Kemmler W, Porzel S, Volkert D, Sieber CC, Bollheimer LC, et al.. Sarcopenic obesity and complex interventions with nutrition and exercise in community-dwelling older persons–a narrative review. *Clin Interv Aging.* (2015) 10:1267–82. 10.2147/CIA.S82454

5. Brady AO, Straight CR, Evans EM. Body composition, muscle capacity, and physical function in older adults: an integrated conceptual model. *J Aging Phys Act.* (2014) 22:441–52. 10.1123/JAPA.2013-0009

6. Maffiuletti NA, Jubeau M, Munzinger U, Bizzini M, Agosti F, De Col A, et al.. Differences in quadriceps muscle strength and fatigue between lean and obese subjects. *Eur J Appl Physiol.* (2007) 101:51–9. 10.1007/s00421-007-0471-2

7. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care.* (٢٠١٨) 11:693–700. 10.1097/MCO.0b013e328312c37d

8. Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Ortolani E, et al.. Sarcopenia: an overview on current definitions, diagnosis and treatment. *Curr Protein Pept Sci.* (2018) 19:633–8. 10.2174/1389203718666170607113459

9. Pérez-Zepeda MU, Sgaravatti A, Dent E. Sarcopenia and post-hospital outcomes in older adults: a longitudinal study. *Arch Gerontol Geriatr.* (2017) 69:105–9. 10.1016/j.archger.2016.10.013

10. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al.. Sarcopenia: European consensus on definition and diagnosis: report of the european working group on sarcopenia in older people. *Age Ageing.* (٢٠١٩) 39:412–23. 10.1093/ageing/afq034

11. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al.. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:601. 10.1093/ageing/afz046

12. Dent E, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, et al.. International Clinical Practice Guidelines for Sarcopenia (ICFSR): screening, diagnosis and management. *J Nutr Health Aging.* (2018) 22:1148–61. 10.1007/s12603-018-1139-9

13. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al.. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. *Report Int Sarcopenia Initiative (EWGSOP and IWGS) Age Ageing.* (2014) 43:748–59. 10.1093/ageing/afu115

14. De Spiegeleer A, Petrovic M, Boeckxstaens P, Van Den Noortgate N. Treating sarcopenia in clinical practice: where are we now? *Acta Clin Belg.* (2016) 71:197–205. 10.1080/17843286.2016.1168064
15. Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Med Direct Assoc.* (2017) 18:553.e551–3.e516. 10.1016/j.jamda.2017.03.019
16. Beckwée D, Delaere A, Aelbrecht S, Baert V, Beaudart C, Bruyere O, et al.. Exercise interventions for the prevention and treatment of Sarcopenia. A systematic umbrella review. *J Nutr Health Aging.* (2019) 23:494–502. 10.1007/s12603-019-1196-8
17. Moore SA, Hrisos N, Errington L, Rochester L, Rodgers H, Witham M, et al.. Exercise as a treatment for sarcopenia: an umbrella review of systematic review evidence. *Physiotherapy.* (2020) 107:189–201. 10.1016/j.physio.2019.08.005
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (20۲۳) 339:b2535. 10.1136/bmj.b2535
19. Bao W, Sun Y, Zhang T, Zou L, Wu X, Wang D, et al.. Exercise programs for muscle mass, muscle strength and physical performance in older adults with sarcopenia: a systematic review and meta-analysis. *Aging Dis.* (2020) 11:863–73. 10.14336/AD.2019.1012
20. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al.. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* (2017) 358:j4008. 10.1136/bmj.j4008
21. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al.. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* (۲۰۲۰) 7:10. 10.1186/1471-2288-7-10
22. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al.. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* (۲۰۲۳) 336:924–6. 10.1136/bmj.39489.470347.AD [
23. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* (2015) 13:132–40. 10.1097/XEB.0000000000000055
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (۲۰۲۲) 315:629–34. 10.1136/bmj.315.7109.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (۲۰۲۱) 327:557–60. 10.1136/bmj.327.7414.557
26. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol.* (2015) 14:263–73. 10.1016/S1474-4422(14)70267-4
27. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al.. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ.* (۲۰۱۸) 343:d4002. 10.1136/bmj.d4002
28. Bohannon RW. Minimal clinically important difference for grip strength: a systematic review. *J Phys Ther Sci.* (2019) 31:75–8. 10.1589/jpts.31.75
29. Bohannon RW, Glenney SS. Minimal clinically important difference for change in comfortable gait speed of adults with pathology: a systematic review. *J Eval Clin Pract.* (2014) 20:295–300. 10.1111/jep.12158
30. Maldaner N, Sosnova M, Ziga M, Zeitlberger AM, Bozinov O, Gautschi OP, et al.. External validation of the minimum clinically important difference in the timed-up-and-Go (TUG) test after surgery for lumbar degenerative disc disease. *Spine*. (2021). 10.1097/BRS.0000000000004128
31. Vlietstra L, Hendrickx W, Waters DL. Exercise interventions in healthy older adults with sarcopenia: a systematic review and meta-analysis. *Australas J Ageing.* (2018) 37:169–83. 10.1111/ajag.12521
32. Hsu KJ, Liao CD, Tsai MW, Chen CN. Effects of exercise and nutritional intervention on body composition, metabolic health, and physical performance in adults with sarcopenic obesity: a meta-analysis. *Nutrients.* (2019) 11:09. 10.3390/nu11092163

33. Yin YH, Liu JYW, Valimaki M. Effectiveness of non-pharmacological interventions on the management of sarcopenic obesity: a systematic review and meta-analysis. *Exp Gerontol.* (2020) 135:110937. 10.1016/j.exger.2020.110937 [
34. Wu PY, Huang KS, Chen KM, Chou CP, Tu YK. Exercise, nutrition, and combined exercise and nutrition in older adults with Sarcopenia: a systematic review and network meta-analysis. *Maturitas.* (2021) 145:38–48. 10.1016/j.maturitas.2020.12.009
35. Maruya K, Asakawa Y, Ishibashi H, Fujita H, Arai T, Yamaguchi H. Effect of a simple and adherent home exercise program on the physical function of community dwelling adults sixty years of age and older with pre-sarcopenia or sarcopenia. *J Phys Ther Sci.* (2016) 28:3183–8. 10.1589/jpts.28.3183
36. Oh MK, Yoo JI, Byun H, Chun SW, Lim SK, Jang YJ, et al.. Efficacy of combined antigravity treadmill and conventional rehabilitation after hip fracture in patients with Sarcopenia. *J Gerontol Seri A-Biol Sci Med Sci.* (2020) 75:e173–81. 10.1093/gerona/glaa158
37. Sen EI, Eyigor S, Dikici Yagli M, Ozcete ZA, Aydin T, Kesiktas FN, et al.. Effect of home-based exercise program on physical function and balance in older adults with sarcopenia: a multicenter randomized controlled study. *J Aging Phys Act.* (2021) 29:1010–7. 10.1123/japa.2020-0348]
38. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al.. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc.* (2014) 15:95–101. 10.1016/j.jamda.2013.11.025
39. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al.. Sarcopenia: an undiagnosed condition in older adults. *J Am Med Direct Assoc.* (20۲۰) 12:249–56. 10.1016/j.jamda.2011.01.003

The effect of exercise for patients with diabetus mellitus

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Abstract
One of the main goals of diabetic therapy is to achieve the best metabolic control to prevent the development and progression of potential complications. A multidisciplinary approach characterized by the combination of diet, physical activity (PA) and drug therapy with oral and injectable (non-insulin) pharmacological agents, is desirable to optimize metabolic control. The aim of this review is to explain the contribution of PA and its beneficial effects on patients affected by type 1 (T1D) and type 2 diabetes (T2D). We provide an overview of evidence on the effects of PA for the main two types of diabetes mellitus (DM) to identify the right level of PA to be recommended. We discuss the physiological and clinical role of PA in people with DM. It can be concluded that the objective of antidiabetic therapy should be the achievement and optimization of metabolic control through a multidisciplinary approach involving non-pharmacological therapy such as diet and PA, which has a crucial role.
Keywords: diabetes, physical activity, exercise, non-pharmacological therapy

1. Introduction

According to the World Health Organization (WHO) diabetes mellitus (DM) is defined as a group of metabolic disorders with different aetiologies characterized by chronic hyperglycaemia associated with alterations in glucose, lipid and protein metabolisms secondary to defects in insulin secretion, action or both. The prevalence of DM has reached epidemic proportions. Currently, almost 390 million individuals worldwide are affected, and more than 590 million individuals are expected to develop this condition by 2035. At the same time, more than half of the diabetic population remains undiagnosed and therefore untreated [1].

Chronic hyperglycaemia is associated with damage, dysfunction and collapse of different anatomical districts [2]. Therefore, continuous interventions to correct blood glucose levels and cardiovascular risk factors are crucial for preventing acute and chronic complications [3].

The non-pharmacological therapy of DM is mainly focused on lifestyle changes in terms of physical activity (PA), diet and smoking habit [4]. Adequate lifestyle changes have beneficial effects on the reduction of anthropometric parameters such as body weight, body mass index (BMI), waist circumference, and also blood parameters related to fat and glucose profiles [5]. Moreover, in people with diabetes, regular PA potentially reduces the amount and dose of antidiabetic therapy and insulin dosage [6].

PA is defined as a subgroup of activities referred to all repetitive, planned and structured movements specifically designed to improve health and physical fitness [7]. Aerobic exercise consists of rhythmic, repeated and continuous movements of the same large muscle groups for at least 10 min [8]. Exercise against resistance consists of activities that use muscle strength to work against a load that offers resistance [9]. The physical fitness term, refers to a series of attributes that can be achieved by training, such as endurance and strength, abilities that are closely related to PA [5]. However, PA in overweight or obese individuals with diabetes often represents an insurmountable problem since these subjects suffer of several musculoskeletal disorders such as osteoarthritis [10], chronic low back pain due to intervertebral disc degeneration [11], and other musculoskeletal disorders [12,13].

The aim of this review is to investigate the beneficial effects of PA in patients affected by type 1 diabetes (T1D) and type 2 diabetes (T2D) through the evaluation and analysis of literature to improve exercise prescription in these delicate population.

2. Type of Physical Activity in Type 1 Diabetes and Type 2 Diabetes Subjects

Several studies have investigated the effects of different types of PA in people with diabetes. Nevertheless, the heterogeneity of these studies suggests that there is no clear evidence. The differences mainly concern the type of PA; its characteristics; the outcomes studied; acute or chronic effects and the pharmacological approach before, during and after PA.

Major types of PA studied in these subjects include aerobic, anaerobic and high-intensity interval training (HIIT).

Aerobic PA, or endurance PA, is characterized by repeated and continuous movement of large muscle groups. Examples of aerobic exercise include cycling, dancing, hiking, jogging/long distance running, swimming and walking [14]. Aerobic exercise activates glycolysis leading to a rapid production of ATP and lactate. In individuals with diabetes, it has been proved to be able to improve insulin sensitivity, lung, immune and cardiovascular function [14], and it is associated with lower risk of cardiovascular diseases and overall mortality [15]. In particular, aerobic exercise improves lipid metabolism and decreases insulin resistance in T1D and reduces blood pressure, triglycerides, insulin resistance and glycated haemoglobin (HbA1C) in T2D [16]. Recommendations suggest that aerobic activity should last at least 150 min/week at moderate to vigorous intensity in people with diabetes [17]. However, aerobic exercise can be performed continuously or as HIIT, which is characterized by short intense bursts with recovery periods interspersed. Similar cardioprotective and metabolic benefits can be obtained by HIIT in younger or more physically fit patients when vigorously performed for 75 min/week [18]. However, HIIT is mainly recommended in clinically stable patients who already perform intense physical activities and under supervision [19].

Resistance or strength training includes exercises with free or body weights, machines or elastic bands. Resistance exercises are able to increase muscle mass and strength, through the induction of muscle hypertrophy and neuromuscular remodelling, and also improvements in physical function, mental and cardiovascular health, insulin sensitivity and lipid metabolism [14]. The effect of resistance exercise on T1D patients is related to the improvement in muscular strength and lipid profile, a better control of blood glucose levels and reduced dose of insulin [20]. In T2D patients, resistance training improves blood pressure and increases muscle mass and strength, which may positively impact insulin responsiveness and metabolic control [21]. Indeed, several randomized clinical studies have shown that metabolic control, lipid and cardiovascular disease risk profile can be enhanced in patients with T2D through resistance training [22]. Recommendations suggest engaging in 2–3 non-consecutive days/week of resistance exercise for adults affected by DM using a variety of strength training modalities [17].

Flexibility exercises, can improve range of motion around joints through stretching, and balance activities can enhance balance and gait preventing falls in older adults [23]. Reduced joint mobility, which may be due to advanced glycation end products, is often found in older individuals with diabetes [24]. Therefore, it is recommended to perform both flexibility and balance activities for 2 or more sessions/week, especially by older adults with peripheral neuropathy [14]. However, flexibility activities do not affect glucose control or insulin action, and they should not replace other recommended exercises such as aerobic and resistance training [25]. A combination of balance, flexibility and resistance activities is represented by Tai Chi and Yoga, which can be performed based on individual preferences. Yoga can help the metabolic control, lipid profile and body composition in T2D patients [26]. On the other hand, Tai Chi in T2D patients with neuropathy can improve neurologic symptoms, balance but also glucose control and quality of life [27].

However, it is crucial to personalize the exercise program according to individual's health status, physical function, exercise responses and goals. Patients who are unable or unwilling to perform PA as recommended can still benefit from exercising at lower levels or reducing total time engaged in sedentary activities.

3. Beneficial Effects of Physical Activity in Type 1 Diabetes

T1D approximately accounts for 5–10% of all people with diabetes. It is related to genetic and environmental factors, even though the latter are still poorly defined [28], and it is characterized by an autoimmune and cell-mediated destruction of pancreatic β-cells leading to insulin deficiency with a tendency to ketoacidosis. The β-cell destruction rate is relatively variable, rapid in childhood and slower in adults [29].

Regular PA in people with T1D produces the same positive effects as for non-diabetics in term of morbidity and mortality. Clinical and experimental studies have shown that the benefits of PA in subjects with T1D are mainly related to the (1) increased insulin sensitivity in skeletal muscle, (2) possible positive effects on glycaemic control, (3) increased antioxidant defences and reduced oxidation, (4) decreased blood pressure, (5) reduction of cardiovascular diseases, (6) optimization of lipid profile and (7) enhancement of renal function [30].

However, one of the main obstacles in regular PA is the fear of hypoglycaemia. Prevention of hypoglycaemia during and after PA remains an important issue in the management of T1D therapy.

Aerobic PA involves several physiological adaptations. Indeed, it can lead to a greater capillary density, greater expression and translocation of GLUT4 towards the plasma membrane, an increased number of muscle fibres which are more sensitive to the action of insulin, changes in the composition of phospholipidic proteins on sarcolemma, an increased activity of glycolytic and oxidative enzymes and an increased use of muscle glycogen [31]. Ebeling et al. evaluated the insulin sensitivity in skeletal muscles of 11 athletes with T1D who participated

in athletic competitions compared to 12 sedentary individuals with diabetes. Glycaemic control, insulin uptake throughout the body and forearm, oxidation of glucose, lipids and muscle glycogen and GLUT4 concentrations were measured. Glucose levels and its oxidation were similar in both groups, while both energy expenditure and lipid oxidation increased in athletes. Lipidic oxidation was inversely related to glycogenosynthesis activity; muscle glycogen and GLUT4 activity were not different in the two groups [32]. Jimenez et al. examined the acute effect of resistance exercise on insulin sensitivity in subjects with T1D [33]. The insulin sensitivity was not significantly different between the trained and untrained group. They concluded that a single period of resistance training does not alter the sensitivity of insulin in people with T1D. Adequate PA can reduce morbidity and mortality in this population [34]. However, to achieve these benefits, individuals with T1D require adjustments in insulin doses.

Patients affected by T1D with poor glycaemic control have higher levels of triglycerides than non-diabetic subjects. Glycaemic control is the main factor interfering with lipid concentration in patients with DM. The benefits of PA on the lipid profile in subjects affected by T1D have been demonstrated, suggesting that this non-pharmacological approach represents an additional alternative therapy [35]. Lehmann et al. showed a better lipid profile, independently from the glycaemic control, in adolescents with T1D who have joined a dietary and training program [36]. Further studies have shown an improvement in lipid profile after physical training in subjects with T1D characterized by a reduction in total cholesterol, LDL cholesterol and triglyceride levels and an increase in HDL cholesterol [37]. Austin et al. reported a reduction or maintenance of levels of high-density lipoprotein LP(a), a cardiovascular risk factor, after a period of physical conditioning in T1D patients [۳۲].

5. Discussion

The objective of non-pharmacological therapy of DM is to change lifestyle by promoting PA and diet. Beneficial effects produced by PA are different in T1D and T2D subjects due to differences in morphotype, aetiology and clinical and pharmacological treatment.

Indeed, PA may have different results in patients affected by T1D and T2D. T1D patients are younger, more active and more prone to PA, which can enhance their insulin sensitivity, glycaemic control, lipid profile, antioxidant defences and renal function and also decrease blood pressure and cardiovascular diseases. Otherwise, T2D patients are adults, who are usually affected by multiple comorbidities such as obesity, metabolic syndrome and musculoskeletal disorders and have a more sedentary life. The therapeutic effect of PA on these patients has been proved to be related to a better control of glucidic and lipidic metabolism, also on blood pressure and cardiovascular diseases, as well as reduction of BMI and an increase of insulin sensitivity in skeletal muscle.

The recommended activities are all pure or predominantly aerobic with the recommendation to avoid a competitive engagement longer than one hour [30]. It is advisable to use a cardiofrequency device that allows instantaneous measurement of the heart rate and to set audible alarms if the set frequency is exceeded. The exercise session should last 30 to 60 min, and blood glucose could be checked one hour after exercise to decide whether or not to take carbohydrates. Anaerobic sports or sports characterized by isometric or strength exercises, fighting sports with physical contact, activities involving frequent head shaking and scuba diving require special caution and should be carefully evaluated on a case-by-case basis.

Moreover, there is a strong link between mental and physical health. Several studies have found a clear relationship between PA, the quality of life and the psychological well-being. Indeed, PA is a major health behaviour with positive effects on mood, self-esteem, cognitive functioning, depression and quality of life, strongly recommended for the prevention and treatment of several non-communicable diseases [۲۰].

PA is now firmly accepted as an effective non-pharmacological treatment of T2D although the specific mechanisms underlying the positive effects of exercise remain unclear. Regular involvement of individuals with diabetes in exercise programs could become a potential way to improve their quality of life reducing the economic expenditure for diabetes treatment and reducing complications that result from it.

6. Conclusions

The goal of DM therapy is certainly to reduce the risk of short-and long-term complications. Drug therapy has beneficial effects on the risk of complications, but it is not sufficient to reverse them. The strongest indication shared by the most recent guidelines and consensus documents on the management of diabetic disease requires continuous attention to the implementation of a correct lifestyle and the necessity of therapy personalization, with the adaptation of pharmacological and non-pharmacological prescriptions (nutritional therapy, PA indications) to the metabolic and clinical profile of the individual patien

References in the text are numbered

References

1. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-۲۰۲۳. *Diabetes Care.* ۲۰۲۳;41:S13–S27. doi: 10.2337/dc18-S002.

2. Harreiter J., Roden M. Diabetes mellitus-Definition, classification, diagnosis, screening and prevention (Update 2019) *Wien. Klin. Wochenschr.* 2019;131:6–15. doi: 10.1007/s00508-019-1450-4.

3. Petersmann A., Muller-Wieland D., Muller U.A., Landgraf R., Nauck M., Freckmann G., Heinemann L., Schleicher E. Definition, Classification and Diagnosis of Diabetes Mellitus. *Exp. Clin. Endocrinol. Diabetes.* 2019;127:S1–S7. doi: 10.1055/a-1018-9078.

4. Khursheed R., Singh S.K., Wadhwa S., Kapoor B., Gulati M., Kumar R., Ramanunny A.K., Awasthi A., Dua K. Treatment strategies against diabetes: Success so far and challengesahead. *Eur.J.Pharmacol.* 2019;862:172625. doi: 10.1016/j.ejphar.2019.172625.

5. Balducci S., D'Errico V., Haxhi J., Sacchetti M., Orlando G., Cardelli P., Vitale M., Bollanti L., Conti F., Zanuso S., et al. Effect of a Behavioral Intervention Strategy on Sustained Change in Physical Activity and Sedentary Behavior in Patients With Type 2 Diabetes: The IDES_2 Randomized Clinical Trial. *JAMA.* 2019;321:880–890. doi: 10.1001/jama.2019.0922.

6. Teich T., Zaharieva D.P., Riddell M.C. Advances in Exercise, Physical Activity, and Diabetes Mellitus. *Diabetes Technol. Ther.* 2019;21:S112–S122. 2019.2509.

7. Huys N., Van Stappen V., Shadid S., De Craemer M., Androutsos O., Lindstrom J., Makrilakis K., de Sabata M.S., Moreno L., De Miguel-Etayo P., et al. Influence of Educational Level on Psychosocial Correlates and Perceived Environmental Correlates of Physical Activity in Adults at Risk for Type 2 Diabetes: The Feel4Diabetes-Study. *J.Phys.Act.Health.* 2019;16:1105–1112. doi: 10.1123/jpah.2019-0003.

8. Johnson N.A., Barwick A.L., Searle A., Spink M.J., Twigg S.M., Chuter V.H. Self-reported physical activity in community-dwelling adults with diabetes and its association with diabetes complications. *J. Diabetes Complicat.* 2019;33:33–38. doi: 10.1016/j.jdiacomp.2018.10.017. [

9. Francesconi C., Niebauer J., Haber P., Weitgasser R., Lackinger C. [Lifestyle: Physical activity and training as prevetion and therapy of type 2 diabetes mellitus (Update 2019)] *Wien. Klin. Wochenschr.* 2019;131:61–66. doi: 10.1007/s00508-019-1457-x.

10. Cannata F., Vadala G., Ambrosio L., Napoli N., Papalia R., Denaro V., Pozzilli P. Osteoarthritis and type 2 diabetes: From pathogenetic factors to therapeutic intervention. *Diabetes Metab. Res. Rev.* 2020;36:e3254. doi: 10.1002/dmrr.3254.

11. Cannata F., Vadala G., Ambrosio L., Fallucca S., Napoli N., Papalia R., Pozzilli P., Denaro V. Intervertebral disc degeneration: A focus on obesity and type 2 diabetes. *Diabetes Metab. Res. Rev.* 2020;36:e3224. doi: 10.1002/dmrr.3224.]

12. Napoli N., Conte C., Pedone C., Strotmeyer E.S., Barbour K.E., Black D.M., Samelson E.J., Schwartz A.V. Effect of Insulin Resistance on BMD and Fracture Risk in Older Adults. *J. Clin. Endocrinol. Metab.* 2019;104:3303–3310. doi: 10.1210/jc.2018-02539.

13. Russo F., Ambrosio L., Ngo K., Vadala G., Denaro V., Fan Y., Sowa G., Kang J.D., Vo N. The Role of Type I Diabetes in Intervertebral Disc Degeneration. *Spine (Phila Pa)* 2019;44:1177–1185. doi: 10.1097/BRS.0000000000003054.

14. Garber C.E., Blissmer B., Deschenes M.R., Franklin B.A., Lamonte M.J., Lee I.M., Nieman D.C., Swain D.P., American College of Sports Medicine American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med. Sci. Sports Exerc.* ۲۰۲۲;43:1334–1359. doi: 10.1249/MSS.0b013e318213fefb.

15. Sluik D., Buijsse B., Muckelbauer R., Kaaks R., Teucher B., Johnsen N.F., Tjonneland A., Overvad K., Ostergaard J.N., Amiano P., et al. Physical Activity and Mortality in Individuals With Diabetes Mellitus: A Prospective Study and Meta-analysis. *Arch. Intern. Med.* ۲۰۱۹;172:1285–1295. doi: 10.1001/archinternmed.۲۰۱۹.3130.

16. Chimen M., Kennedy A., Nirantharakumar K., Pang T.T., Andrews R., Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia* ۲۰۱۲;55:542–551. doi: 10.1007/s00125-011-2403-2.

17. Colberg S.R., Sigal R.J., Yardley J.E., Riddell M.C., Dunstan D.W., Dempsey P.C., Horton E.S., Castorino K., Tate D.F. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care.* 2016;39:2065–2079. doi: 10.2337/dc16-1728.
18. American Diabetes A. 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42:S29–S33. doi: 10.2337/dc19-S003.
19. Levinger I., Shaw C.S., Stepto N.K., Cassar S., McAinch A.J., Cheetham C., Maiorana A.J. What Doesn't Kill You Makes You Fitter: A Systematic Review of High-Intensity Interval Exercise for Patients with Cardiovascular and Metabolic Diseases. *Clin. Med. Insights Cardiol.* 2015;9:53–63. doi: 10.4137/CMC.S26230
20. Ramalho A.C., de Lourdes Lima M., Nunes F., Cambui Z., Barbosa C., Andrade A., Viana A., Martins M., Abrantes V., Aragao C., et al. The effect of resistance versus aerobic training on metabolic control in patients with type-1 diabetes mellitus. *DiabetesRes.Clin.Pract.* ۲۰۱۴;72:271–276. doi: 10.1016/j.diabres.۲۰۱۴.11.011.
21. Gordon B.A., Benson A.C., Bird S.R., Fraser S.F. Resistance training improves metabolic health in type 2 diabetes: A systematic review. *Diabetes Res. Clin. Pract.* ۲۰۲۰;83:157–175. doi: 10.1016/j.diabres.۲۰۲۰.11.024.
22. Strasser B., Siebert U., Schobersberger W. Resistance training in the treatment of the metabolic syndrome: A systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. *Sports Med.* ۲۰۲۳;40:397–415. doi: 10.2165/11531380-000000000-00000.
23. Morrison S., Colberg S.R., Mariano M., Parson H.K., Vinik A.I. Balance training reduces falls risk in older individuals with type 2 diabetes. *Diabetes Care.* ۲۰۲۱;33:748–750. doi: 10.2337/dc09-1699.
24. Abate M., Schiavone C., Pelotti P., Salini V. Limited joint mobility in diabetes and ageing: Recent advances in pathogenesis and therapy. *Int. J. Immunopathol. Pharmacol.* ۲۰۲۲;23:997–1003. doi: 10.1177/039463201002300404.
25. Colberg S.R., Sigal R.J., Fernhall B., Regensteiner J.G., Blissmer B.J., Rubin R.R., Chasan-Taber L., Albright A.L., Braun B., American College of Sports Medicine et al. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. *Diabetes Care.* 2010;33:e147–e167. doi: 10.2337/dc10-9990.
26. Innes K.E., Selfe T.K. Yoga for Adults with Type 2 Diabetes: A Systematic Review of Controlled Trials. *J. Diabetes Res.* 2016;2016:6979370. doi: 10.1155/2016/6979370.]
27. Ahn S., Song R. Effects of Tai Chi Exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type 2 diabetes and neuropathy. *J. Altern. Complement. Med.* 2012;18:1172–1178. doi: 10.1089/acm.2011.0690
28. Barnett R. Type 1 diabetes. *Lancet.* 2018 ;391:195. doi: 10.1016/S0140-6736(18)30024-2.
29. Cnop M., Welsh N., Jonas J.C., Jörns A., Lenzen S., Eizirik D.L. Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: Many differences, few similarities. *Diabetes* ۲۰۲۳;54(Suppl.2):S97–S107. doi: 10.2337/diabetes.54.suppl_2.S97.
30. Riddell M.C., Gallen I.W., Smart C.E., Taplin C.E., Adolfsson P., Lumb A.N., Kowalski A., Rabasa-Lhoret R., McCrimmon R.J., Hume C., et al. Exercise management in type 1 diabetes: A consensus statement. *Lancet Diabetes Endocrinol.* 2017;5:377–390. doi: 10.1016/S2213-8587(17)30014-1.
31. Ebeling P., Bourey R., Koranyi L., Tuominen J.A., Groop L.C., Henriksson J., Mueckler M., Sovijarvi A., Koivisto V.A. Mechanism of enhanced insulin sensitivity in athletes. Increased blood flow, muscle glucose transport protein (GLUT-4) concentration, and glycogen synthase activity. *J. Clin. Investig.* ۲۰۲۲;92:1623–1631. doi: 10.1172/JCI116747.
32. Ebeling P., Tuominen J.A., Bourey R., Koranyi L., Koivisto V.A. Athletes with IDDM exhibit impaired metabolic control and increased lipid utilization with no increase in insulin sensitivity. *Diabetes.* ۲۰۲۱;44:471–477. doi: 10.2337/diab.44.4.471.

The effect of exercise for underweight people

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Introduction/Methods: This systematic review with meta-analysis aims to assess the magnitude of the effects of physical exercise programs on body mass index (BMI) and waist circumference (WC) of individuals with Intellectual and Developmental Disabilities (IDD), metabolic and cardiovascular health markers.

1 Introduction

Obesity is a major public health problem due to its growing prevalence, as it increases the risk of developing various diseases such as cardiovascular or metabolic diseases (de Winter et al., ۲۰۲۱; Vancampfort et al., 2020), increasing mortality in earlier ages when compared to the general population (Hosking et al., 2016). Excessive adiposity results from an imbalance between energy intake and expenditure.

Body mass index (BMI) and abdominal adiposity assessed using waist circumference (WC), body composition and anthropometric variables, are essential markers to assess overweight and obesity and are associated to metabolic disease and QoL (Klein et al., ۲۰۲۰; Kobo et al., 2019). This measure are non-evasive methods widely used in individual with Intellectual and Developmental Disabilities (IDD) to measure nutritional status (Temple et al., ۲۰۲۱; Waninge et al., ۲۰۲۲) and individuals with IDD are more likely to be overweight or obese compared to the general population (Zwierzchowska et al., 2021).

A systematic review with meta-analysis carried out by Maïano and collaborators (Maïano et al., 2016) showed that children and adolescents with IDD were 1.54 and 1.89 times more likely to be overweight and obese, when compared to the population without disability. These results are transversal to all age groups, from children (Wang et al., 2018), to adolescents (Krause et al., 2016) and adults (de Winter et al., ۲۰۲۱). Several factors may influence this prevalence, such as: 1) being female (de Winter et al., ۲۰۲۱); 2) advancing in age (Ranjan et al., 2018); 3) having DS (Krause et al., 2016); 4) having a degree of mild or moderate disability (Ranjan et al., 2018); 5) genetic factors (Wang et al., 2018). Other additional factors such as socioeconomic level, perceptions and attitudes towards physical activity, health problems and other characteristics of the disability itself (McGillivray et al., ۲۰۲۰), may also play a determinant role in this prevalence.

Considering the BMI variable, Temple and collaborators (Temple et al., ۲۰۱۷), when evaluating 11,643 individuals with IDD, verified that 5.5% of the sample was underweight, 36.1% in the normal range, 24.7% overweight, and 32.1% obese. Concluded that levels of overweight and obesity were high. Likewise, Foley and collaborators (Foley et al., 2017), evaluating 4,174 individuals with IDD, he also found that 32% were overweight and 11% were obese. At the same time, 21% of the participants were above the cut-off for abdominal obesity.

High values of BMI and WC, show a high prevalence of overweight and obesity in individuals with IDD. These values are associated with high risk metabolic and cardiovascular disease, excessive health costs (Vohra et al., 2017; Wyszyńska et al., 2017) and increased risk of incidence and mortality (Parra-Soto et al., 2021). On the other hand, BMI and WC are recommended by ACSM (American College of Sports Medicine, 2021) as two possible measures of anthropometric and body composition for individuals with IDD.

The global impact of physical activity and physical exercise on BMI and WC in people with IDD is not known, nor is the most effective type of exercise training for promoting these variables. International guidelines recommend by WHO (World Health Organization, 2020) and ACSM (American College of Sports Medicine, 2021) identify physical activity and exercise as important tools to improve daily life and wellbeing with a positive impact in different age groups (Kim et al., 2019). For these people, the variable mentioned, when practiced regularly, seem to be associated with improvements not only in physical fitness but also in reducing the risk of the appearance of metabolic and cardiovascular disease, reducing health costs and promoting their QoL (Pestana et al., 2018; Jacinto et al., 2021).

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Since all of this work is based on the Guidelines for Exercise Testing and Prescription for individual with IDD (American College of Sports Medicine, 2021), we consider aerobic, resistance and flexibility training. According to ACSM (American College of Sports Medicine, 2021) aerobic exercise is the ability of the circulatory and respiratory system to supply oxygen during sustained physical activity, resistance training is the capacity of muscle to exert force and flexibility is the range of motion available at a joint.

The main purpose of the present systematic review with meta-analysis is to measure the magnitude of effects of different types of physical exercise on BMI and WC, metabolic and cardiovascular health parameter, in individual with IDD aiming to provide relevant information to sport sciences and health sciences professionals when planning, implementing and monitoring exercise intervention programs in people with IDD.

2 Materials and methods

The present systematic review with meta-analysis followed the guidelines defined in the original checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses—PRISMA (Page et al., 2021).

The PICOS strategy (Methley et al., 2014; Nang et al., 2015) was used to ensure rigor defining of the research question, in which: 1) “P” corresponded to participants with IDD of any age, regardless of ethnicity or gender; 2) “I” corresponded to any physical exercise program implemented in the population with IDD (DS included), regardless of the intervention time, according to ACSM (American College of Sports Medicine, 2021); 3) “C” (Comparison) corresponded to the comparison between the CG versus the; 4) “O” corresponded to BMI and WC as the first or second variable in focus; 5) “S” (Study Design) corresponded to randomized controlled clinical trials (RCT).

2.1 Data sources

The search was conducted in the English language, in the following electronic databases: PubMed (title and abstract), Web of Science, and Scopus (title, abstract and key words), accessed between February 2021 and December 2022, using the advanced search option, with randomized exercise intervention studies. The search has been updated until the 10th of December. The search strategy combined Key Medical Subject Heading and indexed search descriptors to refine the data, following the recommendation from the Cochrane Handbook for Systematic Review of Intervention (Higgins and Altman, ۲۰۲۲), as shown in Table 1.

2.2 Eligibility criteria and studies selection

To be included in the present systematic review with meta-analysis, studies must meet the following inclusion criteria: 1) RCT studies with exercise intervention (with intervention group and control group), with any prescription in terms of intensities and duration, according to ACSM guidelines (American College of Sports Medicine, 2021); 2) All participants mut have an IDD diagnosis, whatever the degrees, including other subgroups with IDD (diagnosis by Wechsler Adult Intelligence Scale—Fourth Edition (Wechsler, ۲۰۱۹ or The Wechsler Intelligence Scale for Children—Fifth Edition Integrated (Raiford, 2018); 3) Participants with IDD of any age, gender, race or ethnicity, regarding ACSM (American College of Sports Medicine, 2021); 4) Studies focusing on aerobic, neuromuscular, flexibility or combined capacity (training that combines more than one physical capacity, e.g., strength and aerobic capacity), which recommended by ACSM (American College of Sports Medicine, 2021), Figure 1 shows research content. In turn, all studies with the following characteristics were excluded: 1) Studies published in a language other than English; 2) Studies that do no describe the intervention protocol; 3) Studies with participants with another type of disability or other associated pathologies; 4) Studies in which the intervention is multidimensional (studies involving exercise and nutrition, exercise and health education sessions); 5) Studies that do not show anthropometric data (BMI and WC); 6) Studies that the intervention protocol is through virtual reality (institution where we want to replicate the protocol does not have access to this material, as well as other institutions where most of this population usually spends their day); sports programs. All studies that did not meet the initial selection criteria and did not report results adequately (mean, standard deviation and sample size) or if the respective authors did not reply to our inquiries sent by email, were excluded. Finally, articles presented in abstracts, letters to the editor, systematic reviews, study protocols, and book chapters were excluded.

2.3 Data extraction

Studies were imported into EndNote X7 software, and duplicates were removed. The study selection procedure was carried out in phases. In the first phase, the search for potentially relevant studies was carried out with the participation of two independent reviewers, based on the titles and the abstract. These studies would proceed to the next evaluation phase in case of doubt following. In the second phase, the studies from the previous stage were reviewed by the same independent reviewers based on the application of the previously defined eligibility criteria. In case of doubt or disagreement regarding the inclusion of a study, this was solved through a third reviewer's opinion playing the mediator's role and whose decision was used as a tiebreaker. Finally, the first two reviewers involved in the selection of the studies participated independently in the analysis of the studies extracting all relevant information and characteristics, namely, the author's name, year and country where it was carried out, objective, participants, instruments/techniques, duration/frequency, and results. In this phase, discrepancies about the extracted data were resolved by consensus among reviewers.

2.4 Quality assessment of studies

The PEDro Scale from the Physiotherapy Evidence Database, was used (Maher et al., ۲۰۲۱) to assess the quality of each study. The scale consists of 11 items, which analyse the different characteristics of each study, one of which is not counted (item 1) and the two others are not applicable in the field of sports science (items 5 and 6). The results obtained by both were compared and discussed so that there was a consensus. When there was no consensus, a third researcher was invited to collaborate.

3 Results

3.1 Data search

With the search carried out in different databases PubMed, Web of Science, and Scopus) 329 studies were identified. Subsequently, after eliminating the duplicate studies and reading the titles and abstracts, 47 studies with potential relevance to the study were identified. Considering the eligibility criteria previously defined for this systematic review with meta-analysis, from the complete reading of the articles, a sample of nine studies was constituted for their full analysis .

3.3 Quality of the information

Rosety-Rodriguez and collaborators (Rosety-Rodriguez et al., 2014) were the studies that obtained the lowest quality score (4 points—40%), and the studies with the best scores had 8 points (80%) Shields and Taylor (Shields and Taylor, 2015), showing a good quality of the methodological procedures.

3.4 Participants

The total number of participants included in the different studies was 291, 172 in experimental groups and 119 in CG. The studies included different types of IDD, whether it is DS, autism, or others. In Boer et al. study (Boer et al., 2014), participants were attending 40 secondary school at two Belgian special education school. In Boer and Moss study (Boer and Moss, 2016), participants were recruited from three care centres for persons with IDD. Participants in the Diaz and collaborators study (Diaz et al., 2021) and Ordonez and collaborators (Ordonez et al., 2014) were recruited via community support groups for people with IDD. Also, González-Agüero and collaborators (González-Agüero et al., ۲۰۱۷) recruited participants from different schools and institutions. Ortiz-Ortiz (Boer et al., 2014) and Rosety-Rodriguez and collaborators (Rosety-Rodriguez et al., 2014) does not mention where and how participants were recruited. Shields and Taylor (Shields and Taylor, 2015) recruited participants by contacting family members who were interested and Yu and collaborators (Ortiz-Ortiz et al., 2019) recruited participants from six special schools for adolescents with mild/moderate IDD.

3.5 Duration

The exercise intervention programs ranged from 8 to 36 weeks, however is more prevalent a prescription of 10–12 weeks (Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Boer and Moss, 2016; Diaz et al., 2021), i.e., short duration programs. The two combined exercise programs included in this systematic review lasted for 21–36 weeks (González-Agüero et al., ۲۰۲۱; Yu et al., 2022), one of neuromuscular capacity exercise programs lasted 16 weeks (Ortiz-Ortiz et al., 2019) and other 12 weeks (Diaz et al., 2021) and the five aerobic exercise programs lasted from 8 to 15 weeks, with half being implemented over 10 weeks (Boer et al., 2014; Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Shields and Taylor, 2015; Boer and Moss, 2016).

The frequency varied between 2 and 5 times per week, with most studies implementing 3 times per week (Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Shields and Taylor, 2015; Boer and Moss, 2016; Diaz et al., 2021).

The two combined exercise programs included in this systematic review with meta-analysis have a frequency of 2 times per week (González-Agüero et al., ۲۰۲۱; Yu et al., 2022). Regarding neuromuscular capacity, one of the exercise programs have a frequency of 5 times per week (Ortiz-Ortiz et al., 2019) and other 3 times per week (Diaz et al., 2021). Finally, the 5 aerobic exercise programs have a frequency of 2 and 3 times per week, with the majority implemented 3 times per week (Boer et al., 2014; Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Shields and Taylor, 2015; Boer and Moss, 2016). Regarding the duration of the exercise intervention session, sessions varied between 25 and 65 min including a brief warm-up and a return to calm period. The duration of the training session in the two combined exercise programs varied from 25 to 60 min (González-Agüero et al., 2012; Yu et al., 2022), one of the exercise programs for neuromuscular capacity were implemented for 55 min (Ortiz-Ortiz et al., 2019), with the other one not showing the session duration (Diaz et al., 2021), and from the five aerobic exercise programs four lasted from 30 to 60 min (Boer et al., 2014; Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Boer and Moss, 2016). One of the studies did not mention the duration of the training session, but mentions the weekly volume, namely, 150 min per week (Shields and Taylor, 2015).

3.6 Type of exercise program

Concerning aerobic training, different intensities were reportedfollowingthe global recommendations/guidelines presented of the ACSM (American College of Sports Medicine, 2021) for efforts within the interval of 60%–85% of maximum heart rate (HRmax).

Some studies used an intensity of 40%–65% HRmax (Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Diaz et al., 2021), others used 100%–110% of the ventilatory threshold (Boer et al., 2014) while others reported a 70%–80% maximum oxygen consumption (VO2max) (Boer and Moss, 2016) intensity value, with gradual increments throughout the intervention. These studies use different equipment such as stationary cycling, treadmills, or other materials such as steps or walking/running.

Interval training programs demonstrate a reduced volume compared to continuo training and used periods of 10 s of maximum speed, followed by 90 s of rest (Boer and Moss, 2016) or 15 s of full speed followed by 45 s of rest (Boer et al., 2014) using cycle ergometers or simple walks/runs.

All the exercise programs focused on neuromuscular capacity used a training circuit with different materials. The study by Diaz and collaborators (Diaz et al., 2021) worked at loads of 40%–65% of 8 repetition maximum (RM). One of the combined training programs is based time set (10–30 s per set; 4 sets) and aerobic intensity interval with a HRmax between 30% and 60% (Yu et al., 2022), and a second one is a four-stage circuit based on training with body weight, fitness bands and medicine balls (González-Agüero et al., ۲۰۲۱).

4 Discussion

This systematic review with meta-analysis aimed to assess the magnitude of the effects of different types of exercise programs on BMI and WC, variables related to metabolic and cardiovascular health of individuals with IDD.

The results of exercise programs are varied, depending on the objectives and the assessment tools/techniques. The fact that the present systematic review encompassed people with IDD of varying degrees and diagnoses (DS, autism, or others) may have influenced our results, because subgroups may have different responses to exercise ACSM (American College of Sports Medicine, 2021). However, these different responses to exercise still need further study to determine the optimal exercise intensities and modes for the population. However, taking into account the purposes of this systematic review with meta-analysis, we found that all studies that assess the BMI (Boer et al., 2014; Ordonez et al., 2014; Boer and Moss, 2016; Ortiz-Ortiz et al., 2019; Yu et al., 2022) and WC (Boer et al., 2014; Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Shields and Taylor, 2015; Boer and Moss, 2016; Yu et al., 2022) had a decrease in the values of these same variables through the implementation of exercise programs, except studies by González-Agüero and collaborators (González-Agüero et al., ۲۰۲۱) and Diaz and collaborators (Diaz et al., 2021), where there were an increases in BMI. In the González-Agüero and collaborators (González-Agüero et al., ۲۰۲۱) study, it was natural to see an increase in BMI due to the aim of the study. On the other hand, this increase was beneficial due to the relatively low mean BMI values of the sample, according to the cut-off values, in contrast to most of the literature. In the Diaz and collaborators (Diaz et al., 2021) study, the increase in BMI values may be justified by increases in muscle mass.

All studies used the same paradigm, whereby individuals with IDD were randomly placed in the experimental group (with exercise) or the CG. There is a shortage of exercise programs with randomized controlled methodology that assesses the impact on BMI and WC, along with only the population with IDD. The results were reported regarding the improvement of the BMI or WC.

Exercise was different in the studies, also differing in the physical capacity for training (aerobic training, strength, and/or combined training). The most used training methodology is the continuous aerobic type (Boer et al., 2014; Ordonez et al., 2014; Rosety-Rodriguez et al., 2014; Shields and Taylor, 2015; Boer and Moss, 2016), with observing a reduced or null number of interventions focusing on other physical fitness components. Therefore, which presupposes that the results of this study should be taken with caution.
Considering the present systematic review with meta-analysis, exercise had superior effects in most studies. However, the differences were not significant in some studies. Thus, we can reject the null hypothesis that exercise does not affect the BMI or WC of individuals with IDD, on the other hand, exercise seems decreases BMI and WC values. This is the strength of the study, since previous research shows that exercise interventions did not promote BMI and WC of individuals with IDD (Harris et al., 2015), even multi-component weight management interventions, namely, inclusion of an energy deficit diet, physical activity, and behaviour change techniques, are effective (Harris et al., 2018) and that only exercise and diet interventions could promote the variables under study (Harris et al., 2018; Ptomey et al., 2018). Currently, more researchers interested in promoting the QoL of these individuals may be at the origin of the results of the present study (Schalock et al., ۲۰۲۲), since recommendations for the assessment and prescription of exercise in individuals with IDD are frequently published, adapted, from previously implemented studies (American College of Sports Medicine, 2021). This increased interest increases knowledge of effective strategy and methodologies for QoL improvement. Since individuals with disabilities usually have high levels of overweight and obesity, the results of this study highlight the importance of regular exercise practice by individuals with IDD, to prevent the increase in values such as BMI and WC and, consequently, prevent the onset of metabolic and cardiovascular diseases. On the other hand, a follow-up by the technical of exercise, in order to assess and prescribe exercise in a correct and adapted way should be considered (American College of Sports Medicine, 2021).

According to this systematic review with meta-analysis, combined training appears to be the most efficient method for the promotion of BMI and aerobic training for WC and, in turn, the metabolic health of individuals with IDD. The literature is not clear about the training methodology that best promotes the variables under study. For Skrypnik and collaborators (Skrypnik et al., 2015) there are no significant differences between the different methods. Aerobic training reduces fat mass but has little effect on maintaining fat free mass (Garrow and Summerbell, ۲۰۲۳), and some authors point out that it is effectively the best method to reduce body mass (Willis et al., ۲۰۲۱). However, strength training, which produces fat-free mass gain, also increases resting energy expenditure (Hunter et al., 2000). Exercise combined resistance and aerobic training showed to be a good alternative for increasing fat-free mass and reducing fat mass (Willis et al., ۲۰۲۱), with authors claiming that it is the best method for losing weight and fat mass and maintaining fat free mass (Ho et al., ۲۰۲۱).

This article investigates which type of intervention best promotes BMI and WC in individuals with IDD. However, the small number of articles included and heterogeneity of population and diagnosis in the meta-analysis and a higher prevalence of studies with continuous aerobic methodology may have limited the results. It is recommended to continue implementing exercise programs with different methods, focusing on physical abilities in isolation or combination, so that further studies can measure these results way more precisely and robustly. On the other hand, waist circumference, may be considered a limitation of the present study, despite its usefulness, low cost and wide availability in any clinical setting, due to measurement errors because of its lack of reproducibility (Bouchard, ۲۰۱۶). Several studies are recommending the use of imaging techniques as they are more accurate and reproducible, however, they are also more expensive and complex (El Ghoch et al., ۲۰۱۹). At the same time, we recommend that future studies investigate the impact of a multidisciplinary intervention on these variables. Seeing if it can have more impact than exercise alone. We also recommend that future interventions are aimed at reducing energy intake and not just energy expenditure through the exercise.

5 Conclusion

Based on the results of the systematic review with meta-analysis, we can affirm that exercise programs prevent BMI and WC increments of individuals with IDD. Although without significant results, combined training looks to be more effective in promoting BMI and continuous aerobic training for WC since it had a greater effect size. The interest of various stakeholders in studying the QoL of individuals with IDD has increased, and the results of this systematic review with meta-analysis should be considered when planning interventions with the focus populations, in the sense that exercise programs promote BMI and WC, which, in turn, is associated with metabolic and cardiovascular health. The practice of exercise, in addition to promoting physical capacity, reduces the risk of diseases, being an essential aspect for a better QoL in individuals with IDD.

References are cited in the text

References

1-American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Eleventh, Spiral edition. Philadelphia: LWW; 2023

2-Batterham, A. M., and Hopkins, W. G. (2019). Making meaningful inferences about magnitudes. *Int. J. Sports Physiol. Perform.* 1 (1), 50–57. doi:10.1123/ijspp.1.1.50

3-Boer, P. H., Meeus, M., Terblanche, E., Rombaut, L., Wandele, I. D., Hermans, L., et al. (2020). The influence of sprint interval training on body composition, physical and metabolic fitness in adolescents and young adults with intellectual disability: A randomized controlled trial. *Clin. Rehabil.* 28 (3), 221–231. doi:10.1177/0269215513498609

4-Boer, P. H., and Moss, S. J. (2016). Effect of continuous aerobic vs. interval training on selected anthropometrical, physiological and functional parameters of adults with Down syndrome. *J. Intellect. Disabil. Res.* 60 (4), 322–334. doi:10.1111/jir.12251

5-Bouchard, C. (2022). BMI, fat mass, abdominal adiposity and visceral fat: Where is the 'beef. *Int. J. Obes. (Lond)* 31 (10), 1552–1553. doi:10.1038/sj.ijo.0803653

6-de Winter, C. F., Bastiaanse, L. P., Hilgenkamp, T. I. M., Evenhuis, H. M., and Echteld, M. A. (2019). Overweight and obesity in older people with intellectual disability. *Res. Dev. Disabil.* 33 (2), 398–405. doi:10.1016/j.ridd.2011.09.022

7-de Winter, C. F., Magilsen, K. W., van Alfen, J. C., Penning, C., and Evenhuis, H. M. (2021). Prevalence of cardiovascular risk factors in older people with intellectual disability. *Am. J. Intellect. Dev. Disabil.* 114 (6), 427–436. doi:10.1352/1944-7558-114.6.427

8-Diaz, A. J., Rosety, I., Ordonez, F. J., Brenes, F., Garcia-Gomez, N., Castejon-Riber, C., et al. (2021). Effects of resistance training in muscle mass and markers of muscle damage in adults with Down syndrome. *Int. J. Environ. Res. Public Health* 18 (17), 8996. doi:10.3390/ijerph18178996

9-Egger, M., Smith, G. D., Schneider, M., and Minder, C. (2023). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315 (7109), 629–634. doi:10.1136/bmj.315.7109.629

10-El Ghoch, M., Alberti, M., Milanese, C., Battistini, N. C., Pellegrini, M., Capelli, C., et al. (2018). Comparison between dual-energy X-ray absorptiometry and skinfolds thickness in assessing body fat in anorexia nervosa before and after weight restoration. *Clin. Nutr.* 31 (6), 911–916. doi:10.1016/j.clnu.2012.03.009

11-Foley, J. T., Lloyd, M., Turner, L., and Temple, V. A. (2018). Body mass index and waist circumference of Latin American adult athletes with intellectual disability. *Salud Publica Mex.* 59 (4), 416–422. doi:10.21149/8204

12-Garrow, J. S., and Summerbell, C. D. (2020). Meta-analysis: Effect of exercise, with or without dieting, on the body composition of overweight subjects. *Eur. J. Clin. Nutr.* 49 (1), 1–10.

13-González-Agüero, A., Vicente-Rodríguez, G., Gómez-Cabello, A., Ara, I., Moreno, L. A., and Casajús, J. A. (2021). A 21-week bone deposition promoting exercise programme increases bone mass in young people with Down syndrome. *Dev. Med. Child Neurology* 54 (6), 552–556. doi:10.1111/j.1469-8749.2012.04262.x

14-Harris, L., Hankey, C., Murray, H., and Melville, C. (2019). The effects of physical activity interventions on preventing weight gain and the effects on body composition in young adults with intellectual disabilities: Systematic review and meta-analysis of randomized controlled trials. *Clin. Obes.* 5 (4), 198–210. doi:10.1111/cob.12103

15-Harris, L., Melville, C., Murray, H., and Hankey, C. (2018). The effects of multi-component weight management interventions on weight loss in adults with intellectual disabilities and obesity: A systematic review and meta-analysis of randomised controlled trials. *Res. Dev. Disabil.* 72, 42–55. doi:10.1016/j.ridd.2017.10.021

16-Higgins, J. P., and Altman, D. G. (2018). Assessing risk of bias in included studies in *Cochrane Handbook for systematic reviews of interventions [internet]* (New Jersey: John Wiley & Sons, Ltd). p. 187–241.
17-Higgins, J. P. T., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ* 327 (7414), 557–560. doi:10.1136/bmj.327.7414.557
18-Ho, S. S., Dhaliwal, S. S., Hills, A. P., and Pal, S. (2021). The effect of 12 weeks of aerobic, resistance or combination exercise training on cardiovascular risk factors in the overweight and obese in a randomized trial. *BMC Public Health* 12 (1), 704. doi:10.1186/1471-2458-12-704
19-Hosking, F. J., Carey, I. M., Shah, S. M., Harris, T., DeWilde, S., Beighton, C., et al. (2022). Mortality among adults with intellectual disability in england: Comparisons with the general population. *Am. J. Public Health* 106 (8), 1483–1490. doi:10.2105/AJPH.2016.303240
20-Hunter, G. R., Wetzstein, C. J., Fields, D. A., Brown, A., and Bamman, M. M. (2017). Resistance training increases total energy expenditure and free-living physical activity in older adults. *J. Appl. Physiol. (2017)* 89 (3), 977–984. doi:10.1152/jappl.2000.89.3.977
21-Jacinto, M., Oliveira, R., Brito, J. P., Martins, A. D., Matos, R., and Ferreira, J. P. (2021). Prescription and effects of strength training in individuals with intellectual disability—a systematic review. *Sports* 9 (9), 125. doi:10.3390/sports9090125
22-Kim, K. B., Kim, K., Kim, C., Kang, S. J., Kim, H. J., Yoon, S., et al. (2019). Effects of exercise on the body composition and lipid profile of individuals with obesity: A systematic review and meta-analysis. *J. Obes. Metab. Syndr.* 28 (4), 278–294. doi:10.7570/jomes.2019.28.4.278
23-Klein, S., Allison, D. B., Heymsfield, S. B., Kelley, D. E., Leibel, R. L., Nonas, C., et al. (2021). Waist circumference and cardiometabolic risk: A consensus statement from shaping America's health: Association for weight management and obesity prevention; NAASO, the obesity society; the American society for nutrition; and the American diabetes association. *Am. J. Clin. Nutr.* 85 (5), 1197–1202. doi:10.1093/ajcn/85.5.1197
24-Kobo, O., Leiba, R., Avizohar, O., and Karban, A. (2019). Normal body mass index (BMI) can rule out metabolic syndrome: An Israeli cohort study. *Medicine* 98 (9), e14712. doi:10.1097/MD.0000000000014712
25-Krause, S., Ware, R., McPherson, L., Lennox, N., and O'Callaghan, M. (2016). Obesity in adolescents with intellectual disability: Prevalence and associated characteristics. *Obes. Res. Clin. Pract.* 10 (5), 520–530. doi:10.1016/j.orcp.2015.10.006
26-Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., and Elkins, M. (2021). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys. Ther.* 83 (8), 713–721. doi:10.1093/ptj/83.8.713
27-Maïano, C., Hue, O., Morin, A., and Moullec, G. (2016). Prevalence of overweight and obesity among children and adolescents with intellectual disabilities: A systematic review and meta-analysis: Prevalence of overweight and obesity. *Obes. Rev.*, 17.
28-McGillivray, J., McVilly, K., Skouteris, H., and Boganin, C. (2022). Parental factors associated with obesity in children with disability: A systematic review. *Obes. Rev.* 14 (7), 541–554. doi:10.1111/obr.12031
29-Methley, A. M., Campbell, S., Chew-Graham, C., McNally, R., and Cheraghi-Sohi, S. (2022). PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv. Res.* 14 (1), 579. doi:10.1186/s12913-014-0579-0

The effect of exercise for Digestive disorders

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Summary

This review describes the current state of knowledge on the hazards of exercise and the potential benefts of physical activity on the gastrointestinal tract. In particular, acute strenuous exercise may provoke gastrointestinal symptoms such as heartburn or diarrhoea. A substantial part (20±50%) of endurance athletes are hampered by these symptoms which may deter them from participation in training and competitive events. Nevertheless, these acute symptoms are transient and do not hamper the athlete's health in the long term. The only exception is repeated gastrointestinal bleeding during training and competition, which in the long term may occasionally lead to iron de-ciency and anaemia. In contrast, repetitive exercise periods at a relatively low intensity may have protective eVects on the gastrointestinal tract. There is strong evidence that physical activity reduces the risk of colon cancer by up to 50%. Less convincing evidence exists for cholelithiasis and constipation. Physical activity may reduce the risk of diver-ticulosis, gastrointestinal haemorrhage, and in¯ammatory bowel disease although this cannot be substantiated frmly. Up to now, underlying mechanisms are poorly understood although decreased gastrointestinal blood ¯ow, neuro-immuno-endocrine alterations, increased gastrointestinal motility, and mechanical bouncing during exercise are postulated. Future research on exercise associated digestive processes should give more insight into the relationship between physical activity and the function of the gastrointestinal tract.

Introduction

The impact of exercise and physical activity on the gastro-intestinal tract is an area of emerging interest. During the past two decades research was mainly directed towards the hazards of strenuous exercise, especially gastrointestinal symptoms.1±3 In recent years, however, interest has also focussed on the potential benefts of physical activity on the gastrointestinal tract. Several studies indicate an inverse relationship between physical activity and risk of gastro-intestinal related diseases such as colon cancer,4±6 diverticu-lar disease,7 cholelithiasis,8 9 or constipation.10 While the prevalence of these diseases is relatively high and increases with age, participation in physical activity is relatively low and decreases with age.

This review summarises the current state of knowledge on the hazards of exercise and the potential benefts of physical activity. ªExerciseº is considered as voluntary activation of skeletal muscle leading to short term eVects (for minutes or hours) while ªphysical activityº is considered as repetitive exercise periods leading to long term eVects (for days, weeks, months, or years). We focus on the role of physical activity in the prevention of several diseases of the gastrointestinal tract and the postulated mechanisms by which physical activity in¯uences the gastrointestinal tract. These mechanisms will be discussed more extensively at the end of this review. As potential haz-ards of exercise have been the subject of several reviews (for example, see Moses,11 Peters et al,12 and Brouns and Beck-ers13), they will be discussed only briey.

The role of physical activity in the treatment of gastrointestinal diseases will not be discussed, as the litera-ture on this topic is scarce. Nevertheless, in patients with gastrointestinal diseases physical activity may inhibit mus-cle loss, and improve appetite, functional capacity, and general well being by positive mood changes 5.

Hazards

Gastrointestinal symptoms such as nausea, heartburn, diarrhoea, and gastrointestinal bleeding are common dur-ing exercise, especially during vigorous sports such as long distance running and triathlons.2 13±16 In general, these symptoms are transient and can be considered protective for critical organ damage: its progressive nature

causes the athlete to reduce exercise intensity or duration. Sometimes the symptoms may be so serious that they can limit exercise performance severely1 12 16 and even participation in physi-cal activity.12

Incidence rates during prolonged exercise vary mostly from 20% to 50%, depending on factors such as mode, duration, and intensity of exercise, type of symptom, age, training status, sex, dietary intake, occurrence of gastro-intestinal symptoms at rest, and method of investiga-tion.12 13 15 In particular, exercise intensity seems to be an important factor provoking gastrointestinal symp-toms.12 13 16 The mechanisms by which exercise causes gastrointestinal symptoms are not well known. Decreased gastrointestinal blood ¯ow, increased gastrointestinal motility, increased mechanical bouncing, and altered neu-roendocrine modulation are postulated.11±13 All of these mechanisms are associated with exercise intensity.13 17±20

While most gastrointestinal symptoms do not hamper the athlete's health, gastrointestinal bleeding may be a seri-ous problem. Most often the type of bleeding is occult and transient, although anecdotal case reports document acute massive upper and lower gastrointestinal bleeding.21 Repeated gastrointestinal bleeding during training and competition may contribute to iron defciency and anaemia.22 Also, endotoxaemia, malabsorption, gastro-intestinal tract in¯ammation, and hypersensitivity reac-tions have been postulated to occur.13 14 21 23 All of these eVects, however, can mostly be prevented by appropriate dietary (for example, suYcient ¯uid intake) and other pre-cautions (for example, avoidance of large amounts of aspi-rin and non-steroidal anti-in¯ammatory drugs).12 22

In addition to gastrointestinal symptoms, unfavourable eVects of exercise on liver function11 and peptic ulcer disease24 have been reported. However, in well trained endurance-type sportsmen the increase in liver size can be interpreted as a physiological adaptation to increased energy expenditure rather than an expression of liver dam-age.25 Abnormal high serum levels of bilirubin, aspartate aminotransferase, and alkaline phosphatase are seldom observed in blood, underlining the fact that prolonged strenuous exercise does not lead to serious hepatic damage.

Only under extreme exercise conditions, such as heat shock, may hepatic damage occur.25 In the elderly, long term physical activity even may improve liver function.26 Epidemiological studies24 27 show that physically de-manding occupations may enhance the risk of peptic ulcer disease, independent of several other risk factors such as social class.27 However, these studies were hampered by some limitations and pitfalls which question their conclu-sions. Recently,28 no relationship between a history of pep-tic ulcer and leisure time physical activity was found. Physical activity may even contribute to healing of gastric and duodenal ulcers by normalisation of the microcircula tion at the ulcer regions.29

Benefits

The potential benefts of physical activity concern mainly eVects on cancer risk, cholelithiasis, gastrointestinal haem-orrhage, inammatory bowel disease, diverticular disease, and constipation.

GASTROINTESTINAL CANCERS

To date, the risk of oesophageal, bile duct, or gall bladder cancers have not been examined in relation to physical activity. Concerning stomach cancer, the data are contro-versial: one study reported a reduced risk while two did not.30 No relationship between physical activity and risk of pancreatic cancers has been found,30 31 whereas rectal can-cer risk was unrelated to physical activity in the majority of studies.4 31

In contrast, there is overwhelming evidence that physical activity reduces the risk of colon cancer (for example, see World Cancer Research Fund/American Institute for Can-cer Research,4 Oliveria and Christos,5 and Colditz and col-leagues6). Despite diVerent methods of assessing the amount and diVerent types of physical activity (at work or during leisure time), there is consistent evidence that physically active men and women are at a reduced risk of colon cancer (up to 50% reduction in incidence).6 This eVect is independent of other risk factors such as diet and body weight characteristics. The types of activity that may be of bene®t in preventing colon cancer are largely unknown. Studies analysing dose-response relationships suggest that more intense activity may confer greater pro-tection against the risk of colon cancer than less intense activity.5. 6

The primary postulated mechanism is that physical activity reduces intestinal transit time which would limit the time of contact between the colon mucosa and cancer promoting contents. Enhancing intestinal transit time may indirectly aVect the risk of colon cancer by lowering secondary bile acid concentration or by increasing faecal short chain fatty acids.32 33 Other mechanisms related to colon cancer risk, such as impaired immune function, spe-ci®c dietary intake (for example, large amounts of alcohol or fat, low amounts of dietary fbre), or an increase in body mass index, insulin resistance, prostaglandin and triglycer-ides levels, body iron stores, and/or free radical scavenging enzyme activity, can be altered favourably by physical activity.32

CHOLELITHIASIS

Several studies have been published on the relationship between physical activity and cholelithiasis. While early studies yielded controversial results, most of the later stud-ies suggest a protective eVect of physical activity.8 9 34 Many of the earlier studies in particular are hampered by several methodological drawbacks: no control for potential risk factors other than age (for example, body weight or diet), small sample sizes, limited methods for physical activity assessment, and low variability in physical activity among subjects. Furthermore, it cannot be ruled out that in some studies the level of physical activity was already reduced as a result of the onset of disease. Two recent large prospective studies8 9 showed a relative risk (RR) of cholelithiasis of 0.63 in men and 0.69 in women when comparing the most active with the most inactive subjects, whereas sedentary lifestyle (watching tel-evision or sitting) resulted in an increased risk (RR 1.11±3.32). A clear dose-response relationship was ob-served, independent of several potential risk factors, strongly suggesting that (symptomatic) cholelithiasis can be prevented by physical activity, even beyond its beneft for control of body weight or diet.

The mechanisms by which physical activity may inuence the pathogenesis of gall stones are poorly under-stood but decreased biliary cholesterol secretion, and enhanced gall bladder and colonic motility, all known to be important for gall stone formation at rest,33 are postulated. Moreover, many factors which are related to an increased risk of cholesterol gall stone disease, such as glucose toler-ance, high serum levels of insulin, triglycerides, and various gall bladder regulatory hormones such as cholecystokinin, and low serum levels of high density lipoprotein choles-terol, are favourably altered by physical activity.33 35 36

GASTROINTESTINAL HAEMORRHAGE

The only study which examined gastrointestinal haemor-rhage and physical activity was a prospective cohort study with three years of follow up in 8205 elderly subjects.37 Only severe gastrointestinal haemorrhage was investigated. Physical activity was measured by self reported frequency of walking, gardening, or vigorous physical activity (result-ing in sweating) three years before the study baseline. A summary variable for the three activities was also calculated. For those participants doing the activity at least three times per week, RR was signifcantly lower for walk-ing (0.6) and for the summary variable (0.7) in comparison with sedentary subjects, independent of several other risk factors such as age, sex, mobility, body mass index, or health status. The RR for gardening (0.8) and vigorous physical activity (0.7) was not signi®cantly lower. The authors hypothesised that a relatively increased gastro-intestinal bloodow in physically active subjects reduced the risk of gastrointestinal haemorrhage.37 One should keep in mind that the fndings of this study were restricted to severe haemorrhage in elderly subjects and that no data are available for less severe forms of haemorrhage or for younger subjects.

Conclusions

Strenuous exercise may induce gastrointestinal symptoms such as heartburn or diarrhoea, which may deter people from participating in physical activity. Although many symptoms are acute and transient and do not hamper the athlete's health, repeated gastrointestinal bleeding during training and competition may occasionally lead to iron defciency and anaemia. However, these and other symptoms can often be prevented with appropriate precautions. Physical activity, mostly performed at a relatively low intensity, may also have protective eVects on the gastro-intestinal tract. There is strong evidence that physical activity reduces the risk of colon cancer. Less convincing evidence is found for cholelithiasis and constipation.. Physical activity may reduce the risk of diverticulosis, gastrointestinal haemorrhage, and inammatory bowel disease, although up to now there has been little research to substantiate this. Physical activity does not interfere with the healing process in in¯ammatory bowel disease and will probably not reduce the risk of rec-tal and gastric cancer.

Future research on exercise associated digestive pro-cesses in health or disease should explore the mechanisms involved in the potential benefts and hazards of physical activity and exercise on the gastrointestinal tract.

References are cited in the text

References

1. *Kong F, Singh RP (June ۲۰۲۳). Journal of Food Science.* ***73*** *(5): R67–R80. .*
2. *Encyclopedia Britannica ۲۰۲۱. Retrieved 1 October ۲۰۲۱.*
3. *Hopkins J, Maton A, Charles WM, Susan J, Maryanna QW, David L, Jill DW (۲۰۲۳). Englewood Cliffs, New Jersey, US: Prentice Hall. .*
4. *Pocock G (۲۰۲۳). Human Physiology (Third ed.). Oxford University Press. p. 382*
5. *Macpherson G (۲۰۲۰). Black's Medical Dictionary. A & C. Black Ltd. .*
6. *Frenkel ES, Ribbeck K (January 2015). . Applied and Environmental Microbiology.* ***81*** *(1): 332–338.*

7. *Nanci A, Ten Cate AR (۲۰۲۲). Ten Cate's Oral Histology: Development, Structure, and Function (7th ed.). St. Louis, Mo.: Mosby Elsevier. p. 321.*
8. *Britannica Concise Encyclopedia. Encyclopedia Britannica, Inc. ۲۰۱۸.*
9. *Saladin K (۲۰۱۸). Human Anatomy. McGraw Hill. p. 659*
10. *Dorland WA (۲۰۲۲). Dorland's illustrated medical dictionary (32nd ed.). Philadelphia, PA: Saunders/Elsevier.*
11. *Nanci A (۲۰۲۱). Ten Cate's Oral Histology: Development, Structure, and Function (8th ed.). St. Louis, Mo.: Elsevier. pp. 275–276*
12. Illustrated Anatomy of the Head and Neck, Fehrenbach and Herring, Elsevier, ۲۰۱۹, p. 157
13. *Piludu M, Lantini MS, Cossu M, Piras M, Oppenheim FG, Helmerhorst EJ, et al. (November ۲۰۱۹). "Salivary histatins in human deep posterior lingual glands (of von Ebner)". Archives of Oral Biology. **51** (11): 967–973.*
14. *Maton A (۲۰۲۱-01-01). . Prentice Hall ۲۰۲۱.*
15. *Edgar WM (April ۲۰۲۲). "Saliva: its secretion, composition and functions". British Dental Journal. **172** (8): 305–312*
16. *; Honjo T. (January ۲۰۲۲). "Intestinal IgA synthesis: regulation of front-line body defences". Nature Reviews. Immunology. **3** (1): 63–72.*
17. *Pettit JD, Moss P (۲۰۲۱). Essential Haematology (5e (Essential) ed.). Blackwell Publishing Professional. p. 44.*
18. *Bradbury J (March ۲۰۱۹). PLOS Biology. **2** (3): E64.*
19. *Bowen R. . Hypertexts for Biomedical Sciences. Archived from on 12 December ۲۰۱۹ – via About.com.*
20. *Fejerskov O, Kidd E, Nyvad B, Baelum V, eds. (۲۰۱۸). Dental caries: the disease and its clinical management (2nd ed.). Oxford: Blackwell Munksgaard.*
21. *Jowett A, Shrestha R (November ۲۰۱۹). Journal of Anatomy. **193** (4): 617–618.*
22. *Sherwood L (۲۰۲۲). . Belmont, CA: Wadsworth Pub. Co.*
23. *Saladin K (۲۰۱۸). Human Anatomy. McGraw Hill. pp. 621–622.*
24. *Saladin K (۲۰۱۹). Human Anatomy. McGraw Hill. pp. 674–679*
25. *Hall JE, Hall ME (۲۰۱۷). Guyton and Hall Textbook of Medical Physiology. U.S.: Saunders Elsevier. p. 784.*
26. *Drake RL, Vogl W, Mitchell AW, Richardson P (۲۰۲۱). Gray's Anatomy for students. Philadelphia: Elsevier/Churchill Livingstone. p. 287.*
27. *Retrieved 22 May 2015.*
28. *Ahrens T, Prentice D (۲۰۲۲). Critical care certification: preparation, review & practice exams. Norwalk, CT: Appleton & Lange. p. 265*
29. at the U.S. National Library of Medicine (MeSH)
30. *Read NW, Al-Janabi MN, Holgate AM, Barber DC, Edwards CA (March ۲۰۲۱). 308*
31. *Bowen R. Hypertexts for Biomedical Sciences. Colorado State University. Retrieved April 1, 2020.*
32. *Cummings JH, Macfarlane GT (November ۲۰۱۸). "Role of intestinal bacteria in nutrient metabolism". Journal of Parenteral and Enteral Nutrition. **21** (6): 357–365*
33. *Saladin K (۲۰۲۱). Human Anatomy. McGraw Hill. p. 672. .*

34. *Wood JD (۲۰۲۳). "Gastrointestinal Physiology". In Rhoades RA, Bell DR (eds.). Medical Physiology: Principles for Clinical Medicine (3rd ed.). Philadelphia, PA: Lippincott Williams & Wilkins. pp. 463–496.*
35. *Waaler BA, Toska K (February ۲۰۲۳). "[Digestive system's large and changing needs of blood supply]". Tidsskrift for den Norske Laegeforening.* ***119*** *(5): 664–666.*
36. *Boron WG, Boulpaep EL (۲۰۱۹). Medical Physiology. Elsevier Saunders. p. 883.*
37. *Hall JE (۲۰۱۷). "General Principles of Gastrointestinal Function". Guyton and Hal Textbook of Medical Physiology (12th ed.). Saunders Elsevier. p. 755.*

The effect of exercise in patients with dyslipidemia

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Abstract
Dyslipidemia is the risk of cardiovascular disease, and their relationship is clear. Lowering serum cholesterol can reduce the risk of coronary heart disease. At present, the main treatment is taking medicine, however, drug treatment has its limitations. Exercise not only has a positive effect on individuals with dyslipidemia, but can also help improve lipids profile. This review is intending to provide information on the effects of exercise training on both tranditional lipids, for example, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and new lipids and lipoproteins such as non-high-density lipoprotein cholesterol, and postprandial lipoprotein. The mechanisms of aerobic exercise on lipids and lipoproteins are also briefly described.
Keywords: Aerobic exercise, Coronary heart disease, Dyslipidemia, Lipoprotein

Background

It has been consistently showed that concentration of low-density lipoprotein cholesterol (LDL-C) increasing is associated with an increased risk of myocardial infarction and vascular death [1]. High-density lipoprotein cholesterol (HDL-C) is a strong, consistent, and independent predictor of cardiovascular events, which has been confirmed by many prospective studies on different racial and ethnic groups worldwide [2, 3]. In addition, triglycerides (TG) can enter the arterial wall with a mild to moderate increase concentration (2–10 mmol/L), and then accumulate at there, thus causing the possibility of atherosclerosis [4]. Between 2007 and 2008, an increase in TG was associated with an increased risk of myocardial infarction, ischemic heart disease, ischemic stroke, and all-cause mortality, according to studies in the Copenhagen City Heart Study and Women's Health Study [5–7].
Lowering serum cholesterol can help reduce the risk of coronary heart disease (CHD). Statin therapy has been appropriately emphasized in the current US and European guidelines as the primary treatment for LDL-C reduction because of strong evidence of reduced safety, efficacy and events [8, 9]. However, many people cannot tolerate statins, and statins are contraindicated in pregnant women. Therefore, there is a need to find another non-statin to help more people better reduce LDL-C. There are several novel methods of reducing LDL-C in active studies, such as inhibitors of mipomersen, lomitapide, and proproteinase/subtilisin/kexin 9 (PCSK9). However, their hepatotoxicity, high cost, inconvenience, and a general lack of availability outside the tertiary referral centers imply that their use is limited [10]. Researchers have also attempted to reduce cardiovascular risk by increasing HDL-C concentrations. There are two main approaches currently available: elevation of HDL-C directly, such as with cholesterol ester transfer protein (CETP) inhibitors; or promotion of the reverse cholesterol transport (RCT) pathway, e.g., infusion of apolipoprotein A-I (apoA-I) containing recombinant HDL particles or lipid-poor HDL particles [11]. However, there have been no positive outcomes. For the reduction of TG, more advice comes from changes in lifestyle, such as sugar and the Mediterranean diet [12, 13]. Of course, drugs are also effective [14], such as fibrates, fish oil and niacin [15].

Aerobic exercise with lipids and lipoproteins

Aerobic exercise

In addition to these treatments, aerobic exercise has been shown to improve the prognosis of cardiovascular disease (CVD). Aerobic exercise is defined as any form of physical activity that produces an increased heart rate and respiratory volume to meet the oxygen requirements of the activated muscle. Compared to medications, aerobic exercise is easier to carry out and has fewer side effects. Pedersen and Saltin [16] concluded that exercise can have a positive impact on symptoms and physical health via investigation of multiple meta-analyses about

exercise and lipid profiles. Kokkinos et al. [17] performed a prospective cohort study of exercise and lipid metabolism. Individuals were grouped by evaluating the peak metabolic equivalents (MET) achieved during the exercise endurance test, the adaptation conditions and the different statin treatment. After 10 years, for individuals who took statins, the mortality risk decreased, while their fitness increased; the hazard ratio in patients who were in highly fit for highly fit (>9 MET) was 0.3 when compared with those who were in least fit (<5 MET). Therefore, the authors concluded that the risk of mortality is significantly reduced when combined with statin therapy and aerobic exercise compared to either method alone, and that aerobic exercise is required for individuals with dyslipidemia.

For its low-cost, low-risk and non-drug intervention that can be applied to the vast majority of the public, aerobic exercise is recommended for CHD patients [19]. In 2015, the European Society

Aerobic exercise and LDL-C

Fasting LDL-C is strongly associated with an increased risk of coronary artery disease (CAD), so it is necessary to make clear the effect of aerobic exercise on LDL-C. Unlike HDL-C, the effect of exercise on LDL-C is inconsistent in human and there are even completely contrary results (Table (Table1).1). The results of these different studies may be due to variations in people's weight. Some studies showed that aerobic exercise alone did not change the fasting blood LDL-C levels, unless the weight during this period also changed. In addition, research statistics showed that per kilogram of body weight loss resulting in LDL-C reduced by about 0.8 mg/dL [37].

Although the current results on the LDL-C response to the aerobic exercise are discordant, studies have still indicated the potential occurrence of important cardioprotective improvements in LDL-C subfractions. LDL-C is classified according to their size and density. LDL-C subfractions that directly related to cardiovascular events are smaller, denser LDL particles [١]. Because of the knowledge of different LDL subcomponents, it has become necessary and interesting to explore whether aerobic exercise particularly affects certain LDL subcomponents. In some patients with mild to moderate dyslipidemia, the researchers found that after a few months of aerobic exercise, LDL-C did not change significantly, but the concentration of atherogenic small LDL particles decreased, and the average size of LDL particles increased [٢]. Therefore, the impact of aerobic exercise on LDL-C should not be limited to total LDL-C, but LDL-C subfractions should also be considered. However, Varady et al. [٣] found that the LDL particle volume decreased in patients with hypercholesterolemia after aerobic exercise. Therefore, they worry that aerobic exercise may reduce the LDL particle volume to increase CHD risk. By contrast, Elosua et al. [۴] suggested that aerobic exercise had no effect on LDL particle diameter. Given these discrepant results, additional studies addressing the effects of aerobic exercise on the LDL fraction appear to be necessary.

Plasma Lp (a) is another LDL subunit containing Apo (a). However, unlike other low-density lipoprotein subfractions, Lp (a) is genetically influenced, unaffected by motion, and cannot be improved by any form of exercise [۵].

ApoB is a major component of LDL particles and is essential for the removal of LDL particles in the circulation. About 95% of apoB binds to LDL particles, and each LDL particle binds to only one apoB molecule [۶]. Therefore, the concentration of apoB indirectly reflects the concentration of LDL-C to a certain extent. Because of this, increased apoB concentrations can reflect an increased cardiovascular risk [۷]. The effects of aerobic exercise on apoB concentration are not well confirmed. Crouse et al. [۸] and Laaksonen et al. [۹] both found that after a few months of aerobic exercise, the concentration of apoB in hypercholesterolemic men decreased. However, there were controversies about these findings. For example, Leon et al. [۱۰] found that 20 weeks of aerobic exercise did not affect the concentration of apoB. Others found no change in apoB concentrations during either long (48 weeks) or short (3 weeks) aerobic exercise. Some factors must result in these various outcomes, for example, age. Accordingly, the authors designed a study to determine whether age influenced the results, however, they found that age did not affect apoB or lipoprotein concentrations in response to exercise [۱۱]. Therefore, more studies on aerobic exercise and apoB remain necessary.

Aerobic exercise and TG

It is widely reported that exercise can induce lower plasma TG concentrations However, many studies have shown that sedentary individuals have no change in TG levels after a single exercise session [۱۲]. The reasons for the discrepancies were unclear. It seemed that where there was an exercise with a high energy requirement, there would be more frequent that TG concentrations decreases occur. Actually, TG changes in sedentary subjects did occur regardless of whether the energy consumption is low or moderate [۱۳]. Therefore, the energy consumption may not be the main reason for this distinction. If this is the case, is it the state of the patient before exercise (e.g., sitting or exercise) is the key factor? To our disappointment, the TG did not change significantly in non-active subjects with aerobic exercise. But the results of other studies have been very gratifying. The researchers found that when participants had lower baseline levels of TG, there was only a slight decrease in TG after exercise. While, when TG baseline levels were high, there was a significant reduction. Thus, the TG baseline level may be the key factor influencing the effect of exercise on the TG response.

It has been approved that the baseline level of TG are controversy to that of HDL-C, HDL2-C, and HDL3-C. However, investigators have noted the HDL-C increasing but not TG level decreasing at the same time in subjects after an aerobic exercise training [۱۴]. Numerous studies showed that TG reduction always accompanied with no vary of HDL-C, or HDL-C increased with no apparent improvements of TG level. Likewise, in previous inactive individuals, HDL-C elevation has no relationship with TG level. But, it has been approved that there were both HDL-C increasing and TG decreasing with sedentary hyperlipidemia participants after aerobic exercise training. For instance, Peter et al. noted that after 2 days at the end of the aerobic exercise, the TG decreased with an HDL-C increase approximated to 14%. HDL-C elevation closing to 11% may contribute to the HDL-C concentrations raise [۱۵]. At present, researchers are puzzled the different responses of TG and HDL-C to the aerobic exercise training. It appears that body weight, body fat, cardiovascular fitness, training status, regional lipid concentration, dietary changes, and genetic factors all contribute to it. In addition, exercise intensity, exercise time, as well as blood collection time, blood test technology, subject sample size should also be taken into account.

Aerobic exercise and postprandial lipemia

There are a number of studies that provide important evidence for exercise training in response to lipids. However, almost all of the blood collection is in fasting state. Therefore, it can only reflect the effect of exercise on fasting lipid. As we all know, only a few hours before breakfast can be strictly referred to as fasting state, and the state of time after a meal is far more than fasting state. Therefore, the researchers speculated that postprandial lipid was of more sense in lipid metabolism than fasting state, and postprandial lipid may have a greater role than fasting blood lipids in the prediction of cardiovascular risk factors. In addition, the speculation has been approved by finding that postprandial triacylglycerolemia predicts cardiovascular events better than fasting triacylglycerol (TAG) concentrations [6]. Mestek et al. [۱۶] observed that exercise training reduced the non-fasting TG response to a high-fat diet in individuals with metabolic syndrome. Postprandial blood lipid response to aerobic exercise not only occurred immediately after training in the acute phase, but also lasted to the next day. In addition, there is no need for a specific exercise. Exercise can be done all day. There was no significant difference between continuous aerobic exercise and single-session effectiveness in reducing non-fasting TG levels [۱۷]. Sabaka et al. [۱۸] found that exercise for 4 days resulted in significantly changes of postprandial TG, LDL-C and VLDL remnants. However, there was no significant change in postprandial HDL-C, but some HDL-C subfractions were altered. For example, the authors noted a statistically significant reduction in small and medium HDL particles in the postprandial state after exercise training. Therefore, aerobic exercise does affect postprandial lipid distribution. Another important finding was that only 4 days of physical exercise can lead to significant positive changes in postprandial lipid profile, suggesting that short-term aerobic exercise can improve postprandial lipid distribution. Vigorous exercise training can significantly reduce postprandial lipids, which is more common in healthy and non-obese individuals. To investigate the effects of vigorous exercise on postprandial TG, subjects exercised before a high fat diet, but exercised for longer periods of time and exercised more intensively [۲۰ ۱۹]. As respected, there was substantial lowering of postprandial TG level. However, for most people, especially cardiovascular patients, such a high intensity of exercise is not appropriate. In fact, this intensive training is not necessary. In order to reduce postprandial blood lipids, moderate-intensity aerobic exercise is sufficient. In

addition, low-fitness people only need to use low-intensity aerobic exercise [۲۱]. Therefore, despite the high-intensity aerobic exercise have a very significant impact on postprandial lipid changes, for most people, moderate or lower intensity exercise is sufficient.

Aerobic exercise and non–HDL-C

Recent evidence suggested that non-HDL-C was a better indicator of CVD risk than traditional lipids such as HDL-C, LDL-C, and TG. In addition, studies have shown that, as a predictor of future cardiovascular risk, non-HDL-C was more persuasive than LDL-C to some extent. Given that the potential benefits of aerobic exercise and the risk associated with elevated non–HDL-C levels, meta-analysis has been used to examine the effects of aerobic exercise on non–HDL-C in children and adolescents. However, previous meta-analysis reported that walking reduced adult non-HDL-C by 4% [58]. In contrast, one study reported that non-HDL-C in the exercise training group did not change significantly compared with the control group. The subjects were children and adolescent whose TC and HDL-C levels were essentially normal, and both of which were critical factors in the calculation of non-HDL-C, thus did not achieve the desired positive results. However, few studies have focused on the relationship between aerobic exercise and non-HDL-C levels. Accordingly, more studies should be planned to illustrate the relationship between the two.

Related influencing factors of aerobic exercise on lipids

Many factors lead to different results on the effects of aerobic exercise on lipoprotein levels, such as various training time or training intensities. Some researchers believe that, to keep this effect longer, then, aerobic exercise time also needs longer, as well as the intensity needs more intensive. Dunn et al. [۲۲] suggested that short-term training could also make improvements on plasma lipids, as long as there was enough exercise intensities. Kraus et al. [23] observed that the total energy consumption and exercise intensity was the main factor affecting lipid changes. O'Donovan et al. [24] aimed to study the effect of exercise intensity on lipid changes and found that, in the same amount of exercise, the exercise intensity is higher, the more obvious changes in blood lipids.

The results of these studies suggest that exercise time, exercise volume and exercise intensity all have an effect on exercise-induced changes in blood lipids. HDL-C is the most sensitive to exercise. In order to reduce LDL-C and TG levels more, it is necessary to increase the aerobic exercise intensity. However, this is difficult to achieve in individuals with coronary artery disease who are of limited exercise capacity or other risk factors.

The mechanisms of the effects of aerobic exercise on lipids

Although the mechanism of exercise-induced lipid changes is unclear, exercise itself may increase blood lipid consumption hence to decrease lipids levels [۲۵]. Mechanisms may involve the increased activity of lipoprotein lipase (LPL) - lipoprotein lipase responsible for chylomicrons and VLDL TAG hydrolysis in granules [۲۶]. Most of the catalytically active LPL is located in the vessel wall and then isolated from the endothelium surface and released in the blood after intravenous injection of heparin [۲۷]. Therefore, the detected LPL is often the post-heparin LPL. Ferguson et al. [۲۸] reported that heavy or prolonged aerobic exercise episodes could significantly increase post-heparin plasma LPL activity, thus promoted LPL-mediated TG hydrolysis. However, with several findings showing that pre-heparin LPL concentration indicate the amount of systemic LPL activity [۲۹–۳۰], Tanaka et al. turned the target to pre-heparin LPL, and found that 12 weeks of jogging training increased pre-heparin LPL concentrations in overweight men [۳۱]. Exercise-induced LPL changes were time-delayed, for example, LPL mRNA peak level occurred at 4 h after exercise [۳۲]. Besides, LPL activation elevation could last for 24 h after only a 1 h exercise session in individuals with moderate intensity exercise [۳۳].

In addition to the traditional mechanisms described above, several other discoveries revealed the mechanisms about exercise altering lipids profile from other aspects. Increased expression of ATP-binding cassette transporter A-1 (ABCA1) in macrophages has a strong effect on RCT, plasma HDL-C formation, and protection against atherosclerosis. So far, studies focused on the impact of aerobic exercise on blood ABCA1. Study found that the ABCA1 gene expression was significantly different before and after exercise [۳۴]. Ghanbari-Niaki et al. [۳۵] also found that ABCA1 mRNA expression increased regardless of the intensity of exercise. Therefore, they hypothesized that aerobic exercise may increase the expression of ABCA1 to exert its role in reducing cardiovascular risk. The researchers tested this hypothesis in a recent study [26]. They used human CETP transgenic (CETP-tg) mice to study the effects of aerobic exercise on RCT. Male CETP-tg mice were randomly

assigned to control and exercise groups. Six weeks later, they found ABCA1 protein levels increased 100% in the liver of the exercise group.

Liver X receptor (LXR) is one of the transcription factors of nuclear receptor superfamily that play a key role in liver cholesterol metabolism. A study reported that low intensity exercise resulted in significant increase in LXR expression in human [۲۲]. Study showed that LXRα expression was significantly elevated 2.8 fold in exercised rats than the control group [27]. LXR has been proved involving in regulating the expression of ABCA1. So, exercise may by inducing higher LXR and ABCA1 to improve the RCT process, which resulting in increased plasma HDL-C levels.

PCSK9 is a hot spot in the field of cardiovascular research in recent years as it is a new biomarker of LDL clearance and a new target of CVD therapy. Exercise can reduce plasma LDL-C levels, and PCSK9 plays an important role on the regulation of LDL receptor. Therefore, the investigators have considered that exercise is likely to affect LDL-C by modulating PCSK9. Kamani et al. [۲۴] found a significant decrease in mean PCSK9 levels and mean LDL-C levels in volunteers after 3 months exercise, and concluded that daily exercise is independently associated with a decrease in PCSK9 levels over time. Rideout et al. [۲۸] used C57BL/6 mice as a model, and feed them with high-fat diet, then make them do aerobic exercise. After 8 weeks, the levels of PCSK9 mRNA and sterol regulatory element binding protein 2 (SREBP2) were increased significantly in mice with high-fat diet and exercise training, 1.9 and 1.8 times higher than those only with high-fat diet respectively. In addition, both plasma PCSK9 and cholesterol were reduced by 14% in mice with both high-fat diet and exercise training, while no change with those only with high-fat diet. Accordingly, one means by which aerobic exercise helps improve lipoprotein levels may be via PCSK9 or SREBP2. However, additional mechanistic studies are required to directly link exercise-induced lipid lowering with reduced PCSK9 activity.

Conclusion

Currently, clinicians may be excessively reliant on lipid-lowering drugs (i.e., statins) to treat patients with dyslipidemias. In our opinion, aggressive lifestyle alterations, such as exercise, should not be abandoned. Such knowledge should aid in preventing and treating dyslipidemia while reducing the risks of myocardial infarctions and CAD. Clinicians should encourage as much physical activity as possible.

References in the text are referenced by numbers.

References

1. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55000 vascular deaths. *Lancet.* **۲۰۲۱**;370:1829–1839. doi: 10.1016/S0140-6736(07)61778-4.

2. Toth PP, Barter PJ, Rosenson RS, et al. High-densith lipoproteins: a consensus statement from the National Lipid Association. *J Clin Lipidol.* **۲۰۱۹**;7:484–525. doi: 10.1016/j.jacl.**۲۰۱۸**.08.001

3. Goff DC, Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. **۲۰۱۹**;129(suppl2):S49–S73. doi: 10.1161/01.cir.0000437741.48606.98.

4. Nordestgaard BG, Wootton R, Lewis B. Selective retention of VLDL, ODL, and LDL in the arterial intima of genetically hyperlipidemic rabbits in vivo. Molecular size as a determinant of fractional loss from the intima-inner media. *Arterioscler Thromb Vasc Biol.* **۲۰۲۲**;15:534–542. doi: 10.1161/01.ATV.15.4.534.

5. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA.* **۲۰۲۱**;298:299–308. doi: 10.1001/jama.298.3.299.

6. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglyceride and risk of cardiovascular events in women. *JAMA.* **۲۰۱۹**;298(3):309–316. doi: 10.1001/jama.298.3.309

7. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* **۲۰۲۰**;300:2142–2152. doi: 10.1001/jama.**۲۰۲۰**.621.

8. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomisedtrials. *Lancet***۲۰۲۱**;376:1670–1681.doi: 10.1016/S0140-6736(10)61350-

9. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trial. *Lancet.* **۲۰۲۳**;**380**:581–590. doi: 10.1016/S0140-6736(12)62027-3

10. Ridker PM. LDL cholesterol: controversies and future therapeutic directions. *Lancet.* **۲۰۲۲**;384:607–617. doi: 10.1016/S0140-6736(14)61009-6

11. Rader DJ, Kees Hovingh G. HDL and cardiovascular disease. *Lancet.* **۲۰۲۰**;384:618–625. doi: 10.1016/S0140-6736(14)61217-4.

12. Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol.* **۲۰۱۹**;**2**(8):655–666. doi: 10.1016/S2213-8587(13)70191-8.

13. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* **۲۰۲۱**;**97**:2969–2989. doi: 10.1210/jc.2011-3213.

14. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the Task for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European atherosclerosis Society (EAS) *Eur Heart J.* **۲۰۲۲**;**32**:1769–1818. doi: 10.1093/eurheartj/ehr158.

15. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet.* **۲۰۲۱**;**384**:626–635. doi: 10.1016/S0140-6736(14)61177-6.

16. Pedersen B, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports.* **۲۰۲۳**;**16**(Suppl1):3–63. doi: 10.1111/j.1600-0838.2006.00520.x.

17. Kokkinos PF, Faselis C, Myers J, et al. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. *Lancet.* **۲۰۲۱**;**381**:394–399. doi: 10.1016/S0140-6736(12)61426-3

18. Eklund U, Steene-Johannessen J, Broun WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonized meta-analysis of data from more than 1 million men and women. *Lancet.* **۲۰۲۱**;**388**(10051):1302–1310. doi: 10.1016/S0140-6736(16)30370-1.

19. National Cholesterol Education Program. National Heart Lung and Blood Institute. National Institutes of Health Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation.* **۲۰۱۹**;**106**(25):3143–3421.

20. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC) *Eur Heart J.* 2016;**37**(3):267–315. doi: 10.1093/eurheartj/ehv320

21. LeMura L, von Duvillard S, Andreacci J, et al. Lipid and lipoprotein profiles, cadiovascular fitness, body composition, and diet during and after resistance, aerobic and combination training in young women. *Eur J Appl Physiol.* **۲۰۲۰**;**82**(5–6):451–458. doi: 10.1007/s004210000234.

22. Nybo L, Sundstrup E, Jakobsen M, et al. High-intensity training versus traditional exercise interventions for promoting health. *Med Sci Sports Exerc.* **۲۰۱۸**;**42**(10):1951–1958. doi: 10.1249/MSS.0b013e3181d99203

23. Kraus W, Houmard J, Duscha B, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med.* **۲۰۲۱**;**347**(19):1483–1492. doi: 10.1056/NEJMoa020194.

24. O'Donovan G, Owen A, Bird S, et al. Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate- or high-intensity exercise of equal energy cost. *J Appl Physiol.* **۲۰۲۲**;**98**(5):1619–1625. doi: 10.1152/japplphysiol.01310.2004.

25. Kazeminasab F, Marandi M, Ghaedi K, et al. Endurance training enhances LXRα gene expression in Wistar male rats. *Eur J Appl Physiol.* **۲۰۲۱**;**113**(9):2285–2290. doi: 10.1007/s00421-013-2658-z.

26. Ghanbari-Niaki A, Khabazian BM, Hossaini-Kakhak SA, et al. Treadmill exercise enhances ABCA1 expression in rat liver. *Biochem Biophys Res Commun.* **۲۰۱۸**;**361**(4):841–846. doi: 10.1016/j.bbrc.

27. Kazeminasab F, Marandi M, Ghaedi K, et al. Effects of a 4-week aerobic exercise on lipid profile and expression of LXRα in rat liver. *Cell J.* **۲۰۱۹**;**19**(1):45–49. [

28. Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arcb Intern Med.* **۲۰۱۹**;**167**:999–1008. doi: 10.1001/archinte.167.10.999.

29. Morgan J, Carey C, Lincoff A, et al. High-density lipoprotein subfractions and risk of coronary artery disease. *Curr Atheroscler Rep.* **۲۰۱۴**;**6**:359–365. doi: 10.1007/s11883-004-0047-0.

30. Ballentyne FC, Clark RS, Simpson HS, et al. The effect of moderate physical exercise on the plasma lipoprotein subfractions of male survivors of myocardial infarction. *Circulation.* **۲۰۱۶**;**65**:913–918. doi: 10.1161/01.CIR.65.5.913.

31. Wood PD, Stefanick MK, Dreon DM, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *NEnglJMed.* **۲۰۲۱**;**319**:1173–1179. doi: 10.1056/NEJM198811033191801.

32. Kelley GA, Kelley KS. Aerobic exercise and HDL2-C: a meta-analysis of randomized controlledtrials. *Atherosclerosis.* **۲۰۲۱**;**184**:207–215. doi: 10.1016/j.atherosclerosis.**۲۰۲۱**.04.005.

33. Halverstadt A, Phares DA, Wilund KR, et al. Endurance exercise training raises high-density lipoprotein cholesterol and lowers small low-density lipoprotein and very low-density lipoprotein independent of body fat phenotypes in older men and women. *Metabolism.* **۲۰۱۹**;**56**:444–450. doi: 10.1016/j.metabol.**۲۰۱۹**.10.019.

34. Králová Lesná I, Suchánek P, Kovár J, et al. Life style change and reverse cholesterol transport in obese women. *Physiol Res.* **۲۰۱۸**;**58**(Suppl 1):S33–S38.

35. Välimäki IA, Vuorimaa T, Ahotupa M, et al. Strenuous physical exercise accelerates the lipid peroxide clearing transport by HDL. *Eur J Appl Physiol.* **2016**;**116**(9):1683–1691. doi: 10.1007/s00421-016-3422-y.

36. Tiainen S, Luoto R, Ahotupa M, et al. 6-mo aerobic exercise intervention enhances the lipid peroxide transport function of HDL. *Free Radic Res.* **2016**;**50**(11):1279–1285. doi: 10.1080/10715762.2016.1252040

37. Goldberg AC, Hopkins PN, Toch PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on familial hypercholesterolemia. *J Clin Lipidol.* **۲۰۱۸**;**5**:S1–S8. doi: 10.1016/j.jacl.2011.04.003

38. Davidson MH, Ballantyne CM, Jacobson TA, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. *J Clin Lipidol.* **۲۰۲۲**;5:338–367. doi: 10.1016/j.jacl.2011.07.005.

The effect of exercise for aged people

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Abstract

In this special issue of BioMed Research International, the focus is on lifestyle and in particular physical activity (PA) as a driver for a healthy and long life for older people.

As populations continue to extend life expectancy, a central concern is whether the added time comprises years of healthy life and promotes a high health-related quality of life into old age. PA is defined as any bodily movement produced by skeletal muscles that result in energy expenditure. PA encompasses exercise, sports, and physical activities performed as part of daily living, occupation, leisure, or active transportation. Exercise is a subcategory of PA that is planned, structured, and repetitive and that has as a final or intermediate objective for improvement or maintenance of physical fitness. Physical function is the capacity of an individual to perform the physical activities of daily living. Physical function reflects motor function and control, physical fitness, and habitual PA [1].

Introduction

PA is a protective factor for noncommunicable diseases such as cardiovascular disease, stroke, diabetes, and some types of cancer [2] and PA is associated with improved mental health [3], delay in the onset of dementia [4], and improved quality of life and wellbeing [5, 6]. The health benefits of PA are well documented with higher levels and greater frequency of PA being associated with reduced risk and improved health in a number of key areas [7]. The dose of PA or exercise is described by the duration, frequency, intensity, and mode [8]. For optimal effects, the older person must adhere to the prescribed exercise program and follow the overload principle of training, i.e., to exercise near the limit of the maximum capacity to challenge the body systems sufficiently, to induce improvements in physiological parameters such as VO2max and muscular strength [1].

The effect of exercise for aged people

Improvements in mental health, emotional, psychological, and social well-being and cognitive function are also associated with regular PA. Despite these health benefits, PA levels amongst older adults remain below the recommended 150 min/week [9]. The crude global prevalence of physical inactivity is 21.4% [10]. This translates to one in every four to five adults being physically inactive, or with activity levels lower than the current recommendations from WHO [11]. Inactivity and aging increase the risk of chronic disease, and older people often have multiple chronic conditions (NFH, 2010). The exercise recommendations from WHO include both aerobic exercise and strength exercise as well as balance exercises to reduce the risk of falls. If older adults cannot follow the guidelines because of chronic conditions, they should be as active as their ability and conditions allow [12]. It is important to note that the recommended amount of PA is in addition to routine activities of daily living like self-care, cooking, and shopping, to mention a few.

Inactivity is associated with alterations in body composition resulting in an increase in percentage of body fat and a concomitant decline in lean body mass. Thus, significant loss in maximal force production takes place with inactivity. Skeletal muscle atrophy is often considered a hallmark of aging and physical inactivity. Sarcopenia is defined as low muscle mass in combination with low muscle strength and/or low physical performance [13]. Consequently, low physical performance and dependence in activities of daily living is more common among older people [14, 15]. However, strength training has been shown to increase lean body mass [16], improve physical performance [17, 18], and to a lesser extent have a positive effect on self-reported activities of daily living [18]. These aspects are at focus in the papers of K. Kropielnicka et al. “Influence of the Physical Training on Muscle Function and Walking Distance in Symptomatic Peripheral Arterial Disease in Elderly” as well as G. Piastra et al. “Effects of Two Types of 9-Month Adapted Physical Activity Program on Muscle Mass, Muscle Strength, and Balance in Moderate Sarcopenic Older Women.”

Participation in PA and exercise can contribute to maintaining quality of life, health, and physical function and reducing falls [19–21] among older people in general and older people with morbidities in particular. The increased attention to the relationship between exercise and HRQOL in older adults over the last decade is reflected in a recent review, which showed that a moderate PA level combining multitasking exercise components had a positive effect on activities in daily living, highlighting the importance of physical, mental, and social demands [22]. To reduce falls, balance training is also recommended to be included in physical exercise programs for older adults [12]. Exercise has also been shown to reduce falls with 21%, with a greater effect of exercise programs including challenging balance activities for more than 3 hours/week [23].

The gender perspective and motivators for fall prevention are at focus in M. Sandlund et al. qualitative study "Gender Perspective on Older People's Exercise Preferences and Motivators in the Context of Falls Prevention: A Qualitative Study," in this special issue.

Sports exercises

Exercise training in older people has been associated with health benefits such as decreased cardiovascular mortality [24]. Explanatory mechanism likely to be involved following exercise was a change in the cardiac autonomic balance producing an increase, or a relative dominance, of the vagal component [25]. Furthermore, endurance exercise training in older people decreases resting and submaximal exercise heart rate and systolic and diastolic blood pressure and increases stroke volume [26]. This is especially notable during peak effort in which stroke volume, cardiac output, contractility, and oxygen uptake are increased, while total peripheral resistance and systolic and diastolic blood pressure decreased. Thus lowering after-load in the heart muscle, which in turn facilitates left ventricular systolic and diastolic function, emphasizes the importance of high intensity training also for the elderly. E. Tamuleviciute-Prasciene et al. focus on the frail elderly individuals and exercise in their contribution "Frailty and Exercise Training: How to Provide Best Care after Cardiac Surgery or Intervention for Elder Patients with Valvular Heart Disease."

Exercise may also have benefits for the brain centers that support executive control. It may be that strong executive functioning in itself may facilitate consistency for this challenging activity. Poor executive control has been associated with lower self-reported PA rates over a 2-year period [27, 28]. The executive control's contribution to PA has been found to be 50% greater in magnitude than the contribution of PA to subsequent changes in executive control [29]. In the paper of M. A. McCaskey et al. "Making More of IT: Enabling Intensive MOtor Cognitive Rehabilitation Exercises in Geriatrics Using INFORMATION Technology Solutions," the authors also include new technology to enhance and maintain exercise in cognitive rehabilitation.

In order to attain a high level of cardiorespiratory fitness, it is recommended to be physically active for 6 months or longer. These recommendations may also be applied to balance exercises in order to reduce falls [23]. Many elderly individuals are incapable of sustaining activities for this long on their own. Successful maintenance of PA typically requires substantial support and supervision. Even then, a high percentage of people drop out due to difficulties negotiating everyday costs of activity participation like scheduling conflicts and competing sedentary activities or health issues. This issue is highlighted in the study of T. Adachi et al. "Predicting the Future Need of Walking Device or Assistance by Moderate to Vigorous Physical Activity: A 2-Year Prospective Study of Women Aged 75 Years and Above."

In addition, reduced bodily functions can make it difficult for elderly persons to maintain exercise under different environmental circumstances, which is demonstrated in the contribution of B. N. Balmain et al. "Aging and Thermoregulatory Control: The Clinical Implications of Exercising under Heat Stress in Older Individuals."

In this special issue, we have included papers that focus on the aging process and PA in a broad perspective, focusing on different aspects on PA, exercise, and older people. PA and exercise play an important role in the primary, secondary, and tertiary prevention, in the management of diseases, to counteract sarcopenia and falls as well as improving physical performance and activities of daily living, as these papers illustrate.

Promoting exercise among the older population is an important public health and clinical issue. A core issue is how to get older people with comorbidities to exercise.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References are referenced by numbers in the text

References

1. Garber C. E., Blissmer B., Deschenes M. R., et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine & Science in Sports & Exercise.* ۲۰۲۲;43(7):1334–1359. doi: 10.1249/MSS.0b013e318213fefb.

2. World Health Organization. PA for health. More active people for a healthier world: draft global action plan on PA 2018- 2030. *Vaccine.* 2018 doi: 10.1016/j.vaccine.2018.04.022.

3. Schuch F. B., Vancampfort D., Richards J., Rosenbaum S., Ward P. B., Stubbs B. Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *Journal of Psychiatric Research.* 2016;77:42–51. doi: 10.1016/j.jpsychires.۲۰۱۹.02.023.

4. Livingston G., Sommerlad A., Orgeta V., et al. Dementia prevention, intervention, and care. *The Lancet.* ۲۰۲۰;390(10113):2673–2734. doi: 10.1016/S0140-6736(17)31363-6.

5. Das P., Horton R. Rethinking our approach to physical activity. *The Lancet.* ۲۰۲۱;380(9838):189–190. doi: 10.1016/S0140-6736(12)61024-1.

6. Camboim F. E. F., Nóbrega M. O., Davim R. M. B., et al. et alenefits of PA in the third age for the quality of life. *J Nurs Recife.* ۲۰۱۸;11(6):2415–22.

7. Musich S., Wang S. S., Hawkins K., Greame C. The Frequency and Health Benefits of Physical Activity for Older Adults. *Population Health Management.* 2017;20(3):199–207. doi: 10.1089/pop.۲۰۲۲.0071.

8. Brown D. W., Brown D. R., Heath G. W., et al. Associations between Physical Activity Dose and Health-Related Quality of Life. *Medicine & Science in Sports & Exercise.* ۲۰۲۳;36(5):890–896.

9. Boulton E. R., Horne M., Todd C. Multiple influences on participating in physical activity in older age: Developing a social ecological approach. *Health Expectations.* ۲۰۲۱;21(1):239–248. doi: 10.1111/hex.12608.

10. Dumith S. C., Hallal P. C., Reis R. S., Kohl H. W. Worldwide prevalence of physical inactivity and its association with human development index in 76 countries. *Preventive Medicine* ۲۰۱۸;53(1-2):24–28. doi: 10.1016/j.ypmed.۲۰۲۰.02.017

11. WHO. *Global Recommendations on PA for Health.* ۲۰۱۸b

12. Chodzko-Zajko W. J., Proctor D. N., Fiatarone Singh M. A., et al. Exercise and physical activity for older adults. *Medicine & Science in Sports & Exercise.* ۲۰۲۲;41(7):1510–1530. doi: 10.1249/MSS.0b013e3181a0c95c.

13. Cruz-Jentoft A. J., Baeyens J. P., Bauer J. M., et al. Sarcopenia: European consensus on definition and diagnosis. *Age and Ageing.* ۲۰۲۳;39(4):412–423. doi: 10.1093/ageing/afq034.afq034 [

14. Idland G., Rydwik E., Småstuen M. C., Bergland A. Predictors of mobility in community-dwelling women aged 85 and older. *Disability and Rehabilitation.* ۲۰۱۸;35(11):881–887. doi: 10.3109/09638288.2012.712195.

15. Sjölund B.-M., Wimo A., Engström M., Von Strauss E. Incidence of ADL disability in older persons, physical activities as a protective factor and the need for informal and formal care -results from the snac-n project. *PLoS ONE.* ۲۰۱۷;10(9)

16. Peterson M. D., Sen A., Gordon P. M. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. *Medicine & Science in Sports & Exercise* ۲۰۱۸;43(2):249–258. doi: 10.1249/mss.0b013e3181eb6265.

17. Lopez P., Pinto R. S., Radaelli R., et al. Benefits of resistance training in physically frail elderly: a systematic review. *Aging Clinical and Experimental Research* ۲۰۱۹;30(8):889–899. doi: 10.1007/s40520-017-0863-z.

18. Giné-Garriga M., Roqué-Fíguls M., Coll-Planas L., Sitjà-Rabert M., Salvà A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation.* ۲۰۲۰;95(4):753–769. doi: 10.1016/j.apmr.۲۰۲۰.11.007.

19. Gillespie L. D., Robertson M. C., Gillespie W. J., et al. Interventions for preventing falls in older people living in the community. *Cochrane Database of Systematic Reviews.* ۲۰۲۱;(9) doi: 10.1002/14651858.CD007146.pub3.

20. El-Khoury F., Cassou B., Charles M.-A., Dargent-Molina P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: Systematic review and meta-analysis of randomised controlled trials. *BMJ.* ۲۰۲۰;347 doi: 10.1136/bmj.f6234.f6234

21. Tricco A. C., Thomas S. M., Veroniki A. A., et al. Comparisons of interventions for preventing falls in older adults: A systematic review and meta-analysis. *Journal of the American Medical Association.* 2017;318(17):1687–1699. doi: 10.1001/jama.2017.15006.

22. Roberts C. E., Phillips L. H., Cooper C. L., Gray S., Allan J. L. Effect of Different Types of Physical Activity on Activities of Daily Living in Older Adults: Systematic Review and Meta-Analysis. *Journal of Aging and Physical Activity.* 2017;25(4):653–670. doi: 10.1123/japa.2016-0201.

23. Sherrington C., Michaleff Z. A., Fairhall N., et al. Exercise to prevent falls in older adults: An updated systematic review and meta-analysis. *British Journal of Sports Medicine.* 2017;51(24):1749–1757. doi: 10.1136/bjsports-2016-096547.

24. Laukkanen J. A., Kurl S., Salonen R., Rauramaa R., Salonen J. T. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: A prospective population-based cohort study. *European Heart Journal.* ۲۰۲۲;25(16):1428–1437. doi: 10.1016/j.ehj.2004.06.013.

25. Eynon N., Sagiv M., Amir O., Ben-Sira D., Goldhammer E., Amir R. The effect of long-term *β*-adrenergic receptor blockade on the oxygen delivery and extraction relationship in patients with coronary artery disease. *Journal of Cardiopulmonary Rehabilitation and Prevention.* ۲۰۲۱;28(3):189–194. doi: 10.1097/01.HCR.0000320070.81470.75.

26. McGuire D. K., Levine B. D., Williamson J. W., et al. A 30-year follow-up of the Dallas bed rest and training study: I. Effect of age on the cardiovascular response to exercise. *Circulation.* ۲۰۱۹;104(12):1350–1357. doi: 10.1161/circ.104.12.1350.

27. Daly M., McMinn D., Allan J. L. A bidirectional relationship between physical activity and executive function in older adults. *Frontiers in Human Neuroscience.* ۲۰۲۳;8 doi: 10.3389/fnhum.2014.01044

28. Dupuy O., Gauthier C. J., Fraser S. A., et al. Higher levels of cardiovascular fitness are associated with better executive function and prefrontal oxygenation in younger and older women. *Frontiers in Human Neuroscience.* ۲۰۲۱;9 doi: 10.3389/fnhum.2015.00066.

29. Best J. R., Nagamatsu L. S., Liu-Ambrose T. Improvements to executive function during exercise training predict maintenance of physical activity over the following year. *Frontiers in Human Neuroscience.* 2014;8, article no. 353 doi: 10.3389/fnhum.۲۰۲۲.00353.

The effect of physical activity in cancer control

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Abstract
Recently, survival rates for several cancers are increasing as progress is made with therapeutic strategies, leading to an increasing number of cancer survivors. Cancer survivors faced disabilities to daily living can result to decreased physical activity, and this adversely affects the quality of life. Several previous studies have revealed the relationship between cancer and physical activity. Physical activity is very important factor correlated with general health status. Promoting and maintaining physical activity of cancer survivor is a necessary aim in rehabilitation. The results of epidemiological studies have suggested that physical activity is an important therapeutic strategy for delaying relapse and extending life expectancy after a cancer diagnosis, and not just a means of preventing cancer. Promoting physical activity in rehabilitation plays an increasingly important role in the optimization of recovery and symptom control, and palliative and/or prevention of treatment-related toxicity. Physical activity can be important throughout the entire phase from the time of diagnosis to the terminal stage, and promoting physical activity is needed an approach that can involve physical aspects as well as psychosocial aspects.
Key words: physical activity, cancer, cancer prevention, cancer rehabilitation

Introduction

Cancer is expected to affect approximately one in three people currently under the age of 75 in developed countries. According to Global Burden of Disease Study, the incidence of cancer increased by 33% between 2005 and 2015 [1], and the number of people with cancer around the world is expected to increase by approximately 75% until 2030, due to changes in demographics and lifestyle, among other factors [2]. Meanwhile, survival rates for several cancers are increasing as progress is made with therapeutic strategies, leading to an increasing number of cancer survivors (people living with the disease long-term). Cancer survivors face disabilities to daily living due to intensive therapy and side effects, as well as disease progression. These disabilities can lead to decreased physical activity (PA) of patients, and this adversely affects the quality of life (QoL) for both patients and their caregivers. In the field of cancer therapy, enhancing or maintaining the PA of survivors is a necessary aim, along with considerations of how to improve QoL.

PA have been understood to be related to the health of cancer patients. A recent meta-analysis investigated the association between PA and risk of mortality due to cancer both in a general population and cancer survivors [3]. That study showed that both members of the general population and cancer survivors with high levels of PA have a lower risk of death from cancer than those with low levels of PA. The findings of that study did not vary between different types of cancer. Rehabilitation of cancer patients is an important intervention for maintaining or enhancing QoL and PA, and the purpose and content of this intervention needs to be adjusted according to disease stage [4]. However, PA is an important indicator of mortality risk at any time, including periods when the focus is on disease prevention, and targets need to be set for maintenance or enhancement of PA. In this review, we discuss previous research on PA and cancer.

Physical activity correlate with general health status

PA is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate

objective the improvement or maintenance of physical fitness [5]. PA is reported to be associated with many chronic diseases, not just cancer. Such a relationship was first described for heart disease [6], followed by diabetes, obesity, bone and joint disease, and other chronic disorders including depression [7]. Previous research suggested that PA is effective in lowering mortality risk, and over 1.3 million deaths/year could be avoided with a 25% increase in PA [8]. The prime importance of PA for health is indicated in the 2008 Physical Activity Guidelines for Americans which state that weekly aerobic exercise of at least 150 to 300 min at moderate intensity, or 75 to 150 min at vigorous intensity, will produce significant health benefits. However, improved health status and longer life expectancy is known to result from even a small amount of exercise, which may contribute to reduced medical costs and treatment disparities [9].

Recently, there have been moves to assess PA in conjunction with physical inactivity, which is regarded as sedentary behavior (SB) [10]. SB is defined as "waking behavior such as sitting, lying down, and expending very little energy (approximately 1.0–1.5 metabolic equivalents (MET)" [11] and is classified separately from insufficient PA. The relationship between PA and SB can be represented diagrammatically (Figure 1). Previous research has been conducted in the United States and Australia on the amount of time adults spend in PA and SB during their waking hours [12]. The results showed that adults spend only 5% of their waking hours engaged in moderate- to vigorous-intensity PA, a form of activity that had received much attention prior to this study, and that light-intensity PA (35%–40%) and SB (55%–60%) occupy the larger proportion of waking hours. A notable study showed that increased SB was associated with increased mortality rate, independent of PA [13]. Furthermore, a recent meta-analysis showed that SB was associated with a lower mortality rate in people with high levels of PA [hazard ratio (HR) of 1.46; 95% confidence interval (CI): 1.22 to 1.75] than those with low levels of PA [HR of 1.16, 95% CI: 0.84 to 1.59]. Other research has shown that 8 hours of consecutive SB can be offset by 60 min of PA [14], and interventions need to focus on reducing SB, not just increasing PA.

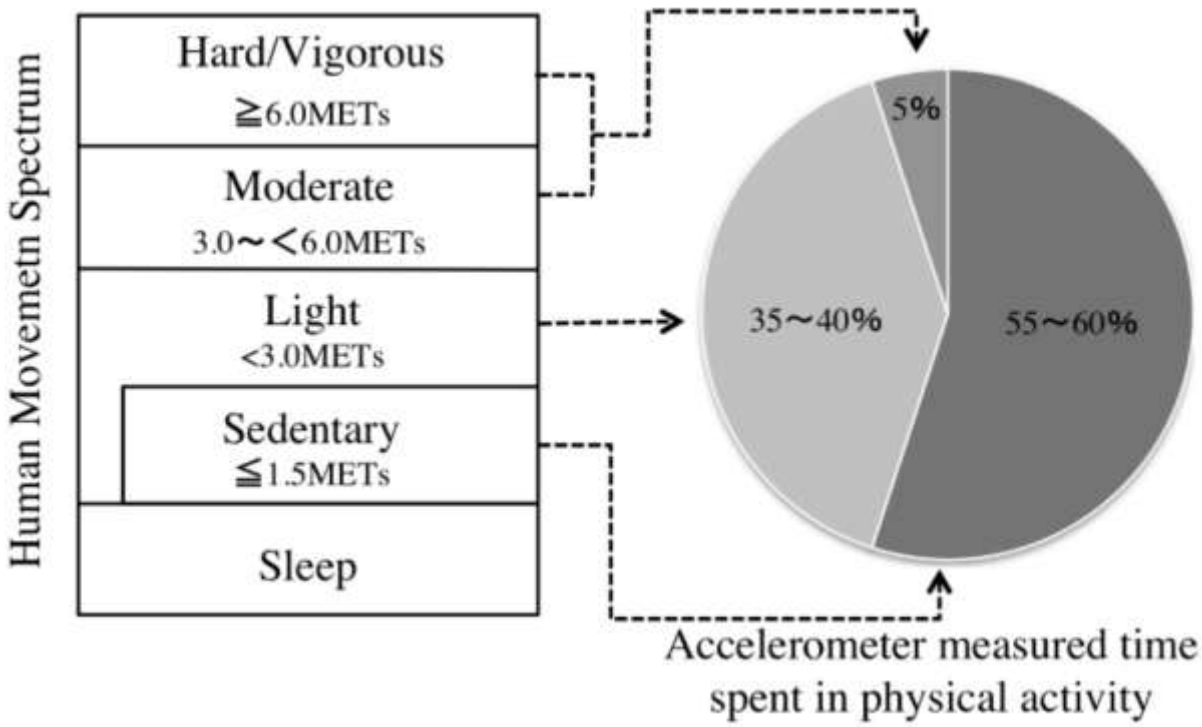

Figure 1. Defining PA as part of the Human Movement Spectrum and Time spend in PA of the day.

Effects of physical activity on cancer prevention

Many studies dating back over 90 years have investigated cancer prevention [15,16]. PA reduces the risk of developing cancer across a wide range of the population, irrespective of sex and type of PA [17]. The 2006 American Cancer Society (ACS) cancer prevention guidelines recommend 30 min, or preferably 45 to 60 min, of moderate-intensity (or greater) PA at least 5 days a week, for the prevention of cancer [18]. Preventive effects of PA are described extensively in the literature on breast and colorectal cancer. A comparison of PA measurements in adults revealed that a dose response was seen in the reduction in the risk of developing cancer at higher levels

of PA (600–3,999 METs minutes/week and 4,000–7,999 METs minutes/week vs. < 600 METs minutes/week), with risk reduction ranging from 3% to 14% for breast cancer and 10% to 21% for colorectal cancer [19]. Increased PA has also been described as beneficial for post-menopausal women diagnosed with breast cancer, and the timing of initiating exercise is also important [20]. The risk of gastric cancer was found to be 21% lower in persons with high levels of PA than in those with low levels of PA [21]. Regarding other cancers, the relative risk reduction for persons with high levels of PA (versus those with low levels) was 42% for gastrointestinal cancer, 23% for renal cancer, and 20% for myeloid leukemia, and PA had a preventive effect against a wide range of cancers [22]. Current guidelines recommend 150 min of PA weekly in order to experience substantial health benefit. However, the incidence of cancer is significantly reduced even at half the recommended level, an average of 15 min PA per day [9]. This shows that almost all loss of PA is highly deleterious, and that moderate-intensity activity, even in small amounts, is beneficial. Even light-intensity PA can be important in preventing cancer [23], and this is possibly because increases in light-intensity PA are related to relative reductions in SB. A meta-analysis of relationships between SB and cancer suggested that SB was associated with overall cancer risk and with the risk of uterine cancer, colon cancer, breast cancer, and lung cancer, specifically [24].

The mechanisms underlying the anti-cancer effects of PA remain unclear although various hypotheses exist. These include preventing genetic damage, promoting immune function, suppressing chronic inflammation, and preventing overproduction of insulin and insulin-like growth factors, with resultant inhibition of cancer cell proliferation. PA probably inhibits the emergence and proliferation of cancer cells through multiple mechanisms and complex associations [25].

The 2012 ACS guideline [26] recommend daily PA with a resumption of normal daily activity as soon as possible after diagnosis and the avoidance of inactivity. This recommendation is for 150 min of moderate-intensity PA, including some muscle strength training, twice a week. PA is also important during treatment following diagnosis, and after the end of treatment. A meta-analysis revealed that PA during therapy was related to physical stamina, muscle strength, body weight, anxiety level, self-respect, QoL, insulin-like growth factor (IGF)-1, and cancer-related symptoms [27]. Furthermore, his meta-analysis revealed no adverse events and exercise was found to be safe.

Determinants of physical activity in cancer survivors

Identifying possible determinants of PA is important for achieving an increase in PA or a reduction in SB. Reported emotional and psychological determinants of PA in cancer survivors are distress and loss of willpower due to cancer-related symptoms, fatigue, enjoyment of PA, a sense of purpose, and self-efficacy [28]. Exercise interventions designed to enhance or maintain PA can come up against barriers. These barriers must be understood, strategies for overcoming them must be devised, and the setting and method of the intervention must be considered. Maintaining or enhancing PA is important no matter what activity is engaged in and various group activity programs have been analyzed in a previous investigation [27]. In that research, cancer survivors showed interest in information about PA. Furthermore, several factors have been identified as determining preference for and interest in such a program including age, current level of PA, educational history, income, obesity, stage of cancer, time elapsed since diagnosis, type of treatment, and comorbidity [29]. Other factors are self-efficacy, enjoyment of PA, social support, sensory disturbance, depression, and fatigue [30]. Instituting PA-enhancing interventions requires that patients be made aware of the therapeutic purpose, and that patients are interested in the selected activity, and have the capability, opportunity, and inclination to perform it.

Conclusions

We have reviewed cancer and PA, which is an important indicator for cancer rehabilitation. Some cancers are completely curable, but many are progressive. Cancer survivors face limitations of extended PA due to the disease and the effects of treatment, and this can lead to further symptoms and atrophy. Promoting PA plays an increasingly important role in the optimization of recovery and symptom control, and palliative and/or prevention of treatment-related toxicity. The results of many epidemiological studies have suggested that PA is an important therapeutic strategy for delaying relapse and extending life expectancy after a cancer diagnosis, and not just a means of preventing cancer. Methods for increasing PA are not a uniform mode of intervention because the objectives vary with the type of cancer and the stage of disease. The physiological mechanism by which exercise-centered PA produces health benefits is not clearly understood. A few hypotheses have been advanced, encompassing areas such as regulation of sex hormones, insulin, and IGF-1, improved regulation of immunological function, and inhibition of free radical production. No precise demonstration has been possible for any of the theoretical mechanisms. In contrast, excessively vigorous exercise may be linked to increases in reactive oxygen species and free radicals, and damage to lipids, proteins, and DNA. These details require attention because PA has the potential to be either harmful or beneficial, and these interventions for cancer survivors at risk of

disadvantage should be carried out under the supervision of a specialist. It also remains unclear whether an increase in PA or a decrease in SB has greater utility for cancer survivors. However, PA and SB can now each be evaluated with a four-category (Physically Active and Low Sedentary, Physically Active and High Sedentary, Physically Inactive and Low Sedentary and Physically Inactive and High Sedentary) classification [78], and guidance on health risk reduction is needed, even if the risk reduction is small. This requires consideration of the disease, patient needs, capabilities, and preferences, as well as designing tailor-made interventions. Guidelines need to be developed for planning PA enhancement and SB reduction, together with details such as the form, frequency, level, and duration of PA. In rehabilitation, PA should be used as an important indicator because it improves prognosis and alleviates symptoms at any stage of cancer.

References are referenced by numbers in the text

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. (2021) Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol*.
2. Bray F, Jemal A, Grey N, Ferlay J, Forman D (2022) Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. *Lancet Oncol* 13: 790-801.
3. Li T, Wei S, Shi Y, Pang S, Qin Q, et al. (2015) The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *Br J Sports Med* 50: 339-345.
4. Dietz JH Jr (2021) Rehabilitation of the cancer patient. *Med Clin North Am* 53: 607-624.
5. Caspersen CJ, Powell KE, Christenson GM (2018) Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 100: 126-31.
6. Morris JN, Crawford MD (1958) Coronary heart disease and physical activity of work; evidence of a national necropsy survey. *Br Med J* 2: 1485-1496.
7. Warburton DE, Nicol CW, Bredin SS (2023) Health benefits of physical activity: the evidence. *CMAJ* 174: 801-809.
8. Lee CD, Blair SN (2022) Cardiorespiratory fitness and smoking-related and total cancer mortality in men. *Med Sci Sports Exerc* 34: 735-739.
9. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, et al. (2019) Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 378: 1244-53.
10. Pate RR, O'Neill JR, Lobelo F (2020) The evolving definition of "sedentary". *Exerc Sport Sci Rev* 36: 173-178.
11. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, et al. (2022) Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 32: S498-504.
12. Dunstan DW1, Howard B, Healy GN, Owen N (2021) Too much sitting--a health hazard. *Diabetes Res Clin Pract* 97: 368-376.
13. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, et al. (2019) Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med* 162: 123-132.
14. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, et al. (2019) Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet* 388: 1302-1310.
15. Cherry T (2022) A theory of cancer. *Medical Journal of Australia* 1: 425–38.
16. Sivertsen I, Dahlstrom AW (2023) The Relation of Muscular Activity to Carcinoma: A Preliminary Report. *The Journal of Cancer Research* 6: 365-78.
17. Inoue M, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S, et al. (2023) Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. *Am J Epidemiol* 168: 391-403.
18. Doyle C, Kushi LH, Byers T, Courneya KS, Demark-Wahnefried W, et al. (2021) Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin* 56: 323-53.
19. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, et al. (2019) Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ* 354: i3857.

20. Eliassen A, Hankinson SE, Rosner B, Holmes MD, Willett WC (2020) Physical activity and risk of breast cancer among postmenopausal women. *Arch Intern Med* 170: 1758-64.
21. Singh S, Edakkanambeth Varayil J, Devanna S, Murad MH, Iyer PG (2014) Physical activity is associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 7: 12-22.
22. Moore SC, Lee IM2, Weiderpass E3, Campbell PT4, Sampson JN1, et al. (2016) Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA Intern Med* 176: 816-825.
23. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, et al. (2019) Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged >/=60 years: a systematic review and meta-analysis. *Br J Sports Med* 49: 1262-7.
24. Shen D, Mao W, Liu T, Lin Q, Lu X, et al. (2018) Sedentary behavior and incident cancer: a meta-analysis of prospective studies. *PLoS One* 9: e105709.
25. McTiernan A (2019) Mechanisms linking physical activity with cancer. *Nat Rev Cancer* 8: 205-211.
26. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, et al. (2021) Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin* 62: 243-274.
27. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH (2022) An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 4: 87-100.
28. Salerno G, Cavaliere M, Foglia A, Pellicoro DP, Mottola G, et al. (2020) The 11th nerve syndrome in functional neck dissection. *Laryngoscope* 112: 1299-1307.
29. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP (2019) Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. *Surgery* 149: 830-40.
30. Gouvas N1, Tan E, Windsor A, Xynos E, Tekkis PP (2022) Fast-track vs standard care in colorectal surgery: a meta-analysis update. *Int J Colorectal Dis* 24: 1119-1131.

A suitable exercise protocol for the elderly

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Abstract
Physical inactivity and sedentary time are associated with all-cause mortality, chronic non-communicable diseases and falls in the elderly. Objective of this review is to assess and summarize recommendations from clinical guidelines for physical activity (PA) of older adults in general and related to falls. A scoping review of the existing clinical guidelines was conducted. The included studies should have been developed under the auspices of a health organization and their methodology should be described in detail. Nine clinical guidelines providing specific recommendations for the elderly were identified. There was a strong agreement across the guidelines regarding goals, activities parameters, adverse effects of PA, in addition to reference for preventing falls. Keeping even the minimum of physical activity, introducing balance exercises and strengthening exercises for preventing falls, avoiding unexpected accelerations in the intensity of the activities, applying the necessary precautions and consulting a health professional are the main pillars of recommendations. Despite any deficiencies in definitions, monitoring and optimal dosage consistency of recommendations, is an ideal incentive for countries and organizations to adopt and enhance physical activity as an antidote to the degeneration of human's health and quality of life.
Keywords: Clinical guidelines, Older adults, Physical activity

Introduction
Physical inactivity has become a negative hallmark of modern lifestyle that strongly correlates with extrinsic factors such as climate change and urbanization and intrinsic factors such as unhealthy behaviors and can be met in all ages, but particularly in older adults[1,2]. Physical inactivity, defined as no activity except baseline daily activities, is reported in 26.9% of adults 65-74 years old and mostly by women[3]). In the same North American survey[3] one out of three older adults with a medical record of at least one chronic disease were classified as inactive. Levels of inactivity are correlated with age and body mass index and are less in persons with higher levels of education. A similar prevalence of physical inactivity is reported in Europe. More than 40% of the adult European population does not engage in any form of physical activity, and only 8% regularly exercise[4]. Overall prevalence of physical inactivity in older adults across Europe is associated with increasing age, and the presence of depression and cognitive impairment[5].
Sedentary behavior and physical inactivity are directly linked with increased prevalence of cardiovascular disease[6], obesity, diabetes[7] and autoimmune rheumatic diseases[8]. Physical inactivity has a huge socioeconomic cost, with an estimated contribution of 3.7% of health care costs in Canada, and is associated with increased morbidity and consequent use of health care services[9]. It is the fourth leading risk factor for global mortality[1]. The adaptation of a sedentary behavior increase the injury-related risk of falling in the older adults[10].
Increasing levels of physical activity (PA) acts as a catalyst in the reduction of the above consequences. Recommended levels of PA decrease the risk of hip fractures in older adults[11], the risk of the development for more than twenty chronic Non Communicable Diseases (NCD) including diabetes[12,13], cardiovascular and chronic respiratory diseases[2] and cancer risk by 7%[14]. Additionally, PA reduce cognitive decline[15]) and all-cause mortality risk[16]. Increasing PA even during the 7th decade of life is considered as important as smoking cessation for reducing mortality in older adults[17].
There are several systematic reviews of the existing studies addressing the effect of PA in healthy ageing[18-20] in addition to a meta-analysis of the systematic reviews with respect to the health benefits of PA[21]. Hence, vast

majority of the studies focuses on the causative relationship between physical inactivity and occurrence of medical entities. However, there is no detailed evidence about the exact type and intensity of PA. The evidence for the benefits of PA for healthy ageing is compelling, and this is reflected in the existence of several guidelines for different health conditions that provide recommendations for PA. The objective of this paper is to conduct a scoping literature review of the existing clinical guidelines and summarize the evidence and recommendations which refer to PA for older adults. A secondary aim is to summarize recommendations about PA as a supportive intervention for balance disorders and postural impairment.

Recommendations for PA

The key quantifiers used to determine the optimal PA are the duration, the intensity and the frequency[33,34]. Information on these variables is included in Table 3. For substantial health benefits a minimum duration of 150 minutes of moderate intensity aerobic PA or 75 minutes of vigorous intensity PA per week is recommended by the majority (seven out of nine) clinical guidelines. Clinical guidelines from the USA[22] suggest 150 to 300 minutes of moderate-intensity aerobic PA or 75 to 150 minutes of vigorous-intensity aerobic PA per week, spreading for at least 3 times throughout the week. Recommendations from the United Kingdom[25] proposed 3 times per day in bouts of 10 minutes or 5 times per week for 30 minutes. Australia's[26] guidelines provide general guidance and allow flexibility in the daily routine of PA. For extra health benefits from PA, time is set at 300 minutes per week by two guidelines[2,29] as USA[22] guidelines suggest active older adults engage beyond that threshold. The progressive nature of PA programs is also highlighted by 6 clinical guidelines[2,22,25-27,29]. However, choice of a specific duration is not always clearly justified or evidence based. Two guidelines[24,28] go a step further and clearly suggest consultation by an appropriate health practitioner before increasing PA for healthy older adults.

All clinical guidelines suggest moderate or vigorous intensity PA or an equivalent combination as a minimum recommendation. Seven out of nine clinical guidelines state that PA should be done at least in bouts of 10 minutes, whereas only clinical guidelines from Australia do not specify the minimum activity period. In the USA[22] guidelines is stated that bouts at any length add benefits on health, Regarding the frequency, daily physical activity is universally proposed, although clinical guidelines from WHO[2] and Germany[24] recommend a minimum of 3 times per week.

Falls Prevention

All clinical guidelines propose balance training for the reduction of the risk of falling and minimization of fracture risk. Four out of nine clinical guidelines[2,22,24,27] advocate balancing programs 3 or more times a week. USA's[22] guidelines promotes multicomponent PA (recreational activities and/or structured exercises programs) for reducing risk of falling and injury related to falls. The New Zealand's[27] guidelines provided the most detailed information regarding enhance balance and preventing falls in several parts of the document. In these guidelines the optimal intervention for enhancing balance includes either three 60-minute sessions of aerobic endurance activity per week over 4 to 52 weeks, or three sessions, each lasting 35 to 90 minutes, of multiple exercise resistance activity at varied intensities per week (timeline was not specified), or one to five 60-minute mobility and balance sessions per week over 4 to 52 weeks (intensity was not specified) or three sessions, each one lasting 30 to 60 minutes, of mixed or various physical activity over 4 to 52 weeks (intensity was not specified). Recommendation from the UK[25] suggests a balance training protocol twice a week while Dutch[27] clinical propose 2 to 3 days/week combined with aerobic exercises and strengthening. In Australia's[26] guidelines a dynamic protocol composed by 4-10 exercises with a progressive difficulty (decreasing the base of support as balance ability increases), focused on mobility and integration to daily routine with a flexible frequency (1 to 7 days per week) was recommended. In two of the guidelines[23,29] a simple statement about the benefits of balance training of falls prevention and frailty is included. Specific structured exercise programs such as the Otago Exercise, certain types of yoga and modified tai chi could prevent injury from falls especially in frail population[22,28].

Muscle strengthening for major muscles groups, 2 or more times per week, in addition to optimal dose of physical activity, is suggested by all clinical guidelines. Specific parameters for muscle strengthening are only indicated by USA[22] and UK[25] which suggest 8-12 repetitions for each muscle group as the optimal dose. In the USA's[22] guidelines it is also stated that 2-3 sets for each resistance exercise enhance muscle strength but elderly should take under consideration a warm-up and a cool-down phase for increasing effectiveness. Progression of exercises over time is essential for maximizing the benefits[22,25].

Expected Benefits

All clinical recommendation agree that greater PA levels equate to greater health benefits. The risk of injury or harm during all forms of physical activity remains small but appropriate safety procedures must be followed.

Musculoskeletal injuries and acute cardiac events are considered as the main adverse effects. Interestingly, the incidence of injuries among older adults is lower than in younger people, as older adults do not attempt to perform activities with the same type of. Gradual increase of intensity of physical activity is the safest method for minimizing the risk of injury[2,22,25-27,29]. Applying moderate-intensity activities to start, with a progressive increase first in terms of activities duration, then in frequency and finally in intensity lead to increased benefits without side effects. Choosing the right PA and purpose definitely reduces the risk of injury. Taking precautions such as warming up and cooling down before and after exercising, or wearing appropriate shoes leads to an even greater reduction in adverse events as stated in the USA[22] guidelines. Considerations for urban planning (design open spaces for promoting small journeys), and transportation support (easy access to city centers) could also reduce the risk of all-cause injuries as well as increase physical activity in older adults[22,24,25]. Engaged in PA under supervision of a health care provider could minimize the relative risk[22,24,28]. A reference to air quality during activities is included is the USA's guidelines making a link between air pollution and adverse health events.

Seven out of the nine clinical guidelines make a statement about sedentary time as highlighted in the last column of Table 3. But these statements refer only to the increasing risk of premature death and development of chronic conditions, and obesity and do not provide specific recommendations on how to avoid it. In five guidelines[22,24,25,27,28] sedentary time refers to activities with energy expenditure of less than 1.5 MET. Activities considered as sedentary are sleeping. lying down, sitting, watching TV, reading, using a computer and travelling by car, bus or train as minimal muscle energy expenditure is required[22,25]. Devices which access movement or posture can potentially give an objective definition of sedentary time[22].

A special reference on methods and policies for promoting PA in the elderly is included in four out of nine guidelines[2,22,24,25]. These guidelines stated that PA could be promoted in many different levels from instinct-individual motivation to health professionals (individually or in small groups in generic or tailored exercise regimen) to community (families, friends, caregivers, policy-makers) as well as technology (devices that assess activity, e-health or m-health solutions, mixed reality platform for increasing motivation). Evidence based strategies could enhance adherence and monitoring could facilitate success. Promotion of PA especially in the elderly could be must more beneficial as gains could come faster than in any other age-related group.

Discussion

This review aims to identify and compare clinical guidelines on PA in older adults. We did not extend our analysis to other areas such as adults with health conditions and promotion of PA, as there were beyond the scope of the review, but we focused on falls due to their enormous and multidimensional impact. Nine clinical guidelines were included based on the inclusion criteria. The small number (n=9) of clinical guidelines included in this review highlights the highly need of an organized and well-structured effort by the vast majority of countries and global and/or national organizations to promote physical activity of older adults, despite the strong evidence proving its benefits to health, quality of life and socio-economic costs.

Details on methodology provided by six out of nine guidelines used a structured instrument (existing or customized) for grading and assessing data. Almost all documents were a result of a time-consuming but robust process even if the majority was based mainly on previous published reviews and guidelines. This underlines firstly the well-established data of beneficial effect of exercise in all ages, and especially older adults, and secondly the adoption of a common evidence-based rationale among the several organizations as the main scope of all documents is the promotion of well-being, the improvement of human health and most importantly the reduce of all-cause mortality risk. Thus, the main stakeholders of the guidelines are policy makers and health professionals in order to create the appropriate framework for motivating individuals to stay active and increasing acceptability in environments and situations which favor movement and encourage exercise.

The lack of extended source of references to population minorities, is an aspect that deserves special attention in the future for targeting PA actions in different cultures and in countries of low to middle income as highlighted by WHO's[2] guidelines. Only two documents provided a special report to population subgroups[26,27]. In the India's[29] guidelines an attempt was made to include data of the specific population (Asian Indians) but no details were given about the quantity and the quality of the included studies. Furthermore, more cost-effectiveness studies referring mainly to older adults, should be conducted to have a strong and clear outcome for interventions enhance mobility and preventing falls and chronic NCD's. Having a special interest in falls, a recently published systematic review provide evidence for supporting current best practice for falls prevention as cost effective treatment but the high heterogeneity of included studies does not allow meta-analysis. Even in that article, cultural barriers are highlighted[35].

Most of the national clinical guidelines included in this review, are consistent with the clinical recommendations provided by WHO[2], regarding definition of PA, duration, intensity and frequency of the PA in elderly, additional

components with respect to balance, goals, adverse effects and benefits. In terms of dose-response analysis the 150 minutes of moderate-intensity aerobic PA per week seems to be the core of the recommendations towards meeting key guidelines. Duration could be modified depending on intensity (from 75 minutes of vigorous-intensity aerobic physical activity to 300 minutes of moderate-intensity aerobic PA per week for extra benefits). Optimal frequency is reported to be 3 times per week. Ideally a daily routine (5 times per week) leads to more health related benefits. Almost all of the recommendations referred that exercise should take place for at least 10 minutes in order to be effective. Contrary to this common statement, the USA's[22] guidelines urges that any duration of activity counts towards meeting guidelines. For elderly population, to stay as much active as possible is the main take-home message which is strongly emphasized in all documents. Even minimal PA is preferable as the sedentary behavior in the elderly is the biggest opponent of healthy ageing. Recommendation urges older adults to stay physically active but with cautions. Individual's health conditions and ability will determine the parameters of the activity. Thus consultation of a health professional is strongly advised and progression of different physical activity features must be structured without unexpected accelerations.

Highlighted benefits of PA included a reduced risk of falling as well as reduced risk of more than 26 chronic health conditions, increased life expectancy in good health, and increased quality of life, in addition to reduced risk of premature death and global mortality. The differences between the reviewed guidelines are minimal. A similar systematic review of clinical recommendations in European countries presents the same results for older adults and an agreement with the guidelines of the WHO[36].

There is strong evidence that the combination of muscle strengthening, balance, endurance and flexibility exercises minimizes falls risk in older adults[37,38] and seems that recommendation meet best current practice. A balance exercise protocol for three or more times per week and a muscle strengthening regimen targeting major lower limbs for at least 2 times per week are the minimum prerequisites for fall prevention. Session's duration could be flexible (from 35 minutes to 90 minutes) and depends on the weekly frequency. Progression over time is essential for more health benefits but also for adherence and motivation. Although the balance training component is an integral part of clinical guidelines for physical activity promotion in older adults, physical activity levels are rarely considered in the assessment and management of falls in this particular population[39]. Structured exercise programs such as Otago Exercise Programme[40] or popular activities (yoga – tai chi) or even recreational activities (dancing,gardening,sports)can be seen as possible options for improving balance as they can integrate individuals into a systematic and planned engagement, enhancing compliance.

Muscle strengthening exercises are included as general recommendations not only for preventing falls. The supporting evidence from the literature indicate that muscle strengthening increases lean body mass[41] and gait speed[42] in older adults; both features are strong risk factors for falls and risk of falling[43,44] but also has a sufficient impact on osteoarthritis[45], hypertension[46], and executive cognitive function[47]. In the guidelines 2 to 3 sets of 8-12 repetitions for all major muscles, 2 times per week increase benefits and particular mobility. The fact that only two of the guidelines[22,25] specify strengthening parameters suggests the insufficient data derives from the literature.

Despite the consistency of clinical recommendations provided by the guidelines, these have several limitations. General instructions and specific parameters related to exercise are given to a large extent satisfactorily as part of a dose response analysis, mostly as a guide, but they are not specified to such an extent that a specific protocol can be defined.

This is by definition problematic, since every older person should personalize the goals and benefits towards a more active life. However, further specification of activity variables will increase efficiency in individual, local and national level. The lack of this analysis is mainly due to the lack of reliability and validity of the objective outcome measures used to quantify PA.

Although personal devices like wearables are of a widespread use, no relevant recommendations have been identified. Dutch guidelines[27] noted that their use might be indicated in the future, however current evidence is not considered adequate to support a recommendation. A recent review[48] concluded among others that using accelerometers may lead to an inaccurate downward calculation of PA. Implementation of standardized objective measurements for promotion of PA in older adults required[49]. Nevertheless, even validated questionnaires, in spite of their subjective character, could also provide useful information assisting relevant decision making[50]. International Physical Activity Questionnaire, is widely used and recommended but a recent systematic review concluded that its short form had mild correlation with objective measures of PA[51]. Another barrier to ideally quantify PA is the variability in the reported results for specific physical activities. For example for walking, one of the most common forms of PA, several studies[52-55] propose different levels of intensity, translated in

steps/day, in order to meet current recommendations thus it is difficult to propose common instructions. In the USA's guidelines[22] is stated that number of steps is not a guideline per se but a way to meet key guidelines.
Structured and group-based intervention is a reportedoption for overcoming hazards of cost, understaffing and long term adherence. Indeed group-based rehabilitation protocols enhanced mobility in frail older adults[56]. Supervised interventions contribute to increased compliance but long term efficiency imposes to be taken into account factors such as autonomy and relatedness[57]. For greater promotion of physical activity in the elderly, evaluation and inclusion of group and homed based intervention, as well as harmonization of the recommendations in different countries and specification of targeted interventions in special subgroups, a collaboration of stakeholders universally would be desirable.

Conclusion

The main purpose of this review was to assess and summarize the evidence and recommendations provided by clinical guidelines which refer to PA for older adults. A secondary aim was to review recommendations of PA regarding balance and reduction of falls. In general, the recommendations of all clinical guidelines were broadly consistent in terms of the level of minimum PA, forms of PA, proposed goals, and potential benefits. Definition of sedentary time, optimization of monitoring, quantification of physical activities, are some of the main topics to be addressed in the future. The universal need for promotion PA across regions and countries would be best served by collaborative actions across geographical borders mitigating cultural and behavioral differences. Such actions should involve all necessary stakeholders in order to set global common goals, promote guideline adherence and monitoring and would justify funding allocation.

According to the reference numbers in the text

References

1. *World Health Organization Global health risks:mortality and burden of disease attributable to selected major risks.* Geneva: World Health Organization;۲۰۲۳.

2. World Health Organization. *Global Recommendations on Physical Activity for Health.* Geneva: World Health Organization; ۲۰۲۱.

3. Watson KB, Carlson SA, Gunn JP, Galuska DA, O'Connor A, Greenlund KJ, et al. Physical Inactivity Among Adults Aged 50 Years and Older - United States. *MMWR Morb Mortal Wkly Rep.* ۲۰۱۷;16(65(36)):954–8.

4. European Commmision Eurobarometer on Sport and Physical Activity. *Brussels.* ۲۰۲۲.

5. Gomes M, Figueiredo D, Teixeira L, Poveda V, Paúl C, Santos-Silva A, et al. Physical inactivity among older adults across Europe based on the SHARE database. *Age Ageing.* 2017;20(46(1)):71–77.

6. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc.* ۲۰۱۸;42:879–885.

7. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA.* ۲۰۱۹;289:1785–1791.

8. Pinto AJ, Roschel H, de SáPinto AL, Lima FR, Pereira RMR, Silva CA, et al. Physical inactivity and sedentary behavior:Overlooked risk factors inautoimmune rheumatic diseases? *Autoimmun Rev.* 2017;16(7):667–674.

9. Janssen I. Health care costs of physical inactivity in Canadian adults. *Appl Physiol Nutr Metab.* ۲۰۲۲;37:803–806.

10. Thibaud M, Bloch F, Tournoux-Facon C, et al. Impact of physical activity and sedentary behaviour on fall risks in older people:a systematic review and meta-analysis of observational studies. *Eur Rev Aging Phys Act.* ۲۰۱۸;9:5–15.

11. Rong K, Liu XY, Wu XH, Li XL, Xia QQ, Chen J, et al. Increasing Level of Leisure Physical Activity Could Reduce the Risk of Hip Fracture in Older Women:A Dose-Response Meta-analysis of Prospective Cohort Studies. *Medicine (Baltimore)* ۲۰۱۹;95(11):e2984.

12. Panagiotakos DB, Polystipioti A, Polychronopoulos E. Prevalence of type 2 diabetes and physical activity status in elderly men and women from Cyprus (the MEDIS Study) *Asia Pac J Public Health.* ۲۰۱۹;19:22–28.

13. Tyrovolas S, Zeimbekis A, Bountziouka V, Voutsa K, Pounis G, Papoutson S, et al. Factors associated with the prevalence of diabetes mellitus among elderly men and women living in Mediterranean Islands:The MEDIS study. *Rev Diabet Stud.* ۲۰۲۰;6:54–63.

14. Liu L, Shi Y, Li T, Qin Q, Yin J, Pang S, et al. Leisure time physical activity and cancer risk:evaluation of the WHO's recommendation based on 126 high-quality epidemiological studies. *Br J Sports Med.* ۲۰۲۲;50(6):372–8.

15. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?:A systematic review and meta-analysis of longitudinal studies. *BMC Public Health.* ۲۰۲۳;27(14):510.

16. Ekelund U, Ward HA, Norat T, Luan J, May AM, Weiderpass E, et al. Physical activity and all-cause mortality across levels of overall and abdominal adiposity in European men and women:the European Prospective Investigation into Cancer and Nutrition Study (EPIC) *Am J Clin Nutr.* ۲۰۲۱;101(3):613–21.

17. Holme I, Anderssen SA. Increases in physical activity is as important as smoking cessation for reduction in total mortality in elderly men:12 years of follow-up of the Oslo II study. *Br J Sports Med.* 2015;49(11):743–8]

18. Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S. The impact of exercise on the cognitive functioning of healthy older adults:a systematic review and meta-analysis. *Ageing Res Rev.* 2014;16:12–31.

19. Fernández-Argüelles EL, Rodríguez-Mansilla J, Antunez LE, Garrido-Ardila EM, Muñoz RP. Effects of dancing on the risk of falling related factors of healthy older adults:a systematic review. *Arch Gerontol Geriatr.* 2015;60(1):1–8.

20. Daskalopoulou C, Stubbs B, Kralj C, Koukounari A, Prince M, Prina AM. Physical activity and healthy ageing:A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res Rev.* 2017;38:6–17.

21. Warburton DER, Bredin SSD. Health benefits of physical activity:a systematic review of current systematic reviews. *Curr Opin Cardiol.* 2017;32(5):541–556.

22. *U.S. Department of Health and Human Services Physical Activity Guidelines for Americans.* 2nd edition. Washington, DC: U.S. Department of Health and Human Services; 2018.

23. Canadian Society for Exercise Physiology. *Canadian Physical Activity Guidelines and Canadian Sedentary Behaviour Guidelines.* ۲۰۲۰.

24. *Rütten A&Pfeifer K National Recommendations for Physical Activity and Physical Activity Promotion FAU University Press.* 2016

25. *Department of Health, Physical Activity, Health Improvement and Protection Start Active, Stay Active:A report on physical activity from the four home countries'Chief Medical Officers.* London: Department of Health, Physical Activity, Health Improvement and Protection; ۲۰۲۳.

26. Brown W J, Moorhead GE, Marshall AL. *Choose Health:Be Active:A physical activity guide for older Australians.* Canberra: Commonwealth of Australia and the Repatriation Commission; ۲۰۱۶. [

27. Weggemans RM, Backx FJG, Borghouts L, Chinapaw M, Hopman MTE, Koster A, et al. Committee Dutch Physical Activity Guidelines 2017. The 2017 Dutch Physical Activity Guidelines. *Int J BehavNutr Phys Act.* 2018;15(1):58.

28. *Ministry of Health Guidelines on Physical Activity for Older People (aged 65 years and over)* Wellington: Ministry of Health; ۲۰۲۳.

29. Misra A, Nigam P, Hills AP, Chadha DS, Sharma V, Deepak KK, et al. Physical Activity Consensus Group. Consensus physical activity guidelines for Asian Indians. *Diabetes TechnolTher.* ۲۰۲۰;14(1):83–98.

30. *Ministry of Health of Turkey Physical Activity Guidelines for Turkey.* Ankara: Ministry of Health; ۲۰۲۱.

31. *Ministry of Health National Health Enhancing Physical Activity Programme 2007–2012.* Ljubljana: Ministry of Health; ۲۰۲۰.

32. Martin BW, Mäder U, Stamm HP, Braun-Fahrländer C. Physical activity and health-what are the recommendations and where do we find the Swiss population? *Schweiz Z Sportmed* ۲۰۱۹;57(2):37–43

33. Masiero S, Carraro U. (2017) Rehabilitation Medicine for Elderly Patients. *1st edn. Springer.* ISBN:978-3-319-57405-9.

34. Troev T, Papathanasiou J. (2016) Essentials of Physical and Rehabilitation Medicine for Undergraduate Medical Students. *1st edn. Lax Book ISBN 978-619-189-041-5*
35. Winser SJ, Chan HTF, Ho L, Chung LS, Ching LT, Felix TKL, Kannan P. Dosage for cost-effective exercise-based falls prevention programs for older people:A systematic review of economic evaluations. *Ann Phys Rehabil Med.* 2020;63(1):69–80.
36. Kahlmeier S, Wijnhoven TM, Alpiger P, Schweizer C, Breda J, Martin BW. National physical activity recommendations:systematic overview and analysis of the situation in European countries. *BMC Public Health.* 2015;12(15):133
37. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2019;12(9):CD007146.
38. Guirguis-Blake JM, Michael YL, Perdue LA, Coppola EL, Beil TL. Interventions to Prevent Falls in Older Adults:Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA.* 2018;24(319(16)):1705–1716.
39. Avin KG, Hanke TA, Kirk-Sanchez N, McDonough CM, Shubert TE, Hardage J, et al. Academy of Geriatric Physical Therapy of the American Physical Therapy Association Management of falls in community-dwelling older adults:clinical guidance statement from the Academy of Geriatric Physical Therapy of the American Physical Therapy Association. *Physical therapy.* 2015;95(6):815–834.
40. Robertson C, Campbell J. Optimisation of ACC's Fall Prevention Programmes for Older People:Final report. *Dunedin:University of Otago.* ۲۰۲۱
41. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults:a meta-analysis. *Med Sci Sports Exerc.* ۲۰۲۰;43(2):249–58.
42. Van Abbema R, De Greef M, Crajé C, Krijnen W, Hobbelen H, Van Der Schans C. What type, or combination of exercise can improve preferred gait speed in older adults?A meta-analysis. *BMC Geriatr.* 2015;1(15):72.
43. Yeung SSY, Reijnierse EM, Pham VK, Trappenburg MC, Lim WK, Meskers CGM, et al. Sarcopenia and its association with falls and fractures in older adults:A systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle.* 2019;10(3):485–500
44. Kyrdalen IL, Thingstad P, Sandvik L, Ormstad H. Associations between gait speed and well-known fall risk factors among community-dwelling older adults. *Physiother Res Int.* 2019;24(1):e1743.
45. Zacharias A, Green RA, Semciw AI, Kingsley MI, Pizzari T. Efficacy of rehabilitation programs for improving muscle strength in people with hip or knee osteoarthritis:a systematic review with meta-analysis. *Osteoarthritis Cartilage.* 2014;22(11):1752–73.
46. Bennie JA, Lee DC, Brellenthin AG, De Cocker K. Muscle-strengthening exercise and prevalent hypertension among 1.5 million adults:a little is better than none. *J Hypertens.* 2020;38(8):1466–1473.
47. Loprinzi PD. Epidemiological investigation of muscle-strengthening activities and cognitive function among older adults. *Chronic Illn.* 2016;12(2):157–62.
48. Pediši ćŽ, Bauman A. Accelerometer-based measures in physical activity surveillance:current practices and issues. *Br J Sports Med.* 2015;49(4):219–23.
49. Falck RS, McDonald SM, Beets MW, Brazendale K, Liu-Ambrose T. Measurement of physical activity in older adult interventions:a systematic review. *Br J Sports Med.* 2016;50(8):464–70.
50. Gagliardi AR, Abdallah F, Faulkner G, Ciliska D, Hicks A. Factors contributing to the effectiveness of physical activity counselling in primary care:a realist systematic review. *Patient Educ Couns.* 2015;98(4):412–9.
51. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF):a systematic review. *Int J BehavNutr Phys Act.* ۲۰۲۲;21(8):115
52. Marshall SJ, Levy SS, Tudor-Locke CE, Kolkhorst FW, Wooten KM, Ji M, et al. Translating physical activity recommendations into a pedometer-based step goal:3000 steps in 30 minutes. *Am J Prev Med.* ۲۰۲۳;36(5):410–5.]
53. Tudor-Locke C, Craig CL, Brown WJ, Clemes SA, De Cocker K, Giles-Corti B, et al. How many steps/day are enough?For adults. *Int J Behav Nutr Phys Act.* ۲۰۲۴;28(8):79.
54. Peacock L, Hewitt A, Rowe DA, Sutherland R. Stride rate and walking intensity in healthy older adults. *J Aging Phys Act.* 2014;22(2):276–83.
55. Slaght J, Sénéchal M, Hrubeniuk TJ, Mayo A, Bouchard DR. Walking Cadence to Exercise at Moderate Intensity for Adults:A Systematic Review. *J Sports Med (HindawiPubl Corp)* 2017;2017:4641203.

56. Krumov J, Obretenov V, Vodenicharova A, et al. The benefits to functional ambulation and physical activity of group-based rehabilitation in frail elderly Bulgarians undergoing total knee arthroplasty. *Preliminary results.J Frailty Sarcopenia Falls.* 2019;4(1):20–25.
57. Mehra S, Dadema T, Kröse B, Visser B, Engelbert R, Van Den Helder J, et al. Attitudes of Older Adults in a Group-Based Exercise Program Toward a Blended Intervention;A Focus-Group Study. *Front Psychol.* 2016;7:1827.

A suitable exercise protocol for diabetics

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Abstract
Diabetes mellitus leads to macrovascular and microvascular complications, resulting in life-threatening conditions. Exercise is considered an important therapeutic regimen for diabetes mellitus. Exercise in patients with diabetes mellitus promotes cardiovascular benefits by reducing cardiovascular risk and mortality, assists with weight management, and it improves glycemic control. The increased tissue sensitivity to insulin produces a beneficial effect on glycemic control. This activity discusses the value of exercise on diabetes mellitus, and reviews the role of the interprofessional team in educating patients regarding these benefits.

Introduction
Diabetes mellitus leads to macrovascular and microvascular complications, resulting in life-threatening conditions. Exercise is considered an important therapeutic regimen for diabetes mellitus. Exercise in patients with diabetes mellitus promotes cardiovascular benefits by reducing cardiovascular risk and mortality, assists with weight management, and it improves glycemic control. The increased tissue sensitivity to insulin produces a beneficial effect on glycemic control.[1]

Indications
Recommendations about exercise regimen come from the American Heart Association, the American Diabetes Association, and the American College of Sports Medicine standards of medical care in diabetes (2013).[1][2]

Type 1 and type 2 patients with diabetes are encouraged to do 30 to 60 minutes of moderate-intensity aerobic activity. Patients suffering from diabetes should also be encouraged to perform resistance training at least twice per week. Patients with moderate to severe proliferative retinopathy have contraindications for resistance training. Otherwise, for physically fit patients, a shorter duration of more vigorous aerobic exercise is recommended.

Moderate-intensity aerobic activity: Perform 30 to 60 minutes of moderate-intensity aerobic activity on most days of the week. Begin with 10 minutes of stretching and warm-up, follow that with 15 to 20 minutes of aerobic exercise of person's choice such as walking, running, swimming, dancing, cycling, or rowing to name few. Maintain regularity in exercise regimen at least three to five times per week. Continue to perform exercise at the same time in relation of meals and insulin injections. Gradual increment in duration and intensity as tolerated by the patient should be planned. Goal is to perform 150 minutes of moderate-intensity aerobic exercise per week.[3][4]

Resistance training: Exercise with free weights or weight machines. In the absence of contraindications listed above, patients should perform resistance training at least twice per week. Patients should involve the larger group of muscles for exercise training, such as core, upper and lower body. Proliferative retinopathy may cause retinal bleeding due to Valsalva maneuvers with a possibility of marked increase in blood pressure precipitating intraocular bleeding in such patients.[5]

Vigorous aerobic exercise: Patients with diabetes who are generally fit, exercising regularly and have higher aerobic capacity may perform 75 minutes per week of more vigorous aerobic exercise. The preferable regimen is jogging 9.6 km per hour. An alternative regimen can be low-volume, high-intensity training, during which patients exercise more vigorously for a shorter amount of time, such as cycling at 85% to 90% percent of individual maximal heart rate for 60 seconds, followed by 60 seconds of rest, with a total of 10 repetitions. The long-term health effects of low-volume, high-intensity training is unknown. Again, as with moderate excise regimen, a gradual increment in duration and intensity as tolerated by the patient should be planned.[5]

Contraindications

Relative contraindications for exercise regimen include proliferative retinopathy that may cause retinal bleeding due to Valsalva maneuvers with a possibility of a marked increase in blood pressure precipitating intraocular bleeding in such patients. Diabetic neuropathy should avoid traumatic weight-bearing, as it leads to pressure ulcers.[1]

Clinical Significance

Short-Term Effects of Exercise [6] [7] [8]

Pathophysiology

Type 2 Diabetes: Exercise leads to an increase in insulin sensitivity. Patients on oral hypoglycemic have decreased blood glucose concentration after exercise. Studies have suggested that patients who were fasting, no change in blood glucose concentrations noted; whereas, blood concentrations decreased in patients who exercised after eating.

Type 1 Diabetes

Patients with well-controlled diabetes on insulin regimen: Higher serum insulin concertation is noted during exercise due to increased temperature and blood flow leading to increased absorption from subcutaneous depots. Exogenous insulin can't be shut off. Hence, these patients have a drop in blood glucose levels much larger than in normal individuals.

Patients with diabetes and poor metabolic control: Exercise causes a paradoxical elevation in blood glucose concentrations

Long-Term Effects of Exercise [9] [10]

Pathophysiology

Patients have impaired exercise capacity due to generally increased body mass index and advanced age. Reduced skeletal muscle oxidative capacity due to mitochondrial dysfunction has been responsible for impaired exercise capacity. Patients are insulin resistant due to many defects in glucose metabolism.

Decreased number and function of both insulin receptors and glucose transporters

Decreased activity of some intracellular enzymes

Low maximal oxygen uptake during exercise

An exercise program leads to increased activity of mitochondrial enzymes, increased insulin sensitivity, and muscle capillary recruitment. Adding resistance training to aerobic exercise provides an additional benefit of increased insulin sensitivity.

Blood Glucose Management During Exercise [11] [12] [13]

General principles for patients with diabetes mellitus for exercise regimens:

Maintain a high level of fluid intake before, during, and after exercise

Maintaining blood sugar logs before, during, and after exercise

If blood glucose is less than 100 mg/dL, it is recommended to ingest food, such as glucose tablets, juice. About 15 to 30 grams of quickly absorbed carbohydrate is recommended to be ingested 15 to 30 minutes before exercise. Extra ingestion of food may be warranted during exercise based on blood glucose testing during the exercise. Immediately after excise slowly absorbed carbohydrates such as dried fruit, granola bars or trail mix are recommended as patients are at risk of late hypoglycemia.

Vigorous exercise is to be avoided in the presence of substantial hyperglycemia greater than 250 mg/dl.

Hypoglycemia is not common in patients with type 2 diabetes not treated with insulin or oral hypoglycemics. Ingestion of extra carbohydrates is not required.

Use insulin about 60 to 90 minutes before exercise to prevent increased insulin absorption along with injecting in a site other than muscle to be exercised. For example, inject into arms when cycling exercise and into the abdomen when the exercise involves both the arms and legs.

Enhancing Healthcare Team Outcomes

Long-Term Compliance and an Interprofessional Approach [14]

Maintenance of the exercise program in patients with type 2 diabetes is an important goal because it is associated with long-term cardiovascular benefits and reduced mortality. Primary care physicians and nursing professional diabetes educators caring for patients play an important role in educating these patients of the importance of exercise regimen as a therapeutic option for the disease management. There have been studies which suggested simple behavioral counseling by clinicians and nurse educators during routine clinic visits gave encouraging results for increasing compliance, although long-term follow-up is needed.

Exercise regimens are difficult to maintain for more than 3 months due to intense nature of the programs requiring extra visits for special classes. In a 10-year study of 255 patients with diabetes enrolled in a diabetes education program emphasizing exercise, the rate of compliance fell from 80% for 6 weeks to less than 50% for 3 months. The compliance rate further dropped to less than 20% at 1 year. A coordinated interprofessional approach with educators working with clinicians will help to maximize compliance. (Level V)

References in the text are referenced by numbers

References

١-Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, Chasan-Taber L, Albright AL, Braun B., American College of Sports Medicine. American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care. ٢٠٢٣ Dec;33(12):2692-6.

٢-Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ., American Heart Association. American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. ٢٠٢٠ Jan 02;115(1):114-26.

٣-Long BJ, Calfas KJ, Wooten W, Sallis JF, Patrick K, Goldstein M, Marcus BH, Schwenk TL, Chenoweth J, Carter R, Torres T, Palinkas LA, Heath G. A multisite field test of the acceptability of physical activity counseling in primary care: project PACE. Am J Prev Med. ٢٠١٩ Mar-Apr;12(2):73-81.

۴-Calfas KJ, Long BJ, Sallis JF, Wooten WJ, Pratt M, Patrick K. A controlled trial of physician counseling to promote the adoption of physical activity. Prev Med. ٢٠٢٢ May-Jun;25(3):225-33.

۵-Bird SR, Hawley JA. Exercise and type 2 diabetes: new prescription for an old problem. Maturitas. ٢٠١٨ Aug;72(4):311-6.

۶-Phielix E, Meex R, Moonen-Kornips E, Hesselink MK, Schrauwen P. Exercise training increases mitochondrial content and ex vivo mitochondrial function similarly in patients with type 2 diabetes and in control individuals. Diabetologia. ٢٠٢٠ Aug;53(8):1714-21.

٧-Kirwan JP, Solomon TP, Wojta DM, Staten MA, Holloszy JO. Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab. ٢٠٢١ Jul;297(1):E151-6.

٨-Winnick JJ, Sherman WM, Habash DL, Stout MB, Failla ML, Belury MA, Schuster DP. Short-term aerobic exercise training in obese humans with type 2 diabetes mellitus improves whole-body insulin sensitivity through gains in peripheral, not hepatic insulin sensitivity. J Clin Endocrinol Metab. ٢٠١٨ Mar;93(3):771-8.

۹-Devlin JT. Effects of exercise on insulin sensitivity in humans. Diabetes Care. ۲۰۱۹ Nov;15(11):1690-3.

۱۰-Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB. Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. Diabetologia. ۲۰۲۱ May;26(5):355-60.

۱۱-Soo K, Furler SM, Samaras K, Jenkins AB, Campbell LV, Chisholm DJ. Glycemic responses to exercise in IDDM after simple and complex carbohydrate supplementation. Diabetes Care. ۲۰۲۲ Jun;19(6):575-9.

۱۲-Grimm JJ, Ybarra J, Berné C, Muchnick S, Golay A. A new table for prevention of hypoglycaemia during physical activity in type 1 diabetic patients. Diabetes Metab. ۲۰۱۹Nov;30(5):465-70.

۱۳-Koivisto VA, Felig P. Effects of leg exercise on insulin absorption in diabetic patients. N Engl J Med. ۲۰۲۰ Jan 12;298(2):79-83.

۱۴-Schneider SH, Khachadurian AK, Amorosa LF, Clemow L, Ruderman NB. Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care. ۲۰۱۷ Nov;15(11):1800-10.

Improve in status of patients with non-alcoholic fatty liver with exercise intervention

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Abstract
Nonalcoholic fatty liver disease (NAFLD) is globally prevalent and characterized by abnormal lipid accumulation in the liver, frequently accompanied by insulin resistance (IR), enhanced hepatic inflammation, and apoptosis. Recent studies showed that endoplasmic reticulum stress (ERS) at the subcellular level underlies these featured pathologies in the development of NAFLD. As an effective treatment, exercise significantly reduces hepatic lipid accumulation and thus alleviates NAFLD. Confusingly, these benefits of exercise are associated with increased or decreased ERS in the liver. Further, the interaction between diet, medication, exercise types, and intensity in ERS regulation is more confusing, though most studies have confirmed the benefits of exercise. In this review, we focus on understanding the role of exercise-modulated ERS in NAFLD and ERS-linked molecular pathways. Moderate ERS is an essential signaling for hepatic lipid homeostasis. Higher ERS may lead to increased inflammation and apoptosis in the liver, while lower ERS may lead to the accumulation of misfolded proteins. Therefore, exercise acts like an igniter or extinguisher to keep ERS at an appropriate level by turning it up or down, which depends on diet, medications, exercise intensity, etc. Exercise not only enhances hepatic tolerance to ERS but also prevents the malignant development of steatosis due to excessive ERS.
Keywords: exercise, fatty liver, lifestyle, NAFLD, treatment, Web-based

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by abnormal fat metabolism in the liver due to nonalcoholic causes [1]. NAFLD undergoes a spectrum of pathologies ranging from simple steatosis earlier to nonalcoholic steatohepatitis (NASH) and hepatic fibrosis at the later period [2]. Obesity-related insulin resistance (IR) and ectopic lipid accumulation cause hepatic steatosis [1], followed by increased lipid toxicity, leading to malignant development of liver inflammation and hepatocyte apoptosis [3]. The “two-hits” hypothesis has been the leading theory on NAFLD [4]. The first hit is the excessive accumulation of fat in hepatocytes, leading to IR. The second hit is the inflammatory response in the liver induced by reactive oxygen species (ROS) following the first hit. Recently, endoplasmic reticulum stress (ERS) has been proposed to understand the pathology of NAFLD [5], in which ERS causes hepatic IR, lipid accumulation, inflammation, and hepatocyte apoptosis. Exercise alleviates NAFLD by reducing hepatic lipid and enhancing insulin sensitivity [۶]. Exercise may modulate ERS levels in multiple organs, leading to improved lipid homeostasis in the liver and even the whole body [۷]. Although there is persuasive evidence that exercise reduces hepatic lipid accumulation in humans and animals, ERS may increase or decrease with exercise in these previous studies. If so, what role does ERS play in hepatic lipid accumulation? In this review, we will focus on understanding the role of up- or downregulation of ERS during exercise in NAFLD.

2. ERS and Unfolded Protein Response

The endoplasmic reticulum (ER) is a cellular organelle required for calcium homeostasis, protein synthesis, and posttranslational modification and trafficking. ER homeostasis is usually disturbed by numerous environmental, physiological, and pathological insults, referred to as ERS, in which misfolded or incomplete folded proteins are accumulated in the ER, termed the unfolded protein response (UPR) [۸]. ERS can be provoked by genetic and environmental factors [۹]. Cell survival or apoptosis is determined by the UPR during ERS. The UPR is regulated

by three transmembrane proteins: protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring protein 1α (IRE-1α), and activating transcription factor 6 (ATF6). All of them are activated by dissociation with glucose regulated protein 78 kD (GRP78) [۱۰].

3. Exercise and Hepatic Steatosis in Patients with NAFLD

3.1. Exercise Types and Diversity

So far, there are no consensual suggestions regarding exercise type to reduce hepatic steatosis. It can be almost inferred from previous studies that each exercise type contributes to liver function, hence avoiding the malignant development of NAFLD. Houghton et al. compared aerobic exercise with resistance exercise for 12 weeks in NAFLD patients, showing that both types of exercise consistently reduced triglyceride (TG) content in the liver and blood glucose [۱۱]. Additionally, 24 weeks of moderate-intensity aerobic exercise improved liver function, as evidenced by serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in NAFLD patients [۱۲]. Likewise, Bacchi et al. suggested that both aerobic exercise such as treadmill exercise and resistance training had a similar effect on hepatic TG content in NAFLD patients [26]. These studies suggest that a wide variety of types of exercise contribute to the reduction of NAFLD.

3.2. Exercise Intensity

Regarding exercise intensity to reduce hepatic steatosis, a study showed that both high-intensity exercises at 60-80% heart rate (HR) and moderate intensity at 45-55% HR reduced hepatic TG content in NAFLD patients [۱۳]. However, vigorous aerobic exercise at 80% of maximal oxygen consumption was deemed to aggravate NAFLD, which might increase lipid accumulation in the liver due to enhanced lipolysis in peripheral tissues after exercise [۱۴]. Another study showed that high-intensity interval training (HIIT) effectively reduced hepatic TG content in NAFLD patients [۱۵], proving that the benefits of exercise are not limited to exercise intensity. Even though the effects of each exercise intensity are analogous in previous studies, the optimal exercise intensity for personalized NAFLD is still confusing [۱۶].

3.3. Exercise Frequency and Duration

The lipid utilization and its beneficial effects may vary with frequency and duration of exercise. However, the frequency and duration of exercise did not limit the risk reduction and development of NAFLD in the follow-up study of NAFLD or non-NAFLD patients. Indeed, the risk reduction and benefit are positively correlated with exercise frequency [۱۷]. Timing exercise bouts to coordinate with individual circadian rhythms might be an effective strategy to optimize the health benefits of exercise [۱۸]. However, an intriguing study showed that the reduction of hepatic TG content did not change with exercise timing [۱۹]. In all, there are still many inconsistencies in the effect of exercise frequency or rhythm on NAFLD. However, exercise with different types, intensity, frequency, and timing has potential to reduce hepatic TG in NAFLD patients, thereby alleviating hepatic steatosis.

4. Overview of the Mechanisms by which Exercise Improves Hepatic Steatosis

A large number of studies suggest that exercise improves NAFLD due to reduced hepatic TG and IR. It can be also attributed to the fact that exercise induces weight loss or normal weight [۲۰]. However, amounts of studies have shown that decreased hepatic TG and serum AST and ALT were not related to body weight or body mass index, suggesting that exercise-induced weight control may not play a critical role in NAFLD [۲۱]. Despite the positive effects of exercise on NAFLD, exercise-treated mice showed more severe hepatic steatosis and metabolic disorders compared with mice without exercise, when given a HFD at the same time after exercise training [۲۲]. These contradictions from human and animal experiments prompted us to further explore the molecular mechanisms on NAFLD. To date, studies regarding underlying mechanisms included improving IR, reducing lipid accumulation, suppressing inflammatory pathways, and strengthening cell function to resist the stress. These results were summarized in Table 1. Although some of these results did not mention ERS, we found that the key signaling molecules of ERS were included in effector molecules of exercise. ERS at the subcellular level must be

an important mediator for exercise to improve IR, reduce lipid accumulation, relieve liver inflammation, and strengthen cell survival.

5. The Up- and Downregulation of ERS in the Liver by Exercise

5.1. GRP78 Expression Depends on the Diversity of Exercise Types

GRP78 is the master protein of the UPR and mediates cellular response to normal or stress conditions. GRP78 was significantly reduced in the liver of elderly NAFLD mice after knee loading exercise for 6 weeks, suggesting that ERS was suppressed by resistance exercise [۲۳]. In contrast, Deldicque et al. showed that endurance treadmill exercise for 6 km/week was not a sufficiently strong stimulus to alter the protein expression of GRP78 in elderly obese mice [17]. Similarly, Kristensen et al. demonstrated that swimming exercise was not able to suppress the increased GRP78 in the liver of HFD mice [55]. Astonishingly, results in the referred studies show that lipid accumulation in the liver is all reduced after exercise. As per previous reports, GRP78 expression in the liver depends on the intensity of treadmill exercise [۲۴], where GRP78 functions as a stress-response protein that needs a threshold intensity of exercise stimulation. In this regard, the up- and downregulation of ERS may be related to different types, intensity, and duration of exercise.

5.2. The Expression of IRE-1α, PERK, and ATF6 Depends on Exercise Conditions

Even though these three signal transducers are activated during ERS, their expression varies greatly under the regulation of exercise. For instance, continuous exhausted exercise reduced ATF6 expression in the liver, while phosphorylation of PERK and IRE-1α was not changed [۲۵]. In contrast, another study showed that long-term aerobic exercise suppressed the expression of IRE-1α and PERK, rather than ATF6 [۲۶]. In addition, diet also affects the regulation of exercise on ERS in the liver. With the same exercise training, HFD-fed mice showed an increased expression of PERK with unaltered IRE-1α and ATF6, while standard diet-fed mice remained unchanged in all these three indicators [۲۷]. Similar results were demonstrated in elderly obese mice [17]. However, 8 weeks of swimming exercise decreased the phosphorylation of PERK in the liver of HFD mice [۲۸]. Several studies with NAFLD rats suggested that swimming exercise, HFD [۲۹], or their combination decreased the expressions of PERK and IRE-1α in the liver [۳۰]. The coactivation of ATF6 and PGC-1α is related to the exercise adaptability of the skeletal muscle [۳۱]. However, there is no effect of exercise on ATF6 in the liver of elderly mice [۳۲]. During the UPR, the ER transmembrane sensor, including IRE-1α, PERK, and ATF6, is activated, by which stress signals are transduced to the outside of the ER, leading to various cell responses including gene induction. In these previous studies, the three sensors had inconsistent responses to exercise, suggesting that the UPR and ERS activation depends on specific exercise and diet conditions (thresholds).

5.3. The Regulation of ERS by Exercise Is Affected by Drugs

Despite the increased knowledge of underlying mechanisms on NAFLD, the design of a standard therapeutic approach for such a complex and multifactorial disease seems to be out of reach so far. Exercise combined with drugs as an unconventional therapy intrigues many scholars. Rutin, a glycoside of quercetin, is a nonnutritive component of many foods such as onions, apples, tea, and red wine [۱۷]. As one of the flavonoids, rutin effectively reversed oxidative stress and inflammation in the liver and prevented chronic progression in metabolic syndrome [۱۸]. Exercise and rutin independently did not change the expression of IRE-1α in the liver of HFD mice, while their combination significantly reduced the expression of IRE-1α [۱۹]. In fact, medication and exercise promote each other to alleviate NAFLD. For instance, an adequate supplement of vitamin D is necessary to achieve the beneficial effects of physical activity [۲۳]. Ezetimibe is useful for treating residual dyslipidemia after exercise intervention in patients with NAFLD [۲۶]. Therefore, it is logically speculated that the combination of exercise and rutin is more useful for NAFLD.

Similar to rutin, resveratrol is a polyphenolic compound, which was regarded as an alternative treatment for NAFLD [۲۷]. Although resveratrol alone has antioxidant, antiapoptotic, and anti-inflammatory properties, combined therapy with interval and continuous training can be more effective to mitigate these abnormalities in NAFLD patients [۲۸]. Exercise combined with resveratrol regulated ERS by different pathways that depend on

exercise intensity in a NAFLD model induced by a HFD [۲۹]. However, no evidence clarified why exercise combined with resveratrol suppressed different branches of the UPR at different exercise intensities. Also, we have screened out the potential NAFLD drugs, which combine with exercise to produce a boost by regulating ERS in the liver. The pharmacological roles of these drugs fall into four broad categories: cytoprotection (e.g., rutin, resveratrol, vitamin D, vitamin E, betaine, pentoxifylline, UDCA, and silymarin), regulation of lipid metabolism (e.g., statins, ezetimibe, metformin, and omega-3 fatty acids), hormonal regulation (e.g., incretin analogues, TZDs, sitagliptin, and vildagliptin), and interactions of systemic metabolism (e.g., angiotensin receptor blockers, probiotics and synbiotics, and orlistat). Meanwhile, it is necessary to identify whether drugs reduce ERS as a result or cause of the improvement of metabolic disorder. In fact, most of these drugs suppress ERS, and exercise that either increases or decreases ERS seems to have beneficial effects on medication. It is interesting to explore the mechanism underlying the combination of drugs and exercise, supposing combination of both may alleviate hepatic ERS in NAFLD.

Together, ERS in response to exercise is associated with exercise types and intensity, diet, drugs, and other factors. The ERS markers may be either increased or decreased after exercise, but the beneficial effect of exercise on NAFLD is almost consistent in previous studies. Exercise always leads to a positive impact on NAFLD by reducing hepatic lipid content. If ERS is induced by unfolded or misfolded proteins, it may be triggered by the accumulation of misfolded proteins to a certain threshold. Aerobic exercise can prevent accumulated misfolded proteins and reduce oxidative damage, heat-shock protein levels, and exercise tolerance [۳۰]. Exercise-induced metabolic stress could activate the UPR, mediating exercise-induced adaptation responses. In fact, moderate-intensity exercise-induced ERS acts as a protective mechanism against current and future stressors. However, biological responses vary according to exercise intensity and therefore induce different degrees of ERS [۳۱]. Thus, three pathways of ERS may be selectively inhibited by different exercise intensities. These results suggest that the regulation of ERS by exercise may ultimately depend on the extent of misfolded protein accumulation in ER.

6. ERS-Related Molecular Mechanism by which Exercise Alleviates NAFLD

6.1. Exercise Reduces Lipid Accumulation in the Liver by Regulating ERS

Lipid ectopic accumulation occurs in the early stage of NAFLD, which leads to ERS in the liver [۱۱]. Unfortunately, ERS further promotes lipid overstore and hepatic steatosis and thus leads to NAFLD [14]. Sliced XBP1s is crucial in hepatic lipogenesis. XBP1 enhanced the protein levels of lipogenesis and resulted in lipid accumulation in the liver [۳۲]. XBP1 knockout mice exhibited hypocholesterolemia, hypotriglyceridemia, and reduced liver lipogenesis [۳۳]. Exercise controls the transcription of XBP1 in the liver. The 6-week wheel running suppressed the increase in XBP1s mRNA in HFD-fed mice [17], and similar results were shown in rats after the 6-week treadmill exercise [58]. Furthermore, swimming exercise decreased the protein levels of IRE-1α and XBP1 and reduced hepatic TG content in rats with NAFLD [۳۴]. However, exercise also offset the age-induced XBP1s reduction, but not the increased hepatic TG content [۳۵]. Contrary to these previous studies, XBP1 has been identified as an antiadipogenic protein in the liver, which reduces hepatic lipogenic gene expression and improves hepatosteatosis in mouse models of obesity and IR [۱۱].

The biosynthesis of fatty acids and cholesterol is controlled by SREBPs. SREBP is regulated by the PERK pathway in the UPR [12, 13]. Eukaryotic initiation factor eIF-2α is phosphorylated by PERK and thus activates SREBP-1c to aggravate hepatic steatosis [14]. ERS induces chronic overexpression of GADD34 [13], dephosphorylates p-eIF-2α to inhibit lipid accumulation in the liver. Lipid accumulation and the expression of SREBP-1c were both reduced in the liver of ATF4 knockout mice [15]. Additionally, ATF4 knockout mice showed reduced lipid accumulation in the liver after HFD [16]. Exercise reduced ATF4 protein and TG content in the liver of NAFLD mice [4], indicating that exercise reduced the lipid accumulation by controlling ATF4 expression. Adenosine 5-monophosphate- (AMP-) activated protein kinase (AMPK) was activated by exercise and suppressed SREBP-1c, thereby reducing lipid accumulation in the liver of HFD mice [1]. Li et al. showed that exercise reduced SREBP-1-induced lipid accumulation in the liver through the AMPK pathway to inhibit the

mammalian target of rapamycin complex 1 and relieve ERS [17]. Collectively, exercise reduced hepatic lipogenesis by the PERK/ATF4/SREBP pathway. These studies suggest that exercise regulates hepatic XBP1 and SREBPs through ERS signaling, thereby reducing lipid accumulation in the liver of NAFLD.

In addition, exercise may regulate ERS in adipose tissue to treat NAFLD. ERS promoted lipolysis in adipose tissue and increased circulating free fatty acid (FFA), and FFA is likely to be transferred to the liver for lipid synthesis [18, 19]. Thus, reducing ERS and FFA output from adipose tissue maybe prevents NAFLD. GRP78, PERK, and ATF6 in the subcutaneous adipose tissue of obese individuals were higher than normal, suggesting a higher level of adipocyte ERS with obesity. These ERS markers were decreased by three months of moderate-intensity aerobic exercise, so Khadir et al. conclude that physical exercise alleviates ERS in obese humans through attenuation of the GRP78 signaling network [20]. The regulation of ERS in the skeletal muscle during exercise aroused several scholars' great interest. Kim et al. emphasized the link between ERS in the skeletal muscle and exercise and suggested that ERS was activated in the human skeletal muscle after exercise [21]. Myokines, such as fibroblast growth factor 21 and interleukin-6 (IL-6), were upregulated by enhanced ERS in the skeletal muscle during a short-term exercise [22,23]. Circulating myokines enhanced β-oxidation and repressed lipogenesis in the liver, increased glucose and lipid uptake in adipocytes, and promoted hepatic glycolysis and lipolysis to fuel the muscle [24, 25]. ERS-activated ATF6 upregulated G protein-coupled bile acid receptor 1 expression and increased energy expenditure in the skeletal muscle during exercise [26].

Together, ERS is the trigger of cellular signaling in multiple organs. In the liver, exercise inhibits lipogenesis directly through UPR-mediated cell signaling. In the fat, exercise suppresses ERS to reduce FFA release into the blood, thus reducing fatty acid transport to the liver. In the skeletal muscle, exercise enhances ERS to promote myokine secretion, thereby targeting the liver to promote lipolysis. Anyway, exercise can reduce lipid accumulation in the liver through the modulation of ERS.

6.2. Exercise Reduces Insulin Resistance in the Liver by Regulating ERS

IR is closely associated with NAFLD, while it is hard to clarify which is the cause and which is the result. ERS is essential for FFA-induced inflammation and IR with PERK and IκB kinase-β (IKKβ) as the critical signaling components. Deficiency of PERK attenuates FFA-induced activation of IKKβ, and deficiency of IKKβ alleviates FFA-induced inflammation and IR [27]. Also, PERK acts oppositely to promote Forkhead box protein O (FOXO) activity via phosphorylation of FOXO1 and results into IR. Inhibition of PERK improves cellular insulin responsiveness at the level of FOXO activity [28]. By the IRE-1α pathway, XBP1s interacts with FOXO1 and thus bypasses hepatic IR independent of its effects on ER protein folding. Modest hepatic overexpression of XBP1s in mouse models of insulin deficiency or IR reduced blood glucose, without improving insulin signaling and ER folding capacity [29]. Activated IRE-1α leads to suppression of insulin receptor signaling through hyperactivation of JNK and subsequent serine phosphorylation of insulin receptor substrate-1 (IRS-1). The IRE-1α-JNK signaling pathway can directly inhibit cytoplasmic insulin signaling because activated JNK phosphorylates IRS-1 at Ser307 [30]. Thus, ERS impairs insulin signaling and results into IR.

Exercise improves IR in the liver by reducing ERS. For instance, swimming exercise led to reduction in PERK and eIF-2α phosphorylation and reduced proinflammatory molecules (JNK, IκB, and NF-κB) in the liver, with enhanced insulin signaling [9]. However, Deldicque et al. found that phosphorylation of JNK and IKK was increased in the liver with unimproved glucose tolerance, although 6-week endurance exercise reduced the phosphorylation of IKK in the obese mice. The authors conclude that the potentiation of the UPR by endurance training may represent a positive adaptation protecting against further cellular stress [17]. These opposite results still show that JNK is linked to the insulin signaling, whether exercise reduces or increases ERS. In line with PERK, the phosphorylation of IRE-1α and JNK decreased in the liver of HFD mice after 16 weeks of treadmill exercise [1]. Thus, an appropriate exercise may improve insulin sensitivity through the PERK/JNK or IRE-1α/JNK pathways to reduce hepatic IR.

Unlike acute exercise, several training sessions weakened ERS in the skeletal muscle. Aging induced oxidative stress and activated ERS-related apoptosis in the skeletal muscle, whereas long-term wheel-running improved redox regulation, ERS adaptation, and attenuated ERS-related apoptosis [31]. Accumulating studies demonstrated that ERS negatively regulated skeletal muscle insulin sensitivity. Overproduction of ATF6 is sufficient to inhibit the expression of glucose transporter 4 in the skeletal muscle [32]. Also, the upregulated Tribbles 3 by ERS, as a pseudokinase in the skeletal muscle [33], inhibited phosphorylation of Akt and repressed glucose uptake [34]. Hepassocin (HPS) is a novel hepatokine that causes hepatic steatosis. ERS induced by palmitate could increase the expression of HPS in hepatocytes and further contribute to the IR in the skeletal muscle via the epidermal growth factor receptor (EGFR)/JNK-mediated pathway [35]. In turn, ERS induced by exercise in the skeletal

muscle could increase the release of myokines such as FGF21 and IL-6 and further reduce hepatic IR in NAFLD ultimately [22, 23].

6.3. Exercise Modulates the Inflammatory Response in the Liver by Regulating ERS

Currently, IR and mild lipid accumulation in the liver are considered common symptoms of reversible NAFLD. However, the UPR cannot restore ER homeostasis in the later stage of NAFLD, and chronic inflammation promotes the further deterioration of fatty liver [36]. ROS-induced lipid peroxidation is more and more serious and triggers inflammation in the liver [37]. In fact, the hepatic inflammation and the UPR occur simultaneously by the IRE-1α and PERK pathways. IRE-1α triggers the JNK inflammatory pathway, thus phosphorylating IκB and activating NF-κB [38]. PERK is activated by ERS, and the resulting eIF-2α phosphorylation is critical for the activation of NF-κB [39], where the decreased IκB/NF-κB ratio promotes inflammation during ERS [40]. Furthermore, increased thioredoxin interaction protein (TXNIP) induced by IRE-1α and PERK, which interacted with ROS, thus aggravated the inflammatory response [41]. In addition, ERS elevated hepatic sensitivity to lipotoxicity and release of inflammatory cytokines to activate more macrophages [42].

For liver inflammation, studies regarding the regulation of exercise on ERS focus on the PERK and IRE-1α pathways. Lifelong exercise significantly reduced the phosphorylation of IRE-1α and JNK in the liver [5], suggesting that exercise might alleviate the inflammation through regulating the IRE-1α pathway. Moreover, endurance exercise decreased JNK, IκB, and NF-κB levels in the liver of obese mice, with a significant reduction of PERK and eIF-2α [9]. In contrast to these results, Deldicque et al. showed that aerobic exercise enhanced ERS and the phosphorylation of JNK, with higher levels of IL-1 and IL-6 in the liver [17]. Interestingly, hepatic metabolic abnormality in these mice was all improved, suggesting that reducing ERS and inflammation may not be necessary for exercise to alleviate NAFLD.

Together, increasing and decreasing ERS with exercise both leads to health benefits. By this way, ERS results in enhancement or reduction of inflammation. For exercise, studies have demonstrated the effects of aerobic exercise on ERS-induced inflammation, while the effects of resistance exercise have not been well-established. Endurance exercise either reduces hepatic ERS as a pathway for reducing inflammation in liver or increases hepatic ERS and inflammation as a stimulus to elevate the anti-inflammatory threshold protecting against further cellular stress. In any case, cells are likely to be protected by exercise. Previous conclusions about exercise effects are contradictory, which may be related to the development stage of NAFLD and exercise conditions. It is worth discussing that the type and intensity of exercise must be highly compatible with the stage of NAFLD or it may backfire.

6.4. Exercise Controls Hepatic Lipoapoptosis by Regulating ERS

A large number of hepatocytes undergo apoptosis and are replaced by fibrosis, leading to severe deterioration in the later stage of NAFLD. Hepatocyte apoptosis with lipotoxicity, referred to as lipoapoptosis, is mainly induced by ERS and the mitochondrial apoptotic pathway in NAFLD [43]. Saturated FFA induces JNK-dependent hepatocyte lipoapoptosis by activating the proapoptotic factor, which triggers the mitochondrial apoptotic pathway. Although saturated and monounsaturated FFAs caused equal cellular steatosis, apoptosis and JNK activation were greater during exposure to saturated versus monounsaturated FFAs [44]. In human and mouse hepatocytes, palmitic acid at a lipotoxic concentration triggered early activation of ERS-related kinases, induced the ERS related-apoptotic transcription factor CHOP, activated Caspase3, and increased the percentage of apoptotic cells [45]. There are three types of lipoapoptosis, which are mediated by UPR, resulted from calcium (Ca2+) disorder in the ER lumen, and induced by an ERS-specific apoptotic protein Caspase12 [43, 46, 47]. Moreover, ERS-mediated lipoapoptosis in the liver is induced by the PERK and IRE-1α pathways.

Exercise reduces hepatocyte lipoapoptosis in mice with NAFLD. Resveratrol, exercise, and their combination reduced the number of apoptotic cells significantly in the liver [48]. Furthermore, moderate-intensity aerobic exercise combined with resveratrol reduced IRE-1α and PERK levels, with their downstream proteins such as JNK1 and CHOP, as well as Caspase3 and Bcl-2-associated X protein (BAX), the apoptosis proteins [8]. This indicates that exercise combined with resveratrol may reduce the hepatocyte apoptosis through the IRE-1α/JNK and PERK/CHOP pathways in mice with NAFLD. 8 weeks of exhausting exercise decreased the expression of Caspase3 and ATF6 in the liver [7]. Consecutive aerobic exercise for 8 weeks with HFD cancellation suppressed CHOP, Caspase12, and JNK, with decreased apoptotic hepatocytes in mice with NAFLD [49]. Thus, exercise reduces lipoapoptosis through the IRE-1α/JNK and PERK/CHOP apoptotic pathways.

However, Deldicque et al. showed that endurance exercise increased PERK and IRE-1α and enhanced Caspase12 in the liver of obese mice [17]. The antiapoptotic factor Bcl-2 was inactivated by the JNK pathway, which may mediate the increasing hepatocyte apoptosis during endurance exercise. Double-KO (proapoptotic Bcl-2 family members BAX and BAK) mice responded abnormally to tunicamycin-induced ERS in the liver, with extensive

tissue damage and decreased expression of the IRE1 substrate XBP1 and its target genes [۴۹]. Another study also showed that low-intensity aerobic exercise could not reduce hepatic lipoapoptosis in mice with NAFLD [8]. As previously mentioned, the effect of exercise on ERS is inconsistent in separate studies. Nevertheless, what is relatively clear is that exercise reduces hepatocyte apoptosis by relieving ERS in NAFLD.

In addition, exercise significantly reduced the expression of Caspase12 in the liver of NAFLD [15], indicating that exercise might decrease Caspase12 to inhibit hepatocyte apoptosis. Also, aerobic exercise with different intensities reduced the expression of Caspase12 and the hepatocyte lipoapoptosis in diabetic mice [6]. However, Kristensen et al. demonstrated no difference in the Bax/Bcl-2 ratio in the livers of untrained and trained older mice, suggesting that exercise did not reduce hepatocyte apoptosis [5]. Additionally, exercise reduced GRP78, CHOP, and cleaved Caspase12 protein in an intensity-dependent manner. Exercise appeared to ameliorate diabetic cardiomyopathy by inhibiting ERS-induced apoptosis in diabetic rats [15]. Dietary obesity could induce prefrontal ERS in rats, and excessive ERS decreases the levels of neuroplasticity-associated proteins. Exercise could reduce GRP78, p-PERK, p-eIF-2α, Caspase12, CHOP, and Bax/Bcl-2 expressions and ERS-induced apoptosis, thus promoting the expression of neuroplasticity-associated proteins [۱۷]. Although these studies were not about NAFLD, the findings suggest that exercise has significant tissue specificity in regulating apoptosis through ERS.

7. Conclusion and Remarks

In conclusion, exercise alleviates NAFLD by reducing lipid accumulation, insulin resistance, hepatocyte lipoapoptosis, and the inflammatory response. These improvements are associated with ERS at the subcellular level in the liver and beyond. However, not all of exercise protocols produce similar ERS. Exercise effects on ERS depend on a variety of conditions, such as the type and intensity of exercise, diet, medications, age, and pathology. Nonetheless, most studies support the benefits of exercise for NAFLD. First, exercise can trigger the UPR to enhance hepatic threshold of ERS tolerance, suggesting that the liver can withstand higher levels of misfolded proteins and raise the protein clearance efficiency. Second, regular exercise can prevent the malignant development of NAFLD by suppressing excessive ERS at the downstream of the UPR. Therefore, ERS must be an intracellular signal of lipid homeostasis for the liver. Too low ERS is not conducive to the clearance of misfolded proteins, whereas too high ERS may activate inflammatory signaling pathways and hepatic apoptosis. Moderate-intensity acute exercise combined with regular exercise produces a moderate level of ERS for hepatic lipid homeostasis. In addition, exercise effects on ERS (up- or downregulation) in the skeletal muscle, fat, and even brain contribute to lipid turnover in the liver through UPR-mediated cytokine secretion. Further studies are needed to explore how the up- and downregulation of ERS in different tissues and organs during exercise are well orchestrated to reduce lipid accumulation in the liver.

References are referenced by numbers in the text

References:

1. C. D. Byrne and G. Targher, “Ectopic fat, insulin resistance, and nonalcoholic fatty liver disease,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 34, no. 6, pp. 1155–1161, ۲۰۲۳.
2. G. N. Zhao, P. Zhang, J. Gong et al., “Tmbim1 is a multivesicular body regulator that protects against non- alcoholic fatty liver disease in mice and monkeys by targeting the lysosomal degradation of Tlr4,” *Nature Medicine*, vol. 23, no. 6, pp. 742–752, 2017.
3. M. Li, C. Xu, J. Shi et al., “Fatty acids promote fatty liver disease via the dysregulation of 3-mercaptopyruvate sulfurtransferase/hydrogen sulfide pathway,” *Gut*, vol. 67, no. 12, pp. 2169–2180, 2018.
4. C. P. Day and O. F. W. James, “Steatohepatitis: a tale of two "hits"?” *Gastroenterology*, vol. 114, no. 4, pp. 842–845, ۲۰۲۱.
5. C. Lebeaupin, D. Vallée, Y. Hazari, C. Hetz, E. Chevet, and B. Bailly-Maitre, “Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease,” *Journal of Hepatology*, vol. 69, no. 4, pp. 927–947, 2018.
6. G. D. Lewis, L. Farrell, M. J. Wood et al., “Metabolic signatures of exercise in human plasma,” *Science Translational Medicine*, vol. 2, no. 33, article 33ra37, ۲۰۲۰.
7. Z. M. Younossi, R. Loomba, M. E. Rinella et al., “Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis,” *Hepatology (Baltimore, Md.)*, vol. 68, no. 1, pp. 361–371, 2018.

8. S. E. Keating and L. A. Adams, "Exercise in NAFLD: just do it," *Journal of Hepatology*, vol. 65, no. 4, pp. 671–673, 2016.
9. D. I. Ogborn, B. R. McKay, J. D. Crane, G. Parise, and M. A. Tarnopolsky, "The unfolded protein response is triggered following a single, unaccustomed resistance-exercise bout," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 307, no. 6, pp. R664–R669, ۲۰۲۰.
10. J. Wu, J. L. Ruas, J. L. Estall et al., "The unfolded protein response mediates adaptation to exercise in skeletal muscle through a PGC-1*α*/ATF6*α* complex," *Cell Metabolism*, vol. 13, no. 2, pp. 160–169, ۲۰۲۲.
11. S. A. Oakes and F. R. Papa, "The role of endoplasmic reticulum stress in human pathology," *Annual Review of Pathology*, vol. 10, no. 1, pp. 173–194, ۲۰۱۹.

View at: H. Urra, E. Dufey, F. Lisbona, D. Rojas-Rivera, and C. Hetz, "When ER stress reaches a dead end," *Biochimica et Biophysica Acta*, vol. 1833, no. 12, pp. 3507–3517, ۲۰۱۸.

12. I. Cakir and E. A. Nillni, "Endoplasmic reticulum stress, the hypothalamus, and energy balance," *Trends in Endocrinology and Metabolism: TEM*, vol. 30, no. 3, pp. 163–176, 2019.
13. M. Wang and R. J. Kaufman, "Protein misfolding in the endoplasmic reticulum as a conduit to human disease," *Nature*, vol. 529, no. 7586, pp. 326–335, 2016.
14. R. Ghemrawi, S. F. Battaglia-Hsu, and C. Arnold, "Endoplasmic reticulum stress in metabolic disorders," *Cells*, vol. 7, no. 6, p. 63, 2018.
15. J. Hwang and L. Qi, "Quality control in the endoplasmic reticulum: crosstalk between ERAD and UPR pathways," *Trends in Biochemical Sciences*, vol. 43, no. 8, pp. 593–605, 2018.
16. L. Deldicque, P. D. Cani, N. M. Delzenne, K. Baar, and M. Francaux, "Endurance training in mice increases the unfolded protein response induced by a high-fat diet," *Journal of Physiology and Biochemistry*, vol. 69, no. 2, pp. 215–225, ۲۰۲۱.
17. X. Zhang, C. Xu, C. Yu, W. Chen, and Y. Li, "Role of endoplasmic reticulum stress in the pathogenesis of nonalcoholic fatty liver disease," *World Journal of Gastroenterology*, vol. 20, no. 7, pp. 1768–1776, ۲۰۲۱.
18. F. Urano, X. Z. Wang, A. Bertolotti et al., "Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1," *Science (New York, N.Y.)*, vol. 287, no. 5453, pp. 664–666, ۲۰۲۰.
19. D. Eletto, D. Eletto, S. Boyle, and Y. Argon, "PDIA6 regulates insulin secretion by selectively inhibiting the RIDD activity of IRE1," *The FASEB Journal*, vol. 30, no. 2, pp. 653–665, 2015.
20. Q. Tong, L. Wu, T. Jiang, Z. Ou, Y. Zhang, and D. Zhu, "Inhibition of endoplasmic reticulum stress-activated IRE1*α*-TRAF2-caspase-12 apoptotic pathway is involved in the neuroprotective effects of telmisartan in the rotenone rat model of Parkinson's disease," *European Journal of Pharmacology*, vol. 776, pp. 106–115, ۲۰۱۹.
21. M. S. Choy, P. Yusoff, I. C. Lee et al., "Structural and functional analysis of the GADD34:PP1 eIF2*α* phosphatase," *Cell Reports*, vol. 11, no. 12, pp. 1885–1891, 2015.
22. F. J. Guo, Z. Xiong, X. Lu, M. Ye, X. Han, and R. Jiang, "ATF6 upregulates XBP1S and inhibits ER stress-mediated apoptosis in osteoarthritis cartilage," *Cellular Signalling*, vol. 26, no. 2, pp. 332–342, ۲۰۲۲.
23. D. Houghton, C. Thoma, K. Hallsworth et al., "Exercise reduces liver lipids and visceral adiposity in patients with nonalcoholic steatohepatitis in a randomized controlled trial," *Clinical Gastroenterology and Hepatology*, vol. 15, no. 1, pp. 96–102.e3, 2017.
24. L. Huabin, S. Pin, and C. Yin, "Research on the intervention of NAFLD by baduanjin," *Journal of Chengdu university of physical education*, vol. 44, pp. 79–83, 2018.
25. E. Bacchi, C. Negri, G. Targher et al., "Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial)," *Hepatology (Baltimore, Md.)*, vol. 58, no. 4, pp. 1287–1295, ۲۰۲۰.

26. H. J. Zhang, J. He, L. L. Pan et al., "Effects of moderate and vigorous exercise on nonalcoholic fatty liver Disease," *JAMA Internal Medicine*, vol. 176, no. 8, pp. 1074–1082, ۲۰۲۱.
27. K. Verboven, R. Stinkens, D. Hansen et al., "Adrenergically and non-adrenergically mediated human adipose tissue lipolysis during acute exercise and exercise training," *Clinical science (London, England: 1979)*, vol. 132, no. 15, pp. 1685–1698, ۲۰۲۲.
28. J. A. Sargeant, S. Bawden, G. P. Aithal et al., "Effects of sprint interval training on ectopic lipids and tissue-specific insulin sensitivity in men with non-alcoholic fatty liver disease," *European Journal of Applied Physiology*, vol. 118, no. 4, pp. 817–828, 2018.
29. N. C. Winn, Y. Liu, R. S. Rector, E. J. Parks, J. A. Ibdah, and J. A. Kanaley, "Energy-matched moderate and high intensity exercise training improves nonalcoholic fatty liver disease risk independent of changes in body mass or abdominal adiposity -- A randomized trial," *Metabolism*, vol. 78, pp. 128–140, 2018.
30. S. E. Keating, D. A. Hackett, H. M. Parker et al., "Effect of aerobic exercise training dose on liver fat and visceral adiposity," *Journal of Hepatology*, vol. 63, no. 1, pp. 174–182, ۲۰۱۹.
31. K. C. Sung, S. Ryu, J. Y. Lee, J. Y. Kim, S. H. Wild, and C. D. Byrne, "Effect of exercise on the development of new fatty liver and the resolution of existing fatty liver," *Journal of Hepatology*, vol. 65, no. 4, pp. 791–797, ۲۰۲۰.
32. B. M. Gabriel and J. R. Zierath, "Circadian rhythms and exercise -- re-setting the clock in metabolic disease," *Nature Reviews Endocrinology*, vol. 15, no. 4, pp. 197–206, 2019.
33. V. W. S. Wong, G. L. H. Wong, R. S. M. Chan et al., "Beneficial effects of lifestyle intervention in non-obese patients with non- alcoholic fatty liver disease," *Journal of Hepatology*, vol. 69, no. 6, pp. 1349–1356, 2018.
34. C. N. Katsagoni, M. Georgoulis, G. V. Papatheodoridis, D. B. Panagiotakos, and M. D. Kontogianni, "Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: a meta-analysis," *Metabolism*, vol. 68, pp. 119–132, 2017.
35. S. Yasari, E. Dufresne, D. Prud'homme, and J. M. Lavoie, "Effect of the detraining status on high-fat diet induced fat accumulation in the adipose tissue and liver in female rats," *Physiology & Behavior*, vol. 91, no. 2-3, pp. 281–289, ۲۰۲۰.
36. G. Ma and Y. Liu, "Effects of endurance exercise on liver NO level, NOS activity and expression in mice with nonalcoholic fatty liver disease," *Journal of Tianjin University of Physical Education*, vol. 23, pp. 516–518, ۲۰۱۸.
37. W. Wu, "Effects of aerobic exercise on AdipoR2 and PPAR protein expression in liver tissues of rats with nonalcoholic fatty liver disease," *Journal of Nanjing university of physical education (Natural Science Edition)*, vol. 14, pp. 33–37, 2015.
38. X. Jin, J. Wei, W. Wu, and J. Zhang, "Effects of aerobic exercise on AMPK protein activity in rat liver tissues with nonalcoholic fatty liver disease," *Chinese Journal of Sports Medicine*, vol. 34, pp. 653–657, 2015.
39. Y. Chen, J. Xie, J. Chen, Y. Zhun, R. Chen, and H. Qu, "Intervention effect of aerobic exercise combined with pigment supplementation of Lycium barbarum on fatty acid oxidation of liver in mice with nonalcoholic fatty liver disease," *Chinese Journal of Sports Medicine*, vol. 38, pp. 201–210, 2019.
40. J. Fu, J. Qi, and J. Zhang, "Swimming activates AMPK pathway in the treatment of non-alcoholic fatty liver disease caused by high-fat diet," *Physical Education & Science*, vol. 39, pp. 84–91, 2018.
41. K. W. Baek, J. A. Gim, and J. J. Park, "Regular moderate aerobic exercise improves high-fat diet-induced nonalcoholic fatty liver disease via monoacylglycerol *O*-acyltransferase 1 pathway suppression," *Journal of Sport and Health Science*, 2018.
42. K. Marcinko, S. R. Sikkema, M. C. Samaan, B. E. Kemp, M. D. Fullerton, and G. R. Steinberg, "High intensity interval training improves liver and adipose tissue insulin sensitivity," *Molecular Metabolism*, vol. 4, no. 12, pp. 903–915, 2015.
43. D. Zhou, B. Sun, and Z. Jing, "Effects of swimming on serum Irisin and PPAR protein expression in rats with nonalcoholic fatty liver disease," *Journal of Nanjing University of Physical Education (Natural Science Edition)*, vol. 15, pp. 68–72, 2016.

44. M. Wu and E. Lu, "Effects of aerobic exercise combined with dietary intervention on plasma SREBP-1c and RBP4 levels in patients with nonalcoholic fatty liver disease," *Chinese Journal of Rehabilitation Medicine*, vol. 30, pp. 132–137, 2015.
45. J. Zhao, M. Zhao, and C. Shi, "Effects of aerobic exercise with different intensity on NAFLD nonalcoholic fatty liver disease in rats based on Sirt-1 axis," *Journal of Sports Science*, vol. 34, pp. 50–59, ۲۰۲۰.
46. H. Ma, Q. Zhang, and J. Yang, "Effects of aerobic exercise on expression of nuclear transcription factor-κB and tumor necrosis factor α protein in rat liver tissues of nonalcoholic fatty liver disease," *Chinese Journal of Rehabilitation Medicine*, vol. 31, pp. 800–802, 2016.
47. N. Kawanishi, H. Yano, T. Mizokami, M. Takahashi, E. Oyanagi, and K. Suzuki, "Exercise training attenuates hepatic inflammation, fibrosis and macrophage infiltration during diet induced-obesity in mice," *Brain, Behavior, and Immunity*, vol. 26, no. 6, pp. 931–941, ۲۰۲۲.
48. H. Ji, "Effects of aerobic exercise on adiponectin and TNF-α mRNA in rats with nonalcoholic fatty liver disease," *Chinese Journal of Rehabilitation Medicine*, vol. 29, pp. 975–977, ۲۰۲۱.
49. P. Ghareghani, M. Shanaki, S. Ahmadi et al., "Aerobic endurance training improves nonalcoholic fatty liver disease (NAFLD) features via miR-33 dependent autophagy induction in high fat diet fed mice," *Obesity Research & Clinical Practice*, vol. 12, no. 1, pp. 80–89, 2018.

The benefits of exercise therapy for patients with diabetic type2

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Abstract

Although physical activity (PA) is a key element in the prevention and management of type 2 diabetes, many with this chronic disease do not become or remain regularly active. High-quality studies establishing the importance of exercise and fitness in diabetes were lacking until recently, but it is now well established that participation in regular PA improves blood glucose control and can prevent or delay type 2 diabetes, along with positively affecting lipids, blood pressure, cardiovascular events, mortality, and quality of life. Structured interventions combining PA and modest weight loss have been shown to lower type 2 diabetes risk by up to 58% in high-risk populations. Most benefits of PA on diabetes management are realized through acute and chronic improvements in insulin action, accomplished with both aerobic and resistance training. The benefits of physical training are discussed, along with recommendations for varying activities, PA-associated blood glucose management, diabetes prevention, gestational diabetes mellitus, and safe and effective practices for PA with diabetes-related complications.

Introduction

Diabetes has become a widespread epidemic, primarily because of the increasing prevalence and incidence of type 2 diabetes. According to the Centers for Disease Control and Prevention, in 2007, almost 24 million Americans had diabetes, with one-quarter of those, or six million, undiagnosed (۱). Currently, it is estimated that almost 60 million U.S. residents also have prediabetes, a condition in which blood glucose (BG) levels are above normal, thus greatly increasing their risk for type 2 diabetes (۲). Lifetime risk estimates suggest that one in three Americans born in 2000 or later will develop diabetes, but in high-risk ethnic populations, closer to 50% may develop it (۳). Type 2 diabetes is a significant cause of premature mortality and morbidity related to cardiovascular disease (CVD), blindness, kidney and nerve disease, and amputation (۴). Although regular physical activity (PA) may prevent or delay diabetes and its complications (۵), most people with type 2 diabetes are not active (۶).

In this article, the broader term “physical activity” (defined as “bodily movement produced by the contraction of skeletal muscle that substantially increases energy expenditure”) is used interchangeably with “exercise,” which is defined as “a subset of PA done with the intention of developing physical fitness (i.e., cardiovascular [CV], strength, and flexibility training).” The intent is to recognize that many types of physical movement may have a positive effect on physical fitness, morbidity, and mortality in individuals with type 2 diabetes.

Treatment goals in type 2 diabetes

The goal of treatment in type 2 diabetes is to achieve and maintain optimal BG, lipid, and blood pressure (BP) levels to prevent or delay chronic complications of diabetes (5). Many people with type 2 diabetes can achieve BG control by following a nutritious meal plan and exercise program, losing excess weight, implementing necessary self-care behaviors, and taking oral medications, although others may need supplemental insulin (۶).

Diet and PA are central to the management and prevention of type 2 diabetes because they help treat the associated glucose, lipid, BP control abnormalities, as well as aid in weight loss and maintenance. When medications are used to control type 2 diabetes, they should augment lifestyle improvements, not replace them.

ACUTE EFFECTS OF EXERCISE

Fuel metabolism during exerciseFuel mobilization, glucose production, and muscle glycogenolysis. The maintenance of normal BG at rest and during exercise depends largely on the coordination and integration of the

sympathetic nervous and endocrine systems (۸). Contracting muscles increase uptake of BG, although BG levels are usually maintained by glucose production via liver glycogenolysis and gluconeogenesis and mobilization of alternate fuels, such as free fatty acids (FFAs) (۹).

Several factors influence exercise fuel use, but the most important are the intensity and duration of PA (۱۰). Any activity causes a shift from predominant reliance on FFA at rest to a blend of fat, glucose, and muscle glycogen, with a small contribution from amino acids (۱۱). With increasing exercise intensity, there is a greater reliance on carbohydrate as long as sufficient amounts are available in muscle or blood (۱۲). Early in exercise, glycogen provides the bulk of the fuel for working muscles. As glycogen stores become depleted, muscles increase their uptake and use of circulating BG, along with FFA released from adipose tissue (۱۳). Intramuscular lipid stores are more readily used during longer-duration activities and recovery (۱۴). Glucose production also shifts from hepatic glycogenolysis to enhanced gluconeogenesis as duration increases (۱۵).

Evidence statement. PA causes increased glucose uptake into active muscles balanced by hepatic glucose production, with a greater reliance on carbohydrate to fuel muscular activity as intensity increases. The American College of Sports Medicine (ACSM) evidence category A (see Tables 1 and and2 for explanation).

Insulin-independent and insulin-dependent muscle glucose uptake during exercise. There are two well-defined pathways that stimulate glucose uptake by muscle (96). At rest and postprandially, its uptake by muscle is insulin dependent and serves primarily to replenish muscle glycogen stores. During exercise, contractions increase BG uptake to supplement intramuscular glycogenolysis (۱۶). As the two pathways are distinct, BG uptake into working muscle is normal even when insulin-mediated uptake is impaired in type 2 diabetes (۱۷). Muscular BG uptake remains elevated postexercise, with the contraction-mediated pathway persisting for several hours (۱۸) and insulin-mediated uptake for longer (۱۹).

Glucose transport into skeletal muscle is accomplished via GLUT proteins, with GLUT4 being the main isoform in muscle modulated by both insulin and contractions (۲۰). Insulin activates GLUT4 translocation through a complex signaling cascade (۲۱). Contractions, however, trigger GLUT4 translocation at least in part through activation of 5′-AMP–activated protein kinase (۲۲). Insulin-stimulated GLUT4 translocation is generally impaired in type 2 diabetes (۲۳). Both aerobic and resistance exercises increase GLUT4 abundance and BG uptake, even in the presence of type 2 diabetes (۵).

Evidence statement. Insulin-stimulated BG uptake into skeletal muscle predominates at rest and is impaired in type 2 diabetes, while muscular contractions stimulate BG transport via a separate additive mechanism not impaired by insulin resistance or type 2 diabetes. ACSM evidence category A.

Postexercise glycemic control/BG levels

Aerobic exercise effects. During moderate-intensity exercise in nondiabetic persons, the rise in peripheral glucose uptake is matched by an equal rise in hepatic glucose production, the result being that BG does not change except during prolonged, glycogen-depleting exercise. In individuals with type 2 diabetes performing moderate exercise, BG utilization by muscles usually rises more than hepatic glucose production, and BG levels tend to decline (191). Plasma insulin levels normally fall, however, making the risk of exercise-induced hypoglycemia in anyone not taking insulin or insulin secretagogues very minimal, even with prolonged PA (۶). The effects of a single bout of aerobic exercise on insulin action vary with duration, intensity, and subsequent diet; a single session increases insulin action and glucose tolerance for more than 24 h but less than 72 h (۲۷). The effects of moderate aerobic exercise are similar whether the PA is performed in a single session or multiple bouts with the same total duration (14).

During brief, intense aerobic exercise, plasma catecholamine levels rise markedly, driving a major increase in glucose production (۱۵). Hyperglycemia can result from such activity and persist for up to 1–2 h, likely because

plasma catecholamine levels and glucose production do not return to normal immediately with cessation of the activity (۱۶).

Evidence statement. Although moderate aerobic exercise improves BG and insulin action acutely, the risk of exercise-induced hypoglycemia is minimal without use of exogenous insulin or insulin secretagogues. Transient hyperglycemia can follow intense PA. ACSM evidence category C.

Resistance exercise effects. The acute effects of a single bout of resistance training on BG levels and/or insulin action in individuals with type 2 diabetes have not been reported. In individuals with IFG (BG levels of 100–125 mg/dl), resistance exercise results in lower fasting BG levels 24 h after exercise, with greater reductions in response to both volume (multiple- vs. single-set sessions) and intensity of resistance exercise (vigorous compared with moderate) (18).

Evidence statement. The acute effects of resistance exercise in type 2 diabetes have not been reported, but result in lower fasting BG levels for at least 24 h after exercise in individuals with IFG. ACSM evidence category C.

Combined aerobic and resistance and other types of training. A combination of aerobic and resistance training may be more effective for BG management than either type of exercise alone (۱۹). Any increase in muscle mass that may result from resistance training could contribute to BG uptake without altering the muscle's intrinsic capacity to respond to insulin, whereas aerobic exercise enhances its uptake via a greater insulin action, independent of changes in muscle mass or aerobic capacity (۱۲). However, all reported combination training had a greater total duration of exercise and caloric use than when each type of training was undertaken alone (۱۳). Mild-intensity exercises such as tai chi and yoga have also been investigated for their potential to improve BG management, with mixed results (۱۴). Although tai chi may lead to short-term improvements in BG levels, effects from long-term training (i.e., 16 weeks) do not seem to last 72 h after the last session (۱۵). Some studies have shown lower overall BG levels with extended participation in such activities (۱۶), although others have not (۱۷). One study suggested that yoga's benefits on fasting BG, lipids, oxidative stress markers, and antioxidant status are at least equivalent to more conventional forms of PA (۱۸). However, a meta-analysis of yoga studies stated that the limitations characterizing most studies, such as small sample size and varying forms of yoga, preclude drawing firm conclusions about benefits to diabetes management (۱۹).

Evidence statement. A combination of aerobic and resistance exercise training may be more effective in improving BG control than either alone; however, more studies are needed to determine if total caloric expenditure, exercise duration, or exercise mode is responsible. ACSM evidence category B. Milder forms of exercise (e.g., tai chi, yoga) have shown mixed results. ACSM evidence category C.

Insulin resistance

Acute changes in muscular insulin resistance. Most benefits of PA on type 2 diabetes management and prevention are realized through acute and chronic improvements in insulin action (۲۰). The acute effects of a recent bout of exercise account for most of the improvements in insulin action, with most individuals experiencing a decrease in their BG levels during mild- and moderate-intensity exercise and for 2–72 h afterward (۱۹).

BG reductions are related to the duration and intensity of the exercise, preexercise control, and state of physical training (۱۸). Although previous PA of any intensity generally exerts its effects by enhancing uptake of BG for glycogen synthesis (40,83) and by stimulating fat oxidation and storage in muscle (۱۱), more prolonged or intense PA acutely enhances insulin action for longer periods (۱۲).

Acute improvements in insulin sensitivity in women with type 2 diabetes have been found for equivalent energy expenditures whether engaging in low-intensity or high-intensity walking (۱۳) but may be affected by age and training status (۱۴). For example, moderate- to heavy-intensity aerobic training undertaken three times a week for 6 months improved insulin action in both younger and older women but persisted only in the younger group for 72–120 h.

Acute changes in liver's ability to process glucose. Increases in liver fat content common in obesity and type 2 diabetes are strongly associated with reduced hepatic and peripheral insulin action. Enhanced whole-body insulin action after aerobic training seems to be related to gains in peripheral, not hepatic, insulin action (۱۴). Such training not resulting in overall weight loss may still reduce hepatic lipid content and alter fat partitioning and use in the liver (۱۵).

Evidence statement. PA can result in acute improvements in systemic insulin action lasting from 2 to 72 h. ACSM evidence category A.

PA AND PREVENTION AND CONTROL OF GDM

As the prevalence of diabetes continues to rise worldwide, it becomes increasingly important to identify high-risk populations and to implement strategies to delay or prevent diabetes onset. Women diagnosed with GDM are at substantially increased risk of developing type 2 diabetes; therefore, PA may be considered a tool to prevent both GDM and possibly type 2 diabetes at a later date (۱۰). Prepregnancy PA has been consistently associated with a reduced risk of GDM (۱۱). Studies during pregnancy are sparse, with only one case-control study (۱۲), one retrospective study (۱۳, and one study of a cohort of Hispanic women (۱۴) observing significant protective effects of PA, while others have not (۱۵).

Engaging in 30 min of moderate-intensity PA (e.g., brisk walking) during most days of the week (e.g., 2.5 h/week) has been adopted as a recommendation for pregnant women without medical or obstetrical complications (۱۶). However, few primary prevention studies have examined whether making a change in PA reduces risk of developing GDM. In 2006, a meta-analysis reviewed four RCTs on GDM in which pregnant women in their third trimester exercised on a cycle or arm ergometer or performed resistance training three times a week for 20–45 min compared with doing no specific program (۱۷). The women involved in exercise had better BG control, lower fasting and postprandial glucose concentrations, and improved cardiorespiratory fitness, although frequency of prescription of insulin to control BG did not differ from nonexercisers, and pregnancy outcomes were unchanged.

Evidence statement. Epidemiological studies suggest that higher levels of PA may reduce risk of developing GDM during pregnancy. ACSM evidence category C. RCTs suggest that moderate exercise may lower maternal BG levels in GDM. ACSM evidence category B.

Supervised training

Initial instruction and periodic supervision by a qualified exercise trainer is recommended for most persons with type 2 diabetes, particularly if they undertake resistance exercise training, to ensure optimal benefits to BG control, BP, lipids, and CV risk and to minimize injury risk (11).

Combined aerobic and resistance and other types of training

Inclusion of both aerobic and resistance exercise training is recommended. Combined training thrice weekly in individuals with type 2 diabetes may be of greater benefit to BG control than either aerobic or resistance exercise alone (۱۲). However, the total duration of exercise and caloric expenditure was greatest with combined training in all studies done to date (۱۳), and both types of training were undertaken together on the same days. No studies have yet reported whether daily, but alternating, training is more effective or the BG effect of isocaloric combinations of training. Milder forms of PA, such as yoga and tai chi, may benefit control of BG (۱۴), although their inclusion is not supported conclusively at this time.

Evidence statement. Medication dosage adjustments to prevent exercise-associated hypoglycemia may be required by individuals using insulin or certain insulin secretagogues. Most other medications prescribed for concomitant health problems do not affect exercise, with the exception of β-blockers, some diuretics, and statins. ACSM evidence category C. ADA C level recommendation.

CONCLUSIONS

Exercise plays a major role in the prevention and control of insulin resistance, prediabetes, GDM, type 2 diabetes, and diabetes-related health complications. Both aerobic and resistance training improve insulin action, at least acutely, and can assist with the management of BG levels, lipids, BP, CV risk, mortality, and QOL, but exercise

must be undertaken regularly to have continued benefits and likely include regular training of varying types. Most persons with type 2 diabetes can perform exercise safely as long as certain precautions are taken. The inclusion of an exercise program or other means of increasing overall PA is critical for optimal health in individuals with type 2 diabetes.

References in the text are referenced by numbers

References

1. Albright A, Franz M, Hornsby G, et al.: American College of Sports Medicine. Position Stand: exercise and type 2 diabetes. *Med Sci Sports Exerc* ۲۰۲۲;32(7):1345–60

2. Aljasem LI, Peyrot M, Wissow L, Rubin RR: The impact of barriers and self-efficacy on self-care behaviors in type 2 diabetes. *Diabetes Educ* ۲۰۲۳;27(3):393–404

3. American Diabetes Association Physical activity/exercise and diabetes. *Diabetes Care* ۲۰۲۱;27(90001):S58–S62

4. American Diabetes Association Diagnosis and classification of diabetes mellitus. *Diabetes Care* ۲۰۱۹;33(1 Suppl.):S62–9

5. American Diabetes Association Standards of medical care in diabetes ۲۰۱۸. *Diabetes Care* ۲۰۱۸;33(Suppl. 1):S11–S61

6. Araiza P, Hewes H, Gashetewa C, Vella CA, Burge MR: Efficacy of a pedometer-based physical activity program on parameters of diabetes control in type 2 diabetes mellitus. *Metabolism* ۲۰۱۹;55(10):1382–7

7. Armit CM, Brown WJ, Marshall AL, et al.: Randomized trial of three strategies to promote physical activity in general practice. *Prev Med* ۲۰۲۱;48(2):156–63

8. Bahr DB, Browning RC, Wyatt HR, Hill JO: Exploiting social networks to mitigate the obesity epidemic. *Obesity* ۲۰۲۲;17(4):723–8

9. Bajpeyi S, Tanner CJ, Slentz CA, et al.: Effect of exercise intensity and volume on persistence of insulin sensitivity during training cessation. *J Appl Physiol* ۲۰۱۹;106(4):1079–85

10. Balducci S, Iacobellis G, Parisi L, et al.: Exercise training can modify the natural history of diabetic peripheral neuropathy. *J Diabetes Complications* ۲۰۲۳;20(4):216–23

11. Balducci S, Zanuso S, Nicolucci A, et al.: Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in type 2 diabetic subjects. A randomized controlled trial: The Italian Diabetes and Exercise Study (IDES). *Arch Intern Med*. In press

12. Barnard RJ, Lattimore L, Holly RG, Cherny S, Pritikin N: Response of non–insulin-dependent diabetic patients to an intensive program of diet and exercise. *Diabetes Care* ۲۰۲۳;5(4):370–4

13. Barnard RJ, Ugianskis EJ, Martin DA: The effects of an intensive diet and exercise program on patients with non-insulin-dependent diabetes mellitus. *J Cardiopulm Rehabil* ۲۰۲۱;12:194–201

14. Baynard T, Franklin RM, Goulopoulou S, Carhart R, Jr, Kanaley JA: Effect of a single vs multiple bouts of exercise on glucose control in women with type 2 diabetes. *Metabolism* ۲۰۲۳;54(8):989–94

15. Bergman BC, Butterfield GE, Wolfel EE, Casazza GA, Lopaschuk GD, Brooks GA: Evaluation of exercise and training on muscle lipid metabolism. *Am J Physiol* ۲۰۱۸;276(1 Pt 1):E106–E17

16. Bernbaum M, Albert SG, Cohen JD: Exercise training in individuals with diabetic retinopathy and blindness. *Arch Phys Med Rehabil* ۲۰۲۱;70(8):605–11

17. Bernbaum M, Albert SG, Cohen JD, Drimmer A: Cardiovascular conditioning in individuals with diabetic retinopathy. *Diabetes Care* ۲۰۲۲;12(10):740–2

18. Black LE, Swan PD, Alvar BA: Effects of intensity and volume on insulin sensitivity during acute bouts of resistance training. *J Strength Cond Res* ۲۰۲۱;24(4):1109–16

19. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr, Gibbons LW, Macera CA: Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA* ۲۰۱۹;273(14):1093–8

20. Bo S, Ciccone G, Rosato R, et al.: Renal damage in patients with type 2 diabetes: a strong predictor of mortality. *Diabet Med* ۲۰۲۲;22(3):258–65

21. Boon H, Blaak EE, Saris WH, Keizer HA, Wagenmakers AJ, van Loon LJ: Substrate source utilisation in long-term diagnosed type 2 diabetes patients at rest and during exercise and subsequent recovery. *Diabetologia* ۲۰۲۰;50(1):103–12

22. Booth GL, Kapral MK, Fung K, Tu JV: Recent trends in cardiovascular complications among men and women with and without diabetes. *Diabetes Care* ۲۰۲۱;29(1):32–7

23. Borghouts LB, Wagenmakers AJ, Goyens PL, Keizer HA: Substrate utilization in non-obese Type II diabetic patients at rest and during exercise. *Clin Sci (Lond)* ۲۰۱۸;103(6):559–66

24. Boule' NG, Haddad E, Kenny GP, Wells GA, Sigal RJ: Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* ۲۰۲۲;286(10):1218–27

25. Boule' NG, Kenny GP, Haddad E, Wells GA, Sigal RJ: Meta- analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* ۲۰۲۱;46(8):1071–81

26. Boule' NG, Weisnagel SJ, Lakka TA, et al.: Effects of exercise training on glucose homeostasis: the HERITAGE family study. *Diabetes Care* ۲۰۲۳;28(1):108–14

27. Braden C: Nephropathy: advanced. In *The Health Professional's Guide to Diabetes and Exercise*. Alexandria (VA): American Diabetes Association; ۲۰۲۳. p. 177–80

28. Braun B, Sharoff C, Chipkin SR, Beaudoin F: Effects of insulin resistance on substrate utilization during exercise in overweight women. *J Appl Physiol* ۲۰۱۹;97(3):991–7

The changes of Complement system during exercise

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Abstract
This study was aimed at examining the impact of common types of physical efforts used to determine the aerobic and anaerobic performance of the participants on the complement system in their peripheral blood. Fifty-one physically active young males aged 16 years old (range 15–21 years) were divided into two age groups (younger, 15–17 years old and older, 18–21 years old) and performed two types of intensive efforts: aerobic (endurance; 20-m shuttle run test; Beep) and anaerobic (speed; repeated speed ability test; RSA). Venous blood samples were collected before and after each exercise (5 and 60 min) to profile the complement system components, namely the levels of C2, C3, C3a, iC3b, and C4. The endurance effort caused a decrease in the post-test C3 ($p < 0.001$ for both age groups) and increase in post-test C3a ($p < 0.001$ and $p < 0.01$ for the younger and older group, respectively), recovery iC3b ($p < 0.001$ and $p < 0.05$ for younger and older group, respectively), recovery C2 ($p < 0.01$ for both age groups), and post-test C4 ($p < 0.05$ and $p < 0.01$ for the younger and older group, respectively) levels, while the speed effort caused a decrease only in the post-test C2 ($p < 0.05$ for younger participants) and post-test C4 levels ($p < 0.001$ and $p < 0.01$ for the younger and older group, respectively) and an increase in the recovery C3a level ($p < 0.05$). Our study provides evidence that different types of physical effort promote different immune responses in physically active young men. Aerobic exercise induced the activation of an alternative pathway of the complement system, whilst the anaerobic effort had little influence. A better understanding of the post-exercise immune response provides a framework to prescribe physical activity to achieve different health outcomes.
Keywords: healthy men, inflammation, progressive effort, endurance test, speed test

Introduction

The complement system is part of the innate immune system, which provides a protective mechanism against pathogens in the absence of specific adaptive immunity [1]. It is a link between the innate and acquired immune systems [2]. Proteins of the complement system are key factors in providing host surveillance and protection through various functions, including targeting inflammatory reactions, phagocyte attraction by chemotaxis, the removal of immune complexes (the scavenging of necrotic and apoptotic debris), activating cells, participating in developmental and regenerative processes, and the modulation of humoral and cell-mediated immune responses [3,4]. The complement system consists of 50 serum and cell surface proteins, which constitute approximately 15% of the globulin fraction, giving more than 3 g/L of protein [۳].

Each feature of the complement system fulfills a specific role in immunity and is activated by different stimuli. Complement C3 plays a key role in a classic and alternative way of activation. A deficiency of C3 leads to impaired work of the immune system, which leads to increased susceptibility to infection [۴]. One of the stages of a well-functioning cascade is the cleavage of the C3 protein into the C3a and C3b components, which is achieved by the C3 convertase known as C4b2a, which also occurs in the lectin activation pathway. In the classical way, the C4 component is cleaved by C1s into two components: C4a and C4b. C4b binds to the cell membrane and connects to C2, which is cleaved into two further subunits, C2a and C2b. Due to fusion of the two C4b and C2a components, a heterodimer called classical-C3 convertase is formed with proteolytic properties, due to the serine protease activity of the C2a element [۵]. The alternative pathway dominates quantitatively over the classical one [۶]. An overactivation of complement activity or incorrect localization can be harmful to the body, leading to serious diseases, including multiple sclerosis, Alzheimer's disease, asthma, sepsis, or hyperacute organ rejection [۷].

One factor influencing the activation of the complement system is physical effort, which is a natural stimulus affecting the defense and immune mechanisms in both specific and cellular and humoral immunity. This interplay is complex, as regular exercise of moderate intensity can have a stimulating effect on the immune system. Conversely, repeated high-intensity exercise (with insufficient recovery), as performed regularly by athletes, can suppress the immune system and increase susceptibility to infections [۸]. Intense physical effort can have strong metabolic effects, increasing oxidative stress, the release of heat shock proteins, catecholamines, cortisol, and insulin-like growth factor 1 (IGF-1) [۹], all of which might contribute to immune stimulation or suppression, depending on other co-factors (e.g., age, fitness level).

The role of the complement system in primary immunodeficiencies, or in defining disease activity in systemic autoimmunity, is well described [۱۰]. However, little research has investigated this system in relation to the acute post-exercise immune response. Knowing that the complement also plays an important role in adaptive immunity involving T and B cells [۱۱], but is also involved in tumor growth [۱۲] and human pathological states such as an atypical hemolytic uremic syndrome, age-related macular degeneration [۱۳], and especially in tissue regeneration [7], it seems that this system must be involved in post-effort immune response. In fact, there are works evidencing its involvement in post-effort immunity [۱۴]. Combining knowledge of T cells in post-effort immune response [۱۵] and the contribution of the complement system to the activation and differentiation of T cells, as well as maintaining immunological memory, could bridge the gap between immunomodulation and immunodepression following an acute bout of intensive exercise. This itself provides a framework to better explain the “open window theory” [۱۶].

The main aim of this study was to examine the impact of two forms of exercise that differ in physical effort on the complement system and post-exercise immune response in young healthy males. To achieve this, the participants performed two bouts of high-intensity exercise (endurance/aerobic and anaerobic) with blood levels of C2, C3, C3a, iC3b, and C4 compared within and between exercise treatments.

Materials and Methods

Participants

Fifty-one young physically active males aged 16 years old (range 15–21 years) were recruited and divided according to their age into two groups: younger (15–17 years old) and older (18–21 years old). The participants reported at least 100 min of physical activity per day, with a median training volume equal to 115 min and a median VO2max equal to 54.62 mL/kg/min. For study inclusion, the following criteria were employed: no history of any metabolic syndrome or cardiovascular diseases, and no medical history of endocrine or immune disorders. All participants were non-smokers and refrained from taking any medications or supplements (except for protein supplements as reported by some of the participants) before the study commenced. The participants and their parents or guardians, when appropriate, were fully informed of any risks and benefits of the experimental procedures before giving their written consent to participate. This study was approved by the Local Ethics Committee at the Regional Medical Chamber in Szczecin (no. 05/KB/VII/2019) in accordance with the Helsinki Declaration.

Experimental Protocols

Prior to exercise testing, participants’ body mass, body mass index (BMI), basal metabolic rate (BMR), percentage of fat (FAT), fat mass (FAT MASS), and total body water (TBW) were determined using a Body Composition Analyzer (Tanita BC-418MA, Tokyo, Japan). All participants performed two types of physical efforts: endurance and speed-based. A maximal multistage 20-m shuttle run test (Beep test) [31,32] was performed for endurance testing. For speed effort, a repeated speed ability test (RSA test) [۱۷] was conducted.

All participants performed both tests (aerobic—Beep test—and anaerobic—RSA test) that started with a standardized warm-up consisting of running at a speed of 5 km/h for 10 min. There was 7 days between each test. The Beep test (maximal multistage 20-m shuttle run test) was performed indoors (athletics hall) at a temperature of 20–23 °C, two hours after light breakfast. Following standard protocols [۱۸], the participants covered 20-m sections in a shuttle format (running back and forth) over several levels of increasing intensity. Each level lasted 60 s in a progressively increasing (by 0.5 km/h) pace, as determined by an audible cue with correspondingly shorter intervals. The test started at a speed of 8.5 km/h. Participants were required to touch their foot (at the 20-

m mark) before the signal sounded. It was acceptable to make up any delay in the next 20-m distance. Each participant was asked to stop after two consecutive failed attempts.
Maximum oxygen uptake (VO2max) was calculated after the Beep test was calculated according to Flouris et al. formula [۱۹] as follows:

$$\mathrm{VO_2\,max}\ \ (\mathrm{mL/min/kg}) = (\mathrm{max.\ \ attained\ \ speed}\ \ (\mathrm{km/h})\ \times 6.65 - 35.8) \times 0.95 + 0.182.$$

The RSA test was conducted in the morning on a 400 m-long athletics track with an ambient temperature of 20–23 °C [33,34], two hours after light breakfast. This test consisted of 10 × 15 m sprints starting every 30 s, with a slow walk (active recovery) between repetitions. Participants were instructed to assume the ready position 5 s before starting the next sprint.

Blood Testing

During each test of physical effort, blood samples were collected at three time points from the cubital vein: before testing (pre-test), no longer than 5 min after exercise (post-test), and about 1 h later, at the end of the lactate recovery period [۲۰]. At each time point, venous blood samples were collected in a 7.5 mL S-Monovette tube for serum separation (SARSTEDT AG & Co., Nümbrecht, Germany). All analyses were performed immediately following blood collection and serum separation.
The biochemical tests were carried out using an Automatic Clinical Chemistry Analyzer (BM-100, BioMaxima S.A., Lublin, Poland). The blood serum component was tested for the concentration of the following analytes. Albumin, total protein (TP), and C-reactive protein (CRP) concentrations were determined using a colorimetric assay kit (BioMaxima S.A., Lublin, Poland) according to manufacturer's protocol. Lactic acid (LA) concentration was determined with the use of a colorimetric assay kit (PZ Cormay S.A., Łomianki, Poland) according to the manufacturer's protocol. C3 and C4 complement components' concentrations were determined using a colorimetric assay kit (QuimicaClinicaAplicada S.A., Amposta, Spain) according to the manufacturer's protocol. All the analyses were verified using a multiparametric control serum and a control serum of a normal level (BioNorm) and a high level (BioPath) (BioMaxima S.A., Lublin, Poland).
Enzyme-linked immunosorbent assay (ELISA) kits were used to determine plasma levels of C2 (Cloud-Clone Corp., Katy, TX, USA), and C3a and iC3b (Quidel Corporation, Athens, OH, USA) according to the manufacturers' protocols. All ELISA tests were performed using a high-throughput microplate reader Synergy H1 (BioTek Instruments, Inc., Winooski, VT, USA).
To compensate for the changes in analyzed blood parameters induced by the exercise test, plasma volume loss (ΔPV) and subsequent correction of those parameters for ΔPV were calculated according to Dill and Costill, and Alis et al.'s equations [39] as follows:

$$\Delta\mathrm{PV}\,(\%) = 100 \times \left(\frac{\mathrm{Hb_{pre}}}{\mathrm{Hb_{post}}} \times \frac{100 - \mathrm{Htc_{post}}}{100 - \mathrm{Htc_{pre}}} - 1\right)$$

where Hbpre—hemoglobin pre-test (g/dL), Hbpost—hemoglobin post-test (or in recovery) (g/dL), Htcpre—hematocrit pre-test (%), Htcpost—hematocrit post-test (or in recovery) (%).

The formula for the correction of blood parameters was as follows:

$$[\mathrm{Corrected\ parameter\ concentration}] = [\mathrm{Uncorrected\ parameter\ concentration}] \times \left(1 + \frac{\Delta\mathrm{PV}\,(\%)}{100}\right).$$

Statistical Analyses

All data are presented as median values (interquartile range), except for age, which is presented as median (minimum–maximum range). The normality of the data was assessed using Shapiro–Wilk test. As a result of non-normal data distribution, non-parametric statistical tests were used. The significance level of differences observed between analyzed time points (pre-exercise versus post-exercise versus recovery) was calculated using Friedman's analysis of variance for repeated measures followed by post-hoc Dunn's test with Bonferroni correction. The significance level of differences in analyzed parameters between the Beep and RSA tests or between younger and older groups was calculated using the Mann–Whitney U-test. Each time, $p < 0.05$ was considered as a significant difference. Statistical analysis was performed using Statistica version 13 software (2017; TIBCO Software Inc., Palo Alto, CA, USA).

Discussion

The role of physical effort as a factor leading to broadly understood changes in the immune system is widely discussed in the literature [۲۱]. Its influence on the immune system gives heterogeneous biological effects, underlying many different dependencies. On one hand, it is assumed that high-intensity physical effort weakens the organism's immunity [۲۲] and their extremely prolonged effect can lead to immunosuppression [۲۳]. On the other hand, regular, moderate-intensity physical activity stimulates the formation and increase in immunity [۲۴]. One of the symptoms of short-term physical exercise is leukocytosis, resulting from the redistribution of tissue cell components into the blood [۲۵]. Disturbances in the functioning of cellular components, such as T lymphocytes or natural killer (NK) cells, are associated with the frequency of high-intensity short-term exercise. This leads to the shift of balance toward an initiation of inflammation, including the secretion of pro-inflammatory and regulatory (anti-inflammatory and multifunctional) signaling factors, causing a violent and aggressive inflammatory response that resembles the immune response to primary antigens [۲۶]. Regular, moderate-intensity exercise is one of the most important factors delaying the senescence of the immune system [۲۷]. Prolonged exercise can have a pleiotropic effect on the immune system. The intensity of effort depends to a large extent on how it will affect the immune system. Intensive physical effort is associated with the activation of cellular components and their rapid redistribution [۲۸]. It can be assumed that short-term physical exertion with an intensity <60% VO2max does not lead to the mobilization of the immune system, but rather, it has modulating effect [9,49] as opposed to high (>70% VO2max) and very high (>90% VO2max) intensity that may contribute to lowering the athletes' immunity [۲۹].

The significant decrease in C4 and C3 proteins is a common observation in both athletes and non-athletes [۳۰]. Interestingly, a significant decrease in C4 level after the RSA test was not in line with C3 activation. No significant changes in C3 level, and its activated forms C3a and iC3b, were demonstrated with RSA testing among older participants at any time after exercise. This may suggest that the signal form C4 protein was not strong enough to activate the complement system. Karacabey et al. [۳۱] found that both aerobic exercise on a treadmill for 30 min and a Wingate (anaerobic) test for 30 s caused a significant decrease in C4 and C3 proteins. Interestingly, only the C3 level in Karacabey et al.'s was comparable with the data for the older group performing aerobic exercise (e.g., 178±6 and 104 ± 3 mg/dL for pre-exercise and post-exercise, respectively in Karacabey et al. versus 198±17 and 99 ± 32 mg/dL in our study, when providing mean ± SD) [23]. However, it must be emphasized that our data are provided as corrected for plasma volume loss that was not provided by Karacabey et al. [23]. The exercises, although being aerobic and anaerobic, were also different between their study and ours. Mashiko et al. [22] reported a similar post-game observation in rugby players. In contrast to our findings for the Beep test, the levels of C3 and C4 after short-term maximal exercise rapidly returned to baseline values [40,54], but they stayed slightly lowered after an ultramarathon [۲۴]. When analyzing the runners, Smith et al. reported that short-term aerobic exercise triggers the activation of C3 and C4 complement components and subsequent increase in C3a and C4a [۲۵]. They suggest that regularly engaged aerobic exercise may cause activation of the classical pathway of complement activation as well as a selective downregulation of C3 synthesis [۲۶]. It is clear that C3 and C4 are proteins that depend on the time of effort application. Berk et al. [۲۷] showed that the C3 basal values are lowered more by long-lasting physical effort than an intermittent one. They also indicate that C4 values are higher in

intermittent exercises than in running [۲۷]. However, they did not examine the activated forms of those proteins (e.g., C3a, C4a). Navarro Sanz et al. observed a significant increase in C3 and C4 levels after intermittent bouts of an 800 m run at a maximal speed with 30 s of recovery in between [۲۸]. Semple et al. analyzed complement components in the cyclists taking part in Vuelta a España [۲۹]. However, their studies were conducted across wide time ranges, since they determined these proteins in two points after an accumulated distance of about 1200 km. They observed no changes in C3 and an increase in C4 but only on the 11th day and not on the 21st day of the race [۳۰]. On the other hand, an 8 mile-long (12.8 km) training run at 70–75% VO2max did not influence the C3 and C4 level both 10 min and 24 h after the exercise [۳۱]. Nieman et al. [۳۲] studied marathon runners and their sedentary counterparts performing graded exercise on a mechanical treadmill. They observed a post-effort increase in C3 and C4 complement components in both studied groups [۳۳]. A similar trend was observed in the case of C4 in older participants performing aerobic exercise in our study. On the other hand, they speculate that these changes were caused by plasma volume reduction [۳۴]. It is known that graded exercise on mechanical treadmill performed by Nieman et al.'s participants does not reflect the physiological demands of a maximal multistage 20-m shuttle run test (Beep test). However, both tests are examples of aerobic exercise. A significant increase in post-exercise C4 level was observed by Cordova et al. after an incremental maximal cycling test using a mechanically braked cycle ergometer [۳۵]. It is in line with our observation in regard to older participants performing aerobic exercise (Beep test).

A significant increase in iC3b component concentration, being liberated during the conversion of opsonin C3b [۲۵], during lactate recovery (versus pre-test values) regarding the age of participants suggests that aerobic exercise using the 20-m shuttle (Beep) test activates C3 convertases. On the other hand, the iC3b fragment, although bound to the cell surface yet unable to form convertase, plays an important role in signal transduction. It binds to complement receptors on immune cells; therefore, it is an important component of the defense system and homeostasis [4]. From this viewpoint, it seems that the endurance effort (Beep test) exerts an immunomodulatory effect among young physically active men. This observation is in line with our previous study describing the impact of endurance-type exercise on T cells in the peripheral blood of young soccer players [۲۶].

The most probable explanation of complement system activity, in the post-effort immune response, is the restoration of homeostasis after high physical effort, which signals cell death pathways in the peripheral cells, as seen in elite athletes [26,۲۰] and firefighters [۱۹]. In turn, this enables the damaged cells to be opsonized before being phagocytized by leukocytes [۱۸]. Artero et al. [۲۲] examined the correlation between muscular fitness and inflammatory parameters, including C3 and C4 complement components, among adolescents. One of the parameters defining health-related fitness was a 20-m shuttle run test (Beep test). They concluded that C3 and C4 levels significantly inversely correlate with the Beep test results [۲۳].

Knowledge of the complement system, in terms of its response trajectory to acute high-intensity exercise, can provide insight regarding mechanisms of exercise immunology and potentially provides a stronger molecular basis for the prevention of cardiovascular diseases (CVD). According to Blankenberg et al. [۲۴], the recruitment of inflammatory cells takes place in CVD impairment and thus, they are candidate particles of higher importance in predicting future CVD events than current risk factors including tobacco smoking, physical inactivity, unhealthy diet, and alcohol abuse. It is known that all-cause and especially CVD mortality negatively correlate with both cardiorespiratory and muscular fitness levels in adults [۲۵]. The research on CRP as the marker of inflammatory status regarding physical activity confirms the anti-inflammatory effects of this protein [۲۰]. In another work [۲۶], Phillips et al. found that C3 concentrations were positively associated with increasing sedentary behavior and negatively associated with increasing moderate to vigorous physical activity. The level of inflammation markers, calculated as a C3/C4 level ratio [۲۱] in our study, indicated that after the Beep test, there was a decreasing C3/C4 ratio (pre-test value 11.8; post-test: 8.4 and recovery: 9.2 in the younger group and 57.9, 11.6, and 11.8 in the older group, respectively), while after the RSA test, the C3/C4 results differed at corresponding

time points (16.0, 25.6, and 21.0 in the case of younger participants and 8.9, 13.9, and 9.0 in the older group, respectively). These results are congruent with the CRP fluctuations observed herein. Delgado-Alfonso et al. [۲۷] also found significant differences in C3 and other inflammatory biomarkers between adolescents who have different physical fitness levels.

Conclusions

Literature data describing the impact of physical effort on complement system activation are not numerous, and the results presented in them are not consistent. Our study attempted to examine the impact of two types of high-intensity physical exercise, generally described as being aerobic and anaerobic in nature on participants' complement systems. We present evidence that each type of effort caused different immune responses in physically active young men regarding the complement system. Knowing that the complement system takes part in the activation and differentiation of T cells, as well as maintaining immunological memory and that different T cell subsets are altered in post-effort immune response depending of the type of exercise [۲۸], it could lead to the speculation that aerobic and anaerobic exercise may have different types of impact on the post-effort susceptibility to upper respiratory illness, which is described as "open window theory". It may be explained by different molecular mechanism with the participation of the complement system.

Regarding the limitations of the study, it was performed on a limited number of participants and only males. One of the reasons was to avoid entering another variable, namely the possible influence of hormone changes during women's menstrual cycles. However, adding a group of women would significantly enrich future studies. The study group consisted of well-trained participants to ensure group homogeneity regarding participants' fitness level, especially VO2max values. However, including less trained or even sedentary participants would give a broader perspective of the influence of aerobic and anaerobic effort on the complement system. Moreover, the analysis of the anti-inflammatory system and cortisol level would give some more perspective on the crosstalk between complement components, as well as inflammatory proteins and the anti-inflammatory response of athletes to a given exercise bout.

Another limitation is the lack of standardized diet for the participants. It was intended so as to not provide any additional stress related to changing the diet, and the participants were asked to keep their daily routine regarding the diet. However, providing a dietician-consulted diet before and during more extensive research would enrich the study .

References are numbered in the text

References

1. Medzhitov R., Janeway C.A., Jr. An ancient system of host defense. *Curr. Opin. Immunol.* ۲۰۲۲;10:12–15. doi: 10.1016/S0952-7915(98)80024-1.

2. Carroll M.C. A protective role for innate immunity in autoimmune disease. *Clin. Immunol.* ۲۰۲۱;95:S30–S38. doi: 10.1006/clim.1999.4813.

3. Schifferli J.A., Ng Y.C., Peters D.K. The role of complement and its receptor in the elimination of immune complexes. *N. Engl. J. Med.* ۲۰۲۳;315:488–495. doi: 10.1056/NEJM198608213150805.

4. Ricklin D., Hajishengallis G., Yang K., Lambris J.D. Complement: A key system for immune surveillance and homeostasis. *Nat. Immunol.* ۲۰۲۲;11:785–797. doi: 10.1038/ni.1923.

5. Walport M.J. Complement. First of two parts. *N. Engl. J. Med.* ۲۰۲۰;344:1058–1066. doi: 10.1056/NEJM200104053441406.

6. Matsuyama W., Nakagawa M., Takashima H., Muranaga F., Sano Y., Osame M. Molecular analysis of hereditary deficiency of the third component of complement (C3) in two sisters. *Intern. Med.* ۲۰۱۹;40:1254–1258. doi: 10.2169/internalmedicine.40.1254.

7. Sarma J.V., Ward P.A. The complement system. *Cell Tissue Res.* 2011;343:227–235. doi: 10.1007/s00441-010-1034-0.

8. Prohászka Z., Kirschfink M., Frazer-Abel A. Complement analysis in the era of targeted therapeutics. *Mol. Immunol.* ۲۰۲۱;102:84–88. doi: 10.1016/j.molimm.2018.06.001.

9. Nieman D.C. Exercise immunology: Practical applications. *Int. J. Sports Med.* ۲۰۲۳;18(Suppl. 1):S91–S100. doi: 10.1055/s-2007-972705.

10. Peake J.M., Neubauer O., Della Gatta P.A., Nosaka K. Muscle damage and inflammation during recovery from exercise. *J. Appl. Physiol.* ۲۰۲۲;122:559–570. doi: 10.1152/japplphysiol.00971.2016.

11. Peake J.M., Neubauer O., Walsh N.P., Simpson R.J. Recovery of the immune system after exercise. *J. Appl. Physiol.* ۲۰۲۱;122:1077–1087. doi: 10.1152/japplphysiol.00622.2016.

12. Pedersen B.K., Hoffman-Goetz L. Exercise and the immune system: Regulation, integration, and adaptation. *Physiol. Rev.* ۲۰۲۳;80:1055–1081. doi: 10.1152/physrev.۲۰۲۳.80.3.1055.

13. Liu X., Zeng Z., Zhao L., Xiao W., Chen P. Changes in inflammatory and oxidative stress factors and the protein synthesis pathway in injured skeletal muscle after contusion. *Exp. Ther. Med.* ۲۰۲۰;15:2196–2202. doi: 10.3892/etm.۲۰۲۰.5625.

14. Skattum L., van Deuren M., van der Poll T., Truedsson L. Complement deficiency states and associated infections. *Mol. Immunol.* ۲۰۱۶;48:1643–1655. doi: 10.1016/j.molimm.۲۰۲۲.05.001.

15. De Cordoba S.R., Tortajada A., Harris C.L., Morgan B.P. Complement dysregulation and disease: From genes and proteins to diagnostics and drugs. *Immunobiology.* ۲۰۱۹;217:1034–1046. doi: 10.1016/j.imbio.۲۰۱۹.07.021.

16. Holers V.M. Complement and its receptors: New insights into human disease. *Annu. Rev. Immunol.* ۲۰۱۸;32:433–459. doi: 10.1146/annurev-immunol-032713-120154.

17. Dunkelberger J.R., Song W.C. Complement and its role in innate and adaptive immune responses. *Cell Res.* ۲۰۲۱;20:34–50. doi: 10.1038/cr.2009.139.

18. Molina H., Holers V.M., Li B., Fung Y., Mariathasan S., Goellner J., Strauss-Schoenberger J., Karr R.W., Chaplin D.D. Markedly impaired humoral immune response in mice deficient in complement receptors 1 and 2. *Proc. Natl. Acad. Sci. USA.* ۲۰۲۲;93:3357–3361. doi: 10.1073/pnas.93.8.3357.

19. Qu H., Ricklin D., Lambris J.D. Recent developments in low molecular weight complement inhibitors. *Mol. Immunol.* ۲۰۱۸;47:185–195. doi: 10.1016/j.molimm.۲۰۱۶.08.032.

20. Wagner E., Frank M.M. Therapeutic potential of complement modulation. *Nat. Rev. Drug Discov.* ۲۰۲۱;9:43–56. doi: 10.1038/nrd3011.

21. Karacabey K., Saygin O., Ozmerdivenli R., Zorba E., Godekmerdan A., Bulut V. The effects of exercise on the immune system and stress hormones in sportswomen. *Neuroendocrinol. Lett.* ۲۰۲۲;26:361–366.

22. Mashiko T., Umeda T., Nakaji S., Sugawara K. Position related analysis of the appearance of and relationship between post-match physical and mental fatigue in university rugby football players. *Br. J. Sports Med.* ۲۰۱۹;38:617–621. doi: 10.1136/bjsm.۲۰۲۰.007690.

23. Karacabey K., Peker İ., Saygın Ö., Cıloglu F., Ozmerdivenli R., Bulut V. Effects of acute aerobic and anaerobic exercise on humoral immune factors in elite athletes. *Biotechnol. Biotechnol. Eq.* ۲۰۱۸;19:175–180. doi: 10.1080/13102818.۲۰۱۸.10817177.

24. Kostrzewa-Nowak D., Nowak R. Analysis of selected T cell subsets in peripheral blood after exhaustive effort among elite soccer players. *Biochem. Med. (Zagreb)* 2018;28:030707. doi: 10.11613/BM.2018.030707. [

25. Kostrzewa-Nowak D., Buryta R., Nowak R. Comparison of selected $CD45^{+}$ cell subsets' response and cytokine levels on exhaustive effort among soccer players. *J. Med. Biochem.* 2019;38:256–267. doi: 10.2478/jomb-2018-0029.

26. Nowak R., Kostrzewa-Nowak D. Assessment of selected exercise-induced $CD3^{+}$ cell subsets and cell death parameters among soccer players. *J. Med. Biochem.* 2019;38:437–444. doi: 10.2478/jomb-2019-0013.

27. Kostrzewa-Nowak D., Nowak R. T helper cell-related changes in peripheral blood induced by progressive effort among soccer players. *PLoS ONE.* 2020;15:e0227993. doi: 10.1371/journal.pone.0227993.

28. Kostrzewa-Nowak D., Ciechanowicz A., Clark Jeremy S.C., Nowak R. Damage-associated molecular patterns and Th-cell-related cytokines released after progressive effort. *J. Clin. Med.* 2020;9:876. doi: 10.3390/jcm9030876.

29. Spielmann G., McFarlin B.K., O'Connor D.P., Smith P.J., Pircher H., Simpson R.J. Aerobic fitness is associated with lower proportions of senescent blood T-cells in man. *Brain Behav. Immun.* ۲۰۱۹;25:1521–1529. doi: 10.1016/j.bbi.۲۰۱۹.07.226.

30. Kakanis M.W., Peake J., Brenu E.W., Simmonds M., Gray B., Hooper S.L., Marshall-Gradisnik S.M. The open window of susceptibility to infection after acute exercise in healthy young male elite athletes. *Exerc. Immunol. Rev.* ۲۰۲۰;16:119–137. doi: 10.1016/j.jsams.۲۰۲۰.10.642.

31. Léger L.A., Lambert J. A maximal multistage 20-m shuttle run test to predict VO_2 max. *Eur. J. Appl. Physiol. Occup. Physiol.* ۲۰۲۱;49:1–12. doi: 10.1007/BF00428958.

32. Metsios G.S., Flouris A.D., Koutedakis Y., Nevill A. Criterion-related validity and test-retest reliability of the 20 m square shuttle test. *J. Sci. Med. Sport.* ۲۰۲۰;11:214–217. doi: 10.1016/j.jsams.۲۰۲۰.12.120.

33. Chaouachi A., Manzi V., Wong D.P., Chaalali A., Laurencelle L., Chamari K., Castagna C. Intermittent endurance and repeated sprint ability in soccer players. *J. Strength Cond. Res.* ۲۰۱۹;24:2663–2669. doi: 10.1519/JSC.0b013e3181e347f4.

34. Ramos-Campo D.J., Martínez-Guardado I., Olcina G., Marín-Pagán C., Martínez-Noguera F.J., Carlos-Vivas J., Alcaraz P.E., Rubio J.Á. Effect of high-intensity resistance circuit-based training in hypoxia on aerobic performance and repeat sprint ability. *Scand. J. Med. Sci. Sports.* 2018;28:2135–2143. doi: 10.1111/sms.13223.

35. Flouris A.D., Metsios G.S., Koutedakis Y. Enhancing the efficacy of the 20 m multistage shuttle run test. *Br. J. Sports Med.* ۲۰۲۱;39:166–170. doi: 10.1136/bjsm.۲۰۲۱.012500.

the changes of immunoglobulin during exercise

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Abstract
The aim of this paper is to describe the structure, production and function of secretory immunoglobulin A (sIgA) as well as changes of its concentration caused by exercise of various intensity and duration. Immunoglobulin A is the main class of antibodies present in the body secreted fluids such as saliva, tears or mucus from the intestines. It is generally recognized that IgA, due to its dominance in the immune system of mucous membranes, is the first line of defence against harmful environmental factors. The secretion and composition of saliva depends on the activity of the sympathetic and parasympathetic nervous systems. Physical activity, stimulating the autonomous nervous system, may reduce the amount of saliva and/or inhibit its secretion. The relationship between physical activity and the suppression of the immune system is not fully understood, but it is known that moderate intensity exercise can improve immune defences, while extreme effort can reduce them by creating an increased risk of upper respiratory tract inflammation (URTI). In athletes, the lowest risk of upper tract infection was connected with the case of moderate intensity exercise. It is now believed that the relationship between exercise volume and the risk of URTI has the shape of the letter "J". This means that both too little and too much physical activity may increase the risk of upper respiratory tract infection. Training optimization and correct balance between exercise and rest periods may reduce the risk of adverse changes in the immune system and decrease the frequency of URTI.
Keywords: immunoglobulins, secretory IgA, exercise

Introduction

Immunoglobulins are a heterogeneous group of proteins of the immune system. All immunoglobulins are composed of four polypeptide chains: two light (L) and two heavy (H), joined by disulfide bonds in macromolecular compound. Numerous studies of the molecules of the immunoglobulin distinguished the variable part (Fab), responsible for recognition and binding of epitopes, and the constant part (Fc). The structural differences within the variable part determine the antigenic specificity of immunoglobulins, while the structural differences observed in the constant part determine their effector functions, associated with the activation of the complement [1].

Based on structural differences in constants heavy chains, immunoglobulins have been divided into five classes (isotypes): IgG, IgA, IgM, IgD, and IgE, in which there are different types of the heavy chain: γ, α, μ, d, and ε, respectively. The result is that individual proteins differ in physicochemical and biological properties. The IgG and IgA classes of immunoglobulins are divided into subclasses: IgG1, IgG2, IgG3, IgG4, and IgA2, IgA1, respectively.

Immunoglobulin A is the main class of antibodies present in the body secreted fluids such as saliva, tears or mucus from the intestines. The meaning of IgA in serum is still unclear. It was postulated that this immunoglobulin performs a complementary role in the neutralization of the pathogens, which defeated the mucosal barrier, as well as macrophage activation, and removal of immune complexes formed with the participation of this isotype [2].

The immunoglobulin M contains a μ heavy chain, which appears together with the peptide J, responsible for the initiation of polymerization to the form of pentamer IgM. Due to the large number of antigen binding sites, the IgM molecule binds very strongly with each pathogen. After binding to the antigen, the Fc portion activates the complement system, leading to the destruction of the pathogen. The immunoglobulin M is the class of antibodies, which appears as the first line of defence in the response to an antigen.

The immunoglobulin D is present on the surface of mature B cells and, in trace amounts, in various body fluids. The function of this class, however, is not entirely clear. The immunoglobulin E, after antigen binding, stimulates the mast cells, which in turn activate eosinophils involved in the elimination of parasites.
In recent years, much research was aimed at explaining how the exercise affects the immune system. It is known that stress induced by sport training causes changes in the lymphatic system, but so far it is not sufficiently clear what other changes occur in the human body.

The human lymphatic system keeps specific biological balance, thereby allowing the body's adaptation to the environment. It also has the ability to neutralize damaging agents stressors. In a healthy subject, the properly functioning immune system comprises lymphatic cells (humoral immunoglobulins) and cells outside the lymph system (components of complement). The correct functioning of these elements determines the proper physiological state of the immune system, and thus a healthy organism.

Structure of IgA

The history of the discovery of IgA goes back to the 1950's, when Slater et al. [3], during the study of globulins, discovered that one of the serum protein fractions demonstrates a particular characteristic during electrophoresis and has specific antigenic properties. In 1955, all these observations led to revealing the presence of a new, previously unknown, class of immunoglobulins.
It is generally recognized that IgA, due to its dominance in the immune system of mucous membranes, is the first line of defence against harmful environmental factors. It is believed that the concentration of secretory IgA (sIgA) varies depending on the physiological state and physical activity.
In each IgA molecule, there is an α chain, which can distinguish a variable part, lying in the N-terminal segment, and a fixed part, comprising the C-terminal segment, organized into domains: CH1, CH2, CH3 as well as the hinge region, and the 18-amino acid peptide, called the tail section. This section is capable of covalent binding to the J chain and the formation of polymers. The immunoglobulin A is secreted in two forms: as a monomer and a dimer. In serum, IgA exists mainly in the monomeric form.
The secretory immunoglobulin A is synthesized locally by subepithelial plasma cells pIgA. After creating a complex with pIgR (transmembrane segment), it undergoes endocytosis and is transported in endosomes to the luminar side of epithelium [50, 56].
Until recently, it was thought that monomeric immunoglobulin A takes the shape of the letter Y [4], but Bohem et al. [5] presented a different structure of this immunoglobulin. They found that the area between the two antigen-binding elements is located at the ends of the Fab arms and is much higher in IgA1 (23 nm) than in IgG (13-16 nm).
The immunoglobulin A class is characterized by considerable heterogeneity. There are two subclasses: IgA1 and IgA2, which differ in structure and distribution, and occur in different proportions in tissues and organs of the human body [5]. The existence of particles IgA2m(1) and IgA2m(2) [6] was established in the 1970's. Subsequent studies confirmed the existence of a third variant isotype: IgA2(n) [9]. Each of these forms occurs in varying degrees of polymerization.
The difference between the subclasses of IgA applies only to 22 amino acids within the hinge region [7]. In the IgA2 molecule, there is a 13-amino acid deletion in this region, however the hinge region of the molecule IgA1 contains from three to five linked oligosaccharide domains, which are not found in IgA2. The immunoglobulin A1 is characterized by the presence of two oligosaccharide chains, connected by N-glycosidic bond in the domains: CH2 (Asn263) and CH3 (Asn459) of the constant α chain. The IgA2 contains two additional oligosaccharide chains, connected by the N-glycosidic bond to asparagine residues of CH1 (Asn166) and CH2 (Asn337) domains. The IgA2m(2) and IgA2(n) are the fifth N-linked region of CH1 domain (Asn211) [8]. The increased number of linked oligosaccharide chains, in particular mannose residues, acts as a soluble receptor of bacterial type 1 fimbriae, weakening bacterial adhesion to epithelial cells [9].
The section linking monomer subunits J chain is a 137 amino acid peptide containing eight cysteine residues, which forms disulfide bridges with the tail section. This chain is involved in regulating the degree of polymerization of locally synthesized immunoglobulins, as well as their translocation through the epithelium onto the mucosal surface. The transcription of the gene encoding the J chain is located on chromosome 4. The main places of synthesis of this peptide are lymphoblasts and plasma cells found in lymphoid tissue, associated with the mucous membranes [10].
The secretory fragment (SC) is a glycoprotein composed of five domains (D1-D5), stabilized with one or two disulfide bridges. This part is synthesized by the epithelial cells of the digestive, respiratory, and genitourinary systems. The SC fragment, located in the cell membrane of the enterocyte, is the extracellular part of the receptor

for polymeric forms of immunoglobulin, and may be a component of the secretory IgA and IgM immunoglobulins or it may exist as a free form [11].

The unique ability of the immunoglobulin A is polymerization, determined by the presence of the tail section, located in the area of C -terminal. It is known that the polymerization also requires the J chain, which probably causes conformational changes. Yoo et al. [12] observed that mutation of cysteine residues in the positions 15 and/or 79 in the J chain prevents the formation of IgA dimers. Another factor enabling the polymerization is the presence of enzymes catalyzing the reactions of forming disulfide bridges and covalent interactions in the tail sections as well as non-covalent interactions between the CH2 and CH3 domains of the monomers.

Production of immunoglobulin A

The immunoglobulin A (IgA) is the major glycoprotein described in recent years. It is produced by mature B cells [13] in the blood and is secreted into bodily fluids [14], such as saliva, tears, as well as nasopharyngeal, bronchial, intestinal and urogenital secretions [15], and it penetrates freely through the mucous membranes.

The human body produces two types of immunoglobulin A: serum and secretory. Their total daily production is 66 mg per kg body weight [16]. The immune response of the IgA is triggered by many pathogens and is mainly induced locally in the mucous membranes.

The IgA secretion into saliva is stimulated by various factors such as stress or physical activity [14]. The secretion and composition of saliva depends on the activity of the sympathetic and parasympathetic nervous systems. The physical activity, stimulating the autonomous nervous system, may reduce the amount of saliva and/or inhibit its secretion [17].

The use of monoclonal and polyclonal antibodies against the IgA subtype IgA1 makes it possible to estimate the level of IgA1 and IgA2. The highest concentrations of immunoglobulins IgA1 was found in the nasal mucosa, where it represents 95%, and the highest concentration of IgA2 was observed in the colon (62%), compared to the total concentration of both subtypes of IgA [18].

In addition to changes in the amount of saliva, physical activity may also induce changes in concentration of some of its components, such as immunoglobulins and α-amylase [4]. Numerous studies have demonstrated an increased level of the total protein in saliva after strenuous exercise [19], explained by the higher activity of β-adrenergic receptors in the salivary glands [20]. Several authors have noted a significant decrease in the concentration of the salivary immunoglobulin A after a maximal intense physical exercise [21], but the sIgA level did not change after the moderate exercise load [22].

The role of IgA in the human organism

It is well known that the salivary IgA is the predominant protein in mucosal humoral response, and it plays a key role in neutralizing toxins and removing pathogenic microorganisms, however, it does not reduce the number of symbiotic bacteria found in human intestine [23]. The secretory IgA is responsible for the agglutination of bacteria, inhibition of bacterial adhesion to epithelial cells of mucous membranes, the absorption of food antigens as well as neutralization of viruses, toxins, and enzymes produced by the microorganism [24], and neutralization of exotoxins [35].

It was also shown that the sIgA has the ability to neutralize and inhibit the intracellular release of virus particles. This occurs during transport of the antibody by epithelial cells with the secretory component (SC), which is a part of the transmembrane receptor protein of the IgA [25]. It has also been demonstrated that the anti-inflammatory role of the dimeric form of the IgA is associated with intracellular neutralization of bacterial antigens (e.g. lipopolysaccharide), involved in the proinflammatory activation of intestinal epithelial cells [26].

The secretory immunoglobulin A is a relatively small particle, secreted in large amounts, and it represents 70% of the total immunoglobulin produced by mammals. The IgA secreted by the intestinal mucosa induces changes leading to the preferential development of symbiotic bacteria in the gastrointestinal tract, which supports the mutualism between microorganisms, although this mechanism is still little understood [7]. The surface of the mucous membranes of the digestive, respiratory, and genitourinary systems of an adult human is more than 400 m2, and is the major route of presentation for infectious, potentially harmful agents, therefore, the immunoglobulin A plays a key role in defence against pathogens.

The salivary immunoglobulin is the first line of defence to prevent colonization and development of pathogens, thus protecting the organism against infection [27]. The decreased level of the salivary immunoglobulin A is associated with an increased incidence of upper respiratory tract illness [28], thus it may be a useful biological marker of clinical predisposition to diseases of the upper respiratory tract [29].

The incidence of upper respiratory tract inflammation (URTI) is associated with sport training, although the nature of the upper respiratory tract infections is not fully explained, particularly among competitive athletes. Although the URTI is the most common cause of the admittance for the elite athletes in the sports medicine clinics, the question arises whether the analyzed respiratory diseases are actually caused by an infection, or whether they reflect other inflammatory conditions associated with exercise. Cox et al. [10] discovered the fundamental genetic polymorphism with high expression of genes encoding proteins with proinflammatory properties, such as interleukin-6. This cytokine increases the frequency of respiratory symptoms, although the same studies also showed that infections were not the only cause of the incidence of upper respiratory tract illness.

It is believed that the upper respiratory tract infections, caused by increased physical activity, are especially common among athletes in endurance sport disciplines. It has been shown conclusively that immunosuppression resulting from physical exercise increases susceptibility to infection, the symptom associated with a subdued immune system [30].

In recent years, there were many reports on the relationship between changes in the immune system and the risk of URTI in both active and sedentary individuals. It was found that there are differences between these groups in the incidence of respiratory disease frequency and in the IgA concentrations in secretions of the body, indicating the relationship between physical activity and the incidence of URTI [21]. In subjects, both who trained and who did not train, there is a negative correlation between the salivary IgA concentration and the risk of URTI [20]. It has been shown conclusively that prolonged exercise resulted in large decreases of the salivary IgA concentrations [22], while the increase in the salivary IgA occurs in response to short-term or moderate exercise [23]. Increasing of the salivary IgA concentration, observed after moderate exercise, can help to reduce susceptibility to URTI [1]. It is believed that the infectious causes of URTI include bacterial infections, which represent about 5% of cases, while the viral illness ranged from 30 to 40% of cases. The bacterial and viral pathogens identified in these studies suggest that infections are caused by typical pathogens, the same as in the entire population of the upper respiratory tract infections [24].

It was noted that in athletes, the exposure to stressors of biological, physical, and psychological origin can induce neurological and endocrine changes, which affect the immune system as well as the increased incidence of symptoms of various illnesses, including respiratory diseases [25]. However, there is not enough direct evidence to support the contention that these are the mechanisms, specific to athletes, associated with susceptibility to infection or upper respiratory tract illness.

The body's response to exercise is also associated with regulation of the production and secretion of cytokines. Cytokines play an important role in the modulation of changes in the immune system during and after exercise, by increasing the risk of infection and the presence of local inflammation in the organism [26].

The effect of physical activity on the salivary IgA concentration

It is well known that a single bout of exercise or regular training may result in numerous changes in the immune system of athletes [30]. Orysiak et al. [31] discovered exercise-induced decrease of white blood cells, which plays a role in defence against bacterial and viral infections. It has been confirmed that the salivary IgA level may depend on both the intensity and duration of training as well as the type of physical activity [32]. On the other hand, there were no changes in the concentration of IgG, IgA, and IgM in serum of young men participating in a 16-week continuous running training [33].

Most of the research shows that intensive, repetitive exercise causes a decrease in the salivary IgA levels and an increased susceptibility to upper respiratory tract infection in athletes [34]. In marathoners participating in a race over a distance of 160 km, Nieman et al. [35] showed that the secretion of the immunoglobulin A in saliva decreased by 10%. The same authors stated that 25% of the runners had developed URTI within two weeks after the end of the race. Gleeson et al. [36] presented the results, which show that long lasting training caused a decrease in the concentration of immunoglobulin A in saliva and an increase in the frequency of URTI. On the other hand, Francis et al. [20] have shown that, in competitive swimmers, the concentration of the salivary immunoglobulin A was significantly higher than in untrained persons. In addition, Wang et al. [16] reported that regular 12-week Tai chi chuan practice improved immune system function, and they demonstrated a lower frequency of incidence of URTI after training compared with sedentary persons.

Laing et al. [17], who studied twelve 28-year old athletes, reported an increase of the salivary IgA level from approximately 400 mg · l-1 to 450 mg · l-1 immediately after training, whereas two hours after the end of training, the IgA concentration was reduced to about 320 mg · l-1. These results confirm the research conducted by

Steerenberg et al. [18] who showed a significant decrease in the salivary IgA concentration in the group of triathletes after a long lasting exercise. Also Libicz et al. [27], who studied athletes practicing triathlon, found a significant decrease in the salivary IgA level after the competition. On the other hand, Slivka et al. [19], studying eight cyclists during 21 days of training, did not observe any changes in the concentration of sIgA in relation to its concentration on the first day of training. A moderate physical effort reduces the risk of infection due to the positive changes taking place in the immune system [21] by increasing the immune response to pathogens [22].

Farzanaki et al. [23] demonstrated that in female gymnasts, aged from 11 to 13 years, low-intensity exercise increases the amount of the salivary immunoglobulin A secretion. On the first day, these gymnasts have been training only in the morning, while on the second day they trained twice, in the morning and in the evening. The physical effort reached the intensity of 60 to 80% of maximum heart rate. The immunoglobulin A concentration on the first day before training had a value above 5.0 mg · dl-1. Immediately after training, it increased to about 11.5 mg · dl-1, and two hours later, it decreased below the initial value (3 mg · dl-1). On the second day after the morning training, the IgA concentration in saliva was 4 mg · dl-1 and it increased to 5 mg · dl-1 immediately after training, however before and after the evening workout the IgA concentrations were 6.2 and 5.0 mg · dl-1, respectively.

Cunniffe et al. [11], leading research on elite rugby players through-out the season, showed that the largest decreases of the sIgA concentration occurred in the months with the highest exercise loads, while at the same time there was an increase in the incidence of URTI.

It is unclear what is the effect of exercise at maximal intensity but short duration on the salivary IgA level. Research, conducted on seven athletes subjected to 30s Wingate test of arms and legs, shows that the maximal effort during leg cycling caused a small increase in the salivary IgA to the value of 112±32 mg · l-1 compared with the value before effort (105±39 mg · l-1), but arm cranking caused a significant increase of the IgA levels, from 125±81 to 147±69 mg · l-1 [25].

The relationship between the concentration of salivary IgA and the URTI risk in trained and untrained subjects has been repeatedly confirmed. It was noted that the risk of URTI varies depending on the volume and intensity of exercise. During prolonged exercise at a high load level, the IgA decreased, and simultaneously the risk of upper respiratory tract infection increased. However, moderate shortterm exercise increases the level of sIgA and decreases the risk of URTI. Klentrou et al. [31] found that the level of salivary IgA after exercise increases after the moderate load and after regular exercise. Fondell et al. [19], who studied 1509 subjects divided into groups of men and women aged 20-60 years, active and physically inactive, have found that physical activity reduces the incidence of upper respiratory tract illness. The risk reduction was observed in both smokers and nonsmokers, and in men and women, regardless of age.

It has been shown that regular exercise can cause favorable changes in the immune system in the elderly, as reported by Akimoto et al. [1] who studied a group of healthy subjects (18 males and 27 females) over 60 years of age, subjected to regular (twice a week) training for one year. Initially, the concentration of immunoglobulin A in saliva was 24.7 µg · ml-1, while after the fourth month there was an increase to 27.2 µg · ml-1, and after 12 months of physical activity the concentration of sIgA was 33.8 µg · ml-1.

Conclusions

The relationship between physical activity and the suppression of the immune system is not fully understood, but it is known that moderate intensity exercise can improve immune defences, while the extreme effort can reduce them by creating an increased risk of URTI. Nieman [43] showed that in athletes the lowest risk of upper tract infection was connected with the case of moderate-intensity exercise. It is now believed that the relationship between the volume of exercise and the risk of URTI has the shape of the letter "J". This means that both too little and too much physical activity may increase the risk of upper respiratory tract infection [22]. Although exercise-induced decrease in defence function of the immune system seems to be transitory, it could be suggested that immediately after training or hard exercise loads the competitors should be isolated from large groups of people [3]. On the other hand, training optimization and correct balance between exercise and rest periods may reduce the risk of adverse changes in the immune system and decrease the frequency of URTI.

References in the text are referenced by numbers

References:

1. Akimoto T, Kumai Y, Akama T, Hayashi E, Murakami H, Soma R, Kuno S, Kono I. Effects of 12 months of exercise training on salivary secretory IgA levels in elderly subjects. *Br. J. Sports Med.* ۲۰۲۱;37:76–79.

2. Allgrove J.E, Gomes E, Hough J, Gleeson M. Effects of exercise intensity on salivary antimicrobial proteins and markers of stress in active men. *J. Sports Sci.* ۲۰۲۲;26:653–661.

3. Baralic I, Miletic I, Djordjevic B, Terzic T, Radojevic-Skodric S, Nikolic G. Effect of sensory stimulation on salivary IgA secretion rate in karate players. *Biol. Sport.* ۲۰۲۲;27:273–278.

4. Bishop N.C, Gleeson M. Acute and chronic effects of exercise on markers of mucosal immunity. *Front. Biosci.* ۲۰۲۳;14:4444–4456.

5. Bohem M.K, Woof J.M, Kerr M.A, Perkins S.J. The Fab and Fc fragments of IgA1 exhibit a different arrangement from that in IgG: a study by X-ray and neutron solution scattering and homology modeling. *J. Mol. Biol.* ۲۰۲۱;286:1421–1447.

6. Brandtzaeg P. Humoral immune response patterns of human mucosae: induction and relation to bacterial respiratory tract infections. *J. Infect. Dis.* ۲۰۲۱;165:167–176.

7. Brandtzaeg P, Nilssen D.E, Rognum T.O, Thrane P.S. Onkogeny of the mucosal immune system and IgA deficiency. *Gastroenterol. Clin. North Am.* ۲۰۲۳;20:391–439.

8. Cavas L, Arpinar P, Yurdakoc K. Possible interactions between antioxidant enzymes and free sialic acids in saliva: a preliminary study on elite judoists. *Int. J. Sports Med.* ۲۰۲۲;26:832–835.

9. Chintalacharuvu K.R, Morrison S.L. Residues critical for H-L disulfide bond formation in human IgA1 and IgA2. *J. Immunol.* ۲۰۱۹;157:3443–3449.

10. Cox A.J, Gleeson M, Pyne D.B, Saunders P.U, Callister R, Fricker P.A. Respiratory symptoms and inflammatory responses to Difflam throat-spray intervention in half-marathon runners: a randomized controlled trial. *Br. J. Sport Med.* ۲۰۲۲;44:127–133.

11. Cunniffe B, Griffiths H, Proctor W, Davies B, Baker J.S, Jones K.P. Mucosal immunity and illness incidence in elite rugby union players across a season. *Med. Sci. Sports Exerc.* ۲۰۱۹;43:388–397.

12. Cunningham-Rundles C. Physiology of IgA and IgA deficiency. *J. Clin. Immunol.* ۲۰۲۱;21:303–309.

13. Czyżewska-Buczyńska A, Lewandowicz-Uszyńska A, Jankowski A. IgA, an essential part of the immune system: selected issues. *Post. Hig. Med. Dosw.* ۲۰۲۲;61:38–47.

14. Daly W, Seegers C.A, Dobridge J.D, Hackney A.C. Relationship between stress hormones and testosterone with prolonged endurance exercise. *Eur. J. Appl. Phsiol.* ۲۰۲۱;93:375–380.

15. Fahlman M.M, Engels H.J. Mucosal IgA and URTI in American college football players: a year longitudinal study. *Med. Sci. Sports Exerc.* ۲۰۱۹;37:374–80.

16. Fahlman M.M, Engels H.J, Morgan A.L, Kolokouri I. Mucosal IgA response to repeated Wingate tests in females. *Int. J. Sports Med.* ۲۰۲۲;22:127–131.

17. Farzanaki P, Azarbayjani M.A, Rasaee M.J, Jourkesh M, Ostoijc S.M, Stannard S. Salivary immunoglobulin A and cortisol response to training in young elite female gymnasts. *Brasilian J. Biomotor.* ۲۰۲۳;2:252–258.

18. Fernandez M.I, Pedron T, Tournebize R, Olivo-Marin J.C, Sansonetti P.J, Phalipon A. Anti-inflammatory role for intracellular dimeric immunoglobulin A by neutralization of lipopolisaccharide in epithelial cells. *Immunity.* ۲۰۲۰;18:739–749.

19. Fondell E, Lagerros Y.T, Sundberg C.J, Lekander M, Balter O, Rothman K.J, Bälter K. Physical activity, stress and self-reported upper respiratory tract infection. *Med. Sci. Sports Exerc.* ۲۰۱۸;43:272–279.

20. Francis J.L, Gleeson M, Pyne D.B, Callister R, Clancy R.L. Variation of salivary immunoglobulins in exercising and sedentary populations. *Med. Sci. Sports Exerc.* ۲۰۲۱;37:571–578.

21. Gleeson M. Mucosal immune responses and risk of respiratory illness in elite athletes. *Exerc. Immunol. Rev.* ۲۰۲۱;6:5–42.

22. Gleeson M, Pyne D.B. Special feature for the Olympics: effects of exercise on the immune system: exercise effect on mucosal immunity. *Immunol. Cell Biol.* ۲۰۲۲;78:536–544.

23. Hübner-Wozniak E, Lutoslawska G, Sendecki W. Effect of training volume on the levels of salivary immunoglobulin A in wrestlers. *Biol. Sport.* ۲۰۲۱;15:129–131.

24. Hübner-Wozniak E, Lutoslawska G, Sendecki W, Sitkowski D. Exercise-induced changes in salivary immunoglobulin A levels. *Biol. Sport.* ۲۰۱۹;14:299–304.

25. Hübner-Wozniak E, Sendecki W, Borkowski L. The effect of maximal 30 s exercise on salivary immunoglobulin A. *Biol. Sport.* ۲۰۲۰;15:61–64.

26. Johansen F.E, Braathen R, Brandtzaeg P. Role of J chain in secretory immunoglobulin formation. *Scand. J. Immunol.* ۲۰۲۱;52:240–248.

27. Kaetzel C.S, Robinson J.K, Chintalacharuvu K.R, Vaerman J.P, Lamm M.E. The polymeric immunoglobulin receptor (secretory component) mediates transport of immune complexes across epithelial cells: a local defense function for IgA. *Proc. Natl. Acad. Sci. USA.* ۲۰۲۳;88:8796–8800.

28. Kerr M.A. The structure and function of human IgA. *Biochem. J.* ۲۰۱۶;271:285–296.

29. Kett K, Brandzaeg P, Radl J, Haaijman J.J. Different subclass distribution of IgA-producing cells in human lymphoid organs and secretory tissues. *J. Immunol.* ۲۰۱۹;136:3631–3635.

30. Kilian M, Reinholdt J, Lomholt H, Poulsen K, Frandsen E.V.G. Biological significance of IgA1 proteases in bacterial colonization and pathogenesis: critical evaluation of experimental evidence. *APMIS.* ۲۰۲۱;104:321–338.

31. Klentrou P, Cieslak T, Neil Mac M, Vintiner M, Plyley A. Effect of moderate exercise on salivary immunoglobulin A and infection risk in human. *Eur. J. Appl. Physiol.* ۲۰۲۰;87:153–158.

32. Koch A.J, Wherry A.D, Petersen M.C, Johanson J.C, Stuart M.K, Sexton W.L. Salivary immunoglobulin A response to a collegiate rugby game. *J. Strength Cond. Res.* ۲۰۱۸;21:86–90.

33. Laing S.J, Gwynne D, Blackwell J, Wiliams M, Walters R, Walsh N.P. Salivary IgA response to prolonged exercise in a hot environment in trained cyclist. *Eur. J. Appl. Physiol.* ۲۰۲۰;93:665–671.

34. Libicz S, Mercier B, Biogu N, Le Gallais D, Castex F. Salivary IgA response of triathletes participating in the French Iron Tour. *Int. J. Sports Med.* ۲۰۱۸;27:389–394.

35. Lycke N, Eriksen L, Holmgren J. Protection against cholera toxin after oral immunization is thymus dependent and associated with intestinal production of neutralizing IgA antitoxin. *Scand. J. Immunol.* ۲۰۲۰;25:413–419.

36. Macpherson A.J, McCoy K.D, Johansen F-E, Brandtzaeg P. The immune geography of IgA induction and function. *Immunology.* ۲۰۲۲;1:11–22.

The effect of exercise on the increase of red blood cells

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Abstract
During exercise the cardiovascular system has to warrant substrate supply to working muscle. The main function of red blood cells in exercise is the transport of O2 from the lungs to the tissues and the delivery of metabolically produced CO2 to the lungs for expiration. Hemoglobin also contributes to the blood's buffering capacity, and ATP and NO release from red blood cells contributes to vasodilation and improved blood flow to working muscle. These functions require adequate amounts of red blood cells in circulation. Trained athletes, particularly in endurance sports, have a decreased hematocrit, which is sometimes called “sports anemia.” This is not anemia in a clinical sense, because athletes have in fact an increased total mass of red blood cells and hemoglobin in circulation relative to sedentary individuals. The slight decrease in hematocrit by training is brought about by an increased plasma volume (PV). The mechanisms that increase total red blood cell mass by training are not understood fully. Despite stimulated erythropoiesis, exercise can decrease the red blood cell mass by intravascular hemolysis mainly of senescent red blood cells, which is caused by mechanical rupture when red blood cells pass through capillaries in contracting muscles, and by compression of red cells e.g., in foot soles during running or in hand palms in weightlifters. Together, these adjustments cause a decrease in the average age of the population of circulating red blood cells in trained athletes. These younger red cells are characterized by improved oxygen release and deformability, both of which also improve tissue oxygen supply during exercise.
Keywords: Hb-O2 affinity, blood gasses, 2,3-DPG, erythropoiesis, hypoxia inducible factor, ATP, NO, intravascular hemolysis

Introduction

The primary role of red blood cells is the transport of respiratory gasses. In the lung, oxygen (O2) diffuses across the alveolar barrier from inspired air into blood, where the majority is bound by hemoglobin (Hb) to form oxy-Hb, a process called oxygenation. Hb is contained in the red blood cells, which, being circulated by the cardiovascular system, deliver O2 to the periphery where it is released from its Hb-bond (deoxygenation) and diffuses into the cells. While passing peripheral capillaries, carbon dioxide (CO2) produced by the cells reaches the red blood cells, where carbonic anhydrase (CA) in tissues and red blood cells converts a large portion of CO2 into bicarbonate ($HCO^{-}3$). CO2 is also bound by Hb, preferentially by deoxygenated Hb forming carboxy-bonds. Both forms of CO2 are delivered to the lung, where CA converts $HCO^{-}3$ back into CO2. CO2 is also released from its bond to Hb and diffuses across the alveolar wall to be expired.
The biological significance of O2 transport by Hb is well-illustrated by anemia where decreased Hb also decreases exercise performance despite a compensatory increase in cardiac output (Ledingham, ۲۰۱۴; Carroll, ۲۰۱۷), and by improved aerobic performance upon increasing total Hb (Berglund and Hemmingson, ۲۰۱۹). The O2 dissociation curves in Figure Figure11 indicate the advantage of normal vs. anemic Hb showing that the O2 content in blood varies with the Hb concentration in blood at any given O2 partial pressure (PO2). Not only its amount but also the functional properties of Hb affect performance. This is illustrated by the observation that an increased Hb-O2 affinity favors O2 loading in the lung and survival in an hypoxic environment (Eaton et al., 2019; Hebbel et al., 2020), whereas a decreased Hb-O2 affinity favors the release of O2 from the Hb molecule in support of oxidative phosphorylation when the ATP demand is high, such as in exercising skeletal muscle (for a recent review see Mairbäurl and Weber, 2018).
Despite O2 transport, red blood cells fulfill a variety of other functions, all of which also may improve exercise performance. Likely the most important one is the contribution of red blood cells in buffering changes in blood pH by transport of CO2 and by binding of H+ to hemoglobin. Red blood cells also take up metabolites such as lactate that is released from skeletal muscle cells during high intensity exercise. Uptake into red blood cells

decreases the plasma concentration of metabolites. Finally, red blood cells seem to be able to decrease peripheral vascular resistance by releasing the vasodilator NO (Stamler et al., 2021) and by releasing ATP which stimulates endothelial NO formation causing arteriolar vasodilation and augments local blood flow (Gonzalez-Alonso et al., 2016).

Oxygen affinity of hemoglobin

A major mechanism optimizing O2 transport by hemoglobin is the change in Hb-O2 affinity. Changes are very fast and actually occur while red blood cells pass through blood capillaries. Effects of altered Hb-O2 affinity on O2 transport are independent of Hb concentration and total Hb mass in circulation and thus add to the adjustment by changes in erythropoiesis.

The intrinsic O2-affinity of hemoglobin is very high (Weber and Fago, 2016). Therefore, allosteric effectors are required that decrease Hb-O2 affinity allowing unloading of O2 from the Hb molecule. The major allosteric effectors modulating Hb-O2 affinity in vivo in human red blood cells are organic phosphates such as 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP), H+ and CO2, and Cl−. A direct role of lactate, which accumulates during exercise, on Hb-O2-affinity is less clear and may be due to a small effect on the Cl− binding by Hb and on carbamate formation (reviewed in (Mairbäurl and Weber, 2021)). Indirect effects of lactate may be caused by affecting the Cl− concentration and by the uptake of H+ together with lactate mediated by MCT-1 (Deuticke, 2018). Another modulator of Hb-O2 affinity relevant to exercise is a change in body temperature (Dill and Forbes, 2017; Mairbäurl and Humpeler, 2018).

The physiological significance of an increased Hb-O2 affinity is an improved O2 binding by Hb when the PO2 is low. It is therefore of significance for people exposed to hypoxic environments, where it prevents exaggerated arterial desaturation. A decrease in Hb-O2 affinity improves O2 delivery to cells with a high O2 demand such as in exercising muscle (see below).

A simple approach to estimate the SO2 from PO2 and vice versa has been published by Severinghaus (2016). The formula was derived from a best fit model of the standard oxygen dissociation curve with an error of SO2 of 0.26% within the physiological range of PO2. The standard half saturation pressure of O2 (P50value) was given as 26.86 mmHg at a plasma pH = 7.4 and 37°C; S is fractional saturation.

$$S = 100 \times \left(\left(\left(PO_2^3 + 150 \times PO_2 \right)^{-1} \times 23400 \right) + 1 \right)^{-1} \text{ or}$$

$$\ln PO_{2,st} = 0.385 \times \ln \left(S^{-1} - 1 \right) + 3.32 - \left(72 \times S \right)^{-1} - 0.17 \times S^6$$

Based on a model proposed by Roughton and Severinghaus (2018), Okada et al. (2016) published a modification of this formula that allows estimating changes in P50 by altered pH, temperature (T; °C), base excess (BE; mEq/Liter), and 2,3-DPG (DPG; molar ration of 2,3-DPG to Hb) with accuracies of P50 values and SO2 of ± 2.5 and ± 5%, respectively.

$$\Delta \log_{50} = 0.48 \times \left(7.4 - pH_{plasma} \right) + 0.024 \times \left(T - 37 \right) + 0.0013 \times BE + 0.135 \times DPG - 0.116,$$

After correction of P50 using this equation to obtain P50,actual, adjusted PO2 (PO2,actual) values can be calculated (Severinghaus, 2020) as

$$PO_{2,actual} = PO_{2,std} \times \frac{P_{50,actual}}{26.86}$$

Then the "Severinhaus-equation" can be used to calculate S from the new PO2 to obtain complete ODCs. A more detailed description of the magnitude of changes in Hb-O2 affinity by allosteric effectors, temperature, and other molecules alone as well as their interactions is reviewed in (Mairbäurl and Weber, 2019).

Oxygen transport capacity

Whereas only 0.03 ml O2 * L−1 * mmHg−1 PO2 at 37°C can be transported in blood in physical solution, one gram of Hb can bind ~1.34 ml of O2. Thus, the presence of a normal amount of Hb per volume of blood increases the amount of O2 that can be transported about 70-fold, which is absolutely essential to meet the normal tissue O2 demand. It is therefore apparent that an increased amount of Hb also increases the amount of O2 that can be delivered to the tissues . In fact, the O2 transport capacity was found to correlate directly with aerobic performance as can be seen from an increase in performance after infusion of red blood cells (Berglund and Hemmingson, 2021) and by the strong correlation between total Hb and maximal O2 uptake (VO2,max) in athletes (for review see Sawka et al., 2018; Schmidt and Prommer, 2019). Calbet et al found that acute manipulations of the O2 carrying capacity also vary performance (Calbet et al., 2019). Thus, it is a clear advantage for aerobic athletic performance to have a high O2 transport capacity.

Parameters required to evaluate O2 transport capacity are the Hb concentration in blood (cHb) and hematocrit (Hct), as well as total Hb mass (tHb) and total red blood cell volume (tEV) in circulation. cHb and Hct are easy to measure with standard hematological laboratory equipment. Together with SO2 they indicate the amount of O2 that can be delivered to the periphery per unit volume of cardiac output. tHb and tEV indicate the total amount of O2 that can be transported by blood. A large tHb and tEV allows redirecting O2 to organs with a high O2 demand while maintaining basal O2 supply in less active tissues. Because they are affected by changes in plasma volume (PV) cHb and Hct allow no conclusion on tHb and tEV, respectively.

Results on cHb, Hct and red blood cell count in athletes and their comparison with values obtained in healthy, sedentary individuals are conflicting due to the fact that red blood cell volume and PV change independently and due to the many factors affecting each of these parameters (see below). Establishing normal values for tHb and tEV for athletes is hampered further by the possibility of use of means to increase aerobic capacity such as blood and erythropoietin (EPO) doping.

Hematocrit in athletes

Many but not all studies show lower Hct in athletes than in sedentary controls (Broun, 2016; Davies and Brewer, 2018; Ernst, 2016; Sawka et al., 2020). However, several studies also report higher than normal Hct. A highly increased Hct increases blood viscosity and increases the workload of the heart (El-Sayed et al., 2014; Böning et al., 2016). It therefore bears the risk of cardiac overload.

Many studies showed that Hct tended to be lower in athletes than in sedentary individuals (Broun, 2019; Davies and Brewer, 2020; Remes, 2018; Magnusson et al., 2017; Selby and Eichner, 2021; Ernst, 2022; Weight et al., 2019). This was verified by Sharpe et al. (2015) in the course of establishing reference Hct and Hb values for athletes. The found that out of ~1100 athletes from different countries 85% of the female and 22% of the male athletes had Hct values below 44%. A tendency for an inverse correlation of Hct with training status, indicated by VO2,max, was also shown (Heinicke et al., 2020). However, a small proportion of sedentary controls and athletes has higher than normal Hct. Sharpe et al. (2021) found that 1.2% of all females and 32% of all males in their study had an Hct > 47%. When following female and male elite athletes and controls over a study period of 43 months Vergouwen (Vergouwen et al., 2015) found 6 males controls and 5 males athletes with a Hct > 50% and 5 females controls but no female athletes with a Hct > 47%.

Hematocrit during exercise Changes in Hct occur rapidly. Hct increases during exercise due to a decrease in PV when fluid replacement during exercise is insufficient (Costill et al., 2020). There is fluid loss due to sweating, a shift of plasma water into the extracellular space due to the accumulation of osmotically active metabolites, and filtration as a consequence of an increased capillary hydrostatic pressure (Convertino, 2019). The resultant increase in plasma protein increases oncotic pressure and thus moderates fluid escape (Harrison, 2018). Changes appear less pronounced during swimming than running exercise, where immersion and the re-distribution of blood volume seem to cause shifts in PV independent of volume regulatory hormones (Böning et al., 2022). An increase in hematocrit due to catecholamine-induced sequestration of red blood cells from spleen is unlikely in humans but has been found in other species (Stewart and McKenzie, 2019).

Long-term changes of hematocrit In a recent review, Thirup (2018) reports a within-subject variability of ~3% when reviewing 12 studies on more than 600 healthy, non-smoking, mostly sedentary individuals, and when measurements were repeated in sampling intervals ranging from days to ~2 months. Sawka et al. summarized data from 18 investigations and found that PV and blood volume increased rapidly after training sessions, whereas red cell volume remained unchanged for several days before it began to increase indicating that Hct values were

decreased for several days (Sawka et al., 2018). The magnitude of Hct change seems to depend on exercise intensity during training sessions and the type of exercise (strength vs. endurance; for review see Hu and Lin, 2021). A few weeks after the training intervention a new steady state had established, and Hct had returned to pre-training values (Sawka et al., 2019). The post-training increase in PV and the increased PV in highly trained athletes (e.g., Hagberg et al., 2017; Sawka et al., 2018 Heinicke et al., 2019; Schumacher et al., 2020) is likely caused by aldosterone dependent renal Na+ reabsorption, and by water retention stimulated by elevated antidiuretic hormone in compensation for the water loss during individual training sessions (Costill et al., 2020; Milledge et al., 2021).

There appear to be quite large seasonal variations in Hct (relative change up to 15%) with lower values in summer than in winter that might result in season-to-season changes from ~42% in summer and 48% in winter as found among several thousand study participants. Seasonal changes depend on climatic effects with larger differences in countries closer to the equator (Thirup, 2016). Studies of seasonal changes in Hct of athletes are sparse but indicate that Hct might be decreased by another 1–2% in summer by addition of a training effect.

The decreased Hct in athletes has been termed "sports anemia." For a long time it had been explained with increased red blood cell destruction during exercise and thus appeared to be the same phenomenon as the well-known march hemoglobinuria (Broun, 2015; Kurz, 2016; Martin and Kilian, 2017). Intravascular destruction of red blood cells occurs at shear stresses between 1000 and 4000 dyn/cm2 (Sutera, 2016; Sallam and Hwang, 2018), values well above physiological values at rest (Mairbäurl et al., 2014). It is related to the intensity and the kind of exercise (Yoshimura et al., 2018; Miller et al., 2021). Foot strike in runners has been the most often reported reason for intravascular hemolysis (Telford et al., 2016), which can be prevented by good shoe cushioning (Yoshimura et al., 2016; Dressendorfer et al., 2014). It also occurred during mountain hiking (Martin et al., 2020), in strength training (Schobersberger et al., 2016), karate (Streeton, 2019), in swimmers (Selby and Eichner, 2020; Robinson et al., 2021), basketball, Kendo-fencing, and in drummers (Schwartz and Flessa, 2020; Nakatsuji et al., 2022). Running exercise has been found to increase plasma hemoglobin from ~30 mg/liter at rest to ~120 mg/liter indicating that about 0.04% of all circulating red blood cells were lyzed (Telford et al., 2003). Exercise had been shown to alter red blood cell membrane appearance in correlation with elevated haptoglobin (Jordan et al., 2018). Senescent red blood cells may be particularly prone to exercise induced intravascular hemolysis as indicated by a decreased mean red blood cell buoyant density and a density distribution curve that was skewed toward younger, less dense cells in trained individuals indicated by increased levels of pyruvate kinase activity, 2,3-DPG and P50, higher reticulocyte counts (Mairbäurl et al., 2016). Other possible reasons for "sports anemia" under discussion are nutritional aspects such as insufficient protein intake and altered profile of blood lipids (for review see Yoshimura et al., 2020), and iron deficiency (Hunding et al., 2021).

Red blood cell mediated vasodilation

Precise control of regional blood flow is required to match substrate demand and removal of metabolites, which is of particular importance when the metabolic activity is high such as in exercising skeletal muscle. Nitric oxide (NO) is an important signaling molecule that causes local vasodilation. It is typically formed in vascular endothelial cells upon a variety of stimuli, the most important during exercise likely being shear stress (Pohl et al.,2016; Shen et al., 2021). Hemoglobin has been shown to tightly bind NO to form nitrosylhemoglobin (Hb-cys-NO; SNO-Hb) in an O2 saturation dependent manner with higher affinity for deoxyhemoglobin, a reaction that also causes formation of Met-Hb (Gow and Stamler, 2021; Grubina et al., 2020). Binding has been interpreted as a sink for NO produced by endothelium to prevent exaggerated and wide-spread vasodilation. However, it has also been hypothesized that Hb not only binds but also releases and/or produces NO from SNO-Hb to cause local vasodilation (Robinson and Lancaster, 2016).

It has been shown experimentally that NO released from red blood cells causes vasodilation when the shear stress is increased and when the tissue is made hypoxic (Ulker et al., 2015). Red blood cells produce bioactive NO equivalents in an O2 saturation, pH, and redox-state dependent manner, which appears to be an allosteric, autocatalytic reaction with characteristics of a nitrite reductase reaction (for review see Gladwin and Kim-Shapiro, 2016). When nitrite is added to fully deoxygenated Hb, NO is released and Met-Hb is formed (Gladwin and Kim-Shapiro, 2018). Bioactivity is indicated by the notion that upon nitrate infusion, NO binding to hemoglobin and vasodilation are tightly coupled and are favored by hypoxia (Crawford et al., 2018). Kleinbongard et al. (2015) presented immune-histochemical and functional evidence of the presence of an endothelial NO-synthase type of enzyme in human and mouse red blood cells indicating the potential to produce NO from L-arginine. It is unclear, however, whether this reaction is active in controlling microcirculation in working skeletal muscle (which generates a low oxygen environment because of its requirement for oxygen).

ATP in plasma is another stimulus for endothelial NO production (Sprague et al., 2021). ATP is released from many cells where it modifies a variety of functions (Praetorius and Leipziger, 2016). Local vasodilation has been shown to depended on the presence of red blood cells (Dietrich et al., 2021). Thus, it has been hypothesized that red blood cells release ATP and cause an NO-dependent increase in blood flow (Gonzalez-Alonso et al., 2015). ATP release is not only an in vitro phenomenon but has also been demonstrated vivo, where elevated ATP has been found in the venous effluent from exercising forearm muscle (Forrester, 2014; Ellsworth et al., 2018). This effect was even enhanced when exercise was performed in hypoxia (Gonzalez-Alonso et al., 2015).

The major stimulus for ATP release from red blood cells seems to be mechanical deformation (Sprague et al., 2014; Ellsworth et al., 2019), where ATP release seems to depend on the shear rate (Mairbäurl et al., 2016). Also in vitro hypoxia stimulates the release of ATP from red blood cells (Bergfeld and Forrester, 2018). Futhermore, hypoxia greatly enhances ATP release induced by shear stress indicating that effects are additive (Mairbäurl et al., 2020). Other stimulators of ATP release from red blood cells are beta adrenergic stimulators and prostacyclin (Olearczyk et al., 2021), and an increase in temperature (Kalsi and Gonzalez-Alonso, 2021). The exact release mechanism is unclear. An involvement of CFTR has been discussed (Sprague et al., 2016) but it is unclear whether CFTR is actually present in human red blood cells. A variety of other mechanisms for ATP release have been described (for review see Praetorius and Leipziger, 2015), some of which seem to involve pannexin1- (Qiu and Dahl, 2015; Qiu et al., 2018). Intravascular hemolysis seems not to contribute significantly to ATP release from erythrocytes exposed to shear-stress (Mairbäurl et al., 2015).

Taken together these results indicate that red blood cells support local vasodilation in tissues with a high O2 demand by directly mediating NO release and enzymatic production and by release of ATP, which causes NO release from endothelial cells by mechanisms, which are greatly enhanced in exercise when shear stress is increased by increased blood flow, O2 is low due to increased consumption, and the increase in temperature.

Conclusion

Red blood cells support local blood flow by providing the vasodilator NO by direct conversion from nitrate and by release of ATP causing endothelial NO release. At any given capillary blood flow the amount of O2 unloaded from Hb to the cells of working muscle can be increased greatly by decreasing Hb-O2 affinity. This happens as the cells enter the capillaries supplying the muscle cells, where they are exposed to increased temperature, H+ and CO2. Training further enhances O2 flux to the working muscle at all levels of regulation: It increases maximal cardiac output, improves blood flow to the muscles by stimulating vascularization, and improves the rheological properties of red blood cells. Training increases total hemoglobin mass by stimulating erythropoiesis, which increases the amount of O2 that can be carried by blood. It also increases red blood cell 2,3-DPG, which increases the sensitivity of Hb-O2 affinity to acidification dependent O2-release. The system appears to be optimized for exercise at low altitude, because in an hypoxic environment the decreased arterial PO2, which is the major determinant for O2 diffusion, cannot be compensated adequately by the above mentioned O2 transport mechanisms resulting in a decrease in performance with increasing degree of hypoxia (Cerretelli and DiPrampero, 2016).

References are cited in the text

References:

1. Arnold H. R., Carrier E. B., Smith H. P., Whipple G. H. (۲۰۲۳). Blood volume studies. *Am. J. Physiol*. 56, 313–327
2. Banfi G., Lundby C., Robach P., Lippi G. (۲۰۱۹). Seasonal variations of haematological parameters in athletes. *Eur. J. Appl. Physiol*. 111, 9–16 10.1007/s00421-010-1641-1
3. Bauer C. (۲۰۲۰). Antagonistic influence of CO_2 and 2, 3 Diphosphoglycerate on the Bohr Effect of human Haemoglobin. *Life Sci*. 8, 1041–1046 10.1016/0024-3205(69)90455-X
4. Benesch R., Benesch R. E. (۲۰۲۲). The effect of organic phosphates from human erythrocytes on the allosteric properties of hemoglobin. *Biochem. Biophys. Res. Commun*. 26, 162–167 10.1016/0006-291X(67)90228-8

5. Bergfeld G. R., Forrester T. (۲۰۱۸). Release of ATP from human erythrocytes in response to a brief period of hypoxia and hypercapnia. *Cardiovasc. Res*. 26, 40–47 10.1093/cvr/26.1.40
6. Berglund B., Hemmingson P. (۲۰۱۵). Effect of reinfusion of autologous blood on exercise performance in cross-country skiers. *Int. J. Sports Med*. 8, 231–233 10.1055/s-۲۰۱۵-1025661
7. Berlin G., Challoner K. E., Woodson R. D. (۲۰۱۵). Low O_2 affinity erythrocytes improve performance of ischemic myocardium. *J. Appl. Physiol* 92, 1267–1276 10.1152/japplphysiol.00194.۲۰۱۵
8. Bert P. (۲۰۲۱). Sur la richesse en hemoglobine du sang des animaux vivant sur les haut lieux. *C. R. Acad. Sci. (Paris)* 94, 805–807
9. Bodary P. F., Pate R. R., Wu Q. O. F., McMillan G. S. (۲۰۲۲). Effects of acute exercise on plasma erythropoietin levels in trained runners. *Med. Sci. Sports Exerc*. 31, 543–546 10.1097/00005768-199904000-00008
10. Böning D., Maassen N., Pries A. (۲۰۲۱). The hematocrit paradox–how does blood doping really work. *Int. J. Sports Med*. 32, 242–246 10.1055/s-0030-1255063
11. Eaton J. W., Skelton T. D., Berger E. (۲۰۲۰). Survival at extreme altitude: protective effect of increased hemoglobin-oxygen affinity. *Science* 183, 743–744 10.1126/science.183.4126.743
12. Eckardt K. U., Boutellier U., Kurtz A., Schopen M., Koller E. A., Bauer C. (۲۰۱۶). Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia.
13. Eckardt K. U., Koury S. T., Tan C. C., Schuster S. J., Kaissling B., Ratcliffe P. J., et al. (۲۰۱۸). Distribution of erythropoietin producing cells in rat kidneys during hypoxic hypoxia. *Kidney Int*. 43, 815–823 10.1038/ki.1993.115
14. Eckardt K. U., Kurtz A. (۲۰۲۰). Regulation of erythropoietin production. *Eur. J. Clin. Invest*. 35, 13–19 10.1111/j.1365-2362.۲۰۲۰1525.x
15. Ellsworth M. L., Ellis C. G., Goldman D., Stephenson A. H., Dietrich H. H., Sprague R. S. (۲۰۲۱). Erythrocytes: oxygen sensors and modulators of vascular tone. *Physiology* 24, 107–116 10.1152/physiol.00038.2008
16. Heinicke K., Wolfarth B., Winchenbach P., Biermann B., Schmid A., Huber G., et al. (۲۰۲۲). Blood volume and hemoglobin mass in elite athletes of different disciplines. *Int. J. Sports Med*. 22, 504–512 10.1055/s-2001-17613
17. Hopkins S. R. (۲۰۲۳). Exercise induced arterial hypoxemia: the role of ventilation-perfusion inequality and pulmonary diffusion limitation. *Adv. Exp. Med. Biol*. 588, 17–30 10.1007/978-0-387-34817-9_3
18. Hu C. J., Wang L. Y., Chodosh L. A., Keith B., Simon M. C. (۲۰۱۶). Differential roles of hypoxia-inducible factor 1alpha (HIF-1alpha) and HIF-2alpha in hypoxic gene regulation. *Mol. Cell Biol*. 23, 9361–9374 10.1128/MCB.23.24.9361-9374.2003
19. Hu M., Lin W. (۲۰۱۹). Effects of exercise training on red blood cell production: implications for anemia. *Acta Haematol*. 127, 156–164 10.1159/000335620
20. Hunding A., Jordal R., Paulev P. E. (۲۰۲۲). Runner's anemia and iron deficiency. *Acta Med. Scand*. 209, 315–318 10.1111/j.0954-6820.1981.tb11598.x
21. Hurtado A. (۲۰۲۲). Some physiological and clinical aspectsof life at high altitudes, in *Aging of the Lung*, eds Cander L., Moyer J. H. (New York, NY: Grune and Stratton;), 257
22. Platt O. S., Lux S. E., Nathan D. G. (۲۰۱۹). Exercise-induced hemolysis in xerocytosis. Erythrocyte dehydration and shear sensitivity. *J. Clin. Invest*. 68, 631–638 10.1172/JCI110297
23. Pohl U., Busse R., Kuon E., Bassenge E. (۲۰۱۶). Pulsatile perfusion stimulates the release of endothelial autacoids. *J. Appl. Cardiol*. 1, 215–235

24. Praetorius H. A., Leipziger J. (۲۰۲۲). ATP release from non-excitable cells. *Purinergic. Signal*. 5, 433–446 10.1007/s11302-009-9146-2
25. Qiu F., Dahl G. (۲۰۲۱). A permeant regulating its permeation pore: inhibition of pannexin 1 channels by ATP. *Am. J. Physiol. Cell Physiol*. 296, C250–C255 10.1152/ajpcell.00433.۲۰۲۱
26. Qiu F., Wang J., Spray D. C., Scemes E., Dahl G. (۲۰۱۸). Two non-vesicular ATP release pathways in the mouse erythrocyte membrane. *FEBS Lett*. 585, 3430–3435 10.1016/j.febslet.۲۰۱۸.09.033
27. Rand P. W., Barker N., Lacombe E. (۲۰۲۱). Effects of plasma viscosity and aggregation on whole-blood viscosity. *Am. J. Physiol*. 218, 681–688
28. Rapoport S. M. (۲۰۱۶). *The Reticulocyte*. Boca Raton, FL: CRC Press, Inc., Boca Raton, FLorida
29. Reinhart W. H., Nagy C. (۲۰۱۹). Albumin affects erythrocyte aggregation and sedimentation. *Eur. J. Clin. Invest*. 25, 523–528 10.1111/j.1365-2362.1995.tb01739.x [
30. Schobersberger W., Tschann M., Hasibeder W., Steidl M., Herold M., Nachbauer W., et al. (۲۰۱۴). Consequences of 6 weeks of strength training on red cell O_2 transport and iron status. *Eur. J. Appl. Physiol. Occup. Physiol*. 60, 163–168 10.1007/BF00839152
31. Schofield C. J., Ratcliffe P. J. (۲۰۲۱). Oxygen sensing by HIF hydroxylases. *Nat. Rev. Mol. Cell Biol*. 5, 343–354 10.1038/nrm1366
32. Schumacher Y. O., Jankovits R., Bultermann D., Schmid A., Berg A. (۲۰۱۸). Hematological indices in elite cyclists. *Scand. J. Med. Sci. Sports* 12, 301–308 10.1034/j.1600-0838.۲۰۱۸.10112.x
33. Schwarz A. J., Brasel J. A., Hintz R. L., Mohan S., Cooper D. M. (۲۰۲۰). Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding protein-3 and its proteolysis in young healthy men. *J. Clin. Endocrinol. Metab*. 81, 3492–3497 10.1210/jc.81.10.3492
34. van der Brug G. E., Peters H. P., Hardeman M. R., Schep G., Mosterd W. L. (۲۰۲۰). Hemorheological response to prolonged exercise–no effects of different kinds of feedings. *Int. J. Sports Med*. 16, 231–237 10.1055/s- ۲۰۲۰۹۷۲۹۹۷
35. Vandewalle H., Lacombe C., Lelievre J. C., Poirot C. (۲۰۱۹). Blood viscosity after a 1-h submaximal exercise with and without drinking. *Int. J. Sports Med*. 9, 104–107 10.1055/s-۲۰۱۹-1024988
36. Vergouwen P. C., Collee T., Marx J. J. (۲۰۲۱). Haematocrit in elite athletes. *Int. J. Sports Med*. 20, 538–541 10.1055/s-۲۰۲۱-8842

Effects of exercise with multiple sclerosis

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Abstract

Multiple sclerosis (MS) can result in significant mental and physical symptoms, specially muscle weakness, abnormal walking mechanics, balance problems, spasticity, fatigue, cognitive impairment and depression. Patients with MS frequently decrease physical activity due to the fear from worsening the symptoms and this can result in reconditioning.

Physicians now believe that regular exercise training is a potential solution for limiting the reconditioning process and achieving an optimal level of patient activities, functions and many physical and mental symptoms without any concern about triggering the onset or exacerbation of disease symptoms or relapse.

Main body

Appropriate exercise can cause noteworthy and important improvements in different areas of cardio respiratory fitness (Aerobic fitness), muscle strength, flexibility, balance, fatigue, cognition, quality of life and respiratory function in MS patients.Aerobic exercise training with low to moderate intensity can result in the improvement of aerobic fitness and reduction of fatigue in MS patients affected by mild or moderate disability.MS patients can positively adapt to resistance training which may result in improved fatigue and ambulation.Flexibility exercises such as stretching the muscles may diminish spasticity and prevent future painful contractions. Balance exercises have beneficial effects on fall rates and better balance.Some general guidelines exist for exercise recommendation in the MS population.The individualized exercise program should be designed to address a patient's chief complaint, improve strength, endurance, balance, coordination, fatigue and so on.

Conclusion

Exercise should be considered as a safe and effective means of rehabilitation in MS patients. Existing evidence shows that a supervised and individualized exercise program may improve fitness, functional capacity and quality of life as well as modifiable impairments in MS patients.

Keywords: Multiple sclerosis, Exercise, Fitness, Balance, Fatigue

Introduction

MS or demyelinating disease of central nervous system is characterized with neurodegeneration, inflammation, axonal demyelination and transaction [1].

This disease has a chronic nature and affects young people, especially women [2]. However, it can be identified in childhood or late adulthood, although this is rare [3].

The chronic course of multiple sclerosis can result in significant mental and physical symptoms and irreversible neurologic deficits, including muscle weakness, ataxia, tremor, spasticity, paralysis, balance disorder, cognitive impairment, loss of vision, double vision, vertigo, impaired swallowing and speech, sensory deficits, bladder and bowel dysfunction, pain, fatigue, and depression [4].

Motor dysfunctions in MS patients are frequently due to muscle weakness, abnormal walking mechanics, balance problems, spasticity and fatigue [5].

MS has an unpredictable progressive nature and defects and restrictions of activities may suddenly occur and proceed further than the expected time [6].

It is reported that nearly 50% of multiple sclerosis patients use a an accessory device for moving following 15 years from the beginning of disease [7]. Patients frequently reduce their activities due to their fear of symptoms exacerbation [8]. Limited activities increase disability,unfitness, mobility, quality of life (QOL),gait abnormalitiesand lack of stability and muscle strenght [9].

Impairments related to the disease process itself are irreversible by exercise, but impairments resulting from deconditioning are often reversible with exercise [10]. Furthermore, inactivity places MS patients in raised possibility of comorbid health dependent conditions.

Hypercholesterolemia, hypertension, obesity, type 2 diabetes, cancer, arthritis, osteoporosis, depression, fatigue and death from cardiovascular diseases are the most frequently reported comorbid health -related conditions [11]. These comorbidities in MS have further been connected with a raised possibility of inability development because of reduced aerobic capacity, decreased muscle strength, increased muscle atrophyas well as further neurologic risks (e.g., stroke, etc) [12].

For many years, physicians advised newly diagnosed persons with MS to avoid anyphysical activity and exercise. But now, we believe that regular exercise and training is a possible solution during disease period by limiting the deconditioning process and achieving an optimal level of patient activity, functions and many physical and mental health benefits without any concern about a triggering onset or exacerbation of disease symptoms or relapse [13]. We review in this paper, therapeutic function of physical training in multiple sclerosis. The aim of this narrative review is to emphasize the current documents in exercise recommendation including aerobic, resistance, balance or combined trainingin MS patients, and to provide instructions for the sensible use of the physical modalities. Another aim is to outline the impacts of exercise on MS patients by summarizing the physiologic and health view of multiple sclerosis disease.

Physiological profile of MS patients

MS patients, especially with more severe impairments, may exhibit some differences in their physiological characteristics in comparison tohealthy age-matched people in terms of cardiovascular and muscle physiology [14].

Decreased aerobic capacity and cardiorespiratory fitness, in expression of VO2maxor maximal oxygen consumption, among MS patients has been about 30% lower than the healthy controls. Respiratory dysfunction due to respiratory muscle weakness and external causes like muscle defect and tiredness are contributing factors in reducing aerobic fitness [15].

Another cardiac factors such as basic heart rate and minimum blood pressure are noted to be increased in multiplesclerosis because of impairments in the autonomic control of cardiovascular function that has been estimated about 7% to 60% among MS patients [13].

Also, decreased muscle force calculated by isokinetic and isometric muscle contractions and endurance,muscle mass in total body and increased muscle atrophy are seen in MS patients [14].

It must be shown that muscle strength defect appears particularly clear in the lower extrimities in comparison to the upper extrimities [8, 13].

Flexibility is another physiological characteristic that has diminished in MS patients specially in those with spasticity [16].

About 80% of MS patients feel high temperature intolerance that may be correlated with temporary exacerbation of clinical manifestations of the MS [22]. This is an important concern about MS and exercise. Physical activity is beneficialand important for people with MS, but it should not causeoverheating symptoms [22, 23].

Benefits of exercise for MS patients

Appropriate exercise can lead to significant and important improvements in different areas of cardiorespiratory fitness (Aerobic fitness), muscle strength, flexibility, stability, tiredness, cognition, quality of life and respiratory function. At this section, the details of benefits are described [3].

Cardiorespiratory fitness

Aerobic training in MS patients is more extensively studied than resistance training. During aerobic training, the patients use multiple muscle acts opposite a low burdon with aim of increasing cardiovascular fitness [16].

In summary, aerobic training of low to moderate intensity is effective on cardiovascular fitness, mood and QOL(quality of life) in multiple sclerosis patients with EDSS < 7. This type of exercise is safe and tolerable in many individuals with MS. multiple sclerosis patients are shown to make favorable gains in cardiorespiratory fitness within a short term of exercise (for example, 4 weeks) [18].

Cardiorespiratory exercise training in MS is associated with increased VO2 Max or VO2peak and working capacity, respiratory function and reduction of fatigue [18, 25].

A number of studies have made better in cardiorespiratory fitness and aerobic capacity in response to exercise interventions. For instance, Rampello et al. (2019) showed that cardiorespiratory training is better than neurorehabilitation in improvement of functional and moving capacity in multiple sclerosis patients with EDSS < 7 [16].

In another study, Swank et al. (2013) showed that structural cardiorespiratory training can cause improvement in quality of life and emotion of multiple sclerosis patients [2].

In addition cardiorespiratory training can can increase aerobic fitness and reduce tiredness in MS patients some degrees of disability [27]. However, it is not clear whether MS patients with sever impairements have similar adaptations to the cardiorespiratory training benefits or not [13].

Muscle strength and endurance

During strength training, the patients use muscle contractions against a load for increasing muscle strength. Some studies have demonstrated the benefits strenght exercises in MS patients [16].

Increased muscular strength and endurance have also been shown following other exercise interventions in multiple sclerosis patients [18]. Increased strength in lower limbs, could be an important benefit of strnght training in MS. Strength of the lower limb is affected by the disease often previously and to a more range than arms and hands [17].

White et al. (۲۰۱۹) revealed the effects of the strenght exercise on leg strength, moving ability and self-reported fatigue and disability and showed significant improvements in knee extensor and plantar flexor muscle forces and thenwalking performance [18].

MS patients can make good adjustments to strenght trainings in accompanying by improvement in moving capacity and tiredness [19]. Gutierrez.et al. (۲۰۲۰) revealed that strenght training is a good intervention to improve moving and functional capacity in MS patients having moderate disabilities [9]. Surakka et al. (۲۰۱۹) reported that cardiorespiratory and strength training improves tiredness in MS patients with some degree of disabilities and the training type was more achievable in women patients with less disability in comparison to men patients with more disabilities [20]. In general, resistance training with moderate intensity can induce improvements in muscle strength and function among moderately impaired persons with MS. Thistype of exercise is safe and well tolerated in multiple sclerosis [21].

Bone health

The use of therapeutic corticosteroids and inactivity may both lead to osteoporosis and pathologic fractures in MS patients. Furthermore, the chronic process of disease and inactivity in multiple sclerosis patients can cause loss of muscle and bone mass. Shabas et al. (2000) showed that among 220 women with MS, 82% had corticosteroid's history of use and 53% had loss of mobility and bone mass [22].

Weight - bearing exercise can slow the loss of muscle and bone mass in MS. For this reason, the resistance training program is recommended for maintaining and developing the muscle and bone mass in the whole of body [23].

Flexibility

People with multiple sclerosis frequently have limitation in joint motion because of spasticity and prolonged inactivity. Goals of flexibility exercises are to lengthen the muscles, enhance joint range of motion, reduce spasticity, and maintain good posture and balance [16, 18].

Avoidance of spasticity in early stages of disease is very noted. Lenghening the muscles can delay coming aching muscle contractions and spasms. Studies regarding the effects of flexibility exercise on MS are limited, but this type of exercise are recommended. These exercises must be performed by using proprioceptive facilitation techniques and stretching tight muscles in pelvis, chest, leg and hip flexores. For preventing spasticity aggravation, activities like for example indicating the toes during traing must be prevented [24].

Balance

Impairments of balance, such as difficulty in maintenance of upright posture, are common in MS patients. Swing during silent standing, moving slowly following postural disturnances and inability to maintain the balance are common in multiple sclerosis and may be related to falling [27].

Some articles showed the effects of balance training in stability of MS patients. Improvements in balance assessed by Berg Balance Scale (BBS), are shown following group aquatic and stability training [25].

Cattaneo et al. (۲۰۱۶) studied the effects of stability training on multiplesclerosis patients and demonstrated that stability training is effective to reduce the falling and improve stability [26].

Generally, balance training has small, but statistically significant effect on improving stability and reducing falling risk in MS patients with some degrees of disabilities. There was limited data on patients with severe MS who are not ambulatory [27].

Tiredness

Tiredness is greatly seen in MS patients and leads to exacerbation of the neurological and other symptoms of MS such as depression, pain, anxiety and cognitive dysfunction [28]. The underlying mechanisms of fatigue are unknown.

Physical inactivity and mental disorders because of MS or comorbidities have been suggested to cause tiredness.

Exercise can cause some changes such as neuroprotection and neuroplasticity, reduction of long-term inactivityand deregulation of hypothalamus-pituitary- adrenal (HPA) axis and then reduction of tiredness in patients [29].

Evidence has revealed that exercise can manage energy and tierdness levels in healthy peoples. Results are much less conclusive with relation to the exercise and tiedness management in MS patients, although several studies provide support for the potential benefits of exercise in these patients [30].

Cardiorespiratory training and neurorehabilitation, energy storage programs and cooling devices and plans have also been shown as good and effective interventions [31]. Petajan et al. showed that regular aerobic exercisecan reduce fatigue in MS patients, and improve both mood and the QOL(quality of life) [32].

Kargarfard et al. (۲۰۲۰), revealed that aquatic training is effective on tierdness and QOL of women with MS [33].

Establishing a safe and effective exercise program may be considered as an important option while planning for treatment of fatigue and should be encouraged [34].

Quality of life

HRQOL(Health-related quality of life) has diminished in MS patients. The reduced QOL may be related with deterioration of symptoms, walking and cognition in patients [14].

Stuifbergen (۲۰۱۸) studied the positive effects of regular exercises in general health, liveliness and function of patients [18]. The results of several studies on patients with MS confirm the effectiveness of exercise on long period improvement in physical and social function and quality of life [16].

In summary, exercise training can cause prominent and positive effects in QOL of persons with MS [3].

CNS morphology and imaging findings

Until now, no evidence has been foundabout the effects of exercise training on brain structure in multiple sclerosis disease. Any way, some studies revealed the effects of cardiorespiratory training on volume of brain grey matter volume and unity of white matter tract as well as functional connectivity of the hippocampus and cortex in people with MS [5]. Despite the limited data on exercise performance on the brain structureon, some studies revealed regular cardiorespiratory training work against brain degeneration in relapsing-remitting type of MS and probably is a protective strategy.

Some studies proposed detection of morphological changes with exercise in the CNS of MS patients by imaging techniques. Although, evidence is still not enoughto demonstrate effects of exercise on brain structure in multiple sclerosis [34].

Implications for practice

The evidence confirms that individuals with MS are less active than healthy individuals [28]. This is important when designing effective exercise programs for both increasing the tendency and adherence to exercise and createing potential beneficial effects.

Despite all the limitations, exercise has beneficial effects on individuals with multiple sclerosis. Furthermore, no side effects from exercise have been seen in most studies [14, 23].

Exercise recommendations

Growing evidence exists in favour of exercise as an effective treatment for MS patients, and therefore it should be recommended in the rehabilitation process [7].

Some general guidelines exist for exercise prescription in the MS population. In this part, we will discuss the practical points for exercise prescription in MS patients.

Exercise program

The individualized exercise program should be designed to address a patient's chief complaint or goal—to improve strength, endurance, balance, coordination, fatigue, etc. It should consider a patient's baseline impairments and capabilities [18]. The prescription should include all the necessary components, such as frequency, duration, intensity, modalities to be used, and precautions to be observed [34].

Risk of falling

Special attention is needed for patients at high risk of falling due to the balance and coordination problems as well as sensory and proprioceptive deficits. These issues should be particularly considered when planning and supervising exercise sessions in MS patients [13, 16].

Conclusion

Exercise should be considered as a safe and effective means of rehabilitation in MS patients. Existing evidence has shown that a supervised and individualized exercise program can improve physical fitness, functional capacity, quality of life and modifiable impairments in MS patients. There are general guidelines that may be followed for exercise prescription for the MS population. These guidelines should be adapted according to the patient's needs, abilities and preferences.

References are given in the form of numbers in the text

References

1. Pilutti LA, Platta ME, Motl R, Latimer-Cheung AE. The safety of exercise training in multiple sclerosis: a systematic review. *J Neurol Sci [review]* ۲۰۲۳;**343**:3–7. doi: 10.1016/j.jns.۲۰۲۳.05.016

2. Swank C, Thompson M, Medley A. Aerobic exercise in people with multiple sclerosis: its feasibility and secondary benefits. *Int J MS Care.* ۲۰۱۹;**15**(3):138–145. doi: 10.7224/1537-2073.۲۰۱۸-037.

3. Motl RW, Sandroff BM. Benefits of exercise training in multiple sclerosis. *Curr Neurol Neurosci Rep.* ۲۰۲۱;**15**(9):62. doi: 10.1007/s11910-015-0585-6.

4. Romberg A, Virtanen A, Aunola S, Karppi SL, Karanko H, Ruutiainen J. Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. *Mult Scler.* ۲۰۲۰;**10**(2):212–218. doi: 10.1191/1352458504ms1001oa.

5. Motl RW, Pilutti LA. The benefits of exercise training in multiple sclerosis. *Nat Rev Neurol.* ۲۰۲۱;**8**(9):487–497. doi: 10.1038/nrneurol.۲۰۲۱.136.

6. Petajan JH, White AT. Recommendations for physical activity in patients with multiple sclerosis. *Sports Med.* ۲۰۱۸;**27**(3):179–191. doi: 10.2165/00007256-۲۰۱۸27030-00004.

7. Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. *J Neurol.* ۲۰۲۰;**261**(9):1651–61. doi: 10.1007/s00415-013-7183-9.

8. White L, McCoy S, Castellano V, Gutierrez G, Stevens J, Walter G, et al. Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult Scler.* ۲۰۲۲;**10**(6):668–674. doi: 10.1191/1352458504ms1088oa.

9. Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance training improves gait kinematics in persons with multiple sclerosis. *Arch Phys Med Rehabil.* ۲۰۱۹;**86**(9):1824–1829. doi: 10.1016/j.apmr.۲۰۱۹.04.008

10. Asano M, Dawes DJ, Arafah A, Moriello C, Mayo NE. What does a structured review of the effectiveness of exercise interventions for persons with multiple sclerosis tell us about the challenges of designing trials? *Mult Scler.* ۲۰۲۱;**15**(4):412–421. doi: 10.1177/1352458508101877.

11. O'Connor P. Key issues in the diagnosis and treatment of multiple sclerosis. *An overview Neurology.* ۲۰۲۱;**59**(6 Suppl 3):S1–33.

12. Grima DT, Torrance GW, Francis G, Rice G, Rosner AJ, Lafortune L. Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler.* ۲۰۲۲;**6**(2):91–98. doi: 10.1177/135245850000600207.

13. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Mult Scler.* ۲۰۲۲;**14**(1):35–53. doi: 10.1177/1352458507079445.

14. Gallien P, Nicolas B, Robineau S, Petrilli S, Houedakor J, Durufle A. Physical training and multiple sclerosis. *Ann Readapt Med Phys.* ۲۰۱۹;**50**(6):373–376. doi: 10.1016/j.annrmp.۲۰۱۹.04.004.

15. Pilutti LA, Platta ME, Motl RW, Latimer-Cheung AE. The safety of exercise training in multiple sclerosis: a systematic review. *J Neurol Sci.* ۲۰۲۰;**343**(1):3–7. doi: 10.1016/j.jns.۲۰۲۰.05.016.

16. Sandoval AE. Exercise in multiple sclerosis. *Phys Med Rehabil Clin N Am.* ۲۰۱۹;**24**(4):605–618. doi: 10.1016/j.pmr.۲۰۱۹.06.010.

17. Feltham MG, Collett J, Izadi H, Wade DT, Morris MG, Meaney AJ, et al. Cardiovascular adaptation in people with multiple sclerosis following a twelve week exercise programme suggest deconditioning rather than autonomic dysfunction caused by the disease Results from a randomized controlled trial. *Eur J Phys Rehabil Med.* 2013;**49**(6):765–74.

18. White LJ, Dressendorfer RH. Exercise and multiple sclerosis. *Sports Med.* ۲۰۲۲;**34**(15):1077–1100. doi: 10.2165/00007256-200434150-00005.

19. Huang M, Jay O, Davis SL. Autonomic dysfunction in multiple sclerosis: implications for exercise. *Auton Neurosci.* ۲۰۱۹;**188**:82–85. doi: 10.1016/j.autneu.2014.10.017.

20. Formica CA, Cosman F, Nieves J, Herbert J, Lindsay R. Reduced bone mass and fat-free mass in women with multiple sclerosis: effects of ambulatory status and glucocorticoid use. *Calcif Tissue Int.* ۲۰۲۱;**61**(2):129–133. doi: 10.1007/s002239900309.

21. Lambert CP, Lee Archer R, Evans WJ. Body composition in ambulatory women with multiplesclerosis. *Arch Phys Med Rehabil.* ۲۰۲۲;**83**(11):1559–1561. doi: 10.1053/apmr.۲۰۲۲.35663.

22. White AT, Wilson TE, Davis SL, Petajan JH. Effect of precooling on physical performance in multiple sclerosis. *Mult Scler.* ۲۰۲۲;**6**(3):176–180. doi: 10.1177/135245850000600307.

23. Brown TR, Kraft GH. Exercise and rehabilitation for individuals with multiple sclerosis. *Phys Med Rehabil Clin N Am.* ۲۰۱۹;**16**(2):513–555. doi: 10.1016/j.pmr.۲۰۱۹.01.005.

24. Mostert S, Kesselring J. Effects of a short term exercise training programme on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. multiple sclerosis. ۲۰۱۸;8(2):161–8.

25. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta AM, MacKibbon KA, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil.* ۲۰۲۱;**94**(9):1800–1828. doi: 10.1016/j.apmr.۲۰۲۱.04.020.

26. Rampello A, Franceschini M, Piepoli M, Antenucci R, Lenti G, Olivieri D, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. *Phys Ther.* ۲۰۲۰;**87**(5):545–555. doi: 10.2522/ptj.20060085.

27. Surakka J, Romberg A, Ruutiainen J, Aunola S, Virtanen A, Karppi SL, et al. Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial. *Clin Rehabil.* ۲۰۲۲;**18**(7):737–746. doi: 10.1191/0269215504cr780oa

28. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. *Mult Scler.* ۲۰۱۹;**11**(4):459–463. doi: 10.1191/1352458505ms1188oa.

29. DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. *Arch Phys Med Rehabil.* ۲۰۲۰;**85**(2):290–297. doi: 10.1016/j.apmr.۲۰۲۰.06.003.

30. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. *Mult Scler J.* ۲۰۱۸;**18**(9):1215–1228. doi: 10.1177/1352458512437418.

31. Shabas D, Weinreb H. Preventive healthcare in women with interferon beta-1b in MS: results of an open label trial. Neurol- multiple sclerosis. *J Womens Health Gend Based Med.* ۲۰۲۲;**9**(4):389–395. doi: 10.1089/15246090050020709.

32. Motl RW, Learmonth YC, Pilutti LA, Gappmaier E, Coote S. Top 10 research questions related to physical activity and multiple sclerosis. *Res Q Exerc Sport.* ۲۰۲۱;**86**(2):117–129. doi: 10.1080/02701367.۲۰۲۱.1023099.

33. Cameron MH, Lord S. Postural Control in Multiple Sclerosis: Implications for Fall Prevention. *Curr Neurol Neurosci Rep.* ۲۰۱۹;**10**:407–412. doi: 10.1007/s11910-010-0128-0.

34. Kargarfard M, Etemadifar M, Baker P, Mehrabi M, Hayatbakhsh R. Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. *Arch Phys Med Rehabil.* ۲۰۲۲;**93**(10):1701–1708. doi: 10.1016/j.apmr.۲۰۲۲.05.006.

۲۹ بهمن ماه ۱۴۰۲
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The Effects of Moderate Interval Training (MIT) and Lithium on Spatial Learning and Memory in Male Wistar Rats

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Abstract:
The most effective non-drug treatment for brain health promotion is physical exercise (EX). Exercise results in benefits such as modulation of autophagy, increased mitochondrial biogenesis, and upregulation of BDNF. The effects of lithium and MIT (moderate interval training) on spatial learning and memory in male Wistar rats were investigated in this study investigated. Also, we evaluated the role of mitochondrial genes and the BDNF protein in this effect. The study protocol included six groups of animals: Control (Ctr.), animals that did not receive the drug; II: Li10 (10 mg/kg/day/i.p.); III: Moderate-intensity training (MIT); IV: Li10 and MIT (Li10+MIT); V: Li40 (40 mg/kg/ip); VI: Li40 and MIT (Li40+ MIT). Our results showed that memory and spatial learning improved as a result of exercise ; nevertheless, lithium administration alone cannot exert this effect. Additionally, rats exposed to a combination of exercise and lithium showed improvement in spatial learning and memory.

Keywords:
exercise, lithium, cognitive.

1. Introduction:

The most effective non-drug treatment for brain health promotion is physical exercise (EX). A wide range of studies, both in animals and humans, have consistently demonstrated the positive effects of exercise on the brain (1, 2). Physical exercise has been demonstrated to enhance spatial learning abilities in individuals without any underlying health condition (3) and reduce neurodegenerative disease symptoms (4), such as those of Parkinson's and Alzheimer's disease and depression (5). Stimulation of neurogenesis is considered to be the cause of the beneficial effects of exercise (6), Exercise has been reported to enhance learning and memory formation (7). In one of the underlying mechanisms, BDNF expression is induced in the hippocampus (8).

exercise of effects positive the supporting evidence of body growing the Despite, of level the exercise in engage to Failure .low alarmingly remains activity physical regular to commitment decline cognitive for factor risk significant a poses, spatial learning, and memory .disorders the ,Furthermorespread of suchyears rise to projected is conditions ahead, with CfrgOVID-19 lifestyles sedentary of issue the exacerbating pandemic (10). Thus, the need for an approach using an alternative substance or an adjuvant is being felt. Lithium supplementation needs to be further studied to determine its long-term effects and optimal doses.

Lithium was first used in treating psychiatric disorders in the 1800s. It was primarily indicated for the treatment of bipolar disorder, a mental health condition characterized by episodes of mania and depression (11, 12, 13, 14, 15). Besides, lithium exerts neuroprotective effects and promotes the generation of new neurons, a process known as neurogenesis, by activating various signal transduction pathways. (16, 17, 18). More evidence is demonstrating that Li has a significant effect on the brain, particularly the hippocampus (19), which is responsible for memory and learning. BDNF (brain-derived neurotrophic factor) is believed to mediate such effects (20, 21). Studies on hippocampal tissue have also revealed the positive impact of lithium on mitochondrial activity (22).

Hence, the investigation into the potential synergistic effects of exercise and lithium on cognitive function in animal models could provide valuable insights for the development of novel therapies for cognitive disorders. Therefore, we designed this study to investigate the simultaneous effects of lithium consumption and moderate-intensity exercise on learning and spatial memory.

2. Material and methods

2.1. Animals

We housed 42 male Wistar rats weighing of 184.4 ± 7.2 g at 23–25 °C (room temperature) with a 12 h light /12 h dark cycle. During the first week, the rats were permitted to acclimatize to the new conditions. The animals had free access to water and suitable chow. The Ethics Committee of Zahedan University of Medical Sciences approved the experiment protocol (ethical code IR.ZAUMS.REC.1401.056).

2.2. Experimental groups:

We assigned the animals to six groups, each of them consisting of 7 animals; Group 1: Control (Ctr), animals that did not receive drugs or exercise, Group 2: Li10 (10 mg/kg/day/IP), Group 3: Moderate-intensity training (MIT), Group 4: Li10 and MIT (MIT+Li10), Group 5: Li40 (40mg/kg/IP), and Group 6: Li40 and MIT (MIT+Li40), (Diagram 1 and 2).

Lithium was dissolved in normal saline and the animals received a daily IP injection of Li at the doses of 10 mg/kg/day (26) and 40 mg/kg/day for six weeks between 8:30 and 10:30 AM (27).

2.3. Exercise Protocol

The MIT group animals practiced and trained for approximately one week prior to the initiation of the 6-week exercise training intervention to be familiarized with running on the treadmill (type USD5000, Form USD4500 Shenyang Sino-King Equipment Imp. & Exp. Co., Ltd.). Moreover, a 10 m/min warmup (5 mins) and cooldown (5 mins) preceded and followed every training session. The protocols for exercise were chosen based on previous studies.

The treadmill speed was used to adjust the intensity of the exercise training. For the MIT, the rats ran for 31 min at 55% of their maximum capacity in week 1, and the duration was slowly raised to 46 min and the speed to 70% by the end of week 6 (28, 29) The treadmill incline was 10% throughout the training period.

The exercise protocol for the six weeks (W) was as follows:

W1 → 31 min at 19 meters per minute
W2 → 31 min at 21 meters per minute
W3 → 37 min at 23 meters per minute
W4 → 40 min at 24 meters per minute
W5 → 46 min at 24 meters per minute
W6 → 46 min at 26 meters per minute

2.2 Body Weight Measurement

A digital weighing balance (Metter) and was used to weigh the rats before and every week after the beginning of the experiment.

2.3 Acquisition trial (learning assessment)

We assessed spatial memory and learning using the MWM (Morris water maze) test (30). Richard Morris designed the MWM in the early 1980s (31). In this test, a hidden platform was placed in the northwest quadrant of a pool to provide a refuge for the animals from water. To help the rats learn the platform's location, we placed doors, windows, and pictures as identifiable landmarks in another maze in the same location. We performed all trials in the 8:00 am–12:00 pm time frame.

In the beginning of every trial, the animals were placed in the water facing the wall of the maze; different quadrants were used as the starting point. The rats were given 120 seconds to locate the submerged platform by swimming in the maze. During the acquisition trials, the platform remained in the same location, the rat was given four training trials within a period of three days to find the platform. The rats were allowed a 20-second rest on the platform after locating it, and they were then returned to the chamber until their next trial. In each trial, different parameters, such as speed, escape latency, and the traveled distance before finding the submerged platform, were calculated and recorded (32).

2.4 Probe trial test (memory assessment)

A probe trial was conducted the day after the rats finished the acquisition stage to evaluate their spatial memory retention. During this phase, after removal of the platform, the rats were released in the water at random locations to try to locate the platform within 60 seconds. A video tracking system counted how often the rats passed where the platform used to be and measured how long they swam within the quadrant where the platform was initially located (32).

2.6. Statistical analysis:

SPSS statistical package ver. 24 (SPSS, Inc., Chicago, Illinois, USA) was used for data analysis. Shapiro-Wilk and Levene's tests were used to check normality and equal variances in data distributions, respectively. The MWM learning rate differences among the groups were assessed by two-way repeated measures ANOVA. One-way

ANOVA was used to analyze and compare the data collected from all the groups in the acquisition and probe phases of the Morris water maze . All post hoc comparisons were done using Tukey's test. The data were reported as mean ± SEM, and the significance criterion was $P < 0.05$.

3. Results:

3.1. The effects of lithium and exercise in the acquisition phase (learning):

In this study, we used the MWM test to assess the rats' spatial memory and learning abilities. The spatial learning rate of the animals was identified by two factors: the distance traveled and the escape latency (time spent) to locate the submerged platform. Two-way repeated measures ANOVA was performed to find the learning rate differences between the groups (considering days and group as factors). Fig. 1A and 1C present the escape latency and traveled distance, respectively, in the three-day acquisition phase. We continue our analysis by comparing the mean values of escape latency and traveled distance (Fig. 1B and Fig. 1D).

According to Fig. 1, the escape latency and traveled distance in the acquisition phase decreased significantly in the exercise (MIT) and MIT+Li10 groups [$F (5, 41) = 10.68$, $P < 0.01$ and $F (5, 41) = 5.16$, $P < 0.01$, respectively] compared to the Ctr group, while the Li10 delivered group only, did not show a significant difference with the Ctr group but exhibited a marked increase compared to exercise group ($P = 0.001$), which revealed the beneficial effects of exercise on the spatial learning, however, Li10 administration alone cannot affect the acquisition phase. The comparison of groups with the MIT group shows a clear upregulation in the escape latency and traveled distance in the Li10, Li40, and MIT+Li40 groups compared to the exercise group [$F (5, 41) = 10.68$, $P < 0.01$), ($F (5, 41) = 5.16$, $P < 0.05$]; which demonstrated that lithium, when used alone in low and high doses and when used at high doses as a supplement to exercise, decreases spatial learning in male rats. Swimming speed was not significantly different between the experimental groups (results not shown).

3.2. The effects of lithium and exercise in the probe phase (memory):

We considered two factors in the MWM test, the mean duration the rat swam in the target quadrant and the times it passed the target quadrant for spatial memory assessment. The results of Tukey's post hoc and one-way ANOVA in Ctr animals showed a significant rise in the percent of frequency and the mean percentage of time spent in the target quadrant in comparison to the Ctr group [$F (5, 41) = 9.29$, $P < 0.01$ and $P = 0.001$, respectively] in the exercise group (MIT) and the MIT+Li10 group, i.e., exercise had a positive effect on spatial memory (Fig 2A and Fig 2B). Besides, the assessed factors were not significantly different for spatial memory between the Li10, Li40, and MIT+Li40 groups compared with the Ctr group.

Another part of our study showed that the mean percentage (%) of time spent in the target quadrant significantly decreased in the Li10, Li40, and MIT+Li40 in comparison to the MIT group [$F (5, 41) = 9.29$, $P < 0.01$]; Nevertheless, there was no meaningful difference in percentage frequency between these groups. According to the Tukey's post hoc and one-way ANOVA tests, speed in the target quadrant was not significantly different among groups (results not shown).

3. Discussion:

The current study results contained valuable information on the potential benefits of exercise and low-dose lithium in improving cognitive function, specifically spatial memory and learning, in male Wistar rats. According to the findings, moderate interval training in combination with low-dose lithium can lead to significant improvements in spatial learning and memory, as measured by the Morris Water Maze test.

The Li10 and Ctr. groups were not significantly different, highlighting the importance of exercise in conjunction with low-dose lithium for optimal spatial learning and memory outcomes.

Our study provides compelling evidence that (EX) can have a positive impact on spatial learning, as demonstrated by the results of the Morris water maze test. These findings are consistent with previous research which has consistently highlighted the beneficial effects of exercise on cognitive function across a range of different populations, including healthy individuals of various ages and animal models of neurological and psychological diseases (34, 35, 36, 37, 38). In addition, extensive research has demonstrated the positive effects of exercise on various aspects of brain function, such as hippocampal plasticity (39), neurogenesis (40), cell proliferation, and dendritic branching (41). Additionally, investigations have consistently demonstrated that memory and learning are improved by regular exercise in both healthy humans (42, 43) and rodents (44,45). These findings highlight the potential of physical exercise as an affordable and accessible approach to enhance cognitive health throughout life. Our study aligns with these findings, as we observed that as a result of moderate-intensity training, the spatial memory and learning of normal rats improved, as there was an increase in time spent in the targeted quadrant and a reduction in escape latency and traveled distance.

Although our study did not investigate the potential negative effects of excessive exercise on neurogenesis, some evidence suggests that high-intensity exercise may not be as beneficial and may even be harmful (38). Furthermore, research has shown that stressful high-intensity exercise can result in increased levels of corticosterone, leading to maladaptive neurological function (46). The variety of training protocols used in the experiments, e.g., differences in the exercise duration and intensity or exercise type (e.g., swimming, wheel, or treadmill) may explain inconsistencies in the findings of different studies (47). Therefore, it is important to find the optimal exercise intensity level that can provide health benefits without causing harm.

We also evaluated the effects of exercise and lithium on spatial memory. Our results showed that exercise and low-dose lithium administration had a positive impact on spatial memory. However, high doses of lithium alone and the combination of exercise and high doses of lithium, decreased the mean percentage of the time the rats stayed in the target quadrant. Consistent with the present study, several reports have shown that, in humans, higher levels of lithium are associated with impaired memory performance in patients with psychosis (48). Research has associated lithium treatment with reduction in memory, learning, and information processing speed in bipolar disorder patients, as well as in control subjects to some extent (49, 50, 51). Additionally, lithium therapy was not found to help bipolar patients with their episodic memory deficit (52). Nevertheless, Certain researchers have reported that long-term administration of lithium boosts spatial working memory in rats (53,54). Additionally, spatial memory and learning were seen to improve by lithium treatment in animals subjected to temporary global cerebral ischemia and cranial irradiation (55) when tested using the Morris water maze. Our results also indicated that MIT was not able to prevent the adverse effects of high doses of lithium on cognitive function.

The variety of training protocols used in the experiments, e.g., the different exercise duration and intensity or exercise types (e.g., swimming, wheel, or treadmill) may explain inconsistencies in findings of different studies (47). Although our study results suggest that lithium 10 alone had a greater effect on gene expression than MIT or MIT+Lit10, Moderate-interval training did lead to an improvement in the spatial memory and learning performance of the mice in the MWM test. The improvement may be caused by other signaling pathways being activated and other genes being expressed, the mechanisms of which, this study did not examine.

Accordingly, Further research is needed to better understand the mechanisms underlying how exercise affects hippocampal gene expression and cognitive function, possibly leading to the development of novel interventions for the prevention and treatment of neurological disorders. Overall, our study provides valuable insights into the potential synergistic effects of exercise and low-dose lithium supplementation on cognitive function and mitochondrial biogenesis. However, caution should be taken when using high doses of lithium, as they may have detrimental effects on cognitive function and BDNF expression. Future studies are needed to further investigate lithium supplementation to determine its long-term effects and optimal dosages in combination with exercise for promoting optimal brain health.

Legend of figures:

Fig1: The effect of exercise and lithium in Morris Water Maze learning phase and comparison of study groups. (A) Escape latency in locating the submerged platform during the three testing days (B) The mean of escape latency in locating the submerged platform (C) Distance traveled for locating the submerged platform during the three testing days, (D) The mean of distance traveled in locating the submerged platform. Data are reported as mean ± SEM (n = 7). $^{**}P < 0.01$ for MIT and MIT+Li10 vs. Ctr, $^{+}P < 0.05$, $^{++}P < 0.01$ and $^{+++}P < 0.001$ for Li10, Li40 and MIT+Li40 vs. MIT. Ctr (control), MIT (exercise), Li10 (lithium 10), Li40 (lithium 40).

Fig2. The effect of exercise and lithium in Morris Water Maze memory phase and comparison of study groups. (A) Comparison of the mean duration of swimming in the target quadrant (%) in study groups. (B) Comparison of the mean of frequency (%) in the study groups. Data are reported as mean ± SEM (n = 7). $^{**}P < 0.01$ and $^{***}P < 0.001$ for MIT and Li10 vs. Ctr, $^{+}P < 0.05$, $^{++}P < 0.01$ and $^{+++}P < 0.001$ for Li10 vs. MIT. Ctr (control), MIT (exercise), Li10 (lithium 10), Li40 (lithium 40).

Fig3. Hippocampus PGC1 and SIRT3 mRNA expression in the experimental groups. Data are reported as mean ± SEM (n = 7). $^{**}P < 0.01$ and $^{***}P < 0.001$ for MIT and Li10 vs. Ctr, $^{+}P < 0.05$, $^{++}P < 0.01$ and $^{+++}P < 0.001$ for Li10, Li40 and ELi40 vs. MIT. Ctr (control), MIT (exercise), Li10 (lithium 10).

Fig4. The BDNF density in the hippocampus in the experimental groups. Data are reported as mean ± SEM (n = 7). $^{**}P < 0.01$ and $^{***}P < 0.001$ for MIT and Li10 vs. Ctr, $^{+}P < 0.05$ for Li10 vs. MIT. Ctr (control), MIT (exercise), Li10 (lithium 10).

References:

1. Cefis M, Prigent-Tessier A, Quirié A, Pernet N, Marie C, Garnier P. The effect of exercise on memory and BDNF signaling is dependent on intensity. Brain Structure and Function. 2019;224(6):1975-85.
2. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proceedings of the national academy of sciences. 2011;108(7):3017-22.
3. Diederich K, Bastl A, Wersching H, Teuber A, Strecker J-K, Schmidt A, et al. Effects of different exercise strategies and intensities on memory performance and neurogenesis. Frontiers in behavioral neuroscience. 2017;11:47.
4. Paillard T, Rolland Y, de Souto Barreto P. Protective effects of physical exercise in Alzheimer's disease and Parkinson's disease: a narrative review. Journal of clinical neurology. 2015;11(3):212-9.
5. Bonanni R, Cariati I, Tarantino U, D'Arcangelo G, Tancredi V. Physical exercise and health: a focus on its protective role in neurodegenerative diseases. Journal of Functional Morphology and Kinesiology. 2022 Apr 29;7(2):38.
6. Van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proceedings of the National Academy of Sciences. 1999;96(23):13427-31.
7. Berchtold NC, Castello N, Cotman CW. Exercise and time-dependent benefits to learning and memory. Neuroscience. 2010;167(3):588-97.
8. Marosi K, Mattson MP. BDNF mediates adaptive brain and body responses to energetic challenges. Trends in Endocrinology & Metabolism. 2014;25(2):89-98.
9. Gusdon AM, Callio J, Distefano G, O'Doherty RM, Goodpaster BH, Coen PM, Chu CT. Exercise increases mitochondrial complex I activity and DRP1 expression in the brains of aged mice. Experimental gerontology. 2017;90:1-13.
10. Okamoto M, Mizuuchi D, Omura K, Lee M, Oharazawa A, Yook JS, et al. High-intensity intermittent training enhances spatial memory and hippocampal neurogenesis associated with BDNF signaling in rats. Cerebral Cortex. 2021;31(9):4386-97.
11. Lee J-H, Kim S-W, Kim J-H, Kim H-J, Um J, Jung D-W, Williams DR. Lithium chloride protects against sepsis-induced skeletal muscle atrophy and cancer cachexia. Cells. 2021;10(5):1017.
12. Won E, Kim YK. An oldie but goodie: lithium in the treatment of bipolar disorder through neuroprotective and neurotrophic mechanisms. International journal of molecular sciences. 2017 Dec 11;18(12):2679.
13. Volkmann C, Bschor T, Köhler S. Lithium treatment over the lifespan in bipolar disorders. Front Psychiatry 11: 377.
14. Yousef M, Kavraal Ş, Artış AS, Süer C. Effects of chronic and acute lithium treatment on the long-term potentiation and spatial memory in adult rats. Clinical Psychopharmacology and Neuroscience. 2019 Mar;17(2):233.
15. Baranowski RW, Skelly LE, Josse AR, Fajardo VA. Exploring the Effects of Greek Yogurt Supplementation and Exercise Training on Serum Lithium and Its Relationship With Musculoskeletal Outcomes in Men. Frontiers in Nutrition. 2021;8:798036.
16. Boyko M, Nassar A, Kaplanski J, Zlotnik A, Sharon-Granit Y, Azab AN. Effects of acute lithium treatment on brain levels of inflammatory mediators in poststroke rats. BioMed research international. 2015 Sep 27;2015.
17. Hajek T, W Weiner M. Neuroprotective effects of lithium in human brain? Food for thought. Current Alzheimer Research. 2016 Aug 1;13(8):862-72.
18. Machado-Vieira R, Manji HK, Zarate Jr CA. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. National Library of Medicine. National Center for Biotechnology Information. PubMed Central. June. 2009.
19. Budni J, Feijó DP, Batista-Silva H, Garcez ML, Mina F, Belletini-Santos T, Krasilchik LR, Luz AP, Schiavo GL, Quevedo J. Lithium and memantine improve spatial memory impairment and neuroinflammation induced by β-amyloid 1-42 oligomers in rats. Neurobiology of Learning and Memory. 2017 May 1;141:84-92.
20. Zanni G, Michno W, Di Martino E, Tjärnlund-Wolf A, Pettersson J, Mason CE, Hellspong G, Blomgren K, Hanrieder J. Lithium accumulates in neurogenic brain regions as revealed by high resolution ion imaging. Scientific reports. 2017 Jan 18;7(1):40726.
21. Stout J, Hozer F, Coste A, Mauconduit F, Djebrani-Oussedik N, Sarrazin S, Poupon J, Meyrel M, Romanzetti S, Etain B, Rabrait-Lerman C. Accumulation of lithium in the hippocampus of patients with bipolar

disorder: a lithium-7 magnetic resonance imaging study at 7 tesla. Biological psychiatry. 2020 Sep 1;88(5):426-33.
22. Singulani MP, De Paula VJ, Forlenza OV. Mini review: Mitochondrial dysfunction in Alzheimer's disease: Therapeutic implications of lithium. Neuroscience Letters. 2021 Aug 24;760:136078.
23. Undi RB, Gutti U, Gutti RK. LiCl regulates mitochondrial biogenesis during megakaryocyte development. Journal of Trace Elements in Medicine and Biology. 2017 Jan 1;39:193-201.
24. Cardillo GD, De-Paula VD, Ikenaga EH, Costa LR, Catanozi S, Schaeffer EL, Gattaz WF, Kerr DS, Forlenza OV. Chronic lithium treatment increases telomere length in parietal cortex and hippocampus of triple-transgenic Alzheimer's disease mice. Journal of Alzheimer's Disease. 2018 Jan 1;63(1):93-101.
25. Yousef M, Kavraal Ş, Artış AS, Süer C. Effects of chronic and acute lithium treatment on the long-term potentiation and spatial memory in adult rats. Clinical Psychopharmacology and Neuroscience. 2019 Mar;17(2):233.
26. Jung SR, Park SY, Koh JH, Kim JY. Lithium enhances exercise-induced glycogen breakdown and insulin-induced AKT activation to facilitate glucose uptake in rodent skeletal muscle. Pflügers Archiv-European Journal of Physiology. 2021 Apr;473:673-82.
27. Ommati MM, Niknahad H, Farshad O, Azarpira N, Heidari R. In vitro and in vivo evidence on the role of mitochondrial impairment as a mechanism of lithium-induced nephrotoxicity. Biological Trace Element Research. 2021 May;199:1908-18.
28. Leite, Allyne Baía, et al. "High-intensity interval training is more effective than continuous training to reduce inflammation markers in female rats with cisplatin nephrotoxicity." *Life Sciences* 266 (2021): 118880.
29. Samadian, Zahra, et al. "Moderate-intensity exercise training ameliorates the diabetes-suppressed spermatogenesis and improves sperm parameters: Insole and simultaneous with insulin." *Andrologia* 51.11 (2019): e13457.
30. Haghparast E, Esmaeili-Mahani S, Abbasnejad M, Sheibani V. Apelin-13 ameliorates cognitive impairments in 6-hydroxydopamine-induced substantia nigra lesion in rats. Neuropeptides. 2018 Apr 1;68:28-35.
31. Morris RG. Spatial localization does not require the presence of local cues. Learning and motivation. 1981 May 1;12(2):239-60.
32. Chahkandi M, Sepehri G, Komeili G, Hadad MK, Haghparast E, Chahkandi M. The different role of G-protein-coupled receptor 30 (GPR30) in the interaction effects of marijuana and estradiol on spatial learning and memory at different ages. Brain Research Bulletin. 2022 Jan 1;178:155-63.
33. Azarian F, Farsi S, Hosseini SA, Azarbayjani MA. Effect of endurance training with saffron consumption on PGC1-α gene expression in hippocampus tissue of rats with Alzheimer's disease. Annals of Military and Health Sciences Research. 2020 Mar 31;18(1).
34. Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. Neurogenesis and neural plasticity. 2013:189-210.
35. Diederich K, Bastl A, Wersching H, Teuber A, Strecker JK, Schmidt A, Minnerup J, Schäbitz WR. Effects of different exercise strategies and intensities on memory performance and neurogenesis. Frontiers in behavioral neuroscience. 2017 Mar 16;11:47.
36. Zang Q, Wang S, Qi Y, Zhang L, Huang C, Xiu Y, Zhou C, Luo Y, Jia G, Li S, Zhang Y. Running exercise improves spatial learning and memory ability and enhances angiogenesis in the cerebral cortex via endogenous nitric oxide. Behavioural Brain Research. 2023 Feb 15;439:114243.
37. Khoury R, Saad J, Jabre V, Ghayad LM, Khalifeh M, Houbeika R, El Ahmad P, Mezher A, El Masri D, Haddad Z, Eid F. Autophagy regulates the release of exercise factors and their beneficial effects on spatial memory recall. Heliyon. 2023 Apr 1;9(4).
38. Diederich K, Bastl A, Wersching H, Teuber A, Strecker JK, Schmidt A, Minnerup J, Schäbitz WR. Effects of different exercise strategies and intensities on memory performance and neurogenesis. Frontiers in behavioral neuroscience. 2017 Mar 16;11:47.
39. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity—exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports medicine. 2010 Sep;40:765-801.
40. Van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. Journal of Neuroscience. 2005 Sep 21;25(38):8680-5.
41. Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. Journal of Comparative Neurology. 2005 May 23;486(1):39-47.

42. Håkansson K, Ledreux A, Daffner K, Terjestam Y, Bergman P, Carlsson R, Kivipelto M, Winblad B, Granholm AC, Mohammed AK. BDNF responses in healthy older persons to 35 minutes of physical exercise, cognitive training, and mindfulness: associations with working memory function. Journal of Alzheimer's Disease. 2017 Jan 1;55(2):645-57.

43. Kandola A, Hendrikse J, Lucassen P J ,Yücel M. Aerobic exercise as a tool to improve hippocampalplasticity and function in humans: practical implications for mental health treatment. Frontiers in human neuroscience2016: 10(373

44. Wang XQ, Wang GW. Effects of treadmill exercise intensity on spatial working memory and long-term memory in rats. Life sciences. 2016 Mar 15;149:96-103.

45. Kim B-K, Shin M-S, Kim C-J, Baek S-B, Ko Y-C ,Kim Y-P, Treadmill exercise improves short-term memory by enhancing neurogenesis in amyloid beta-induced Alzheimer disease rats. Exercise rehabilitation 2014: 10; 2-8.

46. Wu Y, Deng F, Wang J, Liu Y, Zhou W, Qu L, Cheng M. Intensity-dependent effects of consecutive treadmill exercise on spatial learning and memory through the p-CREB/BDNF/NMDAR signaling in hippocampus. Behavioural brain research. 2020 May 27;386:112599.

47. Constans A, Pin-Barre C, Molinari F, Temprado JJ, Brioche T, Pellegrino C, Laurin J. High-intensity interval training is superior to moderate intensity training on aerobic capacity in rats: Impact on hippocampal plasticity markers. Behavioural Brain Research. 2021 Feb 1;398:112977.

48. Bora E, Vahip S, Akdeniz F, Gonul AS, Eryavuz A, Ogut M, Alkan M. The effect of previous psychotic mood episodes on cognitive impairment in euthymic bipolar patients. Bipolar disorders. 2007 Aug;9(5):468-77.

49. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. Psychopharmacology. 2003 Nov;170:225-34.

50. Honig A, Arts BM, Ponds RW, Riedel WJ. Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice. International clinical psychopharmacology. 1999 May 1;14(3):167-71.

51. Stip E, Dufresne J, Lussier I, Yatham L. A double-blind, placebo-controlled study of the effects of lithium on cognition in healthy subjects: mild and selective effects on learning. J Affect Disord. 2000;60:147–157. doi: 10.1016/S0165-0327(99)00178-0

52. López-Jaramillo C, Lopera-Vásquez J, Ospina-Duque J, García J, Gallo A, Cortez V, Palacio C, Torrent C, Martínez-Arán A, Vieta E. Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. The Journal of clinical psychiatry. 2010 Mar 23;71(8):10476.

53. Tsaltas E, Kontis D, Boulougouris V, Papakosta VM, Giannou H, Poulopoulou C, Soldatos C. Enhancing effects of chronic lithium on memory in the rat. Behavioural brain research. 2007 Feb 12;177(1):51-60.

54. Yan XB, Hou HL, Wu LM, Liu J, Zhou JN. Lithium regulates hippocampal neurogenesis by ERK pathway and facilitates recovery of spatial learning and memory in rats after transient global cerebral ischemia. Neuropharmacology. 2007 Sep 1;53(4):487-95.

55. Yazlovitskaya EM, Edwards E, Thotala D, Fu A, Osusky KL, Whetsell Jr WO, Boone B, Shinohara ET, Hallahan DE. Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation. Cancer research. 2006 Dec 1;66(23):11179-86.

56. Whitley KC, Hamstra SI, Baranowski RW, Watson CJ, MacPherson RE, MacNeil AJ, Roy BD, Vandenboom R, Fajardo VA. GSK3 inhibition with low dose lithium supplementation augments murine muscle fatigue resistance and specific force production. Physiological reports. 2020 Jul;8(14):e14517.

57. Martin SA, Souder DC, Miller KN, Clark JP, Sagar AK, Eli ceiri KW, Puglielli L, Beasley TM, Anderson RM. GSK3β regulates brain energy metabolism. Cell reports. 2018 May 15;23(7):1922-31.

58. Rybakowski JK, Suwalska A, Hajek T. Clinical perspectives of lithium's neuroprotective effect. Pharmacopsychiatry. 2018 Sep;51(05):194-9.

59. R.B. Undi, U. Gutti, R.K. Gutti, LiCl regulates mitochondrial biogenesis during megakaryocyte development, J. Trace Elem. Med. Biol. 39 (2017) 193–201,

60. I.T. Struewing, C.D. Barnett, T. Tang, C.D. Mao, Lithium increases PGC-1α expression and mitochondrial biogenesis in primary bovine aortic endothelial cells, FEBS J. 274 (2007) 2749–2765,

61. Wang J, Feng H, Zhang J, Jiang H. Lithium and valproate acid protect NSC34 cells from H2O2-induced oxidative stress and upregulate expressions of SIRT3 and CARM1. Neuroendocrinology Letters. 2013 Jan 1;34(7):648-54.

62. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013 Jun 6;153(6):1194-217.

63. Allen AR, Jones AV, LoBianco FV, Krager KJ, Aykin-Burns N. Effect of Sirt3 on hippocampal MnSOD activity, mitochondrial function, physiology, and cognition in an aged murine model. Behavioural Brain Research. 2023 Apr 27;444:114335.

64. Govindarajulu M, Ramesh S, Neel L, Fabbrini M, Buabeid M, Fujihashi A, Dwyer D, Lynd T, Shah K, Mohanakumar KP, Smith F. Nutraceutical based SIRT3 activators as therapeutic targets in Alzheimer's disease. Neurochemistry International. 2021 Mar 1;144:104958.

65. Wang T, Zhu M, He ZZ. Low-molecular-weight fucoidan attenuates mitochondrial dysfunction and improves neurological outcome after traumatic brain injury in aged mice: involvement of Sirt3. Cellular and molecular neurobiology. 2016 Nov;36:1257-68.

66. Khanna A, Acharjee P, Acharjee A, Trigun SK. Mitochondrial SIRT3 and neurodegenerative brain disorders. Journal of chemical neuroanatomy. 2019 Jan 1;95:43-53.

67. De-Paula VJ, Gattaz WF, Forlenza OV. Long-term lithium treatment increases intracellular and extracellular brain-derived neurotrophic factor (BDNF) in cortical and hippocampal neurons at subtherapeutic concentrations. Bipolar Disorders. 2016 Dec;18(8):692-5.

68. de Sousa RT, van de Bilt MT, Diniz BS, Ladeira RB, Portela LV, Souza DO, Forlenza OV, Gattaz WF, Machado-Vieira R. Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study. Neuroscience letters. 2011 Apr 20;494(1):54-6.

69. Leyhe T, Eschweiler GW, Stransky E, Gasser T, Annas P, Basun H, Laske C. Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's disease. Journal of Alzheimer's Disease. 2009 Jan 1;16(3):649-56.

70. El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, El-Ghandour R, Nasrallah P, Bilen M, Ibrahim P, Younes J. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). Journal of Neuroscience. 2019 Mar 27;39(13):2369-82.

71. García-Mesa Y, Pareja-Galeano H, Bonet-Costa V, Revilla S, Gómez-Cabrera MC, Gambini J, Giménez-Llort L, Cristòfol R, Viña J, Sanfeliu C. Physical exercise neuroprotects ovariectomized 3xTg-AD mice through BDNF mechanisms. Psychoneuroendocrinology. 2014 Jul 1;45:154-66.

72. Kim DM, Leem YH. Chronic stress-induced memory deficits are reversed by regular exercise via AMPK-mediated BDNF induction. Neuroscience. 2016 Jun 2;324:271-85.

73. de Assis GG, Almondes KM. Exercise-dependent BDNF as a modulatory factor for the executive processing of individuals in course of cognitive decline. A systematic review. Frontiers in psychology. 2017 Apr 19;8:584.

74. Salamon A, Torok R, Sumegi E, Boros F, Pesei ZG, Molnar MF, Veres G, Zadori D, Vecsei L, Klivenyi P. The effect of physical stimuli on the expression level of key elements in mitochondrial biogenesis. Neuroscience Letters. 2019 Apr 17;698:13-8.

75. Liu Y, Yan T, Chu JM, Chen Y, Dunnett S, Ho YS, Wong GT, Chang RC. The beneficial effects of physical exercise in the brain and related pathophysiological mechanisms in neurodegenerative diseases. Laboratory Investigation. 2019 Jul 1;99(7):943-57.

76. Azarian F, Farsi S, Hosseini SA, Azarbayjani MA. Effect of endurance training with saffron consumption on PGC1-α gene expression in hippocampus tissue of rats with Alzheimer’s disease. Annals of Military and Health Sciences Research. 2020 Mar 31;18(1).

Changes of interleukins during exercise

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Introduction

It is a well-known fact that regular exercise and physical activities in general are very important for maintaining health and preventing disease. For many years, there was no recommendation for MS patients to participate in sports activities. This issue was due to the fact that some patients had reported symptoms of instability during activity, followed by an increase in body temperature (Vuori, 2004). But currently, prescribing exercise is considered as a useful therapeutic solution to minimize the lack of functional ability in chronic diseases. In many researches, it was stated that exercise in MS patients with mild to moderate intensity has similar physical and psychological benefits to the healthy control group. In recent research, it has been stated that exercise can lead to several therapeutic results, such as improving cardio-respiratory function, muscle function, reducing depression and fatigue and making patients to improve health and quality of life. On the other hand, various researches proved that sports activity causes many physiological changes in the immune system. Exercise regulates immune responses through the production of cytokines, which play a role in regulating the formation of immune and inflammatory responses. In many studies, the effect of short-term exercise on cytokine production in healthy population has been examined (Chan et al., 2019). Research has been done on the effect of sports training on the mentioned patients. The effect of aerobic activity, resistance training (using body weight) and weight training on walking ability, strength, fatigue, functional ability, and personal quality of life of people with MS, a review and the results of each study according to the structure and content of the training program. Selected, differently reported (Lorig et al., 1999). Studies have shown that combined aerobic and strength training has an effect on the level of IL-17 in women with MS, and after a few weeks of training, the anti-inflammatory effects of exercise have reduced IL-17 (Golzari et al., 2010). Few researches have been done regarding the effect of exercise on cortisol changes in MS patients.

For example, Pyatin1 and colleagues (2009) used whole body vibration exercises to improve muscle, nerve and flexibility function and presented reports of increasing

bone density, decreasing the secretion of anabolic hormones and also decreasing cortisol as a beneficial anti-stress effect. These researchers concluded that this type of activity is beneficial for people suffering from osteoporosis and obesity (Green et al., 2023).

and to restore neurological and motor function in patients with Parkinson's disease, MS And stroke is useful. In 2004, Scholes et al., in a study that included 8 weeks of aerobic exercise with 60% of the maximum oxygen consumption on a cycle monitor, controlled factors such as cortisol in MS patients (Winkelman, 2009).

And after the end of the research period, they observed an improvement in the action of cortisol and also concluded that aerobic exercises with pabin levels in MS patients not only improve the quality of life, but also the coordinated performance and physical fitness. But on the other hand, many researches have been done regarding the effect of exercise on cortisol changes in other samples. For example, Pezijablo and colleagues (1390) showed that resistance and endurance training does not have a significant effect on cortisol.

Limoui et al. (2010) showed in research that a session of relaxation training in two times in the morning and in the evening has a significant decrease in cortisol level (Krahn, 2010; Meigal et al., 2021). Hosseini and Agha Alinejad (1388) in research of parallel exercises, it was found that the cortisol levels of the groups did not change significantly (Hosseini et al., 2012). While Sadr al-Ashrafi et al. (2010) showed that the salivary cortisol level increased after a period of rhythmic movement training (Hayes et al., 2013). Few studies have been done regarding the effect of exercise on the factors affecting the health of MS patients. For example, Moradi and colleagues showed that resistance training improves the levels of muscle endurance, strength and balance in MS patients (Anderson & Wideman, 2017).

Maqsoudi and colleagues showed that selected aerobic and strength training leads to a decrease in interleukin-10, tumor necrosis factor alpha and interferon gamma in men and women with MS. Also, Soltani and colleagues reported that a period of aerobic activity in water leads to the improvement of EDSS1 (Physical Disability Scale

in MS patients) of MS patients. These researchers stated that these exercises can be used as a complementary treatment along with drug treatments for MS patients.

Nevertheless, based on our information, few studies have been conducted regarding the effect of sports activities and especially resistance exercises on IL-17 and cortisol levels in MS patients. Therefore, the current study seeks to answer this question, does eight weeks of resistance training have a significant effect on cortisol and IL-17 in MS patients?

Discussion and conclusion

The results of the analysis of the findings of this study showed that eight weeks of resistance training has a significant effect on the reduction of interleukin-17 in patients with MS. Interleukin-17 is a pro-inflammatory cytokine that is secreted by Th-17 cells and causes and strengthens inflammation by inducing various factors (Mosili et al., 2020). The results of Golzari et al.'s research (1389) are in line with the results of the present study. The results of Golzari et al.'s study showed that eight weeks of combined exercises (including warm-up, stretching exercises, aerobic exercises, strength exercises and relaxation program at the end of each session) reduces the level of interleukin-17 in people, which is in line with the results of the present study. Meanwhile, the results of the present study are not in line with the study of (Mosili et al., 2020). The results of Satari Fred's study showed that a session of sports activity in hot weather leads to a significant increase of interleukin-17.

One of the reasons for the inconsistency of the results could be due to the type of training, in the present study it was eight weeks of resistance training, while in the study of Satari Fard et al., the effect of one session of sports activity was examined (Mirzaei et al., 2021). Also, Sattari Fard et al. (2011) showed that a session of sports activity in cold weather does not cause a change in interleukin-17. Also, Dozva et al.1 (2009) stated in research that 12 weeks of intense sports activity increases interleukin-17.

This study is not aligned with the present study. One of the reasons for inconsistency can be the number of training sessions and the type of training. In the present study, eight weeks of resistance training were performed, and the subjects were MS patients, while in the study of Dozva et al., 12 weeks of intense exercise were performed, and their subjects were healthy people (Dozva, 2018).

Due to the fact that intense activities can activate pro-inflammatory cytokines, these cytokines can increase the expression of interleukin-17, so probably one of the reasons that interleukin-17 increased in the study of Dozova et al. can be due to high training intensity. Pedersen and Femen's research results (2001) showed that a session of intense sports activity increases interleukin-17. The results of this research are not in line with the present study. One of the reasons for the inconsistency of the results can be due to the type of exercise. In the present study, it was eight weeks of resistance training, while in the study of Pederson and Ha Femen, the effect of one intense exercise training session was examined (Pederson and Ha Femen 2001). Many researchers stated that in long-term or intense activities, the amount of interleukin-17 production increases, and in the group that performs sports activity with a shorter duration (one week) and moderate intensity, this increase is not observed, and in some cases, it leads to a decrease in interleukin-17. becomes 17 (Dozva, 2018). Probably, the mechanism involved is related to the fact that intense exercise causes the release of pro-inflammatory cytokines, and these cytokines produce anti-inflammatory cytokines such as interleukin-2, interleukin-6, and interleukin-10. It seems that the sequential production of pro-inflammatory and anti-inflammatory cytokines is the reason for the initiation of interleukin-17 production through peripheral blood and skeletal muscle leukocytes (Kumar et al., 2008).

According to the results of various researches, it can be said that the intensity or duration of sports activity is an important factor in increasing or decreasing the production of interleukin-17 (Anderson & Wideman, 2017). In a study, scientists came to the conclusion that consuming too much salt in the diet can be related to the disruption of the body's immune system and the development of autoimmune diseases such as MS. In other words, high salt consumption causes excessive activation and proliferation of 17TH cells, which are a type of T-cell helpers that play a role in stimulating the inflammatory protein interleukin-17 (Yousfi et al. and Vusi et al. 2013).

Also, in research entitled the effect of interferon drug on intervekin 17 of MS patients, it has been found that this cytokine plays a very important role in the symptoms of this disease, as after taking this drug, the level of intervekin o-17 in the MS patients of this research has decreased significantly (Michalowaska et al. 2011).

The results of the analysis of the findings of this study showed that eight weeks of resistance training has a significant effect on reducing the amount of cortisol in patients with MS. The results of the research of Scholes et al. (2004) are in line with the results of the present study. The results of Scholes et al.'s study showed that eight weeks of aerobic training with 60% of the maximum oxygen consumption on a bicycle reduces the cortisol level of people, which is in line with the results of the present study. Also, Sadr al-Ashrafi et al. (1389) stated in research that 8 weeks of rhythmic sports activity increases the cortisol of inactive married women.

The results of this study are not consistent with the present study. One of the reasons for inconsistency can be the type of exercise. In the present study, eight weeks of resistance training were performed, while in the present study, eight weeks of balanced aerobic exercise were performed (Lashgari et al., 2018).

Based on the available information, the history of studies on the effect of exercise on the hormone system of the human body dates back to 1986. The results obtained from the research conducted by Bunt 1 in that year showed that the initial hormonal changes that occur during intense exercise are due to the secretion of catecholamines 2 from the adrenal glands, which start the preparation of sugars and fatty acids. This reaction stimulates other endocrine glands and body cells (anterior and posterior pituitary, adrenal cortex, thyroid, parathyroid, liver, pancreas and kidneys) to secrete secondary hormones that strengthen the mobilization of other reserves and water concentration. and regulate electrolytes.

As exercise continues, the concentration of ions and nutrients also affect hormonal responses. In 1987, Lager and his colleagues 3 designed a study to investigate the rapid responses of hypothalamic-pituitary-adrenal axis hormones to treadmill aerobic exercise and concluded that physical activity is associated with a decrease in the activity of the pituitary-adrenal axis in response to the amount of activity loading. In addition, based on the findings of this research, changes in the hypothalamus-pituitary-adrenal axis continue with a slight increase in cortisol and lead to an increase in depression and competitive anxiety in professional athletes. Doster et al.4 in 1989 studied hormonal and metabolic responses to exercise with three different intensities.

The findings showed that the sympathetic system-adrenal central part 1 is more sensitive to exercise compared to the hypothalamus-pituitary-adrenal axis, which was significantly less sensitive to the absolute load of exercise in trained people. Most of the studies indicate an increase in cortisol along with an increase in exercise intensity. Extremely high amounts of cortisol following long-term training, including marathons, have been observed in subjects, even in activities that have less intensity, if the training period is long enough, plasma cortisol levels increase. In the current research, the results showed that the cortisol level of the subjects in the training group decreased by 9.8% after 8 weeks of resistance training, and this decrease was significant compared to the control group; Therefore, 8 weeks of resistance training has a significant effect on reducing cortisol levels in women with MS. Based on the investigations and the obtained information, the combination of fatigue and depression in this disease has caused So far, little research has been done to discover the physiological causes of excessive fatigue caused by this disease, and for this reason, the physiological causes of fatigue related to this disease remain unknown, and except for a small number of researches, in almost all research cases, fatigue from The behavioral or psychological point of view has been investigated, while based on the few available researches, the problem of excessive fatigue in this disease can also have a physiological factor. According to the available information, excessive and less than normal activity in the hypothalamus-pituitary-adrenal axis has a significant pathophysiological relationship with depression and chronic fatigue syndrome (Netherton et al., 2004). MS is a disease associated with high prevalence of depression.

It has been reported that in both MS and depression, increased levels of cortisol and inflammation are related to disruption of the immune system's endocrine glands. An imbalance in glucocorticoid-mineralocorticoid signaling in the central nervous system is suggested as a mechanism of depression pathogenesis. Regarding the possible mechanisms of the connection between these two diseases, it is possible to mention the increase in sympathoadrenal activity caused by the intensification of HPA axis activity, as well as the increase in HPA activity and the increase in serum cortisol, the size of the adrenal and pituitary glands, and the increase in sympathoadrenal activity in depressed patients (Salomé et al., 2006).

References

Anderson, T., & Wideman, L. (2017). Exercise and the cortisol awakening response: a systematic review. *Sports medicine-open*, *3*(1), 1-15.

Chan, J. S., Liu, G., Liang, D., Deng, K., Wu, J., & Yan, J. H. (2019). Special issue–therapeutic benefits of physical activity for mood: a systematic review on the effects of exercise intensity, duration, and modality. *The Journal of psychology*, *153*(1), 102-125.

Dozva, M. (2018). *The impact of urban street community on young children's educational development in Zimbabwe* University of Pretoria].

Golzari, Z., Shabkhiz, F., Soudi, S., Kordi, M. R., & Hashemi, S. M. (2010). Combined exercise training reduces IFN-γ and IL-17 levels in the plasma and the supernatant of peripheral blood mononuclear cells in women with multiple sclerosis. *International immunopharmacology*, *10*(11), 1415-1419.

Green, C., Jiang, Y., & Isaacs, J. (2023). Robert Gordon University, Aberdeen AB10 7AQ, Scotland c. green1@ rgu. ac. uk. Virtual, Augmented and Mixed Reality: 15th International Conference, VAMR 2023, Held as Part of the 25th HCI International Conference, HCII 2023, Copenhagen, Denmark, July 23–28, 2023, Proceedings,

Hayes, L. D., Grace, F. M., Sculthorpe, N., Herbert, P., Ratcliffe, J. W., Kilduff, L. P., & Baker, J. S. (2013). The effects of a formal exercise training programme on salivary hormone concentrations and body composition in previously sedentary aging men. *Springerplus*, *2*(1), 1-5.

Hosseini, M., Piri, M., Agha-Alinejad, H., & Haj-Sadeghi, S. (2012). The effect of endurance, resistance and concurrent training on the heart structure of female students. *Biology of Sport*, *29*(1), 17-21.

Krahn, L. E. (2010). Circadian Rhythm Sleep Disorders: Physiology of the Circadian Clock. In *Atlas of Sleep Medicine* (pp. 143-156). CRC Press.

Kumar, S. A., Lo, P.-H., & Chen, S.-M. (2008). Electrochemical selective determination of ascorbic acid at redox active polymer modified electrode derived from direct blue 71. *Biosensors and Bioelectronics*, *24*(4), 518-523.

Lashgari, S., Sanatkaran, A., & Rafiee, S. (2018). The Effect of Pilates and TRX Exercises on Non-athletic Women's Mood. *Egyptian Academic Journal of Biological Sciences, E. Medical Entomology & Parasitology*, *10*(1), 95-104.

Lorig, K. R., Sobel, D. S., Stewart, A. L., Brown Jr, B. W., Bandura, A., Ritter, P., Gonzalez, V. M., Laurent, D. D., & Holman, H. R. (1999). Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. *Medical care*, 5-14.

Meigal, A. Y., Tretjakova, O. G., Gerasimova-Meigal, L. I., & Sayenko, I. V. (2021). Program of seven 45-min dry immersion sessions improves choice reaction time in Parkinson's disease. *Frontiers in Physiology*, *11*, 621198.

Mirzaei, E., Azar, F. E. F., Ziapour, A., Azadi, N. A., Qorbani, M., Safari, O., & Mansourian, M. (2021). The impact of educational intervention based on theory of planned behavior for promoting physical activity among middle-aged women referring to Karaj (Iran) health centers. *International quarterly of community health education*, *41*(4), 419-426.

Mosili, P., Maikoo, S., Mabandla, M., Vuyisile, & Qulu, L. (2020). The pathogenesis of fever-induced febrile seizures and its current state. *Neuroscience insights*, *15*, 2633105520956973.

Netherton, C., Goodyer, I., Tamplin, A., & Herbert, J. (2004). Salivary cortisol and dehydroepiandrosterone in relation to puberty and gender. *Psychoneuroendocrinology*, *29*(2), 125-140.

Salomé, N., Viltart, O., Lesage, J., Landgraf, R., Vieau, D., & Laborie, C. (2006). Altered hypothalamo–pituitary–adrenal and sympatho-adrenomedullary activities in rats bred for high anxiety: central and peripheral correlates. *Psychoneuroendocrinology*, *31*(6), 724-735.

Vuori, I. (2004). Physical inactivity is a cause and physical activity is a remedy for major public health problems. *Kinesiology*, *36*(2), 123-153.

Winkelman, C. (2009). Bed rest in health and critical illness: a body systems approach. *AACN advanced critical care*, *20*(3), 254-266.

The effect of regular exercise on the immune system

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Abstract:
The body's immune system is designed and created like an artistic masterpiece. A complex and effective network that connects different parts of the body and millions of specialized cells. The body's immune system is able to identify millions of potential enemies and design and implement different strategies to deal with them. At the same time, this does not mean that this system is not affected by diseases or does not need treatment and medicine. When you're sick, the best way to rebuild your immune system is to give it what it needs to repair itself, and that's nothing more than a healthy diet and regular, moderate-intensity exercise. Exercising is always considered as a health solution. According to the studies conducted in this section, doing moderate to intense sports improves the functioning of the immune system.

Exercise and safety

Physical activity may help flush bacteria from the lungs and airways. This may reduce your chances of getting a cold, flu, or other illness. Exercise causes changes in antibodies and white blood cells (WBCs). White blood cells are immune system cells that fight disease. they do. In exercise, these antibodies or white blood cells circulate faster, so they can detect diseases earlier than before.

A brief increase in body temperature during and immediately after exercise may prevent bacterial growth. This increase in temperature may help the body fight infection better. Exercise reduces the release of stress hormones. Some stress increases the possibility of getting sick. Less stress hormones may protect against disease (Duncan, 2005).

What is aerobic exercise?

When you are exercising and due to a lot of exercise, your heart rate has increased and your body is sweating, and the blood circulation system is working to supply oxygen to your muscles, and because of sufficient oxygen supply, you can continue your activity. And you don't get tired quickly, this flow is called aerobic exercise.

Examples of aerobic sports are: aerobic exercise machines (cardio), pedaling, running, swimming, walking, cycling, cross-country skiing, and sailing, of course there are many other types. Aerobic sports should be of low intensity and activity. It should be moderate, and if the intensity increases, it is no longer aerobic and becomes anaerobic (Spurway, 1992).

These sports have many benefits in terms of health and fitness, and also help to calm the soul and mind. Doing these kinds of sports is recommended to everyone and it reduces the occurrence of some diseases and helps to treat them.

Aerobic exercise program should be simple, practical and realistic. You can use special equipment (such as aerobic exercise machines), but it is not necessary to use this equipment to do aerobic exercise.

The effects of aerobic exercise on health are very effective. When starting this exercise, the first thing that starts to work is breathing. In this exercise, breathing and oxygen supply to the muscles play a vital role, a healthy person normally moves 8 liters of air in his respiratory system in one minute.

During aerobic exercise, when we draw oxygen into the lungs, it passes through the trachea and reaches the air sac, which is the path of oxygen reaching the heart, straight from the air sac. Therefore, it is not possible to perform aerobic sports without the presence of oxygen (Rickhi et al., 2011).

The effects and reactions that occur in the body when doing aerobic activity: By doing these exercises, the heart becomes stronger and delivers more blood to the organs of the body. Every minute they have more heart volume than normal people.

The heart is a muscle and gets bigger with exercise. When you start to exercise, the heart becomes more active and makes the lungs stronger. In the exercise body, the stroke volume increases, because he is active and needs a

lot of oxygen to continue the activity. Therefore, it pumps a lot of blood to deliver oxygen to the muscles of the body.

When we say that athletes have a strong heart, it means that they have a higher stroke volume and a lower heart rate.

Exercises with a primary focus on aerobic exercise are beneficial because they burn fat, improve cardiovascular health and fitness, and improve the body's ability to recover and repair after intense exercise. Changing the composition of muscle fibers in aerobic exercises increases endurance. Aerobic exercise causes muscle recovery and repair after exercise, which in turn helps muscle growth. The increase in myoglobin and mitochondria in muscle tissue caused by aerobic exercises increases aerobic capacity. Aerobic exercises cause several changes, all of which help the body burn more fat (Byrd, 1988).

Anaerobic exercise

Intense and anaerobic training increases the size and quantity of fast-twitch muscles and improves muscle strength and size.

Anaerobic exercise to develop tolerance to lactic acid; which induces fatigue, aids and improves muscle endurance. Metabolic changes resulting from anaerobic activity help increase the amount of energy available to muscles, allowing them to perform faster and more powerfully during exercise. The hormones that cause muscle growth are enhanced by anaerobic exercises (Alipour & Eisazadeh, 2020).

Exercises to strengthen the immune system

Exercise is one of the best ways to boost immunity and immune response. These exercises are designed to detoxify your lymphatic system and energize your body to fight the millions of germs that surround you every day. From moderate to vigorous exercise, anything that gets you up and moving will benefit your immune system.

● Strength training

Weight lifting and strength training stress your body in a way that it is not naturally stressed. It increases blood flow throughout the body and relieves stress. The intensity added to strength training has a significant effect on the body's immune system.

● High intensity interval training (HIIT)

There are few workouts like HIIT that get your heart pumping and act as a steroid for your immune system.

HIIT should only be done a few times a week, as too much exercise can actually backfire on your immune system.

Walking A short walk, about as long as your lunch break, is enough to keep your immune system functioning as it should.

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● Walking A short walk, about as long as your lunch break, is enough to keep your immune system functioning as it should. Plan a brisk walk at least five times a week for at least 30 minutes.

● Rebound Rebounding is an exercise that involves jumping on a mini fitness trampoline. This sport is not only fun, but it is one of the best exercise programs for draining the lymphatic system and detoxifying the body.

According to research in 2019, exercise even affects the body's defense and immune response so that the risk of contracting diseases decreases and inflammation decreases. This study focused on moderate-to-vigorous exercise lasting less than an hour.

Researchers claim that the human body has a small number of immune cells that are circulating throughout the body. These cells are usually found in tissues and lymphatic organs, including the spleen. In these organs, the body fights and destroys viruses, germs and bacteria that cause disease. The researchers concluded that by exercising and increasing blood circulation, you can increase the circulation of immune cells in the body so that they can deal with viruses and bacteria more quickly (Shirini Pargami et al., 2018).

Apart from this, exercise can also activate special immune cells to make the body safer. In the research we mentioned, some people did 45 minutes of brisk walking and were able to face an increase in the circulation of immune cells throughout the body up to three hours after exercise.

Although the immune system immediately becomes stronger and the body safer when exercising, this effect will eventually wear off. But if you exercise regularly, you can always benefit from this increased immunity. This event can be compared to eating. If you eat a meal, your hunger will disappear. But after a few hours you get hungry again and you have to eat again. The relationship between exercise and body immunity is the same. You should have proper and regular exercise throughout the week to keep your immune system high. Doing aerobic and stretching exercises is the best way to raise the body's immunity level. Among these sports, we can mention sitting and stretching, stretching, butterfly movements, running and even walking (McHeyzer-Williams, 1997).

The relationship between aerobic and resistance exercise and body immunity

Aerobic exercises increase the heart rate, and as the heart rate increases, more microphages are produced in the body and create a defense barrier against viruses and help to destroy them. For this reason, aerobic and resistance sports will help to increase the immunity of people.

The effect of walking on the immune system the effect of walking on the immune system is very significant. A gentle walk or a fast and professional walk, both can improve the body's immune status and effectively prevent many diseases. One of the main benefits of walking will be helping to lose weight, which will help reduce the body's resistance to viral and microbial diseases.

According to the U.S. Institute of Health. National Institute of Health Exercises not only help the immune system to fight disease and common bacteria and arterial infections and cause more synthesis of white blood cells and increase the body's overall resistance, but also reduce the risk of heart disease, cancer, and reduces osteoporosis. Also, the adaptation caused by sports exercises develops the defense system of the human body (Bayigga et al., 2014).

Studies recently published in the American Journal of Medicine show that women who walk for 30 minutes during the day catch colds less than others. Recent studies in America have shown that women who walk regularly catch colds less than others. Previously, studies have shown that people over 65 years of age who exercise regularly, their immune system is as healthy as people who are half their age.

Moderate intensity exercise is beneficial for the immune system. If the exercise is intense, it may cause the destruction of the cells of the immune system or create a difference in the efficiency of the immune system. Therefore, intense exercise, despite having many benefits, weakens the immune system until the end of recovery. After complete recovery, the immune system returns to normal.

Jumping is a very good way to strengthen the body's immune system because movement and physical activity are useful for strengthening the immune system, and it is also much softer than running and is stress-free.

The reason why jumping with a trampoline and rebounding strengthens your immune system is that this device increases the metabolism and metabolic rate in your body and increases the blood circulation system and
the flow of lymph fluid in the body. This blood circulation makes the lymphocytes and antibodies in the blood, that is, the army and the body's resistance system, move faster in the body and cleanse the body of pollution and pathogens faster and even before complications occur.

When you are stressed, your immune system is disrupted. Since it is practically impossible to live without stress in today's modern day-to-day life, we can use methods to reduce and release our stress during the day. Trampoline provides you with a natural way to release your daily stress. Soft jumps and oscillations on the springboard of the trampoline will loosen your muscles and lubricate your body joints. With this simple massage method, your daily stress will be relieved to a great extent and you will feel much better after using it, and you will sleep more comfortably at the end.

At the same time, by jumping on the trampoline, more oxygen reaches your body and the release of endorphins, which is a factor of good morals and cheerfulness, is accelerated. All these factors will make you feel better after using the trampoline.

Many studies have investigated the effect of aerobic exercise on the immune system, and the result is that aerobic exercise has a positive effect on immune function and can even reduce the risk of upper respiratory tract infections, such as colds. But heavy sports or long-term sports such as marathons have the opposite effect because it weakens the body's defense against infection by increasing the possibility of getting infected with annoying viruses. The biggest detriment to immune performance is training hard and intensely without giving the body a chance to recover.

The lymphatic system plays a very important role in your immune system. Bacteria, toxins, cancer cells are collected in the lymph nodes before being discharged from the body. Jumping several times in situ is an excellent way to increase the flow of lymph fluid in the body and strengthen the immune system.

If you have little movement during the day or your work with little movement is like the work that you have to sit at the desk; Your risk of infection is 2 to 3 times higher than others. Research shows that those who exercise continuously, the chance of catching respiratory infections such as colds is reduced by nearly a third. On the other hand, after a period of intense and long-term exercise, the chance of getting an infection and becoming a A patient increases. This member of the British Society of General Microbiology emphasized: Exercising in a balanced way helps to strengthen the function of the body's immune system cells and controls the hormonal changes that occur due to stress, etc., but excessive exercise can be just as harmful, so if you have a disease, for example Avoid exercising if you have a cold.

The increasing effect of tiring exercises followed by other intense exercises has a negative effect on the immune system. Exercising too much without adequate rest and recovery suppresses the activity of killer cells, the cells

that fight viruses and help keep tumor cells from gaining a foothold in the body. You probably don't want to weaken these guard cells. Exercising in moderation benefits the immune system and killer cell function, while exercising too much will impair their ability (Abd El-Kader & Al-Shreef, 2018).

Bodybuilding and immune system

Most of the studies that have studied the effect of exercise on the immune system have focused on endurance exercise. Health and safety are a very important issue in the field of sports, especially for people who do heavy sports such as marathons. But few studies have studied the effect of bodybuilding exercises on the body's immune activity, one of the oldest of which dates back to 1996.

Strength training temporarily increases the number of circulating immune cells that help protect the body against infections. These cells are part of the body's internal system and include certain types of white blood cells and killer cells. In this small study, 22 people participated in the bodybuilding program. Half of them were young (between 20 and 30 years old) and the rest were older (between 65 and 80 years old). Some of these people were healthy and others had rheumatoid arthritis. Their weight training program consisted of lifting weights at 80% of one repetition maximum with 8 repetitions per set (three sets per session). They trained three times a week for 12 weeks. There was also a control group that did not exercise.

When the researchers measured various indicators of the immune system, they found that there was no significant difference between the exercise group and the control

group. That is, strength training using relatively high resistance could not affect people's safety performance, but this was only a study!

More recent research shows that strength training temporarily increases the number of circulating immune cells that help protect the body against infections. These cells are part of the body's internal system and include certain types of white blood cells and killer cells. This enhancement of immune activity has been less pronounced in older people because aging itself affects the immune system.

Just like other parts of the body, our immune system ages through a process called immunosenescence. Research shows that the enhanced activity of immune cells after bodybuilding can be a way to increase the immune response that elderly people face. But not much research has been done on what type of exercise is best, and there are still many questions about exercise and the immune system.

In another study, the researchers of Zahedan University of Medical Sciences, by examining 155 athletes aged 19 to 54, to measure the power of the immune system,

evaluated the number of antibodies produced in their bodies in response to the injection of the influenza vaccine. (In simple words, in fact, the researchers They wanted to measure the amount and level of defense of the white blood cells of the tested athletes by introducing influenza germs into the bodies of the tested athletes compared to normal people.)

In this research, the researchers divided the athletes into 3 categories with normal, moderate and intense activity based on the intensity of the exercise.

Based on this research, the results of which were presented in the 9th Congress of Immunology and Allergy of Iran. Finally, it was found that exercise increases the response of the immune system to the influenza vaccine. This study also shows that the greater the intensity of exercise, the greater the effect on strengthening the immune system.

In addition to its physical benefits, exercise is the most important factor in eliminating depression or preventing these types of diseases. It has been proven that continuous daily exercises reduce anxiety, depression, regulate and adjust the amount of stress and even personality changes (the emergence of a more positive view of life).

As mentioned, many times, physical activity reduces nervous tension, relieves stress and fights depression, since depression is known to produce suitable conditions for tiring the body's immune system, and most of the time, people suffering from various types of depression diseases are, their immune system will suffer and they are ready to get physical diseases. So, by exercising and doing physical activity, while making our psyche resistant to mental stress, we also strengthen our body's immune system and reduce the risk of contracting various diseases.

According to researchers, today's modern life, which is very stressful at times, has harmful effects on both health and thinking of people. When a person is tired, he needs to rest and sleep comfortably, but when he is stressed and anxious, he cannot rest properly, and this lack of rest causes irreparable problems in the human mind and body (Kim & Kim, 2023).

Strengthening cellular immunity with exercise

Doing sports activities naturally increases body temperature. For this reason, sweating during exercise is considered a very natural phenomenon. After your exercise is over, your body temperature is still a bit high so

you can gradually return to normal conditions. Many bacteria and pathogenic agents are unable to grow at high temperature and will be destroyed if present.

For this reason, increasing body temperature can greatly help the body's immune system. This issue will actually create a fever-like function in the body. Of course, don't forget that fever has a stronger effect in this section. Temporary body heat after exercise can be a helpful tool for your immune system, so use it in a special way (Jee, 2020).

Strengthening body immunity by reducing stress through exercise

Stress and anxiety are the root of many physical and mental problems that cause many problems for you. The release of stress hormones causes restlessness and frequent discomfort. Studies have proven that high stress weakens the body's immune system. Exercising plays an important role in reducing the release of stress hormones, which is suggested as an excellent solution. Exercise brings with it freshness and a good feeling. During exercise, happy hormones such as serotonin start to be released. As a result, a person's stress level also decreases a lot. By weakening the immune system, depression and anxiety create conditions for the occurrence of various infections. For this reason, if you have a professional plan for your exercise, you can fight various diseases more easily (Jee, 2020).

Reduce inflammation with regular exercise

One of the special effects of exercise is that it can reduce the amount of inflammation in the body. Inflammation occurs when your body is fighting toxins and pathogens. Inflammation is basically the body's natural response that is used for treatment. Inflammations in themselves are not considered a special problem, but when they become chronic, they will cause a lot of trouble.

One of the best ways to reduce inflammation is to exercise regularly. In order for the body's immune response to reach its lowest level, you must have planned exercise. It is important to mention that intense and long-term sports can aggravate inflammation. For this reason, be sure to strictly and professionally follow the sports standards (Wilund, 2007).

Exercise conditions during illness

Exercising during the illness when the immune system is weakened should be done in a controlled manner. In many cases, exercising can aggravate your disease. It is also possible that the recovery period will be longer. If you have symptoms such as high fever, it is better to rest most of your time. Of course, the severity of the disease will be very effective in the amount of your exercise. However, if your disease is mild, you can do light sports activities. In this case, the body's immune system works better (Primos Jr, 1996).

Improving sleep and immune system with exercise

Having regular physical activity can be effective in regulating your sleep. Lack of sleep causes the number of antibodies in your blood to decrease. This causes the risk of cardiovascular diseases to increase. Also, lack of sleep causes the power of the body's immune system to decrease. All these things together make us realize the importance of sleep. People who exercise regularly sleep

better. If you have a proper exercise plan, you will maintain your health easily (Primos Jr, 1996).

Conclusion

Exercise has many benefits for physical and mental health, and everyone should try to have more physical activity in their lives. Although other healthy habits such as eating fruits and vegetables, managing stress and mental problems, quality sleep and having a healthy lifestyle can also help to reduce the risk of diseases, but it can be said that exercise is the best and most effective way to improve the health of the body and the environment. Staying is one of various diseases. The need for physical activity to strengthen the immune system of the elderly is certain, there must be a regular exercise and physical activity program for all age groups (both men and women).

References:

(Duncan, 2005)

Abd El-Kader, S. M., & Al-Shreef, F. M. (2018). Inflammatory cytokines and immune system modulation by aerobic versus resisted exercise training for elderly. *African health sciences*, *18*(1), 120-131.

Alipour, A., & Eisazadeh, F. (2020). The Impact of Spirituality and Religion on the Immune System: A Review. *Journal of Quran and Medicine Volume*, *5*(2).

Bayigga, L., Nabatanzi, R., Sekiziyivu, P. N., Mayanja-Kizza, H., Kamya, M. R., Kambugu, A., Olobo, J., Kiragga, A., Kirimunda, S., & Joloba, M. (2014). High CD56++ CD16-natural killer (NK) cells among suboptimal

immune responders after four years of suppressive antiretroviral therapy in an African adult HIV treatment cohort. *BMC immunology*, *15*(1), 1-8.
Byrd, R. C. (1988). Positive therapeutic effects of intercessory prayer in a coronary care unit population.
Duncan, W. (2005). Prayer and spirituality in health: Ancient practices, modern science. *CAM at the NIH-Focus on Complementary and Alternative Medicine*(1).
Jee, Y.-S. (2020). Physical exercise for strengthening innate immunity during COVID-19 pandemic: 4th series of scientific evidence. *Journal of Exercise Rehabilitation*, *16*(5), 383.
Kim, J.-H., & Kim, J.-S. (2023). Effect of bodybuilding athletes' weight loss method on performance factors and immune function. *Journal of Exercise Rehabilitation*, *19*(6), 357.
McHeyzer-Williams, M. G. (1997). Immune response decisions at the single cell level. Seminars in immunology,
Primos Jr, W. A. (1996). Sports and exercise during acute illness: recommending the right course for patients. *The Physician and sportsmedicine*, *24*(1), 44-54.
Rickhi, B., Moritz, S., Reesal, R., Xu, T. J., Paccagnan, P., Urbanska, B., Liu, M. F., Ewing, H., Toews, J., & Gordon, J. (2011). A spirituality teaching program for depression: a randomized controlled trial. *The International Journal of Psychiatry in Medicine*, *42*(3), 315-329.
Shirini Pargami, B., KHalatbari, J., Tavakol, M., & Tarkhan, M. (2018). Prediction of warning signs of immune deficiency through Psychological Indicators by mediation Personality Characteristics in Nurses. *QUARTERLY JOURNAL OF HEALTH PSYCHOLOGY*, *7*(25), 74-94.
Spurway, N. (1992). Aerobic exercise, anaerobic exercise and the lactate threshold. *British Medical Bulletin*, *48*(3), 569-591.
Wilund, K. R. (2007). Is the anti-inflammatory effect of regular exercise responsible for reduced cardiovascular disease? *Clinical science*, *112*(11), 543-555.

The effect of exercise on improving the immune system and reducing the risk of various diseases

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Abstract

Purpose: This research was prepared to investigate the role of exercise in improving the body's immune system and reducing the incidence of disease. Human body and mental health is a goal that all people strive to achieve. One of the important factors in maintaining health and improving body condition is exercise (Brien SE, 2007). In addition to helping muscles and cardiovascular function, exercise has a great effect on improving the body's immune system and reducing the risk of various diseases (Foster C, 2018). Exercise increases blood flow in the body, which in turn increases the number of white blood cells, protein substances and other components of the immune system. These components strengthen the body's immune system and make the body better able to deal with external factors such as bacteria, viruses and other infectious diseases (Williams PT, 2007). Exercise can be used as a method of preventing infectious diseases. Exercise also has a positive effect on reducing the risk of various diseases. According to scientific research, exercise reduces the risk of heart disease, type 2 diabetes and obesity-related diseases (Gibala MJ, 2006). Also, exercise increases the level of antioxidants in the body, which reduces the complications of aging-related diseases such as arthritis, Alzheimer's and cancer-related diseases (Pedersen BK, 2000).

Method: Using the review method, 20 articles were reviewed and then their summary was written in this abstract.

Results: Various sports can help improve the body's immune system. Resistance sports such as bodybuilding increase the number of white blood cells and other components of the immune system. Also, aerobic sports such as running and swimming increase the blood flow in the body and strengthen the muscles and cardiovascular system, which improves the immune system (Anderson L, 2016). In addition, mental exercises such as yoga and breathing exercises can also help improve the body's immune system. Exercise is introduced as a simple and

efficient way to improve the body's immune system and reduce the risk of contracting various diseases. By increasing blood flow, strengthening muscles and increasing the number of white blood cells, exercise has a positive effect on the immune system. In addition, exercise reduces the risk of chronic diseases such as heart disease and diabetes. Therefore, it is recommended that every person have a regular exercise program on weekdays to improve his immune system and reduce the risk of diseases.

Keywords: exercise, immune system, diseases, body.

References

List of Persian sources:
Tavakli, M., Movahdi, K. 1401.. The 7th International Conference on Psychology, Educational Sciences and Child Rights in the Islamic World, Tehran.

Hakimi, L. 1381.. Iranian Journal of Children's Diseases.

Khaliqpour, H., Mofazal Jahrami, M., Alwar, Abuzar. 2019.. The first national online seminar on managing the Corona crisis, focusing on sports for health, Ahvaz.

Ulamazadeh, M., Faramarzi, M. 2019.. Journal of Isfahan Faculty of Medicine, page 477-488.

Melanuri Shamsi, M., Amani Shalamzadi, p. 2019.. Sports physiology (research in sports sciences), page 17-40.

Miri, M., Ghasemi, A. 2019.. The 5th International Conference on New Researches in Sports Sciences and Physical Education, Hamadan.

List of Latin sources:
Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016; 67(1): 1-12.

Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol 2012; 2(2): 1143-211.

Brien SE, Katzmarzyk PT, Craig CL, Gauvin L. Physical activity, cardiorespiratory fitness and body mass index as predictors of substantial weight gain and obesity: The Canadian physical activity longitudinal study. Can J Public Health 2007; 98(2): 121-4.

Fiuza-Luces C, Santos-Lozano A, Joyner M, CarreraBastos P, Picazo O, Zugaza JL, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. Nat Rev Cardiol 2018; 15(12): 731-43.

Foster C, Shilton T, Westerman L, Varney J, Bull F. World Health Organisation to develop global action plan to promote physical activity: Time for action. Br J Sports Med 2018; 52(8): 484-5.

Gibala MJ, Little JP, van Essen M, Wilkin GP, Burgomaster KA, Safdar A, Raha S, Tarnopolsky MA. Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. Journal of Physiology. 2006; 575(Pt 3): 901-911.

Katzmarzyk PT, Powell KE, Jakicic JM, Troiano RP, Piercy K, Tennant B. Sedentary behavior and health: Update from the 2018 physical activity guidelines advisory committee. Med Sci Sports Exerc 2019; 51(6): 1227-41.

Low WY, Lee YK, Samy AL. Non-communicable diseases in the Asia-Pacific region: Prevalence, risk factors and community-based prevention. Int J Occup Med Environ Health 2015; 28(1): 20-6.

Nocon M, Hiemann T, MullerRiemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. European Journal of Cardiovascular Prevention & Rehabilitation. 2008; 15: 239-246.

Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiological Review. 2000; 80(3): 1055-1081

Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P. Position statement. Part one: Immune function and exercise. Exercise Immunology Review. 2011; 17: 6-63.

Williams PT. Physical fitness and activity as separate heart disease risk factors: A meta-analysis. Med Sci Sports Exerc 2001; 33(5): 754-61.

Wilund KR. Is the anti-inflammatory effect of regular exercise responsible for reduced cardiovascular disease? Clin Sci (Lond) 2007; 112(11): 543-55.

Physical activities and neurophysiological changes in brain

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Abstract

Introduction: Regular physical activity can reduce the risk of cognitive decline, including dementia. With no exercise, the brain may be more vulnerable to the effects of this age-related decline. Physical activity can help everyone think, learn, problem-solve, and enjoy an emotional balance. It can also improve memory and reduce anxiety or depression. In this short article some neurochemical changes in nerves' system during physical activity will be introduced.

Methods: The present study briefly introduces the neurophysiological and neurochemical changes of the brain during physical activity. Information has been collected from various articles.

Results and Discussion: resistance and endurance exercises evoke substantial functional brain changes, especially in the frontal lobe, which were accompanied by improvements in executive functions. Furthermore, physical activities by changing the levels of neurochemicals can influence the expression level of some genes and finally neuroplasticity can appear.

Keywords: Physical activity, Brain, Neurophysiological changes

Introduction:

Endurance and resistance exercises: Endurance training is what refer to as aerobic exercise. It may involve bicycling, it may involve walking on a treadmill, and it may involve swimming. Resistance training is a form of exercise intended to increase muscular strength and endurance. It involves exercising muscles using some form of resistance. This resistance could be weights, bands, or even everyone bodyweight working against gravity (Swank, Ann Marie, 1996).

Physical activity and central nervous system plasticity:

Physical activity is an effective determinant of brain neurophysiology and can be seen as a broadly practiced behavior that enacts molecular and cellular cascades which bolster and keep up brain versatility. These changes are interceded by upregulation of a few development components or growth factors, counting vascular endothelial growth factor, and brain-derived neurotrophic factor (BDNF) (Russo L, 2003). BDNF could be a key protein in controlling upkeep, development, and indeed survival of neurons (, and has been appeared to be an imperative activity-dependent modulator of synaptic transmission and, in turn, of synaptic versatility (Khairrunnuur and Rahimah, 2022). Besides, BDNF appears to intercede exercise-induced neurogenesis, i.e., the method by which modern neurons multiply and create (Khairrunnuur and Rahimah, 2022). Exercise can moreover advance physiological changes within the brain. Past transcranial Doppler research reported that high-impact exercise can be advantageous for the support of cerebral blood flow (CBF) (Jianxiu Liu et al, 2023). Amid physical movement, CBF increments to supply satisfactory oxygen to the brain and the direction of CBF shows up pivotal for the upkeep of cardiovascular homeostasis. Chronic exercise has also the potential to influence the brain and motor function. Neuroplasticity refer to the capacity of the brain and central nervous system (CNS) to adjust to natural changes by adjusting neural network and function, such as physical activity doing that.

Myokines and brain

A myokine is one of a few hundred cytokines or other little proteins and proteoglycan peptides that are delivered and discharged by skeletal muscle cells in reaction to strong contractions (Pedersen BK, et al, 2007). They have autocrine, paracrine and/or endocrine effects. Mykines's receptors are found on muscle, fat, liver, pancreas, bone, heart, resistant, and brain cells (Delezie et al, 2018). These molecules involved in exercise-associated metabolic changes, as well as within the metabolic changes taking after preparing adaptation. They too take an interest in tissue recovery and repair, immunomodulation and cell signaling, expression and differentiation (Pedersen BK, et al, 2007).During endurance and resistance exercise, muscle synthesis, and release myokines (e.g., brain-derived neurotrophic factor, BDNF), as well as of metabolites (such as lactate) into the blood circulation. Myokines can cross the blood–brain barrier (BBB) and influence the functions of both neurons and glial cells. These molecules modify neurotransmission in different parts of the brain. For example at the cellular level, it was reported that treadmill exercise can increase hippocampal neurogenesis in aged mice (Lezi et al, 2014). Exercise can also affect the size, function and the rate of astrocytes proliferation (Li et al, 2005 and

Saur et al, 2014). Consequently the number and localization of neuronal synapses will be changed. So long term potentiation (LTP) and episodic memory can be influenced (Chen and Russo, 2009).

Physical activity and Neurotransmitters:

Exercise has been shown to improve brain function in animal models and an increasing number of human clinical studies. Exercise has a number of mechanisms that contribute to its brain-enhancing effects, such as vascularization, antioxidation, neuroinflammation, energy adaptation, and regulation of neurotrophic factors and neurotransmitters. Exercise is known to modulate three major monoamine neurotransmitters: dopamine (DA), noradrenaline (NE), and serotonin (Lin and Kuo, 2013).

The regulation of some genes during exercise

Numerous pieces of evidence point to the regulation of gene expression and muscle plasticity by muscle contraction in and of itself. Since the most significant signal during muscle contraction is undoubtedly changes in intracellular [Ca^{2+}], it is very likely that Ca^{2+} is what triggers the aforementioned changes in fiber phenotype and, more generally, muscle adaptation to PA. Excitation-contraction coupling (ECC) is actually the mechanism underlying contractility, as is the intricate interaction between voltage-gated and ligand-gated channels, contractile proteins (like myosin), buffer proteins that bind calcium (like calreticulin, parvalbumin, and calsequestrin), calcium-sensor proteins (like calcineurin and calmodulin), and calcium-dependent ATPases (Gehlert et al, 2015). Calcium ions can also control glycolysis by releasing glucose through the breakdown of glycogen; in muscle cells, the calcium/calmodulin (CaM) complex, which makes up its δ subunit, activates glycogen phosphorylase kinase (PhK), the enzyme that phosphorylates and activates the glycogen-breaking enzyme phosphorylase (GP) (Cohen, 1980 and Dasgupta et al, 1989).Furthermore, CaM has the ability to interact with PFK-M, the pacemaker of glycolysis, which is an isoform specific to muscles (Sola et al, 2010). An increase in ATP synthesis and the energy conversion potential are also brought about by Ca^{2+} influx into mitochondria (Gehlert et al, 2015).

Effects of Physical activity on neurodegeneration

In recent years, there has been an increasing body of evidence supporting the idea that regular exercise can help prevent and even treat neurological disorders. Simultaneously, a great deal of research is being done to determine the optimal patient protocols, with an emphasis on the mechanisms that underlie physical activity (PA)'s capacity to ameliorate the symptomatology of neurodegenerative diseases. Exercise-produced lactate and brain derived neurotrophic factor (BDNF) appear to have stimulating effects on learning and memory processes (Tari et al, 2019). Cathepsin B is a cysteine protease that is involved in multiple aspects of Alzheimer's disease pathogenesis. It is noted the endogenous inhibitor of this enzyme, cystatin B (CSTB) crosses the blood-brain barrier and may enhance learning and memory by stimulating hippocampal neurogenesis. Nevertheless, since Alzheimer disease (AD) patients have elevated blood levels of this enzyme, its precise function in AD is still up for debate (Tari et al, 2019). It has also been reported recently that in a mouse model of AD, 4 weeks of exercise can reverse the induction of genes encoding proteins involved in inflammation and apoptosis in the hypothalamus. Improvements in glucose metabolism were also noted after six weeks, and after eight weeks, there was a noticeable decrease in apoptosis in certain hypothalamic neuron populations (Do et al, 2018). Lastly, it has been proposed that the benefits of aerobic exercise for early AD patients stem from the exercise-dependent improvement of cardiorespiratory fitness, which is linked to better memory function and less hippocampal atrophy (Morris et al, 2018).

Conclusion: the beneficial effects of exercise on neurochemicals and improving neuro-cognition, neurogenesis, and brain functions have been reported. Regular exercise at a moderate intensity improves neurochemicals in all three classes and influences mental health and well-being.

References:

Chen M.J., Russo-Neustadt A.A. Running exercise-induced up-regulation of hippocampal brain-derived neurotrophic factor is CREB-dependent. Hippocampus. 2009; 19:962–972.

Cohen P. The role of calcium ions, calmodulin and troponin in the regulation of phosphorylase kinase from rabbit skeletal muscle. Eur. J. Biochem. 1980; 111:563–574.

Dasgupta M., Honeycutt T., Blumenthal D.K. The gamma-ubunit of Skeletal Muscle Phosphorylase Kinase Contains Two Noncontiguous Domains That Act in Concert to Bind Calmodulin. J. Biol. Chem. 1989; 264:17156–17163.

Delezie, Julien; Handschin, Christoph (2018). "Endocrine Crosstalk Between Skeletal Muscle and the Brain". Frontiers in Neurology. 9: 698.

Do K., Laing B.T., Landry T., Bunner W., Mersaud N., Matsubara T., Li P., Yuan Y., Lu Q., Huang H. The effects of exercise on hypothalamic neurodegeneration of Alzheimer's disease mouse model. PLoS ONE. 2018; 13:e0190205.

Gehlert S., Bloch W., Suhr F. Ca^{2+}-dependent regulations and signaling in skeletal muscle: From electro-mechanical coupling to adaptation. Int. J. Mol. Sci. 2015; 16:1066–1095.

Jianxiu Liu, Leizi Min, Ruidong Liu, Xiaoyu Zhang, Meiting Wu, Qian D. Xindong Ma. The effect of exercise on cerebral blood flow and executive function among young adults: a double-blinded randomized controlled trial. Scientific Reports , 2023, volume 13, Article number: 8269.

Khairunnuur Fairuz Azman and Rahimah Zakaria. Recent Advances on the Role of Brain-Derived Neurotrophic Factor (BDNF) in Neurodegenerative Diseases. Int J Mol Sci. 2022 Jun; 23(12): 6827.

Lezi E., Burns J.M., Swerdlow R.H. Effect of high-intensity exercise on aged mouse brain mitochondria, neurogenesis, and inflammation. Neurobiol. Aging. 2014; 35:2574–2583.

Li J., Ding Y.H., Rafols J.A., Lai Q., McAllister J.P., 2nd, Ding Y. Increased astrocyte proliferation in rats after running exercise. Neurosci. Lett. 2005; 386:160–164.

Lin TW and Kuo YM. Exercise Benefits Brain Function: The Monoamine Connection. Brain Sci. 2013 Mar; 3(1): 39–53.

Morris J.K., Vidoni E.D., Johnson D.K., Van Sciver A., Mahnken J.D., Honea R.A., Wilkins H.M., Brooks W.M., Billinger S.A., Swerdlow R.H., et al. Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. PLoS ONE. 2017; 12:e0170547.

Pedersen BK, Akerström TC, Nielsen AR, Fischer CP (September 2007). "Role of myokines in exercise and metabolism". Journal of Applied Physiology. 103 (3): 1093–8.

Russo L. The Forgotten Revolution. Springer; Berlin/Heidelberg, Germany: New York, NY, USA: 2003.

Saur L., Baptista P.P., de Senna P.N., Paim M.F., do Nascimento P., Ilha J., Bagatini P.B., Achaval M., Xavier L.L. Physical exercise increases GFAP expression and induces morphological changes in hippocampal astrocytes. Brain Struct. Funct. 2014; 219:293–302.

Sola-Penna M., Da S.D., Coelho W.S., Marinho-Carvalho M.M., Zancan P. Regulation of mammalian muscle type 6-phosphofructo-1-kinase and its implication for the control of the metabolism. IUBMB Life. 2010; 62:791–796.

Swank, Ann Marie. Exercise Physiology: Human Bioenergetics and its Application, 2nd Edition. Medicine & Science in Sports & Exercise 28(11):p 1442,1443, November 1996.

Tari A.R., Norevik C.S., Scrimgeour N.R., Kobro-Flatmoen A., Storm-Mathisen J., Bergersen L.H., Wrann C.D., Selbæk G., Kivipelto M., Moreira J.B.N., et al. Are the neuroprotective effects of exercise training systemically mediated? Prog. Cardiovasc. Dis. 2019; 62:94–101.