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Tailored Exercise Intervention in Metabolic Syndrome: Enhancing Cardiovascular Health Beyond Weight Loss and Diet

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Abstract: Background: Metabolic syndrome (MS) is a cluster of cardiovascular and metabolic risk factors that increase the likelihood of both acute events and chronic conditions. While exercise has been shown to improve individual risk factors associated with MS; research on its effects on MS as an integrated condition remains limited. This study aims to evaluate the effectiveness of a 6-month Adapted Personalized Motor Activity (AMPA) program in improving health outcomes in individuals with MS. **Methods:** Seventy-one sedentary participants with MS (mean age: 63 ± 9.4 years; 46.5% female) completed a 6-month intervention incorporating moderate-intensity aerobic and resistance training. Each participant received a personalized exercise plan prescribed by a sports medicine physician. Training was monitored via telemetry to ensure safety. No dietary recommendations were provided during the intervention. Baseline and post-intervention assessments included Cardiopulmonary Exercise Testing (CPET); anthropometric measurements; blood pressure; heart rate; lipid profile (total cholesterol; HDL; LDL; and triglycerides); fasting glucose; and HbA1c. **Results:** Significant improvements were observed in fasting glucose (-10.6%; $p < 0.001$); HbA1c (-3.88%; $p < 0.001$); HDL cholesterol (+20.8%; $p < 0.001$); LDL cholesterol (-25.1%; $p < 0.001$); and VO_2 max (+8.6%; $p < 0.001$). Systolic and diastolic blood pressure also decreased significantly; with reductions of -12% ($p < 0.001$) and -5.9% ($p < 0.001$); respectively. Reductions in weight and waist circumference were statistically significant but modest and clinically irrelevant; showing no correlation with improvements in cardio-metabolic parameters. Logistic regression and correlation matrix analyses were performed to identify key predictors of changes in individual risk factors. **Conclusions:** While personalized exercise alone may not fully control individual risk factors of metabolic syndrome; its overall effect is comparable to low-intensity pharmacological polytherapy with minimal adverse effects. These benefits appear to be independent of dietary habits; gender; and both baseline and post-intervention physical performance and anthropometric measures

Keywords: Metabolic Syndrome; Personalized Exercise; Lipid Metabolism; Cardiovascular Health; Moderate-Intensity Training

1. Introduction

Metabolic syndrome (MS) refers to a combination of cardiovascular (CV) risk factors, including hyperglycemia, elevated blood pressure, dyslipidemia and central obesity. Considering that cardiovascular diseases alone are responsible for nearly one-third of deaths globally [1], the prevention and the management of MS is a significant public health issue, especially if we consider that the estimated global prevalence of MS ranges from 12.5% to 31.4% [2,3]. Studies reveal that regular exercise can deliver results similar to those achieved with blood pressure or blood sugar-

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lowering medications, benefiting both sedentary non-MS individuals and those with MS [4,5]. Exercise provides a wide range of benefits for subjects with and without MS. One of the most important factors is an individual's ability to deliver and utilize oxygen during physical activity, known as maximal oxygen uptake (VO_{2max}) [6]. Higher VO_{2max} levels are strongly associated with lower overall mortality rates in healthy individuals and those with chronic conditions [7]. This means that improving VO_{2max} through regular endurance exercise can play a critical role in enhancing cardiovascular fitness, reducing the risk of disease progression, and ultimately increasing longevity in both healthy sedentary and MS populations [7]. Endurance training helps to improve body composition by boosting daily energy expenditure and reducing visceral fat [4,6,8]; resistance training prevents muscle loss during weight reduction, increase fat-free mass, as well as maximal strength, muscular efficiency and energetics [6]. In addition to aiding weight loss, exercise enhances glucose metabolism by lowering blood sugar levels and reducing the risk of type 2 diabetes [9]. It increases skeletal muscle insulin sensitivity, improving the signaling for Glucose Transporter type 4 (GLUT4) translocation, and enhances mitochondrial protein expression [10]. While physical activity alone has a limited effect on cholesterol management, pairing it with lipid-lowering medication can maximize the outcomes [11]. Exercise primarily improves high-density lipoprotein cholesterol (HDL-C) levels, with minimal impact on low-density lipoprotein cholesterol (LDL-C) [12]. However, it can slow the progression of atherosclerosis by increasing the average size of atherogenic small dense LDL-C particles [13] and improving their ability to resist oxidative processes [14]. Regular physical activity also helps lower blood pressure similar to common antihypertensive medications, especially for systolic blood pressure (SBP) [5]. This is obtained through two mechanisms: firstly, exercise reduce vascular resistance through an increased expression of endothelial nitric oxide synthase, a reduction of either nervous sympathetic activity and arterial stiffness; secondly, physical activity acts on renin-angiotensin-aldosterone system decreasing water retention [15,16]. Despite the strong long-term effects, exercise training is often unobserved and the its applicability on a large scale remains a major limitation. Among the various training programs proposed, Adapted Personalized Motor Activity (AMPA) is a structured intervention designed to improve VO_{2max}, muscle mass, strength, and flexibility in patients with noncommunicable diseases. Notably, AMPA is one of the few programs that has been successfully implemented in large patient cohorts showing a good adherence rate, making it a valuable framework for further investigation [17,18]. Given that exercise targets multiple disrupted mechanisms in patients with metabolic syndrome, we hypothesize that the long-term effects of exercise are more pronounced in this population compared to sedentary individuals without the condition. Furthermore, we propose that the impact of exercise on cardiovascular risk may differ between these groups. Therefore the present study aims to evaluate the extended effects of a six-month AMPA program on metabolic syndrome patients and quantify its overall efficacy independently from gender, dietary habits and medications. Changing of anthropometric, cardiopulmonary and CV risk factor are considered.

2. Materials and Methods

2.1. Subjects

The study initially enrolled 230 subjects who met the inclusion criteria and had no contraindications to the physical activity outlined in the protocol. Following the 6-month AMPA program, the study population was defined by selecting individuals diagnosed with metabolic syndrome according to IDF criteria [19,20].

The inclusion criteria were:

- Aged between 40 and 75;
- Diagnosis of metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III [21] criteria;
- No participation in structured physical activity programs within the six months prior to the study.

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The exclusion criteria included:

- History of musculoskeletal, neurological, or orthopedic disorders in the preceding six months that could hinder participation in the experimental protocol;
- Acute cardiovascular conditions contraindicating physical activity;
- Active cancer, infectious diseases, chronic obstructive pulmonary disease or active smoking
- Inability to provide informed consent.

The study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the relevant ethics committee (protocol n° 1538, version 3). All participants provided informed consent after receiving detailed information about the potential risks, benefits, and procedures involved.

2.2. Experimental Design

This study utilized a prospective observational design, aiming to assess the effects of the AMPA program on various health outcomes. The primary objectives were to evaluate the impact of the exercise program on:

- Metabolic parameters (fasting glycemia, HbA1c, LDL cholesterol, HDL cholesterol and triglycerides)
- Anthropometric measures (wight, BMI, waist and hip circumference)
- Cardiopulmonary performance (HR, blood pressure, FVC, FEV1 and VO_2)

These outcomes were evaluated both at baseline and after 6 months of participation in the exercise program. Participants underwent a baseline medical screening that included the collection of medical history, a complete clinical evaluation, anthropometric measurements, blood tests, and cardiopulmonary assessments. Anthropometric measurements included body weight (kg), height (cm), and waist circumference (cm). Body weight and height were measured in light clothing without shoes using a calibrated scale and stadiometer, respectively, to the nearest 0.1 kg and 0.5 cm. Body Mass Index (BMI, kg/m^2) was calculated. Cardiopulmonary fitness was assessed using a maximal graded exercise test on a cycle ergometer [22]. VO_2 max (mL/kg/min) was measured to determine cardiorespiratory fitness. Heart rate, blood pressure, and oxygen saturation were monitored throughout the test.

2.3. Training Protocol

The experimental group participated in a six-month tailored exercise program, combining aerobic and resistance exercises. The program followed the guidelines of the American College of Sports Medicine (ACSM), with sessions supervised by exercise specialists to ensure safety, adherence, and proper progression [6].

- **Aerobic Training**:

Conducted three times per week, focusing on moderate-intensity exercises aimed at 55–70% of VO_2 max or 60–80% of the participant's maximum heart rate. Aerobic activities included:

- Treadmill walking
- Cycling
- Elliptical training

Each session lasted 25–30 minutes, gradually increasing in intensity as the participants' fitness improved [6,23].

- **Resistance Training**:

Conducted twice per week, focusing on strengthening the major muscle groups. The resistance training regimen included:

- 2–3 sets of 8–15 repetitions for each major muscle group, with 1–3 minutes of rest between sets.
- The resistance load was set at 50–70% of the participant's one-repetition maximum (1-RM) [6,24].

Weight machines were used to ensure correct form and safety during the exercises.

Each session included:

- **Warm-up**: 5–10 minutes of low-intensity aerobic exercise to prepare the body for the workout [6].
- **Cool-down**: A 5–10-minute recovery phase, consisting of light aerobic exercise and stretching [6].

2.4. Statistical Analysis

Continuous variables are presented as mean ± SD or median with range, depending on the distribution (assessed by the Shapiro-Wilk test). Comparisons between groups for normally distributed data were performed using Student's t-test or paired t-test, as appropriate. Welch's t-test was applied for variables with unequal variances. Nominal variables are presented as counts and percentages, with group comparisons made using the chi-square test or Fisher's exact test. Correlations between continuous variables were assessed using Pearson or Spearman correlation coefficients. Linear and logistic regression models were applied as appropriate. A p-value of <0.05 was considered statistically significant. A**nalysis** was performed using Jamovi software [25,26].

3. Results

In the AMPA project, 230 sedentary participants were enrolled, of whom 178 (77.4%) completed the 6-month exercise program. Among these, 71 participants met at least three of the five criteria for metabolic syndrome diagnosis, as defined by the International Diabetes Federation (IDF). The cohort had a mean age of 63 ± 9.4 years, with 33 participants (46.5%) being female. The prevalence of individual risk factors was as follows: arterial hypertension in 63 participants (88.7%), hypertriglyceridemia in 25 (35.2%), low HDL cholesterol in 51 (71.8%), visceral obesity in 58 (81.2%), and impaired fasting glucose in 61 (85.9%). Additionally, 39 participants (54.9%) were classified as obese (BMI > 30 kg/m²), and 23 (32.4%) had type 2 diabetes (Figure 1). Regarding the distribution of metabolic syndrome diagnostic criteria, 34 participants (47.9%) met three criteria, 25 (35.2%) met four criteria, and 12 (16.9%) met all five criteria. Moreover, exercise-induced hypertension was observed in 28 subjects (39.4%) during the cardiopulmonary exercise test.

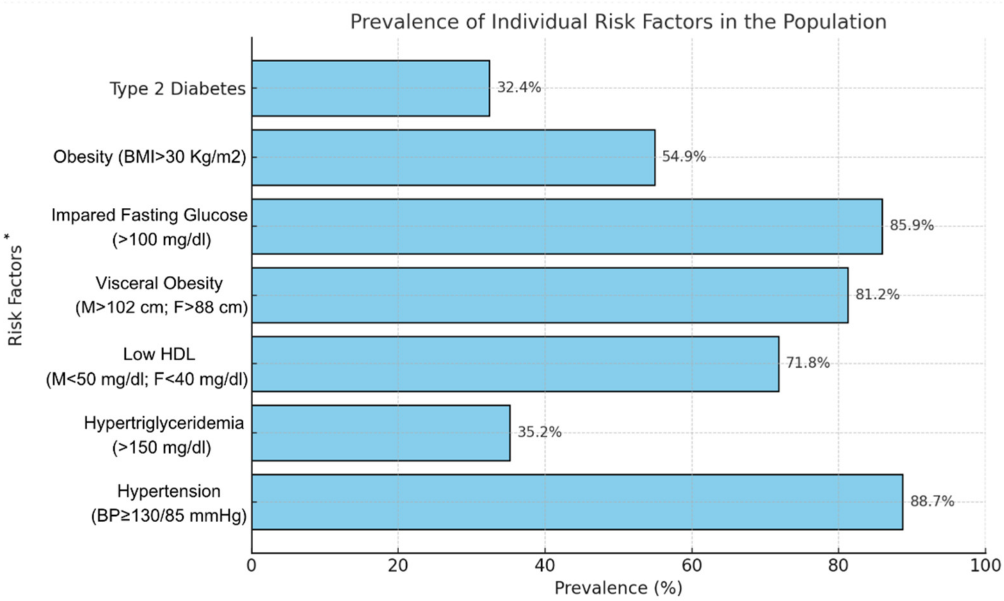

Figure 1. Prevalence of individual metabolic syndrome risk factors in the study population. BMI: body mass index; HDL: high density lipoprotein; *A risk factor is considered present even when the patient is undergoing specific treatment for that condition.

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A significant improvement was observed in most of the parameters pre- and post-intervention, including anthropometric characteristics, glucose and lipid metabolism, and cardiorespiratory performance (Figure 2). However, the most notable effect sizes were observed in the following: fasting glucose (-10.6%, p<0.001), total cholesterol (-10%, p<0.001), HDL cholesterol (+20.8%, p<0.001), LDL cholesterol (-25.1%, p<0.001), forced vital capacity and forced expiratory volume in 1 second (both +6.6%, p<0.001), VO_2 max (+8.6%, p<0.001), indexed VO_2 max (+8.8%, p<0.001), aerobic threshold (+10.4%, p<0.001), maximal oxygen pulse (+7.6%, p<0.001), resting heart rate (-7.6%, p<0.001) and recovery phase heart rate (-6%, p<0.001), as well as resting systolic and diastolic blood pressure (-12% and -5.9%, respectively, both p<0.001), recovery phase systolic and diastolic blood pressure (-8% and -6.7%, respectively, both p<0.001), and diastolic blood pressure at peak exertion (-5.9%, p<0.001). No significant difference was observed in heart rate or systolic blood pressure at peak exertion, suggesting that the cardiopulmonary tests were maximal both at baseline and after the intervention. Significant but clinically negligible changes were observed in the number of pills taken, anthropometric characteristics, ventilatory reserve, Tiffeneau index, relative peak power output, and age-adjusted peak power output.

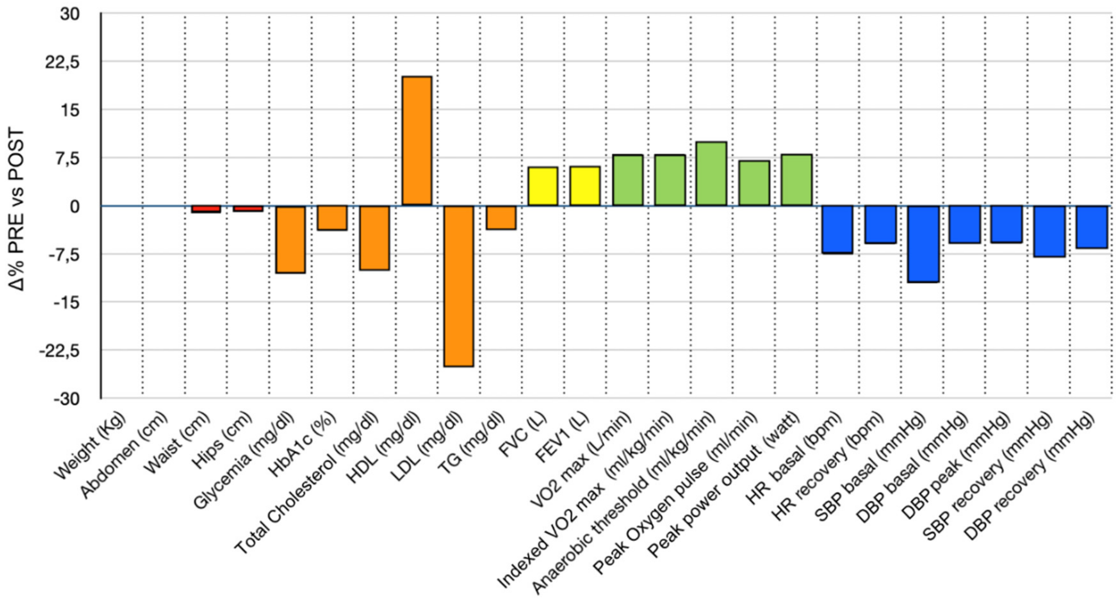

Figure 2. Percentage changes in the main variables observed after the AMPA intervention. HbA1c%: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; VO_2max: maximum oxygen consumption rate; Indexed VO_2 max: maximal oxygen consumption rate normalized to body weight; HR: hart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The clinical characteristics, the results of the biochemical and instrumental tests at baseline and after 6 months of AMPA, as well as the absolute and percentage changes of these variables between pre- and post-intervention, are shown in Table 1.

Table 1. Clinical characteristics, laboratory tests, and instrumental assessments at baseline and after 6 months of the AMPA program.

	PRE INTERVENTION Mean (± SD) or Median (min-max)	POST INTERVENTION Mean (± SD) or Median (min-max)	p	Δpre-post Mean (± SD) or Median (min-max)	Δ%pre-post Mean (± SD) or Median (min-max)
N° of pills	3.0 (0–15)	3.0 (0–15)	0.025	0 (-3–2)	-
Weight (Kg)	84.0 (47–125)	84.0 (48–125)	0.03	0 (-11–5)	0 (-15.3–4.8)
Waist (cm)	103.0 (65–131)	102.0 (68–132)	< .001	-1 (-12–6)	-1.1 (-13.5–8.5)
Hips (cm)	106.0 (74–142)	104.0 (85–142)	0.008	-1 (-14–11)	-1 (-14.6–12.9)
Glycemia (mg/dl)	120.0 (86–340)	107.0 (78–246)	< .001	-11 (-144–65)	-10.6 (-73.5–34.9)
HbA1c (%)	6.6 (2.83–14.6)	6.4 (4.9–9.7)	< .001	-0.2 (-6.2–1.8)	-3.88 (-73.8–18.6)
Total Cholesterol (mg/dl)	205.0 (79–324)	182.0 (115–278)	< .001	-19 (-87–98)	-10 (-54–55)
HDL (mg/dl)	41.5 (± 11.3)	53.9 (± 13.4)	< .001	12.47 (±11.64)	20.8 (±18.6)
LDL (mg/dl)	148.9 (± 34.8)	121.6 (± 25.8)	< .001	-27.3 (±33.3)	-25.1 (±30.3)
TG (mg/dl)	152.0 (46–403)	141.0 (58–459)	0.18	-5 (-206–89)	-3.6 (-191.7–52.5)
Uric acid (mg/dl)	5.9 (± 1.3)	5.6 (± 1.1)	0.012	-	-
Creatinine (mg/dl)	0.83 (0.53–1.55)	0.87 (0.62–1.74)	0.48	-	-
FVC (L)	3.27 (2.04–5.95)	3.51 (1.77–6.07)	<.001	0.2 (-1.59–1.73)	6.6 (-50–39.7)
FVC %	104.5 (56–196)	111.7 (62–157)	<.001	-	-
FEV1 (L)	2.50 (1.1–4.4)	2.68 (1.35–4.66)	< .001	0.18 (-1.65–1.87)	6.6 (-64.7–42.6)
FEV1 %	95.5 (62–205)	106.5 (62–154)	< .001	-	-
Tiffeneau Index	0.78 (0.48–0.91)	0.78 (0.65–0.95)	0.083	-	-
PEF (L)	6.32 (2.72–13.54)	6.42 (3.01–11.17)	0.74	-	-
PEF%	93.5 (55–141)	95.6 (49.2–134)	0.70	-	-
VO_2max (L/min)	1.42 (0.75–2.76)	1.51 (0.81–2.90)	< .001	0.150 (-0.660–0.790)	8.6 (-31.4–33.8)
iVO2 max (ml/kg/min)	16.8 (10.8–27.6)	18.6 (12.3–33.9)	< .001	1.7 (-6.6–11.1)	8.8 (-39.8–32.8)
AT (ml/kg/min)	12.83 (± 2.45)	14.28 (± 2.75)	< .001	1.61 (±1.92)	10.4 (-47.5–39)
Peak O_2 pulse (ml/min)	12.0 (6–22)	13.0 (7–23)	< .001	1 (-8–12.5)	7.6 (-57.1–54.4)
Ventilatory reserve (%)	52.91 (± 12.70)	50.86 (± 11.78)	0.19	-2.06 (±13.24)	-2.06 (±5.4)
Age-adjusted PPO (watt)	137.0 (63–262)	134.0 (65–262)	0.01	0 (-48–10)	0 (-27.1–5.5)
PPO (watt)	110.0 (60–224)	125.0 (75–250)	< .001	12 (-29–56)	8.3 (-19.3–32.7)
Relative PPO (watt/Kg)	1.46 (± 0.39)	1.61 (± 0.39)	< .001	0.16 (± 0.32–0.61)	0 (-27.1–5.47)
HR basal (bpm)	68.0 (48–98)	61.0 (46–83)	<.001	-5 (-29–15)	-7.6 (-49.2–22.4)
HR peak (bpm)	121.5 (± 17.2)	122.1 (± 16.5)	0.7	-	-
HR recovery (bpm)	89.4 (± 15.9)	83.8 (± 11.3)	<.001	-5.6 (± 10.1)	-6 (-40.9–20.3)
SBP basal (mmHg)	140.0 (110–160)	120.0 (105–160)	<.001	-15 (-55–30)	-12 (-52.4–20)
DBP basal (mmHg)	80.0 (70–110)	80.0 (60–95)	<.001	-5 (-35–15)	-5.9 (-50–17.7)
SBP peak (mmHg)	195.0 (150–250)	190.0 (155–240)	0.2	-	-
DBP peak (mmHg)	85.0 (55–110)	80.0 (60–110)	0.004	-5 (-30–30)	-5.9 (-38.5–27.8)

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SBP recovery (mmHg)	139.6 (± 13.8)	129.3 (± 12.0)	<.001	-10 (-40–25)	-8 (-30.4–17.2)
DBP recovery (mmHg)	80.0 (55–105)	75.0 (50–95)	<.001	-5 (-25–15)	-6.7 (-41.7–17.7)

HbA1c%: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; PEF: peak expiratory flow; VO_2max: maximum oxygen consumption rate; iVO_2max: indexed maximal oxygen consumption rate; AT: aerobic threshold; PPO: peak power output; HR: hart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Correlations

A significant positive correlation was observed between the percentage changes in triglycerides and baseline HDL cholesterol (r=0.454, p < 0.001), suggesting that participants with lower baseline HDL cholesterol experienced greater reductions in triglyceride levels. Conversely, a significant negative correlation was identified between age and percentage changes in diastolic blood pressure (r=−0.348, p = 0.003), indicating that older participants showed more substantial improvements in this parameter.

Gender Differences

Significant baseline differences were found, with men taking a higher number of pills (ES=0.66, p=0.007), having higher fasting glucose levels (ES=0.50, p = 0.042), lower HDL cholesterol (ES=0.633, p = 0.010), higher triglycerides (ES=0.62, p = 0.039), and a lower resting heart rate (ES=0.60, p = 0.014) compared to women. In men, beyond higher fasting glucose levels, a history of type 2 diabetes was also more common (44.7% in men vs. 21.2% in women; χ^2 = 4.37, p=0.037). Conversely, a higher incidence of exercise-induced hypertension was observed in women (26.3% in men vs. 54.5% in women; χ^2 = 5.89, p=0.015). Beyond the notable baseline anthropometric, laboratory and cardiopulmonary fitness differences (data not shown), no significant gender differences were observed in the percentage changes of most of anthropometric measures, blood exams and cardiopulmonary fitness. However, men showed greater reductions in triglycerides (ES=0.69, p = 0.022) and experienced less reduction in systolic blood pressure at peak exercise (ES=0.7, p = 0.004) and during recovery (ES=0.57, p = 0.019).

Linear Regression Models

Regression models evaluated the relationship between baseline values of risk factors and their percentage changes, with separate models constructed for each percentage change. Each model was adjusted for baseline values, including the baseline of the variable undergoing change, and included age and gender as covariates. Notably, gender did not significantly influence any of the percentage changes in the variables studied.

Key findings from the models include the following:

LDL cholesterol: the percentage change in LDL was significantly associated with its baseline level (β=−0.377, SE=0.110, p=0.001), indicating that higher baseline LDL levels were associated with greater reductions.

Triglycerides: changes in triglycerides showed significant associations with both baseline triglyceride levels (β=−0.233, SE=0.081, p=0.007) and fasting glucose (β=−0.411, SE=0.129, p=0.003). Higher baseline values of these variables were linked to greater reductions in triglycerides.

HDL cholesterol: The percentage change in HDL was significantly associated with age (β=−0.655, SE=0.252, p=0.013) and baseline HDL levels (β=−0.847, SE=0.279, p=0.004). Older age and higher baseline HDL levels were associated with smaller percentage increases in HDL.

These results highlight that baseline levels and age are key determinants of changes in these risk factors, while gender showed no significant influence.

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Table 2. Summary of Linear Regression Models for Percentage Changes in Risk Factors.

Outcome	Baseline Predictors	β	SE	p-value
LDL cholesterol (%Δ)	Baseline LDL	−0.377	0.110	0.001
Triglycerides (%Δ)	Baseline triglycerides	−0.233	0.081	0.007
	Baseline fasting glucose	−0.411	0.129	0.003
HDL cholesterol (%Δ)	Age	−0.655	0.252	0.013
	Baseline HDL	−0.847	0.279	0.004
Fasting glucose (%Δ)	Baseline fasting glucose	−0.295	0.061	<0.001
Systolic blood pressure (%Δ)	Baseline LDL	0.089	0.045	0.057
Diastolic blood pressure (%Δ)	Baseline triglycerides	0.037	0.020	0.077

HDL: high density lipoprotein; LDL: low density lipoprotein.

4. Discussion

In this study, we evaluated the effects of adapted and monitored exercise in 71 MS patients, following ACSM's guidelines [6]. Our results show that Adapted Personalized Motor Activity (AMPA) [18] **positively impacts MS and cardiovascular risk factors. Adherence to the program was high (77.4%), with less than one-fourth of participants unable to complete the six-month exercise program. Other studies reported higher dropout rates** [27,28]**.** We attribute the low dropout rate to a one-month familiarization period with low-intensity exercises included in the assisted AMPA program, and a variety of gym equipment. The program comprised resistance and aerobic exercises three times a week for 50–60 minutes per session. Moderate-intensity exercise (150 minutes weekly) is known to improve MS, with better results at higher intensity/volume levels [29]. After the familiarization, in AMPA, aerobic intensity was initially moderate, progressing to 75% of VO2max, while resistance training intensity ranged from 50–70% of maximum voluntary muscle contraction. The recent CardioRACE trial [30] found that heart rate reserve (HRR)-based combined aerobic and resistance training reduced cardiovascular disease risk but did not significantly affect SBP or LDL cholesterol. In contrast, our CPET-based and personalized training in MS patients showed superior outcomes compared to HRR-based or standardized training [27]. The most significant effect of AMPA was on lipid profiles, particularly a reduction in LDL levels (-27.3 mg/dL). Higher baseline LDL was associated with greater reductions, with new perspectives on emphasizing the benefits of physical activity in MS. A recent meta-analysis reported a -7.22 mg/dL LDL reduction with exercise training [31], though it excluded patients with CV diseases and found moderate-to-high heterogeneity among studies. Interestingly, older participants exhibited lower increases in HDL, showing an inverse correlation between age and HDL levels, confirming that exercise may have a reduced impact on lipid profiles in the elderly [32]. However, participants with low baseline HDL experienced better lipid improvements, particularly in triglyceride reduction among men, highlighting the importance of exercise for MS patients with poor lipid profiles. On the other hand, physical activity is known to reduce visceral adipose tissue (VAT) and influence lipid metabolism (i.e., lipoprotein lipase, PCSK) [33] and inflammation [34]. While our patients showed significant reductions in weight and waist circumference, these changes did not correlate with cardio-metabolic improvements. Our study corroborates [10] that exercise positively influences body composition and metabolism even without anthropometric changes. Since the aim of the study was to isolate the effects of exercise, no dietary modifications were implemented, as diet plays a critical role in reducing MS components [35]. Cardiovascular fitness improved significantly, with increases in VO_2 max (+8.6%), AT (+10.4%), and peak O_2 pulse (+8.8%). VO_2 max is an independent CV risk factor in MS [36,37], correlating with lipid profiles [38]. CPET confirmed normal ventilatory reserve before and after AMPA, and training improved resting pulmonary function parameters FVC and FEV1 [39]. No ventilatory limitations were detected. Greater fitness improvements were observed with AMPA compared to non-monitored exercise programs [28] or HRR-based aerobic exercise [27]. Sedentary lifestyles contribute to non-transmittable chronic diseases development, with exercise recognized as medicine for these conditions [40]. Cardiorespiratory fitness in MS does not improve by merely reducing sedentary behavior [41]. Medication use remained unchanged after AMPA, with exercise effects comparable to low-intensity pharmacological polytherapy [42]. The program also reduced serum uric acid, associated with insulin resistance, hypertension [43] and its related cardiomyopathy [44]. Fasting blood glucose and HbA1c also improved (-10.6% and -3.88%), with greater effects in those with higher baseline values. It is known that aerobic exercise increases glucose uptake in skeletal muscle [45], while resistance training enhances insulin sensitivity by increasing muscle mass [46]. No significant gender differences were observed in anthropometric, blood, or fitness changes, likely due to our mainly postmenopausal female cohort [47]. However, men exhibited greater triglyceride reductions, and higher fasting glucose levels correlated with greater triglyceride decreases. In fact, reduced insulin resistance is related to improvements in skeletal muscle fatty acid oxidation [48]. These data support that physical activity can act on different metabolic pathways with pleiotropic effects in MS [49] as well as on cardiorespiratory fitness parameters (i.e., VO_2 max). [50]: the latter aspect is of particular interest in MS because higher VO_2 max may protect from hypertension development ( ). SBP and DBP decreased significantly (-12% and -5.9%), with older participants showing greater DBP reductions, possibly due to lower initial fitness and arterial stiffness modulation [51]. Data on duration of intervention to gain effectiveness are conflicting (3, 6, 12 months) [52,53] but in the specific setting of MS as in our cohort, 6 months seems to have a significant reduction of blood pressure in the elderly [54] Exercise-induced hypertension (EIH) was more common in women, yet AMPA led to a reduction in peak SBP, confirming its safety and effectiveness [55]. Remarkably, EIH has been correlated with sudden cardiac death, CV accidents [56], and pathological vascular stiffness in middle-aged women. [57]. AMPA likely improved blood pressure via nitric oxide modulation **[57]** and insulin sensitivity.[58]. Similarly, the effects of lower sympathetic tone positively influenced resting heart rate (-7.6%), recovery heart rate (-6%), and blood pressure [58].

5. Conclusions

Our study demonstrates that improvements in CV risk factors among patients with MS - including lipid profiles, fasting blood glucose, and blood pressure - are not significantly influenced by gender or weight loss, even in the absence of dietary intervention. However, individuals with higher CV risk experience greater benefits from combined, tailored, and supervised exercise training. A key limitation of our study is the lack of body composition measurements, which could play a crucial role in reducing CV risk. Nevertheless, our findings highlight a significant reduction in CV risk markers among MS adults, suggesting that the overall effect of Adapted Personalized Motor Activity (AMPA) is comparable to that of low-intensity pharmacological polytherapy. Future research should focus on personalized exercise prescriptions for MS, employing a long-term, multi-omics approach to better understand the complexity of this condition and the potential variability in therapeutic exercise responses. Based on our results, we strongly advocate for the integration of CPET-based, tailored exercise prescriptions in clinical practice especially for MS patients at high CV risk.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

MS	Metabolic Syndrome
AMPA	Adapted Personalized Motor Activity
CPET	Cardiopulmonary Exercise Testing
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
HbA1c	Glycated Hemoglobin
VO_2max	Maximum Oxygen Consumption
BMI	Body Mass Index
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume in 1 Second
HR	Heart Rate
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
ACSM	American College of Sports Medicine
RM	Repetition Maximum
IDF	International Diabetes Federation

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