Exercise Reduces Medication for Metabolic Syndrome Management: A 5-Year Follow-up Study

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ABSTRACT

MORALES-PALOMO, F., A. MORENO-CABAÑAS, M. RAMIREZ-JIMENEZ, L. ALVAREZ-JIMENEZ, P. L. VALENZUELA, A. LUCIA, J. F. ORTEGA, and R. MORA-RODRIGUEZ. Exercise Reduces Medication for Metabolic Syndrome Management: A 5-Year Follow-up Study. *Med. Sci. Sports Exerc.*, Vol. 53, No. 7, pp. 1319–1325, 2021. **Purpose:** This study aimed to determine the effects of a 5-yr exercise intervention on metabolic syndrome (MetS) and health-related variables and medication use for MetS management. **Methods:** Participants were randomly assigned to an exercise intervention (n = 25, 54 ± 2 yr, 20% women) or control group (n = 26, 54 ± 2 yr, 38% women). The intervention lasted 4 months per year and consisted of high-intensity interval training on a cycloergometer thrice a week. Outcomes were MetS z-score and medication use score, MetS-related variables (including blood pressure, blood glucose homeostasis, and lipid profile), and cardiorespiratory fitness (CRF, as determined by maximal oxygen uptake). **Results:** MetS z-score was similarly reduced over time in both groups (P = 0.244 for group–time interaction). A quasi-significant and significant group–time interaction was found for MetS number of factors (P = 0.004) and CRF (P < 0.001), respectively. Thus, MetS factors tended to decrease over time only in the exercise group with no change in the control group, whereas CRF increased from baseline to 5-yr assessment in the exercise group (by 1.1 MET, P < 0.001) but decreased in the control group (−0.5 MET, P = 0.025). Medicine use score increased twofold from baseline to 5-yr follow-up in the control group (P < 0.001) but did not significantly change (10%, P = 0.52) in the exercise group (P < 0.001 for group–time interaction). The proportion of medicated patients who had to increase antihypertensive (P < 0.001), glucose-lowering (P = 0.036), or total medication (P < 0.0001) over the 5-yr period was lower in the exercise than that in the control group. **Conclusions:** Exercise training can attenuate the increase in medication that would be otherwise required to manage MetS over a 5-yr period. **Key Words:** METABOLIC DISORDERS, CARDIOVASCULAR DISEASE, EXERCISE, DRUG INTERACTIONS, HEALTH CARE

Metabolic syndrome (MetS) affects one third of the adult population in the United States (1). Owing to the multisystemic nature of this disorder, more than 35% of affected people take two or more drugs daily (2,3). Polypharmacy is defined as routinely taking a minimum of five medicines daily and represents an important medical problem (4). Indeed, most drugs have adverse effects, and dosage must be frequently increased over the years to maintain the desired effect, with subsequent saturation of metabolizing processes, drug accumulation, and exacerbation of side effects (5). Polypharmacy also imposes a burden on the public health system (6). Implementation of lifestyle strategies aiming at reducing medicine use without affecting—and ideally improving—disease management are thus paramount from both an individual and a public health perspective (7).

A major lifestyle intervention with multisystemic benefits that can mimic—at least partly—drug effects on cardiometabolic conditions is physical exercise (8–10). Although reductions in medicine use is not a direct aim for the inclusion of

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exercise into a lifestyle, sometimes it induces that reduction by improving some health risk factor (11,12). We recently showed that a 4-month exercise intervention implemented twice during two consecutive years prevented the increases in medication that would be otherwise needed to normalize blood glucose levels in patients with MetS (3). In the present follow-up study, we aimed to determine the effects of maintaining this type of intervention during three more years on MetS and health-related variables, as well as on the use of medication for MetS management.

METHODS

Experimental Design and Participants

The present study is a follow-up of a randomized controlled trial (3) with 64 participants (middle-age men and women with MetS who were physically inactive, <150 min·wk^{-1} of moderate-intensity physical activity [13]) allocated to an exercise (see below) or standard care group with a block on age, number of MetS factors, and body mass index (BMI). MetS was defined according to updated International Diabetes Federation 2009 criteria (14). Exclusion criteria were having untreated cardiovascular or renal disease, or any condition associated with exercise intolerance. All subjects provided written informed consent. The study was approved by the local Hospital's Ethics Committee and was performed in accordance with the Declaration of Helsinki.

For the present study, we analyzed data at baseline and after a 5-yr follow-up, with results of a previous 2-yr follow-up published elsewhere (3). To account for seasonal effects on MetS (15), participants were consistently tested in the same month (beginning of November). Assessors were blinded to group allocation. All participants received attention from the Spanish health care system, which included medical counseling and lifestyle advice every 6 months.

Intervention

Both groups received usual care, and participants in the exercise group also performed a supervised exercise program (3 sessions per week [Monday, Wednesday, and Friday]) consisting of high-intensity interval training on stationary bikes (Tomahawk S-Serie, Nürnberg, Germany [16]) 4 months per year (from mid-November [after assessment] to mid-March) during a total of five consecutive years. Exercise sessions were performed in the facilities of the Universidad de Castilla–La Mancha (Toledo, Spain). All subjects underwent a training familiarization session before intervention onset. Each session included a 10-min warm-up at 70% of peak heart rate (HR_{max}) followed by 4 × 4-min intervals at 90% of HR_{max} interspersed with 3-min active recovery at 70% of HR_{max} and a 5-min cooldown period. HR was continuously displayed on a large screen (Seego Realtrack Sytems, Almería, Spain), and participants self-adjusted the workload to reach their individual HR target value. Each session was supervised by a member of the research team for compliance with the training scheme.

Outcomes

MetS components and other health indicators. Patients arrived at the laboratory in the morning after an overnight fast. Nude body weight (Hawk; Metler, Toledo, OH), height (Stadiometer; Secca 217, Hamburg, Germany), and waist circumference were measured using a nonelastic measuring tape. Fat mass and fat-free mass were determined by bioelectrical impedance analysis (Tanita BC-418; Tanita Corp., Tokyo, Japan). After 10 min of supine rest, blood pressure (BP) was measured in triplicate using a calibrated ECG-gated electrosphygmomanometer (Tango; SunTech Medical Inc., Morrisville, NC).

Thereafter, a 7-mL blood sample was collected to determine serum glucose, insulin, and lipid levels (triglycerides, total, HDL, and LDL cholesterol [17]). Insulin sensitivity was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) (18). Sex-specific z-scores were calculated for each MetS criterion using the group SD, with the sum of the z-scores for each MetS component divided by five to compile the MetS risk score with units of SD (19). The equations used to calculate MetS z-score are as follows:

$$\begin{aligned}\text{Men's MetS } z\text{-score} = {} & [(40 - \text{HDL cholesterol})/\text{SD}] \\ & + [(\text{triglycerides} - 150)/\text{SD}] \\ & + [(\text{glucose} - 100)/\text{SD}] \\ & + [(\text{waist circumference} - 94)/\text{SD}] \\ & + [(\text{mean arterial pressure} - 100)/\text{SD}]\end{aligned}$$

$$\begin{aligned}\text{Women's MetS } z\text{-score} = {} & [(50 - \text{HDL cholesterol})/\text{SD}] \\ & + [(\text{triglycerides} - 150)/\text{SD}] \\ & + [(\text{glucose} - 100)/\text{SD}] \\ & + [(\text{waist circumference} - 80)/\text{SD}] \\ & + [(\text{mean arterial pressure} - 100)/\text{SD}]\end{aligned}$$

Participants underwent a maximal graded cardiopulmonary exercise test on a cycle ergometer (Ergoselect 200; Ergoline, Bitz, Germany) with indirect calorimetry (Quark b^2; COSMED, Rome, Italy) and electrocardiogram monitoring (Quark T12, COSMED) to assess HR_{max} and maximal oxygen uptake ($\dot{V}O_{2max}$), which consisted of 3 min of warm-up at 30 W for women and 50 W for men. Then workload was increased every minute (15 W women and 20 W men) until volitional exhaustion. This test was followed by a verification test at 110% of the maximal workload reached to ensure the achievement of actual $\dot{V}O_{2max}$ (20).

Medication. Participants were under the supervision of their primary care physician following the guidelines of the Spanish society of family and community medicine for the treatment of MetS (21). These guidelines include lifestyle advice, blood analysis every 6 months, and pharmacological prescription adjusted to blood chemistry, BP values, and body weight evolution. Physicians were blinded to group allocation. Participants brought all prescription medication to the laboratory at each of the two assessment visits (baseline and 5-yr follow-up) to ensure recording accuracy. Only medicines to

control MetS factors (i.e., hyperglycemia, hypertension, and hyperlipidemia) were registered. Evolution in the number and dose of medicines taken was assessed as follows (3):

$$\text{Medicine use score} = [\text{medicine 1 (subject used dose/Anatomical Therapeutic Chemical (ATC) recommended dose)}] + [\text{medicine 2 (subject used dose/ATC recommended dose)}] + \ldots + [\text{medicine } n \text{ (subject used dose/ATC recommended dose)}]$$

where recommended dose for adults was based on the posology listed in the ATC of the World Health Organization adapted for medications sold in Spain (22) (see Table, Supplemental Digital Content 1, Example of calculation for the medicine use score, http://links.lww.com/MSS/C244).

Other outcomes (nutrition and activity levels). After the preliminary testing and before the onset of the training program, participants filled out a 3-d nutritional diary analyzed for calorie intake and macronutrient composition (CESNICD v1.0; Barcelona, Spain). To monitor physical activity, participants wore a wristband activity monitor (Polar Electro Oy, Kempele, Finland) during 48 h to monitor their daily number of steps, standing time, and supine resting time.

Statistical Analysis

We used per-protocol analysis, with only patients who completed the 5-yr follow-up included in the statistical analysis. Data are presented as mean ± SEM. Smirnov–Kolmogorov test revealed that data were normally distributed. Between-group comparisons at baseline were performed with an unpaired Student's *t*-test and the chi-square (χ^2) test. A repeated-measures two-factor (group [exercise and control], time [baseline and 5-yr follow-up]) ANOVA was used to assess the effects of the exercise intervention on MetS *z*-score, number of MetS factors, medication use score, and MetS and health-related variables (anthropometric variables, glucose homeostasis, blood lipid profile, $\dot{V}O_{2max}$, and nutrition and activity levels). To minimize the risk of statistical type I error, *post hoc* pairwise comparisons (with the Bonferroni test) were only performed within groups and only if a significant group–time interaction effect was found. We also compared the proportion of participants who needed to increase medication over the 5-yr follow-up between the two groups using the χ^2 test. The Statistical Package for the Social Sciences software (version 22; IBM Corporation, Armonk, NY) was used for statistical analyses. To minimize the risk of statistical type I error, the *P* value was corrected

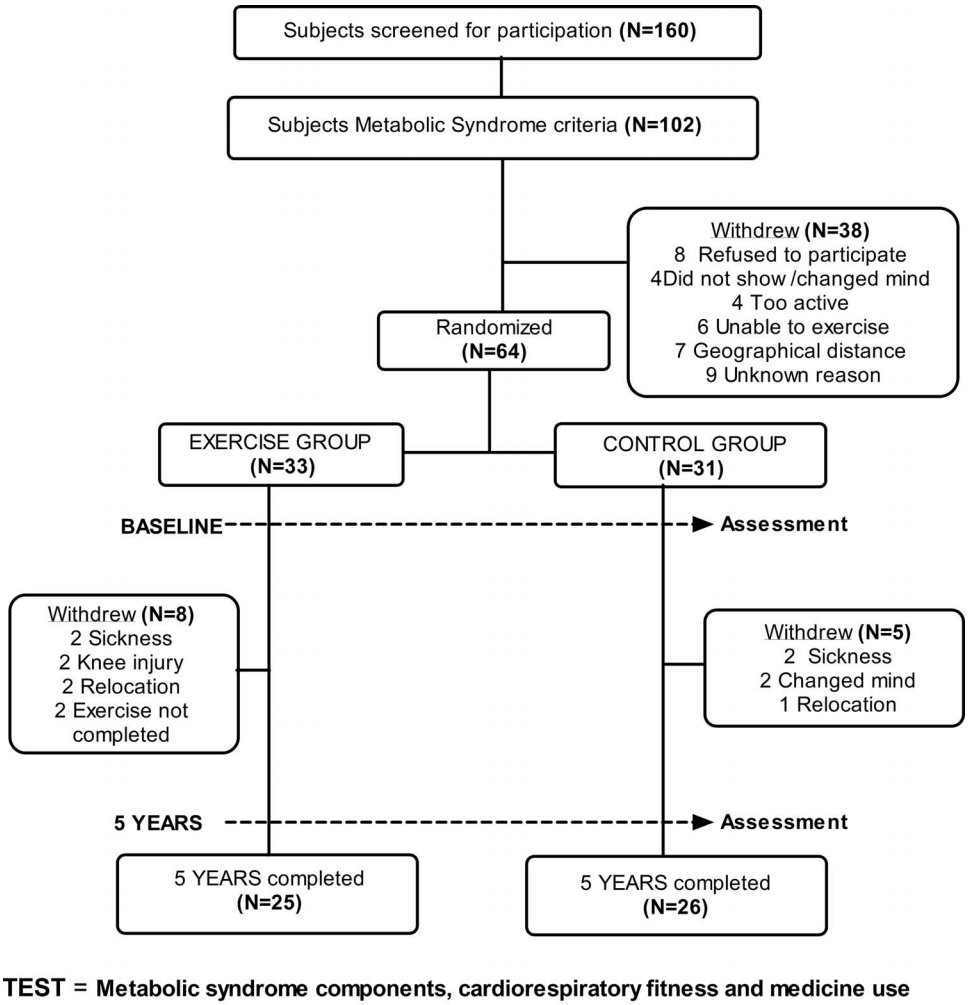

FIGURE 1—Flow diagram of study participants.

with the Bonferroni method (i.e., 0.05 divided by number of comparisons).

RESULTS

A flow diagram of study participants is shown in Figure 1. A total of 25 and 26 participants completed the study in the exercise and control group, respectively. All participants were Caucasians and 29% were women (all postmenopausal). The mean age at baseline was 54 ± 2 versus 52 ± 2 in the exercise and control group, respectively ($P = 0.46$), with 20% and 38% of women ($P = 0.15$). During the 5-yr follow-up, all participants attended at least 90% of the prescribed exercise sessions, and no exercise-related adverse effects were noted. During the months without supervised exercise (8 months per year), subjects declared no involvement in regular physical activity.

MetS components and health-related outcomes. MetS *z*-score was similarly reduced over time in both groups ($P = 0.244$ for group–time interaction effect; Fig. 2A). The effects of the exercise intervention on the different MetS components and health-related parameters are shown in Table 1. A significant time effect ($P < 0.001$) was observed for LDL cholesterol and BP (systolic, diastolic, and mean BP), with a decrease over the 5-yr period in both groups. A quasi-significant and significant group–time interaction effect was found for MetS number of factors ($P = 0.004$) and $\dot{V}O_{2max}$ ($P < 0.001$), respectively. Thus, MetS number of factors tended to decrease over time only in the exercise group with no change at all in the control group, whereas $\dot{V}O_{2max}$ increased from baseline to 5-yr assessment in the exercise group (by 3.69 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% confidence interval [CI] = 2.14 to 5.23, $P < 0.001$) and decreased in the control group (−1.74 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI = −3.26 to −0.23, $P = 0.025$).

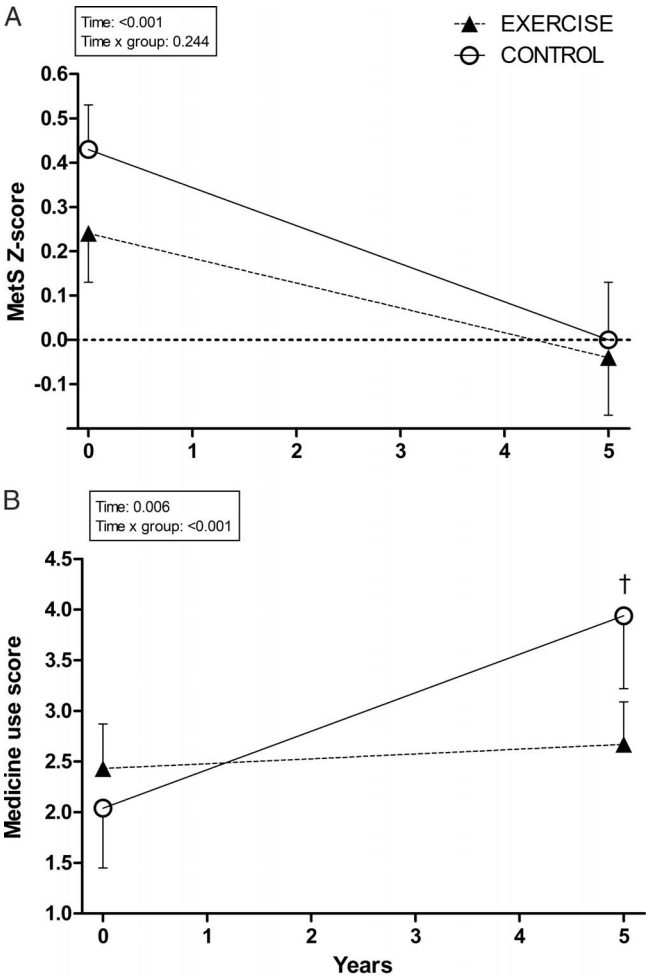

FIGURE 2—Evolution of metabolic syndrome (MetS) *z*-score (A) and medicine use score (B) during the 5-yr follow-up. Data are presented as mean ± SEM. †Significant change from baseline within each group ($P < 0.001$).

Medicine use. A significant group–time interaction effect was found ($P < 0.001$), with medicine use score increasing from baseline to 5-yr follow-up in the control group (by 1.89, 95% CI = 1.19 to 2.60, $P < 0.001$) but showing no significant change in the exercise group (0.23, 95% CI = −0.48 to 0.95, $P = 0.52$) (Fig. 2B).

The proportion of patients under treatment who had to increase antihypertensive ($P < 0.001$), glucose-lowering ($P = 0.036$), and total medication ($P < 0.0001$) over the 5-yr period was significantly lower in the exercise than that in the control group (Fig. 3).

Nutrition and activity levels. Data are shown in Table 2. There were no significant differences in time or group–time interaction in caloric intake or physical activity at any time point ($P > 0.05$).

DISCUSSION

This study aimed to examine the efficacy of a long-term exercise training program on the clinical management of MetS. After a 5-yr follow-up, individuals in the exercise group did not have to take substantially more medicines to manage their condition compared with baseline (i.e., no significant change in the medicine use score from baseline to 5-yr assessment), whereas their controls showed nearly a twofold increase in the medicine use score (Fig. 2B).

The effects of lifestyle interventions on MetS evolution can be finely assessed because thresholds for each MetS component are well defined and specific to sex and populations (14). By using a continuous MetS *z*-score, we (3,19,23,24) and others (25) have reported improvements in MetS with exercise training. However, MetS *z*-score is deceiving when individuals have their medication altered by their health care providers. For instance, increased metformin dose to control hyperglycemia could be confounded as a positive effect of the concurrent training intervention. Conversely, unchanged MetS *z*-score in the face of increase medication use should be interpreted as a worsening of their MetS condition and not a stabilization. It is not clear how to integrate medicine use into the *z*-score evolution, and in this article, we have graphically displayed both variables in Figure 2 for a complete evaluation of MetS management. Interestingly, *z*-score improved similarly in control and exercise group, which could be interpreted to mean that supervised exercise training during 4 months per year does not add anything to the effect of the standard care

TABLE 1. MetS components and other health parameters by group.

	Control Group (n = 26)		Exercise Group (n = 25)		P (η^2)	
	Baseline	5 yr	Baseline	5 yr	Time	Time–Group
MetS (number of factors)	3.5 ± 0.2	3.5 ± 0.2	3.7 ± 0.2	3.0 ± 0.2	0.040 (0.08)	0.004 (0.16)
Anthropometric variables						
Waist circumference (cm)	109.5 ± 2.4	112.1 ± 2.9	107.7 ± 2.4	107.2 ± 1 0.9	0.262 (0.03)	0.099 (0.05)
BMI ($kg \cdot m^{-2}$)	34.0 ± 0.9	33.6 ± 1.1	32.7 ± 1.0	31.7 ± 0.9	0.046 (0.08)	0.313 (0.02)
Weight (kg)	91.9 ± 3.8	90.9 ± 4.5	94.3 ± 3.1	91.6 ± 2.6	0.055 (0.07)	0.363 (0.02)
Fat mass (kg)	34.8 ± 1.8	33.9 ± 2.2	31.3 ± 1.7	28.8 ± 1.6	0.052 (0.08)	0.343 (0.02)
Fat-free mass (kg)	57.1 ± 2.5	57.0 ± 2.7	62.3 ± 2.1	62.3 ± 1.9	0.885 (0.00)	0.888 (0.00)
Glucose control						
Glucose ($mg \cdot dL^{-1}$)	113 ± 4	110 ± 5	114 ± 5	113 ± 6	0.420 (0.01)	0.845 (0.00)
Insulin ($\mu IU \cdot mL^{-1}$)	12.6 ± 1.0	12.8 ± 1.4	11.6 ± 1.0	9.3 ± 0.9	0.080 (0.06)	0.049 (0.08)
HOMA-IR	3.5 ± 0.3	3.5 ± 0.4	3.2 ± 0.3	2.6 ± 0.3	0.148 (0.04)	0.140 (0.05)
Lipids						
HDL cholesterol ($mg \cdot dL^{-1}$)	43 ± 4	44 ± 3	43 ± 2	49 ± 3	0.009 (0.02)	0.048 (0.08)
Triglycerides ($mg \cdot dL^{-1}$)	197 ± 7	185 ± 6	193 ± 9	181 ± 7	0.336 (0.16)	0.968 (0.00)
Total cholesterol ($mg \cdot dL^{-1}$)	197 ± 7	185 ± 6	193 ± 9	181 ± 7	0.004 (0.16)	0.979 (0.00)
LDL cholesterol ($mg \cdot dL^{-1}$)	122 ± 6	110 ± 5	128 ± 6	112 ± 5	**<0.001** (0.25)	0.577 (0.01)
BP						
MAP (mm Hg)	101 ± 3	93 ± 2	99 ± 2	92 ± 2	**<0.001** (0.34)	0.883 (0.00)
SBP (mm Hg)	132 ± 3	123 ± 3	134 ± 3	124 ± 2	**<0.001** (0.29)	0.956 (0.00)
DBP (mm Hg)	85 ± 2	78 ± 1	82 ± 2	75 ± 2	**<0.001** (0.33)	0.842 (0.00)
$\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	21.9 ± 0.9	20.2 ± 0.9	24.1 ± 1.4	27.8 ± 1.2†	0.077 (0.06)	**<0.001** (0.34)

Data are presented as mean ± SEM. To minimize the risk of statistical type I error, the threshold P value was obtained by dividing 0.05 by the number of comparison (thus, threshold P value = 0.05/17 = 0.002).

†Significant change from baseline within each group (P = 0.001). Significant P values for time or group–time interaction effect are in bold.

BMI, body mass index; DBP, diastolic BP; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; SBP, systolic BP; $\dot{V}O_{2max}$, maximal oxygen uptake.

provided by family physicians. Only when medicine use is integrated (Fig. 2), it emerges that z-score reductions in control group paralleled the doubling of medicine use. Thus, our data suggest that exercise training prevented the doubling of medication use that otherwise occurs in people with MetS in 5 yr.

Some studies, most of them conducted in patients with type 2 diabetes, have reported reduction or discontinuation of medication with lifestyle interventions (12,26). In the U-TURN study, a 12-month intervention consisting of both physical exercise and dietary counseling resulted in the discontinuation of glucose-lowering medication in 56% of the patients in the intervention group (vs 15% in controls) (27). In the Look AHEAD study, a lifestyle intervention of physical activity and diet induced a reduction in the number of medications, of 14% and 6.2% after 1 (11) and 10 yr, respectively (26). In turn, a reduction in diabetes medication has been reported in a study that applied a combination of both hypocaloric diet and high training loads (15 to 20 $h \cdot wk^{-1}$ [28]). A common characteristic to all these studies is the combination of both exercise and dietary interventions, resulting in significant reductions in body weight (ranging from 5.7% to 8.5%). In this regard, our results suggest for the first time that an exercise intervention alone might prevent the increase in medication even with no need to achieve remarkable body weight losses (i.e., only 3% on average in the exercise group).

The reducing effect of exercise on medication use was especially remarkable and significant for BP-lowering drugs (Fig. 3), which is in accordance with previous research. Notably, a recent network meta-analysis of 391 randomized controlled trials (n = 39,742) found that both exercise interventions and antihypertensive drugs were similarly effective in reducing systolic BP in people with hypertension (29). In this regard, no other lifestyle intervention and certainly no drug or even drug combination acts on so many potential BP-reducing mechanisms at the multisystemic level than exercise, particularly aerobic exercise (i.e., loss of adiposity, especially visceral adiposity, increased insulin sensitivity, attenuated oxidative stress and inflammation with subsequent improvements in vascular endothelial function, vascular remodeling with increase in the luminal diameter of conduit and resistance arteries, and improved arterial baroreflex control and thus autonomic balance [30]).

Another finding of the present study was that the exercise program prevented the decline (−8% or −0.5 MET) in cardiorespiratory fitness (CRF, as assessed by $\dot{V}O_{2max}$) observed in the control group after 5 yr. In a recent study, we showed that 16 wk of an aerobic interval training program similar to the one

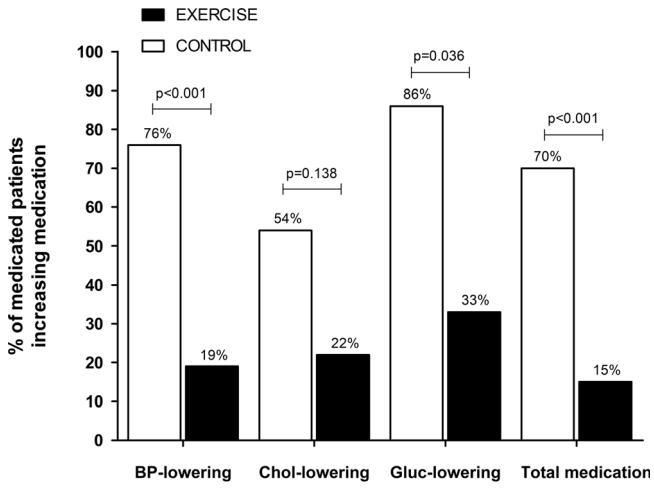

FIGURE 3—Comparison between groups in the proportion of medicated participants with an increase in medication/s over the 5-yr study period. Comparisons were not performed for triglyceride-lowering drugs because of the low number of participants under this specific type of treatment. CHOL, cholesterol; GLU, glucose.

TABLE 2. Nutrition and activity levels by group.

	Control Group (n = 26)		Exercise Group (n = 25)		P (η^2)	
	Baseline	5 yr	Baseline	5 yr	Time	Time–Group
Total calorie intake (kcal·d^{-1})	2308 ± 99	2273 ± 86	2407 ± 89	2298 ± 78	0.174 (0.04)	0.498 (0.01)
% Carbohydrate	46 ± 2	49 ± 2	44 ± 4	50 ± 3	0.079 (0.08)	0.333 (0.02)
% Fat	35 ± 1	33 ± 2	33 ± 2	29 ± 2	0.245 (0.02)	0.363 (0.02)
% Saturated fat	40 ± 2	41 ± 4	38 ± 1	38 ± 2	0.761 (0.00)	0.872 (0.00)
% Protein	19 ± 1	18 ± 3	23 ± 3	21 ± 2	0.544 (0.01)	0.410 (0.01)
Physical activity (steps·d^{-1})	5430 ± 260	6005 ± 277	5898 ± 255	6109 ± 309	0.092 (0.05)	0.675 (0.01)
Time standing (min·d^{-1})	195 ± 119	207 ± 95	203 ± 113	197 ± 100	0.458 (0.01)	0.519 (0.01)
Time in supine rest (min·d^{-1})	517 ± 190	517 ± 190	524 ± 167	516 ± 156	0.598 (0.01)	0.766 (0.00)

Data are presented as mean ± SEM. To minimize the risk of statistical type I error, the threshold P value was obtained by dividing 0.05 by the number of comparison (thus, threshold P value = 0.05/8 = 0.006).

we applied here increased the activity of mitochondrial oxidative muscle enzymes (i.e., citrate synthase and 3-hydroxyacyl-CoA dehydrogenase) in patients with MetS (31), which reinforces the benefits of physical exercise on the aerobic fitness of this patient population. CRF is usually low in individuals with MetS (23), and a low CRF might be associated with the cardiometabolic abnormalities that compose this syndrome (32,33). Of note, in the present study, the exercise intervention resulted in an increase in CRF after the 5-yr period of 1.1 METs, resulting in a final mean CRF of ~8 METs. This finding is potentially relevant given that CRF is a strong, independent predictor of cardiovascular mortality and all-cause mortality, with each 1-MET increase in CRF conferring a 12% improvement in survival in men (34) and a CRF above the 8-MET threshold associated with substantially lower rates of all-cause mortality and cardiovascular events compared with lower CRF values (35).

A main limitation of our study is that the intervention only included aerobic exercise training, with growing evidence that the inclusion of strength training could further improve MetS (36), particularly insulin sensitivity (37) and fasting hyperglycemia (38). In turn, a major strength and novelty was that we performed a 5-yr follow-up of a randomized controlled trial and we could thus assess the sustainability of exercise benefits over the years based on the highest level of evidence. Furthermore, we took into account activity levels outside the intervention and caloric intake, which did not differ between groups.

CONCLUSION

Exercise training can attenuate the increase in medication that would be otherwise required to manage MetS over a 5-yr period. These findings have potential for translation into a real-life scenario because benefits were observed with only 4 months of supervised training per year and with no concomitant body weight loss or dietary intervention.

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The authors state that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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