Cardiorespiratory Fitness and Components of the Metabolic Syndrome in Sedentary Men

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Key Words

Fitness · Sedentary men · Metabolic disease

Summary

Objective: To investigate the relationships between fitness and components of the metabolic syndrome in sedentary men. **Subjects and Methods:** 39 subjects (34–53 years) were evaluated for fitness ($\dot{V}O_{2\max}$) and anthropometric, metabolic, and skeletal muscle phenotypes. $\dot{V}O_{2\max}$ was assessed on a bicycle ergometer whereas other variables were obtained from an oral glucose tolerance test (OGTT), hydrostatic weighing, and a muscle biopsy. **Results:** Pearson and partial correlations adjusted for fat mass (FM), waist circumference (WC), muscle enzyme activities (citrate synthase (CS), cytochrome c oxidase (COX)), and capillary density were used to investigate the independent relationships between variables. Negative correlations between $\dot{V}O_{2\max}$ and WC as well as blood pressure and OGTT test were observed. When adjusted for FM, correlations remained between $\dot{V}O_{2\max}$ and WC ($r = -0.46$, $p < 0.01$) and systolic blood pressure ($r = -0.35$, $p < 0.05$). When adjusted for WC and CS activity, all correlations were lost except for high-sensitivity C-reactive protein (hs-CRP) ($r = -0.34$, $p < 0.05$) which remained when adjusted for CS activity. Adjustment for COX activity failed to remove correlations with hs-CRP ($r = -0.36$, $p < 0.05$), age ($r = 0.34$, $p < 0.05$), WC ($r = -0.35$, $p < 0.05$), and blood pressure. Negative correlations persisted when fitness was adjusted for the mean number of capillaries. **Conclusion:** The effects of fitness on components of the metabolic syndrome in sedentary men are explained by abdominal obesity and muscle phenotypes.

Introduction

The metabolic syndrome is defined as a clustering of atherosclerotic risk factors simultaneously occurring in the same individual [1–3]. Major components of the metabolic syndrome include central obesity, abnormal glucose metabolism, dyslipidemia, and hypertension [1, 3]. Regular physical activity has been recommended as an effective preventative approach to modulate the metabolic syndrome, the benefits of which are believed to occur in part from the improvement of physical fitness [4, 5]. For example, Laaksonen et al. [6] showed that men who are less fit have a 7-fold greater chance of developing the metabolic syndrome compared to fit and physically active men. Also, higher levels of cardiorespiratory fitness were shown to be associated with a decreased risk of having the metabolic syndrome independently of the amount of visceral and subcutaneous fat, highlighting the potential benefits of increased fitness in the obese [7, 8].

However, fitness levels vary significantly between subjects, and this is true even when adjustments are made for physical activity. This phenomenon likely results from interindividual differences in the genetic background as well as from the cumulative effects of many small differences in everyday behavior. In sedentary subjects, it is not fully understood which impact a high level of cardiorespiratory fitness might have on components of the metabolic syndrome.

Accordingly, the aim of this study was to investigate if a higher level of cardiorespiratory fitness ($\dot{V}O_{2\max}$) in sedentary men could impact components of the metabolic syndrome. Also, we investigated if the impact of fitness could be explained by related anthropometric and/or skeletal muscle phenotypes that are known to influence oxygen consumption. We hypothesized that sedentary men with higher levels of fit-

ness would be protected against metabolic perturbations usually found in the metabolic syndrome and that this protection would occur independently of the level of obesity and of the oxidative potential of skeletal muscle.

Subjects and Methods

Subjects

A total of 39 sedentary men aged between 34 and 53 years participated in this cross-sectional study. Of these, 11 were normal weight controls ($\text{BMI} \leq 25 \text{ kg/m}^2$), 12 were obese ($\text{BMI} > 30 \text{ kg/m}^2$) with normal glucose tolerance, and 16 were obese with impaired glucose tolerance. Sedentary lifestyle was defined by the absence of participation in regular leisure-time or intense physical activity over the 3 previous months or longer. Specifically, this included activities involving an energy expenditure of 8 metabolic equivalents (METs) or more and activities lasting 30 min or more, for more than once a week [9]. All potential subjects underwent a medical examination, a medical history questionnaire, and a 75 g oral glucose tolerance test (OGTT) prior to inclusion. Individuals with diabetes (fasting plasma glucose concentration $> 7.0 \text{ mmol/l}$ and/or 2 h plasma glucose $\geq 11.1 \text{ mmol/l}$ after bolus glucose ingestion), body weight fluctuation of $\pm 2 \text{ kg}$ in the last 6 months, smokers, heavy alcohol consumers, asthmatics under steroid therapy, or those with liver, renal, or uncontrolled thyroid disorders were excluded. Subjects were also excluded if they were medicated with steroid hormones, alpha- or beta-blockers, diuretics, or other modulators of lipid metabolism (thiazolidinediones, statins, insulin). Those on calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists were not excluded if they had been on stable doses in the last 3 months. Any history or physical findings of coronary heart disease, peripheral vascular disease, hypertension (diastolic blood pressure $> 90 \text{ mm Hg}$, systolic blood pressure $> 140 \text{ mm Hg}$), or intolerance to exercise resulted in exclusion of the participants. Physical activity levels were quantified with the ARIC/Baecke questionnaire [10], a modified version of the original Baecke questionnaire [11]. Tests were usually administered in the aforementioned order and over a 3- to 4-week period. The research protocol was approved by the Université Laval ethics committee, and all subjects provided written informed consent.

Body Composition

Body mass was measured to the nearest 0.1 kg using a calibrated scale including a tension gauge (Intertechnology Inc., Don Mills, ON, Canada) and a Digital Panel Indicator (Beckman industrial series 600; Beckmann Coulter Canada Inc., Mississauga, ON, Canada). Standing height was measured to the nearest millimeter using a wall stadiometer. Lean body mass and fat mass (FM) were evaluated by the hydrostatic weighing technique as previously described [9]. Waist circumference (WC) was measured in duplicate at the mid-distance between the iliac crest and last rib margin with a flexible steel metric tape to the nearest 0.1 cm. Resting blood pressure was measured using a mercury manometer and is reported as the average of 4 measurements on the right arm of subjects sitting for 30 min or more.

Oral Glucose Tolerance Test

After an overnight fast, an OGTT with a 75 g glucose load was performed. Blood samples were collected through a venous catheter from an antecubital vein at -15, 0, 30, 60, 90, and 120 min following glucose ingestion for the determination of plasma glucose, C-peptide, and insulin concentrations [12]. Plasma glucose was measured enzymatically, whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation [13, 14]. Subjects were classified as glucose-tolerant if fasting plasma glucose and 2 h post-bolus injection glucose levels were < 7.0 and

$< 7.8 \text{ mmol/l}$, respectively. Subjects were glucose-intolerant if their plasma glucose level was $\geq 7.8 \text{ mmol/l}$ 2 h following bolus ingestion.

Cardiorespiratory Fitness ($\dot{V}O_{2\text{max}}$)

Maximal oxygen consumption was measured using an incremental exercise test on a bicycle ergometer (Ergo-Metrics 800s; SensorMedics, Yorba Linda, CA, USA). Following a 5-min warm-up period between 50 and 75 W, subjects were submitted to an incremental test starting between 100 and 150 W, with an increase of 25 W every 2 min. Direct measurements of O_2 (Ametek S-3A with a Zircon cell) and CO_2 (Anarad AR-411 infrared gas analyzer) were taken every 30 s. During the test, subjects were instructed to maintain at least 70 revolutions per min. The test was ended when participants could not maintain the required speed or upon the appearance of a usual indicator for the termination of exercise testing [15]. Blood pressure and perceived exertion (Borg analogue scale) were measured every 2 min [16].

Plasma Lipid-Lipoprotein and C-Reactive Protein

The plasma lipid-lipoprotein profile and C-reactive protein (as an indicator of systemic inflammation and risk for heart disease) were analyzed from blood samples collected from the antecubital vein into vacutainer tubes containing EDTA after an overnight fast. Cholesterol and triglyceride concentrations were determined enzymatically in plasma with a Technicon RA-500 analyzer (Bayer Corporation Inc., Tarrytown, NY, USA) and enzymatic reagents obtained from Randox (Randox Laboratories, Crumlin, UK) [17]. Plasma very low density lipoprotein (VLDL) (density $< 1.006 \text{ g/ml}$) were isolated by ultracentrifugation [18]. The HDL fractions (HDL_2 , HDL_3) were obtained after precipitation of LDL in the infranantant (density $> 1.006 \text{ g/ml}$) with heparin and MnCl_2 [18]. Plasma apolipoprotein A-I (apo A-I) and apolipoprotein B (apoB) concentrations were measured by the rocket immuno-electrophoretic method of Laurell [19]. The lyophilized serum standards for apolipoprotein measurements were prepared in the core laboratory at the Lipid Research Center of Laval University Medical Center and calibrated with reference standards obtained from the Centers for Disease Control. Plasma high-sensitivity C-reactive protein (hs-CRP) levels were measured on plasma stored at -80°C using the Behring latex-enhanced high-sensitivity assay on a Behring BN-100 nephelometer (Behring Diagnostics, Westwood, MA, USA) and the calibrators (N Rheumatology Standard SL) provided by the manufacturer.

Muscle Biopsies and Analyses

After a standardized evening meal (macronutrient content: 17% protein, 38% lipid, and 45% carbohydrate) followed by an overnight (12–14 h) fast, biopsy samples were taken from the middle region of the vastus lateralis (15 cm above the patella) and 2 cm away from the fascia by the use of the percutaneous needle biopsy technique as previously described by Evans et al. [20] and regularly used in our laboratory [21]. Spectrophotometric assays of the maximal enzyme activities of citrate synthase (CS; EC 4.1.3.7) and cytochrome c oxidase (COX; EC 1.9.3.1) and histochemical determination of fiber type distribution and capillary supply were performed as previously described [22, 23].

Statistical Analyses

Statistics were performed using JMP 5.0.1 software (SAS Institute, Cary, NC, USA). Comparison of variables between lean, normal glucose-tolerant and glucose-intolerant obese was done by analysis of variance (ANOVA). Tukey HSD post-hoc tests were used to test significant differences revealed by ANOVA. The impact of body weight and fat free mass (FFM) on maximal oxygen consumption was also assessed using ANCOVA. Pearson correlations were used to examine relationships between $\dot{V}O_{2\text{max}}$ and other variables. Partial correlation analyses (adjusted for FM, WC, COX, CS, and mean capillaries per fibers) were performed between $\dot{V}O_{2\text{max}}$ and variables relating to metabolic health. The normal-

Table 1. Physical characteristics of the subjects

Variable	Lean (n = 11)	Obese normal glucose-tolerant (n = 12)	Obese glucose-intolerant (n = 16)	ANOVA p value
Age, years	44 ± 1	45 ± 2	42 ± 1	0.26
Body mass, kg	73.9 ± 1.8 ^a	99.5 ± 3.6 ^b	107.9 ± 3.3 ^b	<0.0001
BMI, kg/m ²	23.9 ± 0.5 ^a	31.8 ± 1.0 ^b	35.1 ± 1.0 ^c	<0.0001
Waist circumference, cm	88.7 ± 2.0 ^a	110.1 ± 3.0 ^b	117.5 ± 2.3 ^b	<0.0001
FFM, kg	59.1 ± 1.5 ^a	67.8 ± 1.5 ^b	73.9 ± 1.9 ^c	<0.0001
FM, kg	14.7 ± 0.9 ^a	31.8 ± 2.6 ^b	34.0 ± 2.4 ^b	<0.0001
Body fat, %	19.9 ± 1.0 ^a	31.4 ± 1.5 ^b	31.1 ± 1.5 ^b	<0.0001
$\dot{V}O_{2max}$, ml/kg/min	38.2 ± 1.6 ^a	32.1 ± 1.0 ^b	29.7 ± 1.2 ^b	0.0002
$\dot{V}O_{2max}$, ml/kg FFM/min	47.8 ± 1.8	46.9 ± 1.0	43.1 ± 1.3	0.05
ARIC/Baecke total activity index	8.52 ± 0.57	7.08 ± 0.36	7.36 ± 0.34	0.06
	Lean (n = 10)	Obese normal glucose-tolerant (n = 11)	Obese glucose-intolerant (n = 13)	
Systolic blood pressure, mm Hg	115 ± 2 ^a	120 ± 2 ^a	130 ± 2 ^b	<0.0001
Diastolic blood pressure, mm Hg	78 ± 1 ^a	81 ± 1 ^a	86 ± 1 ^b	0.0002

Values are means ± SE. Values that share the same letter are not statistically different using the Tukey HSD post-hoc test.

ity of the distribution of the data was assessed with the Shapiro-Wilk W test and, where appropriate, transformations were used to normalize the distribution of raw data or residuals prior to statistical analyses. Values are presented as means ± standard error (SE) of untransformed data throughout the text. Differences with p values < 0.05 were considered statistically significant.

Results

Subject Characteristics, Cardiorespiratory Fitness, and Physical Activity

The physical characteristics of the age-matched sedentary subjects are shown in table 1. As expected, anthropometric characteristics were significantly different between the 2 obese groups and the lean subjects. Obese glucose-intolerant subjects were also characterized by higher (but subclinical) systolic and diastolic blood pressure.

Cardiorespiratory fitness ($\dot{V}O_{2max}$), when expressed relatively to total body mass (expressed in ml/kg/min), was significantly higher in lean men when compared to those in both obese cohorts (table 1). However, when expressed relatively to FFM (ml/kg FFM/min), in order to better demonstrate the actual O₂ extraction capacity of lean tissue, the difference between groups was largely lost, albeit a tendency (p = 0.05) for a smaller value in the obese groups remained. ANCOVA results, however, confirm that when adjusted for body mass or FFM, there are no differences between groups in maximal aerobic power (p values of 0.51 and 0.12 for the group term, respectively). Thus, per unit of active tissue during exercise (muscle), no large functional difference at the level of O₂ consumption was found between our obese and lean groups. In terms of total physical activity levels (work, leisure, and sport) of the cohorts, no significant difference was found between

groups when assessed using the ARIC/Baecke total activity index.

Typical of obese men, higher (approximately 2-fold) triglyceride levels and lower HDL cholesterol concentrations (lesser by approximately 25%) were observed in our 2 cohorts of obese subjects (table 2). No differences were observed in total and low density lipoprotein (LDL) cholesterol levels between groups. Also, hs-CRP levels were found to be significantly higher in our obese groups (table 2). Using American Heart Association guidelines, average hs-CRP levels in the lean group (<1 mg/l) were consistent with a low risk, whereas those of the obese cohorts (>1.0 and <3.0 mg/l) indicated an average risk of developing cardiovascular disease. Within our obese glucose-tolerant cohort, 27% (3 of 11) of the subjects were found to have levels >3 mg/l, indicating a high risk for cardiovascular disease. This increased to 40% (6 of 15) of the subjects in our obese glucose-intolerant group.

Consistent with our classification of subjects by glucose tolerance status following OGTT, fasting plasma glucose was not different between the 3 groups, but obese glucose-intolerant men had significantly greater fasting and 120 min plasma insulin (approximately 2-fold) and plasma C-peptide (approximately 2-fold) levels when compared to lean subjects (table 2). Obese subjects with normal glucose tolerance were found to have intermediate values of fasting and 120 min insulin and C-peptide.

The enzyme activity of COX in the vastus lateralis was similar between groups, whereas the activity of CS was found to be lower in obese groups, with the lowest values observed in obese glucose-intolerant subjects. Histochemical analyses revealed that the mean number of capillaries per fiber was similar in the 3 groups (table 2).

Table 2. Metabolic and skeletal muscle (vastus lateralis) characteristics of the subjects

Variable	Lean (n = 11)	Obese normal glucose-tolerant (n = 11)	Obese glucose-intolerant (n = 15)	ANOVA p value
<i>Metabolic characteristics</i>				
Triglycerides, mmol/l	1.1 ± 0.2 ^a	2.1 ± 0.2 ^b	2.7 ± 0.2 ^b	<0.0001
Total cholesterol, mmol/l	4.7 ± 0.2	5.1 ± 0.3	5.3 ± 0.2	0.18
HDL cholesterol, mmol/l	1.3 ± 0.1 ^a	1.0 ± 0.1 ^b	1.0 ± 0.1 ^b	0.0004
LDL cholesterol, mmol/l	3.0 ± 0.2	3.2 ± 0.2	3.3 ± 0.1	0.55
hs-CRP, mg/l	0.65 ± 0.12 ^a	2.10 ± 0.48 ^{a,b}	2.70 ± 0.56 ^b	0.013
	Lean (n = 10)	Obese normal glucose-tolerant (n = 12)	Obese glucose-intolerant (n = 16)	
Glycemia, mmol/l				
Fasting	5.5 ± 0.2	5.8 ± 0.1	5.9 ± 0.1	0.19
120 min	5.2 ± 0.5 ^a	6.5 ± 0.2 ^b	9.1 ± 0.2 ^c	<0.0001
Insulinemia, mmol/l				
Fasting	75.6 ± 9.7 ^a	105.6 ± 15.8 ^{a,b}	163.7 ± 23.7 ^b	0.003
120 min	526 ± 93 ^a	724 ± 129 ^a	1,277 ± 177 ^b	0.002
C-peptide, mmol/l				
Fasting	743 ± 68 ^a	1,061 ± 86 ^{a,b}	1,305 ± 195 ^b	0.005
120 min	3,906 ± 546 ^a	4,992 ± 437 ^{a,b}	6,690 ± 658 ^b	0.006
	Lean (n = 11)	Obese normal glucose-tolerant (n = 10)	Obese glucose-intolerant (n = 14)	
<i>Skeletal muscle characteristics</i>				
CS activity, U/g	6.2 ± 0.8 ^a	4.5 ± 0.3 ^{a,b}	4.2 ± 0.4 ^b	0.04
COX activity, U/g	4.9 ± 0.5	4.2 ± 0.4	4.2 ± 0.5	0.53
Mean number of capillaries/fiber	3.6 ± 0.2	4.4 ± 0.3	4.0 ± 0.2	0.07

Values are means ± SE. Values that share the same letter are not statistically different using the Tukey HSD post-hoc test.

Relationship of Anthropometric and Metabolic Variables with Cardiorespiratory Fitness

WC and blood pressure (systolic and diastolic) were found to correlate negatively with fitness ($\dot{V}O_{2\max}$) (table 3). Negative correlations were also observed between fitness and glucose, insulin, and C-peptide levels during the OGTT (table 4). Similar results were obtained with fasting blood total triglycerides ($r = -0.32$, $p < 0.05$), VLDL triglycerides ($r = -0.34$, $p < 0.05$) as well as levels of hs-CRP (table 4). No correlations were observed between cardiorespiratory fitness and other fasting blood lipid and lipoprotein levels (NEFA, total cholesterol and cholesterol subfractions, triglyceride VLDL, LDL, HDL, and HDL subfractions, apo A-I and apoB subfractions). Positive correlations between fitness and activities of CS ($r = 0.43$, $p < 0.01$), COX ($r = 0.60$, $p < 0.001$), and the mean number of capillaries per fiber ($r = 0.38$, $p < 0.05$) were observed, however, no such relationship was found for the mean fiber area irrigated per capillary ($\mu\text{m}^2/\text{cap}$) (data not shown). These data indicate that a higher level of fitness in sedentary men is correlated with some anthropometric, metabolic, and skeletal muscle aerobic metabolic potential characteristics.

As relationships were found between fitness and obesity and muscle aerobic metabolic potential, and since the latter are known to impact on metabolic health, we used partial cor-

relations in an attempt to elucidate the independent contributions of fitness to markers of metabolic health. When adjusted for FM, most correlations of elements of the metabolic syndrome with fitness were lost. Only those with WC and systolic blood pressure remained. Remarkably, all correlations lost significance when data were adjusted for WC in the partial correlation analyses. Relative to muscle characteristics, all correlations between fitness and metabolic health except those with hs-CRP (table 4) were lost when $\dot{V}O_{2\max}$ was adjusted for citrate synthase activity. Following adjustment for cytochrome c oxidase activity, correlations remained between fitness and hs-CRP (table 4) as well as with age, WC, and systolic and diastolic blood pressure. Finally, when $\dot{V}O_{2\max}$ was adjusted for the mean number of capillaries per fiber, almost all correlations persisted except for those with age, the ARIC/Baecke total activity index, fasting glycemia, fasting C-peptide, and hs-CRP (table 4).

Discussion

An active lifestyle clearly improves health outcomes. The American College of Sports Medicine recommends increasing the volume of aerobic physical activity to prevent the meta-

Table 3. Correlation coefficients (r values) between cardiorespiratory fitness and characteristics of the subjects, $\dot{V}O_{2\max}$ (ml/kg FFM/min)

	Pearson correlation	Partial correlation adjusted for				
		FM	WC	CS	COX	Mean cap
Age, years (n = 39)	NS	NS	NS	NS	0.34 ^a	NS
BMI, kg/m ² (n = 39)	NS	NS	NS	NS	NS	-0.45 ^a
WC (n = 39)	-0.38 ^a	-0.46 ^b	–	NS	-0.35 ^a	-0.51 ^a
FM, kg (n = 39)	NS	–	NS	NS	NS	-0.38 ^a
% FM (n = 39)	NS	NS	NS	NS	NS	-0.40 ^a
ARIC/Baecke total activity index (n = 39)	NS	NS	NS	NS	NS	NS
Systolic blood pressure, mm Hg (n = 34)	-0.40 ^a	-0.35 ^a	NS	NS	-0.39 ^a	-0.43 ^a
Diastolic blood pressure, mm Hg (n = 34)	-0.36 ^a	NS	NS	NS	-0.40 ^a	-0.39 ^a

FM = Fat mass; WC = waist circumference; CS = citrate synthase activity; COX = cytochrome c oxidase activity; Mean cap = mean number of capillaries per fiber; NS = not significant.

^ap < 0.05.

^bp < 0.01.

Table 4. Correlation coefficients (r values) between cardiorespiratory fitness and OGTT variables and circulating hs-CRP; $\dot{V}O_{2\max}$ (ml/kg FFM/min); n = 39

	Pearson correlation	Partial correlation adjusted for				
		FM	WC	CS	COX	Mean Cap
Glycemia, mmol/l						
Fasting	NS	NS	NS	NS	NS	NS
120 min	-0.34 ^a	NS	NS	NS	NS	-0.39 ^a
Insulinemia, mmol/l						
Fasting	-0.32 ^a	NS	NS	NS	NS	-0.36 ^a
120 min	-0.38 ^a	NS	NS	NS	NS	-0.36 ^a
C-peptide, mmol/l						
Fasting	NS	NS	NS	NS	NS	NS
120 min	-0.32 ^a	NS	NS	NS	NS	-0.36 ^a
hs-CRP, mg/l	-0.40 ^a	NS	NS	-0.34 ^a	-0.36 ^a	-0.52 ^b

FM = Fat mass; WC = waist circumference; CS = citrate synthase activity; COX = cytochrome c oxidase activity; Mean cap = mean number of capillaries per fiber; NS = not significant.

^ap < 0.05.

^bp < 0.01.

bolic syndrome based on epidemiological, prospective, and randomized control trial studies that have shown reduced cardiovascular disease, type 2 diabetes, and metabolic risk factors with this type of training [5, 6, 24–28]. Increasing muscle mass through resistance training could also positively affect insulin resistance and fatty acid metabolism as well as decrease FM [29, 30], further enforcing the message that physical activity in general is beneficial to counter metabolic dysfunctions.

Although the benefits of increased physical activity in preventing or treating these conditions are clear, the impact of greater cardiorespiratory fitness without regular physical activity is not. Studies have established that sedentary individuals or those with a low cardiorespiratory fitness are more susceptible to suffer from or develop the metabolic syndrome [6, 31], but how fitness relates to components of the metabolic syndrome remains unclear. The purpose of this study was to

investigate if cardiorespiratory fitness in sedentary men was associated with elements of the metabolic syndrome.

Our simple correlation data suggest that a higher level of fitness in sedentary men matched for overall levels of physical activity potentially protects against obesity, hypertension, a deteriorated blood lipid-lipoprotein profile, and inflammation. This would seem to indicate that those sedentary individuals who benefit from an elevated cardiorespiratory fitness might be protected from metabolic dysfunction.

However, the relationships between fitness, obesity, and skeletal muscle characteristics observed in our study introduce a potentially important confounding effect [32]. We chose to study the contributions of fitness beyond those of obesity and skeletal muscle phenotypes by using partial correlation analyses. When adjusted for FM, most correlations between fitness and markers of metabolic health were lost, with the exception

of systolic blood pressure. This would suggest that high fitness can protect against hypertension in sedentary men with varying levels of obesity. Even more dramatic, however, were the effects of adjusting for abdominal obesity, where all relationships between fitness and elements of the metabolic syndrome and health were lost. This suggests that no matter the fitness level of a sedentary subject, the effects of increased abdominal obesity will always prevail over metabolic health. Our results also showed that, when adjusted for the potential for oxidative metabolism of muscle, almost all relations between fitness and the markers of metabolic health were lost except for that with the inflammatory marker hs-CRP. This suggests that the oxidative potential of muscle also has a more important effect on these markers of metabolic health than fitness. Moreover, these relations suggest that inflammation could be attenuated by better fitness independently of muscle oxidative potential.

The negative relationship between cardiorespiratory fitness and abdominal obesity could be indicative of a causal link. Evidence of a significant impact of obesity on the machinery solicited during fitness testing is found in the literature. For instance, a number of studies have shown skeletal muscle perturbations in obesity, changes typically observed in the machinery relating to energy metabolism. Notably, muscle from obese individuals displays reduced oxidative enzyme activities and reduced electron transport chain activity [33, 34]. At least some of these changes can occur following weight gain, as revealed in an overfeeding study [35]. Our results that show a tendency for a decreased $\dot{V}O_{2\max}$, when expressed per kg of FFM in obese men, could derive at least in part from such changes to skeletal muscle metabolic potential.

The present study has some limitations. Our findings are limited to a population of relatively healthy sedentary men and need to be confirmed in a larger cohort of subjects that should include women and younger individuals. Our small

sample size could have limited our ability to discern minor contributions of fitness to metabolic health, although we are confident we can rule out major effects. Also, if these results apply to a population of severely metabolically deteriorated individuals, such as those suffering from type 2 diabetes, remains to be demonstrated. Finally, it also remains to be shown how fitness impacts on other metabolic aspects related to obesity and diabetes, such as insulin resistance.

The results from this study should not be used to diminish the well-established importance of regular physical activity in the struggle against metabolic disease. Instead, they should be considered as cautionary and be used to stress the need for regular physical activity even in those individuals who are found to have high fitness levels with little or no training. Physical activity has been demonstrated to impact on abdominal obesity as well as the aerobic metabolism potential of skeletal muscle, and in light of our results, this might be of particular importance for those men who suffer from a deteriorated metabolic profile.

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Disclosure

All authors who participated in this study have no conflict of interest to declare.

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