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Effects of exercise on insulin sensitivity, inflammatory cytokines, and serum tartrate-resistant acid phosphatase 5a in obese Chinese male adolescents

Kuang-Chung Shih[a], Anthony J. Janckila[b,c], Ching-Fai Kwok[d,e,*], Low-Tone Ho[f,g], Yu-Ching Chou[h], Tsu-Yi Chao[i,*]

[a]*Division of Endocrinology and Metabolism, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[b]*Special Hematology Laboratory, Department of Hematology, Veterans Affairs Medical Center, Louisville, KY, USA*
[c]*Department of Microbiology and Immunology, University of Louisville, School of Medicine, Louisville, KY, USA*
[d]*Division of Endocrinology and Metabolism, Department of Medicine, Taipei-Veteran General Hospital, Taipei, Taiwan*
[e]*Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[f]*Department of Medical Research, Taipei-Veteran General Hospital, National Yang-Ming University, Taipei, Taiwan*
[g]*Department of Education, Taipei-Veteran General Hospital, National Yang-Ming University, Taipei, Taiwan*
[h]*School of Public Health, National Defense Medical Center, Taipei, Taiwan*
[i]*Division of Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

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Abstract

The benefits of exercise on glucose metabolism, inflammation, and serum tartrate-resistant acid phosphatase 5a (TRACP 5a) protein levels in Chinese male adolescents have not been extensively analyzed. Therefore, we examined the effects of a 12-week exercise program on weight, adiposity, insulin sensitivity (IS), and inflammatory marker expression, including the novel macrophage marker TRACP 5a, in obese Chinese male adolescents. A total of 106 male adolescents were recruited from the Army Academy in Taiwan and classified as lean (body mass index [BMI], 20.9 ± 0.2 kg/m^2) or obese (BMI, 27.7 ± 0.2 kg/m^2). Body composition, IS, and inflammatory markers were measured in both groups at baseline and in the obese group after completion of a 12-week exercise program. Body weight, BMI, waist circumference, body fat mass and percentage, homeostasis model assessment for insulin resistance, fasting plasma glucose, fasting serum insulin, 2-hour postchallenge plasma glucose concentration, interleukin-6, C-reactive protein, and serum TRACP 5a were significantly higher in the obese group as compared with the lean group. In addition, serum TRACP 5a was positively correlated with body mass and fat indices. After completion of the exercise program, significant reductions in all anthropometric, metabolic, and inflammatory indicators, with the exception of serum TRACP 5a were observed. Although the obese participants remained obese, exercise training significantly improved IS and reduced interleukin-6 and C-reactive protein. Tartrate-resistant acid phosphatase 5a remained unaffected by exercise training, consistent with our hypothesis that it is associated with increased adipose tissue in obese individuals.

1. Introduction

Rising prevalence of childhood obesity and its associated cardiometabolic complications are increasingly becoming major health care issues. It is possible that the greatest future health burden will result from type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), both of which are major complications that result from obesity. Previously considered a disease of adolescents and adults, T2DM [1] and CVD [2] are now increasingly diagnosed in children. Although fatal episodes occur later in life, the early pathologic manifestations of CVD appear in childhood. Accordingly, effective early interventions for the treatment of obesity and its metabolic abnormalities are urgently needed.

* Corresponding authors. Tsu-Yi Chao is to be contacted at Tel.: +886 2 87927208; fax: +886 2 87927209. Ching-Fai Kwok, Division of Endocrinology and Metabolism, Department of Medicine, Taipei-Veteran General Hospital, Taipei, Taiwan, Tel.: +886 2 28757774; fax: +886 2 28724982.
E-mail addresses: cfkwok@vghtpe.gov.tw (C.-F. Kwok), tsuyi@ndmctsgh.edu.tw (T.-Y. Chao).

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Insulin resistance (IR) is a precursor of T2DM [3]. Abdominal adiposity is associated with both IR and T2DM in adults [4,5] as well as children [6,7]. Improvements in IR have been observed in adults upon participation in exercise programs [8,9]; however, similar studies in overweight and obese children are limited [10-12].

The link between adiposity and insulin sensitivity (IS) may be mediated through certain adipokines and other inflammatory mediators. Insulin resistance is associated with high levels of serum interleukin-6 (IL-6) and C-reactive protein (CRP) [13,14]. Obesity is associated with increased macrophage infiltration into adipose tissue, which leads to a chronic inflammatory state and contributes to IR [15,16]. Measurement of the aforementioned cytokines and acute phase reactants may be used to assess the severity of chronic inflammation, disease risk, and treatment response. Regular exercise and/or weight loss may result in decreased IL-6 and CRP levels in adults according to some studies, and these changes have been associated with improved IS [17,18].

In addition to these inflammatory biomarkers, a novel marker of chronic inflammation, serum tartrate-resistant acid phosphatase 5a (TRACP 5a), is expressed and secreted by activated or inflammatory macrophages in vitro [19,20]. Significantly increased levels of serum TRACP 5a were found in one fourth to one third of patients with established rheumatoid arthritis [21,22], particularly those with nodular disease [23], implicating it as a marker of disease severity and systemic macrophage burden. Recently, it was shown that TRACP messenger RNA and a monomeric TRACP protein, equivalent to serum TRACP 5a, were more abundantly expressed in adipose-derived macrophages from obese adults compared with those of lean individuals [24]. In the same report, a TRACP transgenic mouse subline was developed that preferentially expressed monomeric TRACP 5a–like protein in adipose tissue macrophages and displayed spontaneous insulin-sensitive obesity [24]. Therefore, similar to rheumatoid arthritis, serum TRACP 5a protein may be a useful biomarker to assess the severity of obesity-related disorders as well as their response to treatment.

We sought to test this hypothesis in Chinese male adolescents with no evidence of other acute or chronic inflammatory conditions. We first established the degree of IS and inflammatory status, including the analysis of serum TRACP 5a levels, in an obese group compared with a lean group. We then measured the effect of a 12-week exercise program on anthropometric measures of total body mass indices and adiposity, parameters of glucose metabolism and IS, and serum markers of inflammation in the obese participants.

2. Subjects and methods

2.1. Subjects

One hundred six male adolescents from the Army Academy of Taiwan were enrolled. Fifty-five were classified as being of normal weight (18.5 kg/m^2 ≤ BMI < 23.0 kg/m^2), and 51 were classified as obese (25.0 kg/m^2 ≤ BMI < 30.0 kg/m^2, Table 1). The definitions of overweight and obesity based on the criteria developed by the Taiwan National Institutes of Health [25] were used in this study because morbidity and mortality are observed at lower BMIs in the Asian population. The study subjects were similar in age (15-17 years) and maturity stage (Tanner stage ≥IV). Staging was assigned by physical examination by a physician and/or nurse practitioner using Tanner classification for genital development and pubic hair [26]. All volunteers had not participated in a weight loss program for at least 6 months before the study, were not taking any medication, and were nonsmokers. Exclusion criteria included diagnosed heart disease, diabetes, renal disease, secondary obesity, or underlying genetic syndromes. The study was approved by the Taipei-Veterans General Hospital Institution Review Board. After explaining the study procedures and protocol to the participants and their parents or legal guardians before the physical examination and initiation of the study, informed written consents were obtained from the subjects and their parents or legal guardians. After fulfilling the inclusion criteria, all subjects were asked to maintain their eating habits and to record a baseline diet log before initiation of the study. Two subjects from the lean group did not complete the study because of transfer to another school; all other subjects completed the study.

2.2. Protocol design

Participants were analyzed between 8:00 and 8:30 AM after a 12-hour fast. A short questionnaire was administered to both the participants and their parents or legal guardians to verify that the guidelines regarding maintenance of their dietary habits and activity level were followed. Specifically, participants were asked to follow a prescribed weight-maintaining high-carbohydrate diet and to refrain from hard exercise 3 days before the baseline anthropomorphic

Table 1
Anthropometric data in the lean (n = 53), pretraining obese (n = 51), and posttraining obese (n = 51) groups

	Lean group (n = 53)	Obese group (n = 51)	
		Pretraining	Posttraining
Age (y)	15.8 ± 0.1	15.9 ± 0.1	15.9 ± 0.1
BH (cm)	170.7 ± 0.8	172.1 ± 0.6	172.9 ± 0.6
BW (kg)	61.1 ± 0.8	82.8 ± 0.9*	78.4 ± 1.1†,‡
BMI (kg/m^2)	20.9 ± 0.2	27.7 ± 0.2*	26.5 ± 0.3†,‡
WC (cm)	72.5 ± 0.6	90.4 ± 0.7*	86.9 ± 0.7†,‡
BFP (%)	14.1 ± 0.6	24.9 ± 0.5*	18.1 ± 0.6†,‡
BFM (kg)	8.7 ± 0.4	20.6 ± 0.5*	14.3 ± 0.6†,‡
Fat-free mass (kg)	52.4 ± 0.7	62.2 ± 0.8*	64.2 ± 0.8†,‡

Data were expressed as mean ± SEM.
* $P < .001$, lean group vs pretraining obese group.
† $P < .001$, pretraining obese group vs posttraining obese group.
‡ $P < .001$, lean group vs posttraining obese group.

analysis. After each participant emptied his bladder, body height (BH), body weight (BW), and waist circumference (WC) were measured by trained staff. Body mass index (BMI) was calculated as BW (in kilograms) divided by BH squared (in square meters). The body fat percentage (BFP) and body fat mass (BFM) were obtained using a bioelectrical body composition analyzer (Quantum X; RJL System, Clinton Township, MI). An electrocardiogram was used to evaluate cardiac function in all subjects, and blood samples were taken from the antecubital vein of the arm at 9:00 AM. A 2-hour oral glucose tolerance test (OGTT) was then performed according to a standardized procedure. These specific measurements were also determined in the obese participants after completion of the 12-week exercise intervention program.

2.3. Exercise training intervention

Exercise training, which was supervised by an experienced physical education instructor, was performed 5 times per week (Monday through Friday) for 12 weeks. Each session lasted 40 minutes and included the following: 10 minutes of warm-up, 25 minutes of physical training, and 5 minutes of cooldown. During the first 5 minutes, subjects performed warm-up/flexibility exercises (such as push-ups and sit-ups) followed by 5 minutes of physical activities consisting of progressive stretching techniques. For the following 25 minutes, subjects participated in slow running activities; slow running involved movement of the total BW to ensure maximum caloric expenditure. Participants were vigorously encouraged by the physical education instructor to perform to the limit of their tolerance during the high-intensity phases of the program that occurred in the final 5 minutes. After each session, the participants cooled down for approximately 5 minutes by slow walking. One session per week was monitored by the physician and legal guardians. Thus, the participants were actively monitored during the 12-week intervention period. However, diet-related lifestyle changes were not monitored.

2.4. Oral glucose tolerance test

Volunteers consumed a weight-maintaining diet containing 250 g of carbohydrates per day and refrained from vigorous physical activity 3 days before the OGTT. An antecubital vein of the arm was cannulated for blood sampling at 8:50 AM. Baseline fasting blood samples were obtained after approximately 10 minutes of rest after the placement of the cannula. An OGTT was then performed with the administration of 75 g of glucose [2]. All subjects consumed 300 mL of water with 75 g of dextrose in 5 minutes. Blood samples were drawn for plasma glucose and serum insulin determination every 30 minutes for 2 hours.

2.5. Laboratory measurements

All sera were stored at −80°C and thawed at room temperature immediately before biochemical parameters were measured. A venous blood sample was taken after a 12-hour fast for plasma glucose (FPG), serum insulin (FSI), CRP, IL-6, and serum TRACP 5a measurements. Fasting plasma glucose was detected using the glucose oxidase method (Model 2300 STAT; Yellow Springs Instrument, Yellow Springs, OH). Fasting serum insulin was determined by a microparticle enzyme immunoassay using the AxSYM system from Abbott Diagnostics (Abbott Laboratories, Dainabot, Tokyo, Japan). The homeostasis model assessment for insulin resistance (HOMA-IR) was applied to estimate the degree of IR (HOMA-IR = FSI × FPG/22.5, where insulin is expressed in microunits per milliliter and glucose in millimoles per liter) [27]. Circulating CRP levels were determined using a sandwich enzyme-linked immunosorbent assay. This in-house immunoassay uses peroxidase-labeled and unlabeled commercial rabbit polyclonal antiserum to human CRP and pure human CRP protein as a standard (Dako Denmark, Copenhagen, Denmark). Interleukin-6 concentration was measured using the RayBio human IL-6 enzyme-linked immunosorbent assay kit (RayBiotech, Atlanta, GA). Immunoassays for serum TRACP 5a were done according to previously published methods [21-23].

2.6. Statistical analysis

Differences in the lean and pretraining obese groups as well as the lean and posttraining obese groups were analyzed using a Student *t* test. Pretraining and posttraining obese group differences were assessed using the paired *t* test for dependent samples. Multivariate linear regression analysis was also performed with IR and IS parameters as dependent variables and TRACP 5a, IL-6, and CRP as independent variables. A P value $< .05$ was considered statistically significant. Data were expressed as mean ± SEM. All statistical analyses were performed using SPSS version 14.0 statistical software (Chicago, IL).

3. Results

3.1. Effects of exercise on obesity

Anthropometric data for the lean group were compared with data for the pretraining and posttraining obese groups (Table 1). As expected and by definition, all measures of total body mass indices (BW, BMI, and WC) and adiposity were significantly higher in the obese group before training. Although all of these measures declined significantly after completion of the exercise program, none achieved lean group levels. Although significant, the reductions in BMI were small, ranging from 4% to 6%. In contrast, measures of body fat (BFP and BFM) declined from 27% to 31%, suggesting a selective loss of body fat as a result of the training program. Nevertheless, after training, the participants remained obese by definition.

3.2. Effect of exercise on IR

As shown in Table 2, IR indices (HOMA-IR, FPG, FSI, and 2-hour postchallenge plasma glucose concentration [PCPG]) were all significantly elevated in the obese group compared with the lean group. After the exercise program, all IR indices significantly declined to levels observed in the lean group, indicating a full correction in glucose metabolism.

3.3. Effect of exercise on inflammatory markers

Inflammatory markers were significantly elevated in the obese group compared with the lean group at baseline (Table 3). After training, serum IL-6 and CRP declined significantly; but similar to anthropometric measures, they did not fall to levels observed in the lean group. Uniquely, serum TRACP 5a levels remained unchanged as a result of training.

3.4. Effects of inflammatory cytokines expression on IR and IS

To test the hypothesis that changes in inflammation result in altered IS or IR, regression analysis for all subjects was performed with IR and IS parameters as dependent variables and TRACP 5a, IL-6, and CRP as independent variables (Table 4). Both FPG and PCPG were significantly associated with TRACP 5a levels, whereas CRP was associated with FPG only. In addition, IL-6 was significantly associated with PCPG. Taken together, these results indicate that inflammatory cytokine levels are associated with measures of IS.

3.5. Serum TRACP 5a levels and body mass and fat indices

To determine if serum TRACP 5a levels were associated with body mass and fat indices, serum TRACP 5a levels were determined in the lean (n = 53) and obese (n = 51) groups at baseline. Serum TRACP 5a levels were positively associated with BW (Fig. 1A), BMI (Fig. 1B), WC (Fig. 1C), BFP (Fig. 1D), and BFM (Fig. 1E). Specifically, for each 1-kg increase in BW, serum TRACP 5a increased by 0.11 μg/L (serum TRACP 5a protein = −3.87 + 0.11 × BW, Fig. 1A); and for each 1-kg/m^2 increase in BMI, serum TRACP 5a increased by 0.36 μg/L (serum TRACP 5a = −4.67 + 0.36 × BMI, Fig. 1B). For each 1-cm increase in WC, serum TRACP 5a increased by 0.12 μg/L (serum TRACP 5a = 0.12 − 6.13 × WC, Fig. 1C); and a 1% increase in BFP represented a 0.20 μg/L increase in serum TRACP 5a (serum TRACP 5a = 0.19 + 0.20 × BFP, Fig. 1D). Finally, for each 1-kg increase in BFM, serum TRACP 5a increased by 0.21 μg/L (serum TRACP 5a = 1.01 + 0.21 × BFM, Fig. 1E).

Table 2
Insulin sensitivity in the lean (n = 53), pretraining obese (n = 51), and posttraining obese (n = 51) groups

	Lean group (n = 53)	Obese group (n = 51)	
		Pretraining	Posttraining
HOMA-IR	0.051 ± 0.004	0.108 ± 0.017*	0.054 ± 0.004†,‡
FPG (mg/dL)	79.2 ± 1.0	89.6 ± 1.1*	81.6 ± 1.1†,‡
FSI (μU/mL)	4.62 ± 0.31	8.47 ± 1.27*	4.76 ± 0.35†,‡
PCPG (mg/dL)	93.3 ± 2.5	125.6 ± 2.1*	94.6 ± 2.2†,‡

Data were expressed as mean ± SEM.
* $P < .01$, lean group vs pretraining obese group.
† $P < .01$, pretraining obese group vs posttraining obese group.
‡ $P > .05$, lean group vs posttraining obese group.

Table 3
Inflammatory cytokine levels in the lean (n = 53), pretraining obese (n = 51), and posttraining obese (n = 51) groups

	Lean group (n = 53)	Obese group (n = 51)	
		Pretraining	Posttraining
IL-6 (pg/mL)	1.02 ± 0.26	4.06 ± 0.44*	2.79 ± 0.23†,‡
CRP (μg/mL)	0.78 ± 0.20	2.63 ± 0.35*	1.36 ± 0.31†,‡
TRACP 5a (μg/L)	2.645 ± 0.294	5.362 ± 0.163*	5.584 ± 0.167‡

Data were expressed as mean ± SEM.
* $P < .001$, lean group vs pretraining obese group.
† $P < .01$, pretraining obese group vs posttraining obese group.
‡ $P < .05$, lean group vs posttraining obese group.

4. Discussion

To our knowledge, this is the first study to demonstrate that a short 12-week exercise program may significantly

Table 4
Multivariate linear regression models using HOMA-IR as the dependent variable and FPG, FSI, 2-hour PCPG, and the other measurements as independent variables as indicated

			Intercept	TRACP 5a	IL-6	CRP
HOMA-IR	R^2	0.091				
	ANOVA	0.066				
	Coefficients		0.738	0.192	0.079	−0.099
	Standard error		0.558	0.130	0.085	0.098
	P value		.190	.144	.355	.318
FPG	R^2	0.326				
	ANOVA	<0.001				
	Coefficients		78.325	1.710	0.599	−1.195
	Standard error		2.369	0.551	0.361	0.418
	P value		<.001	.003	.101	.005
FSI	R^2	0.078				
	ANOVA	0.106				
	Coefficients		3.840	0.744	0.319	−0.348
	Standard error		2.331	0.542	0.355	0.411
	P value		.104	.174	.372	.400
PCPG	R^2	0.339				
	ANOVA	<0.001				
	Coefficients		88.748	4.436	2.658	−1.369
	Standard error		5.993	1.395	0.912	1.057
	P value		<.001	.002	.005	.199

Tartrate-resistant acid phosphatase 5a in micrograms per liter, IL-6 in picograms per milliliter, CRP in micrograms per milliliter, FPG in milligrams per deciliter, FSI in microunits per milliliter, PCPG in milligrams per deciliter. ANOVA indicates analysis of variance.

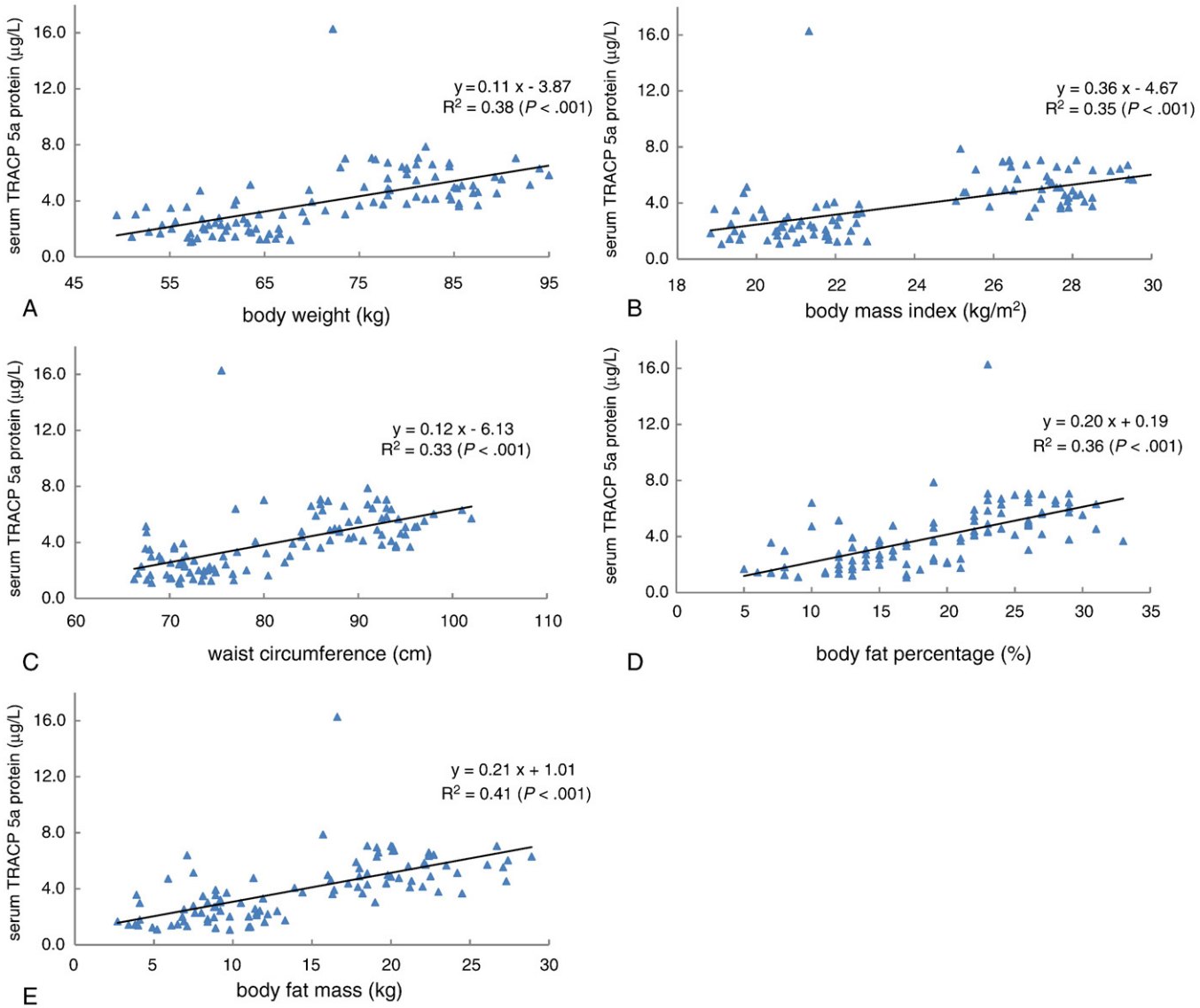

Fig. 1. Serum tartrate-resistant acid phosphatase 5a levels and body mass and fat indices. Correlation between serum TRACP 5a levels and BW (A), BMI (B), WC (C), BFP (D), and BFM (E). The TRACP 5a levels were measured in the lean group (n = 53) and the obese group (n = 51) at baseline.

enhance IS and reduce acute inflammatory risk factors in obese Chinese male adolescents. After the 12-week exercise intervention, BW and BMI were reduced by 5.3% and 4.3%, respectively, whereas BFP and BFM values declined by 27.3% and 30.6%, respectively. Fasting plasma glucose, PCPG, and HOMA-IR improved by 9%, 25%, and 50%, respectively. Finally, FSI decreased by 44%, which is in agreement with studies of adult participants [28].

The effect of physical training on IS in overweight and obese children and adolescents is limited, and studies investigating the relationship between body fat and IR after exercise have shown mixed results. Some studies reported no changes in body composition after completion of an exercise training program [29,30], whereas others observed exercise-induced fat mass reduction and acquisition of lean body mass [31,32]. In Landt et al [33], 12 weeks of aerobic training resulted in a 23% improvement in IS, as determined by using the euglycemic clamp technique, and a 4% (or 2 kg) increase in lean body mass in 16-year–old children with type 1 DM. Although BFM values were not reported, BW remained unchanged. Consequently, the significant increase in glucose utilization after exercise training reflects increased IS, attributable to the exercise program. The absence of any change in glucose utilization rates at baseline and after 12 weeks in control subjects further underscores that the observed changes were due to excise training and not to psychologic or other adjustments in undergoing the clamp procedure. Alternatively, no change in 2-hour glucose concentrations was observed in 11-year–old overweight boys and girls after 8 weeks of aerobic training in a study by Kelly et al [34]. Although BW and body composition remained unchanged after exercise, improvements in

endothelial function were observed. This was further supported by Green et al [35] who observed that an 8-week exercise program had an independent effect on arterial health. Another study observed that an 8-week exercise training program improved IR in obese children in the presence of improved exercise capacity, but in the absence of changes in BW or body composition [11]. Duration and/or intensity of the exercise program as well as characteristics of the study population might influence the outcomes of these studies and account for some of the discrepancies reported. For example, some studies involved children of a particular sex, whereas others did not; and some included participants spanning a large age range that may be affected by puberty influences on IR. In the present study, male participants of a particular age (15-17 years) were included; and pubertal status as assessed by Tanner staging remained clinically unchanged for the duration of the study.

In the present study, we observed that a 12-week exercise training program improved IR and body composition in obese adolescents, effecting a more pronounced reduction in body fat than in BW. Regular physical activity has the potential to reverse IR, improve cardiovascular function and the blood lipid profile, and control high blood pressure. Overweight individuals can obtain these important benefits even if BW is not completely normalized during a program of regular physical activity. This should help alleviate problems of diabetes, heart disease, and hypertension often associated with being overweight [36,37]. However, weight loss and improvements of metabolic factors are not linearly related possibly because exercise increases muscle mass, and the specific weight of muscle is much higher than fat.

The correlation between adipocyte size rather than adipose tissue mass and insulin malfunction has been previously observed [38]. Adipocyte enlargement may not have pathophysiologic significance alone but rather be a manifestation of other pathogenetic factors leading to IR [39], such as increased adipocyte lipolysis, resulting in elevated fatty acid production, which in turn causes IR [40]. On the other hand, enlarged adipocytes may be pathogenic themselves (ie, altered production of adipokines and cytokines) [41]; cytokine production may mediate adipose inflammation and IR.

Recently, both TRACP messenger RNA and monomeric TRACP protein expression levels were found to be increased by 400% among obese subjects compared with lean subjects [24]. Certain macrophages in adipose tissue secrete monomeric TRACP, inducing insulin-sensitive obesity by forming new, small adipocytes (ie, hyperplastic obesity) [24]. Elevated levels of serum TRACP have been positively correlated with serum insulin levels in studies using T2DM rat models [42]. Because adipose tissue from obese subjects contains increased number of inflammatory macrophages, which might be associated with IR [43], we predicted that the level of TRACP 5a expression would be increased in the obese participants. Indeed, elevated serum TRACP 5a levels were observed in the obese group compared with lean group. In addition, serum TRACP 5a was positively correlated with body mass and fat indices; however, it remained unchanged after the exercise intervention. These data may appear to be in contrast to the findings reported by Suzuki et al [42]. Using a non–insulin-dependent diabetes mellitus rat model, elevated serum TRACP activity was correlated with increased serum insulin [42]. However, the method used to assess serum TRACP activity was biased toward osteoclastic TRACP 5b, thereby reflecting a correlation between serum insulin and osteoclasts and bone resorption. In this study, the TRACP 5a isoform, which is not derived from osteoclasts and is unrelated to bone resorption, was specifically measured [44]. Thus, the increased serum TRACP 5a levels observed in obese male adolescents were a consequence of increased inflammatory macrophages in adipose tissue and were not directly linked to IS.

This study has several limitations. The effects of exercise training on anthropometric measurements and IS in obese participants were compared with the lean group. No posttest measurements of dependent variables were performed in the lean group or for obese individuals not receiving the exercise training. Thus, the effects of age, growth, maturation, attention, and seasonal variations on the dependent variables were not assessed. In addition, diet logs were only assessed at baseline. Furthermore, examination of adipose tissue histology in lean and obese subjects was not performed, although this may be the focus of future investigations. In addition, the relationship between both subcutaneous and visceral loads and atherogenic biomarkers was not determined, but may individually play a role in total adiposity burden. Finally, although HOMA was used to assess in vivo IS, we acknowledge that it only represents an approximation of systemic IR [45]. Further study is needed to confirm our finding.

Despite these limitations, we have shown that obese male adolescents carry inflammatory and metabolic risk factors for diabetes and CVD. Significant attenuation of inflammatory cytokine production and improvement in IS were observed upon completion of a 12-week exercise program. Exercise did not influence serum TRACP 5a levels in the obese participants, suggesting that elevated serum TRACP 5a was independent of IS and most likely reflects adipose-associated macrophage infiltration. These findings support the idea that increased physical activity may ameliorate the hazards of obesity in Chinese male adolescents.

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