

6-7-2017

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Combined exercise training reduces blood pressure, arterial stiffness, and insulin resistance in obese prehypertensive adolescent girls

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To cite this article: Won-Mok Son, Ki-Dong Sung, Leena P. Bharath, Kong-Jib Choi & Song-Young Park (2017) Combined exercise training reduces blood pressure, arterial stiffness, and insulin resistance in obese prehypertensive adolescent girls, *Clinical and Experimental Hypertension*, 39:6, 546-552, DOI: <https://doi.org/10.1080/10641963.2017.1288742>

ABSTRACT

Childhood obesity is strongly linked to pathological processes for cardiovascular diseases in later adulthood. Obese adolescent girls with high blood pressure (BP) are reported to have increased arterial stiffness, which is associated with the development of hypertension and atherosclerosis. The present study sought to examine the impact of combined resistance and aerobic exercise (CRAE) training on BP, brachial-ankle pulse wave velocity (baPWV), insulin resistance (IR), and body composition in obese prehypertensive girls. Forty girls (age, 15 ± 1 years; systolic BP, 132 ± 2 mmHg, diastolic BP, 80 ± 5 mmHg) were randomly assigned to either a combined exercise (EX, $n = 20$) or no exercise group (CON, $n = 20$). The EX group performed CRAE for 12 weeks, 3 times per week. BP, baPWV, blood nitrite/nitrate, endothelin-1 (ET-1), homeostasis model assessment for insulin resistance (HOMA-IR), and body composition were measured before and after the exercise intervention. BP ($\Delta -7.3 \pm 2.67$ mmHg), baPWV ($\Delta -1.23 \pm 0.49$ m/s), ET-1 ($\Delta -14.35 \pm 1.76$ $\mu\text{mol/mL}$), nitrite/nitrate ($\Delta 0.5 \pm 0.09$ μM), HOMA-IR ($\Delta -1.4 \pm 0.07$), percent body fat ($\Delta -1.35 \pm 0.9\%$), and

waist circumference were significantly improved ($P < 0.05$) in the EX group after 12 weeks of training versus the CON group. These findings indicate that 12 weeks of CRAE improves BP, HOMA-IR, and arterial stiffness and reduces central adiposity in obese adolescent girls with prehypertension. Thus, this study provides evidence that CRAE can be a useful therapeutic treatment for high BP, IR, and central adiposity, thereby reducing the likelihood of pathological development for cardiovascular diseases in later adulthood.

KEYWORDS

Adolescent; arterial stiffness; combined resistance and aerobic exercise; hypertension; obesity

Introduction

Obesity is associated with higher prevalence of cardiovascular diseases in both adults and children (1). Increased abdominal body fat, in particular, is positively associated with high blood pressure (BP), arterial stiffness, and hyperinsulinemia (2,3). Additionally, previous studies have reported that obesity or obesity-related insulin resistance (IR) is closely linked with increases in arterial stiffness in adolescents (4,5). Brachial-ankle pulse wave velocity (baPWV), an index of systemic arterial stiffness, has been associated with high BP in children (6). Recent studies have reported that early development of atherosclerotic lesions is strongly linked to overweight and obesity in childhood (7). Additionally, children and adolescents with high BP are at a significantly increased risk of developing coronary heart disease in adulthood (8).

Previous studies suggested that exercise-mediated reduction in fat mass in obese individuals is accompanied by improved IR. These studies recommend that 40 minutes of moderate-to-high intensity aerobic exercise 3–5 days/week is required to improve vascular function (9–11). Aerobic exercise training has also been shown to improve arterial stiffness via increasing nitric oxide (NO) bioavailability and reducing endothelin-1 (ET-1) levels in adults (12,13). Recently,

we and other research teams have suggested that improved muscular strength and mass resulting from combined resistance and aerobic exercise (CRAE) programs have greater beneficial effects on reducing baPWV in comparison to traditional aerobic exercise in older adults (14,15). However, to our knowledge, no prior studies have examined the impact of CRAE training on arterial stiffness, BP, IR, and body composition in prehypertensive adolescent girls. Thus, the aim of this study was to examine the impact of 12 weeks of CRAE on arterial stiffness, BP, blood nitrite/nitrate, ET-1 levels, homeostasis model assessment for insulin resistance (HOMA-IR), and body composition in obese adolescent girls with prehypertension. We hypothesized that CRAE would reduce arterial stiffness, BP, IR, and ET-1 levels, which would be accompanied by improved nitrite/nitrate levels and decreased central adiposity.

Materials and methods

Participant characteristics

Forty adolescent girls (Tanner 2–3 stage) from Busan, South Korea, were recruited and categorized as obese (age, 14–16 years, body mass index (BMI), ≥ 30 kg/m², 95th percentile based on the Centers for Disease Control and Prevention Child & Teen BMI chart) with prehypertension (systolic $140 \geq$ BP ≥ 120 mmHg and diastolic $90 \geq$ BP ≥ 80 mmHg), hyperinsulinemia (>12.0 μ U/ml), and abdominal obesity (waist > 80 cm) (16,17). All participants were sedentary, defined as having less than 1 hour of regular exercise training per week, and were not on a weight loss diet within the last 6 months. Exclusion criteria included pulmonary, cardiovascular, renal, adrenal, pituitary, severe psychiatric, and thyroid diseases. Participants were also excluded if they were on any medication. All of the participants and their guardians signed a written informed consent approved by the Institutional Human Research Committee of Pusan National University (PNU IRB/2013-2), carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to the study.

Table 1. Combined resistance and aerobic exercise program.

Weeks	Order	Exercise	Duration	Intensity	Frequency
	Warm-up	Static stretching	5 min		
1-4	Main exercise	Left and right side stroke 1 line 1 jump Foot changing run jump Cross jump Right and left jump Box jump Weight squat jump Jump rope Badminton game	30 min 20 min	40-50% HRR (RPE 11-12)	3 times/week
5-8	Main exercise	Left and right side stroke 1 line 1 jump Foot changing run jump Cross jump Right and left jump Box jump Weight squat jump Jump rope Badminton game	30 min 20 min	50-60% HRR (RPE 13-14)	3 times/week
9-12	Main exercise	Left and right side stroke 1 line 1 jump Foot changing run jump Cross jump Right and left jump Box jump Weight squat jump Jump rope Badminton game	30 min 20min	60-70% HRR (RPE 15-16)	3 times/weeks
	Cool-down	Static stretching	5 min		

Study design

Blood samples and body composition were evaluated at baseline and at 12 weeks for this research. After baseline measurements, the participants of the study were randomly assigned to either the control group (CON, $n = 20$) or the combined exercise group (EX, $n = 20$) by using a two-armed, parallel design. The participants in the EX group performed a combined exercise program (60 minutes per day, 3 times per week, for 12 weeks). All participants were sedentary (less than 1 hour of regular exercise per week in the previous year). Participants were requested not to make changes to their diet and physical activity habits for the duration of the study, with the exception of refraining from nitrate/nitrite-containing foods. Guardians of participants recorded food and physical activity logs, and also all the participants were supervised and educated by trainers every 2 days for their diet and physical activity.

Volunteers reported to the laboratory between 8:00 and 8:30 AM after a 10- to 12-hour fast for blood sampling. Additionally, volunteers were advised to refrain from the nitrate/nitrite-containing foods. Participants in the CON group did not participate in any supervised or unsupervised exercise protocol and were asked to maintain their regular lifestyle habits (diet, activity levels, etc.) for the duration of the study. There was no dropout of participants reported. All experiments were examined in accordance with the protocol approved by the Public Institutional Review Board, designated by the Ministry of Health and Welfare (P01-201511-11-001).

Combined exercise training

Participants in the EX group trained using CRAE for 12 weeks, 3 days per week, 60 minutes each day. This CRAE program was divided into warm-up (5 minutes), the main exercise (30 minutes of various exercises and 20 minutes of playing badminton), and cool-down (5 minutes). The warm-up and cool-down included static stretching. Furthermore, CRAE consisted of seven exercises (left- and right-side stroke, 1 line 1 jump, cross-jump, right and left jump, box jump, weighted squat jump, and jump rope) and badminton. Intensity of the exercise was gradually increased from 40–50% heart rate reserve (HRR) and rated perceived exertion (RPE) 11–12 within the first 1–4 weeks to 60–70% HRR and RPE 15–16 in 9–12 weeks. All of the sessions were fully supervised by the researchers. The heart rate (HR) of each subject was monitored using a wearable polar device (Electro, Oy, Kempele, Finland) during the entire training session so as to maintain the correct training intensity. The program is shown in Table 2.

Blood sample analysis

Fasting blood samples were collected around 8:00 AM from an antecubital vein into ethylenediaminetetraacetic acid (EDTA)- containing tubes, centrifuged for 15 minutes at 3,000 rpm, and the plasma was stored at -80° C until analysis. Each sample was run in duplicate according to the manufacturer's instructions using the provided reagents (18).

Table 2. Descriptive characteristics of the study participants.

	Control (n = 20)		Exercise (n = 20)	
	Pre	Post	Pre	Post
Age, years	15±1		15±1	
Height, m	156.9±6.28		157.99±5.94	
Tanner stage	2-3		2-3	
Weight, kg	72.29±9.84	70.26±9.7	72.86±10.27	68.37±9.07
BMI, kg/m ²	30.31±0.76	28.31±0.74	30.36±0.69	27.39±0.71
Body fat, %	33.84±2.41	33.85±2.41	33.75±2.36	30.4±1.61*
Lean body mass, %	43.13±4.4	42.93±4.28	41.76±4.81	42.51±5.1*
Systolic blood pressure, mmHg	130.2±1.4	130.6±1.39	134±2.41	123.7±2.13*, †
Diastolic blood pressure, mmHg	82±2.45	82.4±1.99	76.3±3.63	79.8±1.48
Pulse pressure, mmHg	48.2±2.16	48.2±2.07	53.7±2.56	46.9±1.55*
MAP, mmHg	98.07±1.9	98.47±1.53	95.53±3.04	95.43±1.56
Glucose, mg/dL	91±3.2	94±2.7	86.3±1	86.8±2.1*, †
Insulin, mU/L	11.6±1.4	12.5±1.2	14.4±1.2	9.1±0.3*, †
HOMA-IR	2.6±0.5	2.9±0.2	3.3±0.2	1.9±0.1*, †
Waist circumference, cm	85.4±0.7	86.3±1	86.6±0.7	84.5±0.7*, †
*, † P < 0.05 versus pre				
*, † P < 0.05 versus control.				

Levels of ET-1 in blood samples were measured by commercially available enzyme immunoassay technique (Endothelin-1 Enzyme Immunoassay Kit, Cayman Chem, Ann Arbor, MI, USA). The detection range for ET-1 using this assay was from ≥ 1.5 $\mu\text{mol/ml}$.

To assess the NO production, total nitrite/nitrate concentration was assayed using a commercially available Griess assay kit from Cayman Chemical (Ann Arbor, MI, USA). The amount of nitrite/nitrate produced in the reaction mixture was determined spectrophotometrically at 540 nm (OD540) using a microplate reader (19).

Blood glucose concentrations were evaluated with a kit from Raichem (San Diego, CA, USA). Serum insulin was measured by enzyme-linked immunosorbent assay (ELISA) from Millipore (Billerica, MA, USA). The HOMA-IR was calculated from the fasting plasma blood glucose and insulin levels according to the model from Matthews et al. (20).

Blood pressure and arterial stiffness

Systolic BP (SBP) and diastolic BP (DBP) were measured using automatic sphygmomanometer (HEM-7113 INT; Omron Corp., Kyoto, Japan). baPWV (m/s), an

indicator of arterial stiffness, was measured using a commercially available applanation tonometer (SphygmoCor CPV system, AtCor Medical Ltd, Sydney, Australia), followed by data analysis using analysis software (version 8.0, SphygmoCor Cardiovascular Management Suite). Two measurements were collected, one at each time point, and averaged as previously described (21,22).

Anthropometry and body composition

Height was measured to the nearest 1.0 cm while participants were barefoot. Body weight was measured to the nearest 0.1 kg, with the participants wearing light clothes. BMI was calculated according to the common formula, weight (kg) divided by the square of height (m²). Body fat (%) and lean body mass (%) were determined for all of the participants using bioelectrical impedance analysis (InBody 230, Biospace, Seoul, Korea) (23).

Data analysis

The Shapiro–Wilk test was performed to examine the normality of the data. Unpaired t-tests were used to determine the differences at baseline between groups. A two-way analysis of variance with repeated measures [group (CON and EX) × time (before and after 12 weeks)] was used to compare the difference of changes at pre- and post-CRAE training program within and between groups. Bonferroni correction was used to determine the effects of CRAE over time. When a significant interaction or main effect was noted, univariate analysis was used for post-hoc comparisons. All analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as the mean ± SEM. Statistical significance was set at $P < 0.05$. Based on the previous literature, we estimated that 40 participants would enable 90% power to detect a 5% decrease in baPWV after CRAE (15,24).

Results

Participants' characteristics before and after 12 weeks for the CON and EX groups are presented in Table 2 (data are shown as means ± SE). Baseline parameters between the two groups were not significantly different ($P > 0.05$).

Blood Pressure

SBP was significantly reduced in the EX group after 12 weeks of training (Δ -8.3 \pm 2.67 mmHg, $P < 0.05$) (Figure 3A). However, DBP was not significantly different from baseline to post-exercise training values in both CON and EX groups (Figure 3B).

Bapwv

As shown in Figure 2, baPWV was significantly decreased in the EX group (Δ -1.23 \pm 0.49 m/s, $P < 0.05$), whereas baPWV in the CON group had no change.

Total nitrite/nitrate levels

Total nitrite/nitrate levels of the EX group were significantly increased (Δ 0.5 \pm 0.09 μ M, $P < 0.05$) after the CRAE training, while there was no statistical time effect in the CON group (Figure 1A).

Endothelin-1

There was a significant decrease in ET-1 levels after the exercise training by 14.35 \pm 1.76 μ mol/mL ($P < 0.05$). No difference was observed in the CON group (Figure 1B).

Glucose, Insulin, and homa-ir

Baseline insulin and glucose levels in our subjects were similar to those found in obese adolescents with IR and hyperinsulinemia in previous studies (10,25,26). Glucose (Δ -3.9 \pm 1.01 mg/dL, $P < 0.05$), insulin (Δ -5.3 \pm 0.39 mU/L, $P < 0.05$), and HOMA-IR (Δ -1.4 \pm 0.07, $P < 0.05$) were reduced after the training. Furthermore, glucose, insulin, and HOMA-IR were significantly decreased in the EX group when compared to the CON group ($P < 0.05$). This data is shown in Table 2. Significance was set at $P < 0.05$.

Body composition

No significant difference was observed between the CON and EX groups in

age, height, weight, or BMI (Table 2). 12 weeks of CRAE training significantly decreased percent body fat (EX pre vs. post: $\Delta -1.35 \pm 0.9\%$, $P < 0.05$) and increased percent lean body mass (EX pre vs. post: $\Delta 0.75 \pm 2.22\%$, $P < 0.05$) (Table 2). Additionally, waist circumference (WC) was significantly reduced in the EX group (EX pre vs. post: $\Delta -2.2 \pm 1.4$ cm, $P < 0.05$).

Discussion

There are several interesting and novel findings in the present study. First, 12 weeks of CRAE training reduces the mean arterial BP and arterial stiffness in obese adolescent girls with prehypertension. Additionally, we found that there is an increase in blood nitrite/nitrate levels, which is a marker for NO. NO has vasodilatory, anti-inflammatory, and antioxidant properties, which are associated with improved vascular function. We also observed a decrease in ET-1, which is a potent vasoconstrictor. This evidence shows that exercise-induced decreases in BP and arterial stiffness are mainly due to the improved vasodilatory function. Second, IR and HOMA-IR were decreased in conjunction with reduced fat percentage after 12 weeks of CRAE training. To our knowledge, this is the first study which demonstrates the beneficial effects of the CRAE training on both cardiovascular and metabolic functions in obese adolescent girls with prehypertension. Therefore, these findings imply that CRAE training is a useful therapeutic treatment to reduce high BP and IR in this population.

Exercise has been suggested as a non-pharmacological treatment to improve cardiovascular function in both young and older individuals (15,27), and previous studies reported that aerobic exercise improves cardiovascular health in obese adolescent girls (28,29). We previously reported that BP and baPWA were reduced after 12 weeks of CRAE training in older obese women (15). In the present study, we extend the use of this distinct exercise modality to obese girls with prehypertension. The novel finding is that CRAE training reduces both BP (SBP: -9 mmHg) and arterial stiffness (-1.23 m/s) by improving vasodilatory function. Importantly, the magnitude of reduction in SBP observed in the present study is clinically relevant as well as comparable to the reduction observed following

antihypertensive drug treatment in obese adolescents with hypertension (30). Additionally, a reduction in SBP greater than 5 mmHg has been shown to reduce the risks for cardiovascular events and mortality (31).

The CRAE training-mediated decrease in BP is likely due to improved vasodilatory function, especially an improvement in vascular endothelial cell function, as indicated by increased blood nitrite/nitrate and reduced ET-1 levels. Nitrite/nitrate level is a well-validated marker of circulating NO, a potent endothelial-produced vasodilator. Additionally, ET-1, an endothelial-derived vasoconstrictor, was significantly reduced. This is important because elevation in ET-1 indicates a decline in endothelial cell function (32,33). Previous studies reported that increased NO bioavailability promotes a decrease in vascular resistance and eventually results in a decrease in BP (34,35). In agreement with these previous studies, our results demonstrate that CRAE training increases circulating NO and decreases ET-1, which could significantly contribute to the decrease in BP (32,33). Additionally, increased NO may reduce arterial stiffness by structural “remodeling” of endothelium, which would result in the reduction in BP and arterial stiffness in these prehypertensive study participants. Therefore, these results highlight that CRAE training can be a useful therapeutic method for lowering high BP in obese individuals.

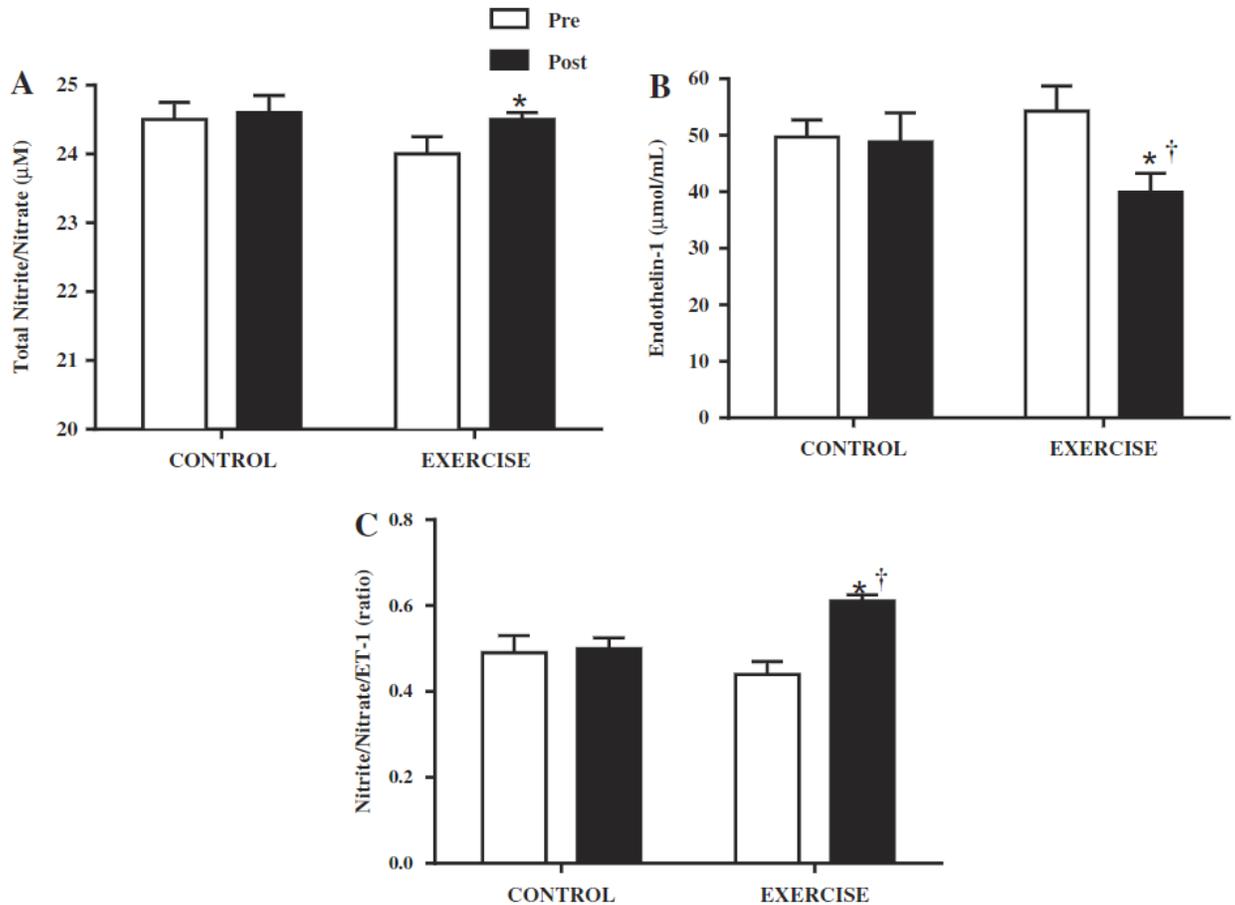


Figure 1. Total nitrite/nitrate (A), endothelin-1 (B), and the ratio of nitrite/nitrate and ET-1 (C) before and after 12 weeks of combined exercise training (EX, $n = 20$) or no exercise (CON $n = 20$) in obese girls with prehypertension. * $P < 0.05$, time effect; † $P < 0.05$, group effect. Values are presented as mean \pm SEM. ET-1, endothelin-1.

Previous studies reported that reducing body fat, especially central fat, is crucial for reducing the risks of cardiovascular disease in obese and obese with high BP populations (28,29). Our exercise training program successfully reduced percent body fat and increased percent lean muscle mass in our subjects. This improved body composition would promote an improvement in the metabolic milieu which may be associated with reduced IR. Previous studies reported that 12 weeks of both aerobic and resistance exercise training reduced body fat, but no change was observed in IR in obese adolescents (36,37). Giannopoulou et al. suggested that a 14-week aerobic exercise training program is required to have a clinical reduction of IR in obese girls (9). Although neither of these exercise training regimens could efficiently correct IR in obese adolescents, our results

demonstrated that the CRAE program effectively reduced IR in our participants to the levels found in lean adolescents (25,26,38). Interestingly, our exercise program reduced both fasting plasma glucose and insulin levels. Therefore, the improved IR after exercise intervention may be due to improvements in both skeletal muscle glucose uptake and hepatic insulin sensitivity (38).

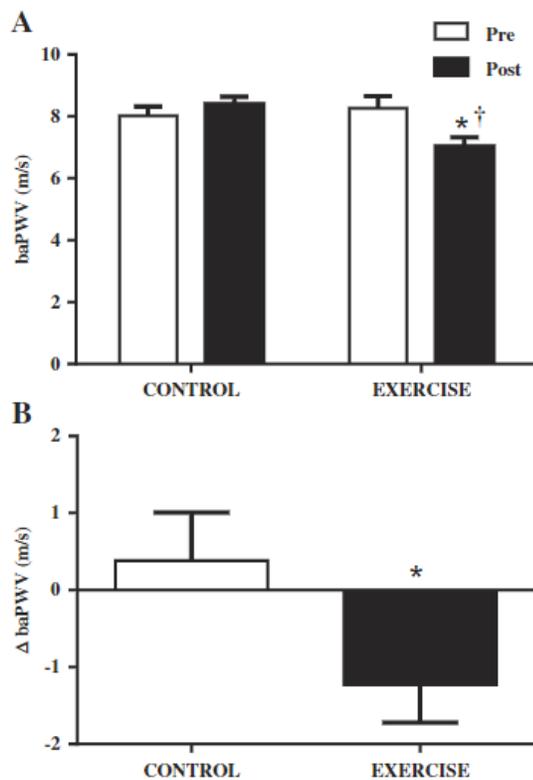


Figure 2. baPWV (A) and Δ baPWV (B) before and after 12 weeks of combined exercise training (EX = 20) or no exercise (CON = 20) and in obese girls. * $P < 0.05$, time effect; † $P < 0.05$, group effect. Values are presented as mean \pm SEM.

Previous studies suggested that elevated abdominal fat is associated with IR in both adults and adolescents (26,39). WC is a well-validated indicator of central adiposity and abdominal fat in adolescents (40). Moreover, abdominal fat appears to mediate the association between IR and cardio-vascular disease in adolescents (41,42). The links between IR and elevated BP can be explained by IR-mediated elevations in inflammation, which results in endothelial dysfunction. Moreover, this IR-mediated endothelial dysfunction attenuates NO bioavailability and eventually elevates BP by reducing vascular conductance. As we

reported (Table 2), our participants fall in the pediatric definition of metabolic syndrome, WC criterion ≥ 80 cm (43). We observed that our exercise training program reduced WC by ~ 2.2 cm, along with a reduction of HOMA-IR. This notable finding demonstrates that a reduction of ~ 2.2 cm in WC could promote a reduction in IR in adolescents. However, this finding warrants to be investigated with a larger sample size of subjects.

In conclusion, our findings suggest that 12 weeks of CRAE training reduces BP, arterial stiffness, IR, and percent body fat in obese girls with prehypertension. Reductions in BP, arterial stiffness, and IR occurred in conjunction with decreases in ET-1 levels and abdominal adiposity, as well as an increase in nitrite/nitrate levels. These findings suggest that CRAE training is a useful therapeutic intervention for treating high BP and IR. Additionally, regular practice of CRAE training can be an efficient precaution for reducing the risks of future obesity-related metabolic complications and cardiovascular diseases in obese adolescent girls.

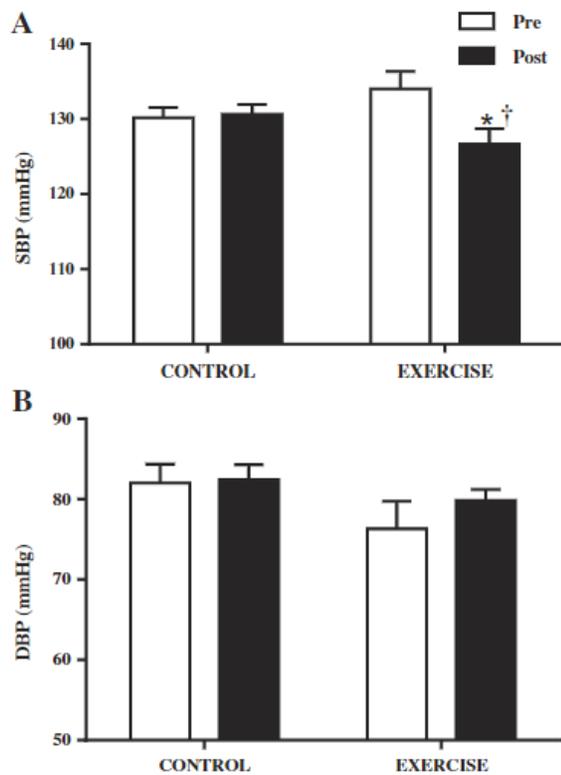


Figure 3. SBP (A) and DBP (B) before and after 12 weeks of combined exercise training (EX = 20) or no exercise (CON = 20) and in obese girls. * $P < 0.05$, time effect; † $P < 0.05$, group effect. Values are presented as mean \pm SEM. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Acknowledgments

The authors are grateful to the subjects for participating in this study.

Author disclosure statement

There is no conflict of interest/financial disclosure.

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