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Aerobic exercise is an independent determinant of levels of inflammation and oxidative stress in middle-aged obese females

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The purpose of this study was to investigate the effects of a 4-week moderate-intensity aerobic exercise on changes of body composition and markers of inflammation and oxidative stress independent from weight loss in middle-aged obese females. Thity-five obese females were randomly assigned to either an exercise (EX, N = 16) or control (CON, N = 19) group. The EX performed moderate intensity aerobic exercise on the treadmill for 60 min at 55% of maximal oxygen consumption (VO_{2max}) for 4 weeks (3 days/wk). Body composition measurement with dual-energy x-ray absorptiometry and blood collection were conducted before and after the 4-weeks intervention. Blood samples were used to measure levels of tumor necrosis factor-alpha (TNF-α), C-reactive protein, adiponectin, total antioxidant status (TAS), and 8-hydroxydeoxyguanosine. Four weeks of aerobic exercise intervention significantly increased VO_{2max} in EX ($P < 0.001$). EX also observed a decrease in TNF-α ($P = 0.033$) and an increase in TAS ($P = 0.028$) without changes in body weight and fat mass after 4 weeks of aerobic exercise training. No changes were observed in CON after the intervention. Results of this study indicate that moderate aerobic exercises may contribute, at least a part, to reductions of inflammation and oxidative stress independently from fat loss. Therefore, it may reduce risks of obesity-associated disorders in middle-aged obese females.

Keywords: Aerobic exercise, Obesity, Body composition, Inflammatory cytokines, Oxidative stress

INTRODUCTION

The prevalence of obesity and obesity-related diseases has increased significantly over the past two decades to pandemic proportions (Cao, 2014; Tumova et al., 2013). Obesity is considered to increase the risk for many diseases such as cancers, cardiovascular disease, and type 2 diabetes mellitus (Bell et al., 2014; Hatoum et al., 2012), which often results from lack of exercise, good diet, and maintaining a healthy lifestyle (Pérez-Escamilla et al., 2017; van Rossum, 2017).

Excess body fat, acting as an active endocrine organ, is associated with elevated levels of proinflammatory cytokines and oxidative stress in the blood (Beavers et al., 2015; Bruun et al., 2006) which are known to induce cancers, type 2 diabetes, and cardiovascular diseases. Therefore, the inflammatory pathway with oxidative stress is pointed out by researchers as a potential therapeutic approach targeting for lifestyle interventions designed for obese populations to reduce diseases and disabilities (Wang and He, 2018; You et al., 2004; Zatterale et al., 2020).

There is mounting evidence that aerobic exercise is as an effective and preventive countermeasure to chronic diseases. Previous studies reported that aerobic exercise training reduced cardiovascular risk factors and improved insulin sensitivity, which was accompanied by reductions in proinflammatory cytokines and oxidative stress in overweight and obese population (Abramson and Vaccarino, 2002; Adamopoulos et al., 2001; Church et al., 2002; Conraads et al., 2002). Results of these studies suggest that aerobic exercise training may improve the inflammatory profile and oxidative stress independently from weight loss. However, most studies failed to confirm the effects of exercise on inflammatory

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cytokines and oxidative stress (Beavers et al., 2015; Fatouros et al., 2004; Kelishadi et al., 2008; Marcell et al., 2005) independent from fat mass, therefore, it is generally accepted that a reduction in fat mass is required to induce decreases in markers of proinflammatory cytokines and oxidative stress.

Even though the mechanism which links exercise training to these inflammatory markers are not fully understood yet, a few recent studies provided evidence that physical activities may, independently from weight loss or fat mass, suppress oxidative stress (Samjoo et al., 2013), the production of inflammatory markers (Starkie et al., 2003), enhance the anti-inflammatory indices (You et al., 2013).

With given information of the relation between obesity and cardiovascular risk factors, insulin resistance, and inflammation, it is important to understand whether systemic inflammation and oxidative stress can be in part explained by the physiologic benefits of exercise and whether exercise can be used as a potential therapeutic intervention for overweight and obese individuals to prevent the prevalence of chronic diseases. Therefore, the purpose of this study was to investigate the effects of exercise training on inflammatory biomarkers in the absence of weight loss and fat loss by conducting a short-term, a 4-week exercise training intervention.

MATERIALS AND METHODS

Subjects

A total of 38 obese Hispanic females aged 34–46 years old, were recruited from the Hispanic community in the United States. Participants were considered eligible if they were nonsmokers, premenopausal, obese (% body fat >30%), physically inactive; did not have any known chronic disease; did not take medication that would alter metabolic, cardiovascular, or immune function; and had no musculoskeletal limitations. Participants who did not have menses during the last 2 months were excluded from this study. This study was approved by the Institutional Review Board (TAMIU-IRB-20131203) and the subjects provided written informed consent and the medical history forms prior to performing any study protocols.

Study design

During the initial visit, the subjects were randomly assigned to either an exercise (EX: N = 19) or control (CON: N = 19) group. Subjects were assessed 2 times: before the intervention (PRE) and after the 4 weeeks of intervention (POST). Subjects were asked to maintain a normal dietary regimen and refrain from any forms of aerobic or anaerobic physical activity other than the exercise treatment throughout the study period. For each test, subjects arrived at the testing center between 08:00 and 09:00 hr after 12 hr of fasting and underwent anthropometric measurements, measurement of body fat and visceral adipose tissue mass, blood sample collection, and maximal oxygen consumption (VO_{2max}) test. Total three subjects in exercise group were excluded due to missing more than 3 days of training. Therefore, a total of 35 subjects (16 EX, and 19 CON) completed this study.

Anthropometric measurements

All measurements were completed in duplicate by a trained technician. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with the participants wearing indoor clothes without shoes.

Body composition assessment

Total and multicompartment body composition was measured by dual-energy x-ray absorptiometry (Hologic Discovery Series, Bedford, MA, USA) at PRE and POST. This allows for estimation of total lean mass and fat mass within specific regions, including the visceral depot. Subjects lied on the table and the entire body were scanned. The subject lied flat on her back for the duration of the scan without difficulty, pain, or shortness of breath. Subjects were asked to wear a gown and to remove all metal objects (glasses, jewelry, and cell phones). The scans were performed following the standard clinical protocol.

VO_{2max} test

VO_{2max} test was conducted in each testing day and the result of VO_{2max} test at PRE was used to determine exercise intensity (55% of VO_{2max}) for subjects in exercise group. VO_{2max} was measured during a continuous, progressive, treadmill running protocol on a level grade, with which subjects started to walk at 4 km/hr and speed was increased 0.8 km/hr every 2 min.

Blood collection and analyses

Five milliliter of venous blood was drawn from an antecubital vein right after body fat measurement in each testing day. Collected blood sample was centrifuged in serum separating vacutainer tubes at 1,000×g for 15 min (Allegra X-15R Refrigerated Centrifuge, Beckman Coulter, Irving, TX, USA). The serum was then stored at -80°C until blood chemical analyses were conducted.

Tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP),

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adiponectin, total antioxidant status (TAS), and 8-hydroxydeoxyguanosine (8-OHdG) in blood were measured using the enzyme-linked immunosorbent assay. All these variables were determined with commercial kits (Cayman Chemical Co., Ann Arbor, MI, USA) using a microplate reader (EL 808, BioTek Co., Winooski, VT, USA). The mean intra-assay coefficients of variation (CVs) were 6.5%, 5.8%, 5.6%, and 6.7% and Interassay CVs were 6.9%, 7.9%, 8.5%, 7.4%, and 7.5% for TNF-α, CRP, adiponectin, TAS, and 8-OHdG, respectively.

Exercise intervention

Subjects assigned to the exercise group performed walking exercise on a treadmill at a predetermined exercise intensity (heart rate at 55% VO_{2max}) for 60 min, 3 days a week for 4 weeks. During each exercise session, the subjects' heart rate was monitored using the Polar heart rate monitor (Polar, Lake Success, NY, USA) and recorded every 10 min to ensure their target exercise intensity. As each subject's fitness level improved, the exercise speed on treadmill was increased on the basis of heart rate in order to maintain a heart rate at 55% VO_{2max}. Speed was adjusted when average heart rate was decreased by more than 5 beats per minute on 2 consecutive training sessions. All the exercise sessions were supervised by research assistants. The subjects in the control group did not perform any physical activity throughout the study period.

Data analysis

The sample size was calculated by G*Power 3.1.0 software, given an alpha level at 0.05, an effect size of 0.40, and power at 0.80. The appropriate sample size was estimated to be 15 subjects for the current study. All statistical analyses were conducted using Sigmaplot 13 (Systat Software, Inc., San Jose, CA, USA). Two-way analysis of variance (ANOVA) was used to analyze changes in body composition, inflammatory cytokines, and markers of oxidative stress. *post hoc* tests were performed using Tukey *post hoc* test and statistical significance was set at $P < 0.05$.

RESULTS

We conducted two-way repeated measures ANOVA with Tukey *post hoc* test since all variables in this study passed Shapiro–Wilk normality test and Brown–Forsythe equal variance test. Results of these two tests indicate that there is no baseline difference found in all variables measured in this study. Significant time and interaction effects were found only in VO_{2max}, TNF-α, and TAS.

The physical characteristics of 35 subjects at baseline (PRE) and after the 4 weeks of exercise intervention (POST) are presented in Table 1. There were no significant differences found between EX and CON groups at PRE. EX group observed an increase in VO_{2max} (time×interaction: $P < 0.001$, $F = 9.265$) at POST along with no changes in body weight, BMI, % body fat, and visceral adipose tissue mass. None of these variables were significantly changed in CON group over the 4-week intervention.

Changes in inflammatory cytokines and markers of oxidative stress are found in Table 2. EX group observed a significant decrease in TNF-α (time×interaction: $P = 0.033$, $F = 3.742$) and an increase in TAS (time×interaction: $P = 0.0298$, $F = 4.12$) at POST, meanwhile, levels of adiponectin and CRP were unaltered. CON group did not observe any changes in these variables.

Table 1. Physical characteristics of subjects at baseline (PRE) and after 4 weeks of aerobic exercise intervention (POST)

Variable	EX (n=16)		CON (n=19)	
	PRE	POST	PRE	POST
Age (yr)	39.4±3.2		40.3±3.7	
Height (cm)	162.7±5.6	-	161.5±4.9	-
Weight (kg)	89.2±14.1	89.0±14.3	90.4±15.3	90.3±15.6
BMI (kg/m^2)	34.2±4.6	34.0±4.9	34.7±4.8	34.6±5.3
% Body fat (%)	42.1±5.2	41.9±5.4	42.6±5.2	42.5±5.8
VAT (kg)	0.8±0.2	0.9±0.3	0.9±0.3	0.9±0.3
VO_{2max} (mL/kg/min)	23.5±4.1	26.7±4.9**	22.9±4.1	23.3±4.8##

Values are presented as mean±standard deviation.
EX, exercise group; CON, control group; BMI, body mass index; VAT, visceral adipose tissue mass; VO_{2max}, maximal oxygen consumption.
**Significantly different from PRE within group ($P<0.01$). ##Significantly different from EX at the same measurement point ($P<0.01$).

Table 2. Changes in markers of inflammation an oxidative stress at baseline (PRE) and after 4 weeks of aerobic exercise intervention (POST)

Variables	EX (n=16)		CON (n=19)	
	PRE	POST	PRE	POST
Adiponectin (μg/mL)	6.21±0.24	6.30±0.29	6.29±0.22	6.29±0.25
CRP (mg/L)	4.13±0.25	4.12±0.26	4.07±0.26	4.08±0.27
TNF-α (pg/mL)	4.57±0.24	4.29±0.28*	4.49±0.29	4.55±0.33#
TAS (mM)	1.76±0.10	1.92±0.10*	1.77±0.10	1.78±0.10#
8-OHdG (ng/mL)	1.92±0.21	1.87±0.26	1.88±0.28	1.88±0.32

Values are presented as mean±standar error.
EX, exercise group; CON, control group; CRP, C-reactive protein; TNF-α, tumor necrosis factor-alpha; TAS, total antioxidant status; 8-OHdG, 8-hydroxydeoxyguanosine.
*Significantly different from PRE within group ($P<0.05$). #Significantly different from CON at the same measurement point ($P<0.05$).

DISCUSSION

The present study investigated effects of a 4-week treadmill exercise training at moderate intensity on changes in % body fat, visceral adipose tissue mass, and markers of inflammation and oxidative stress independently from fat loss in middle-aged obese females. The 4-week exercise training resulted in a significant decrease in TNF-α and elevation of TAS in EX along with an increase in VO_{2max} when no changes were found in body weight, BMI, % body fat, and visceral adipose tissue mass.

Obesity is known as a risk factor for cardiovascular diseases and metabolic syndrome, which may contribute to increases in circulating inflammatory markers (Beavers et al., 2015; Bruun et al., 2006; de Ferranti and Mozaffarian, 2008) and oxidative stress (Dennis et al., 2013; Zguira et al., 2019) in blood. Regular exercise training at low to moderate intensity is considered as an effective therapeutical treatment of the deleterious effects of obesity (Alcazar et al., 2019; Simioni et al., 2018).

Beneficial effects of exercise training to oxidative stress have been reported in previous studies, in which changes in markers of oxidative stress and antioxidant status were observed following a 24 weeks of endurance exercise training in adults (Park et al., 2005), a 16-week moderate exercise training in elderly population (Fatouros et al., 2004; Mota et al., 2019), a 6-week physical activity in children (Kelishadi et al., 2008), and a 3-week high-intensity interval training in young male (Bogdanis et al., 2013). However, it is not clear whether these beneficial effects of exercise training occur independently from changes in fat mass because the relation between oxidative stress and fat loss was not reported in these studies. For instance, reductions in body weight following exercise training were observed (Fatouros et al., 2004; Kelishadi et al., 2008), body weight information was not provided in other two studies (Bogdanis et al., 2013; Park et al., 2005), and the change in fat mass was not measured (Mota et al., 2019) in the studies above.

Moreover, results of recent studies indicate that a decrease in oxidative stress is associated with reductions in % body fat and fat mass. Kelly et al. (2007) following an 8 weeks of endurance exercise training in overweight children found no changes in fat mass and a marker of oxidative stress, 8-isoprostane. This result is supported by Kanikowska et al. (2021) who investigated effects of an 8 weeks of caloric restriction on changes in fat mass and markers of oxidative stress and found that significant decreases in oxidative stress markers were accompanied by reductions in fat mass and % body fat in this study.

We found only two studies reported the therapeutic effect of regular exercise on oxidative stress in the absence of fat loss (Samjoo et al., 2013; Vincent et al., 2006). Samjoo et al. (2013) observed decreases in markers of oxidative stress following 3-month cycling exercise training in obese men in the absence of changes in % body fat and fat mass, emphasizing therapeutic effects of endurance exercise training by enhancing antioxidant capacity and reducing oxidative stress in blood. A similar result was found following a 6-month resistance exercise training in obese older adults (Vincent et al., 2006), in which markers of oxidative stress decreased following resistance training along with improvement in muscular strength and cardiovascular function.

In the present study, we observed that the level of TAS elevated after 4 weeks of moderate-intensity training along with an increase in VO_{2max} when % body fat and VAT were not changed. Results of the present study correspond to previous studies (Samjoo et al., 2013; Vincent et al., 2006), indicating that an enhancement in physical fitness may contribute, at least a part, to the increase in TAS regardless of changes in fat mass. Vezzoli et al. (2014) suggest for this result that repeated-aerobic exercise training induces antioxidant enzyme adaptation, therefore, reduces reactive oxygen species, and increases antioxidant defenses.

It is generally accepted that proinflammatory cytokines have a direct correlation with increased level of obesity, which causes an increase in the volume and number of adipocytes produced resulting in the creation of a proinflammatory state in the human body (Beavers et al., 2015; Marcell et al., 2005; Nicklas et al., 2004). In contrast, some studies reported that inflammatory status can be improved with lifestyle interventions such as exercise (Balducci et al., 2010; You et al., 2004), diet (Rajaram et al., 2010) or combination of exercise and diet (Lambert et al., 2008). However, the mechanisms by which each lifestyle intervention positively affects inflammatory cytokines are unclear.

Recent studies reported that the reductions of proinflammatory cytokines are not achieved by the exercise interventions but are directly associated with loss of fat mass (Beavers et al., 2015), suggesting that more than 5% of fat loss is required to observe significant reductions in proinflammatory cytokines. Two other studies found that an elevation of adiponectin (Marcell et al., 2005) and decreases in proinflammatory cytokines (Nicklas et al., 2004) are not associated with the improvement of physical fitness, but positively related to the weight loss. Results of these studies suggest that exercise training alone does not change the levels of inflammatory cytokines. Furthermore, it is not clear whether changes in inflammatory cytokines following exercise training is caused by physiological benefits of exercise training or by weight loss ac-

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companied to exercise since most of the studies that reported significant changes in inflammatory cytokines by exercise training reported weight loss and/or fat loss concomitantly.

Nonetheless, a few studies recently reported the independent effects of exercise training on inflammatory cytokines from more controlled experiments. You et al. (2004) found that the diet plus exercise intervention decreased CRP and TNF-α, while the diet only group failed to show the same result although the similar amount of reduction in fat mass was observed. A similar result was reported by Balducci et al. (2010), which observed that 12 months of exercise programs at high intensity (aerobic or aerobic+resistance exercises) significantly reduced levels of proinflammatory cytokines such as CRP and TNF-α and increased the level of adiponectin even in the absence of changes in body weight and fat mass, while these changes were not observed in low-intensity aerobic exercise or control group. It is suggested that regular exercise can significantly attenuate mortality risk in obese individuals even in the absence of fat loss, especially when the exercise intensity is high.

Current evidence provides potential mechanisms by which exercise trainings, independently from fat loss, may suppress the production of inflammatory markers (Shaw et al., 2018; Starkie et al., 2003), and enhance the anti-inflammatory indices (You et al., 2013). Starkie et al. (2003) observed elevations of interleukin-6 (IL-6) and epinephrine and a decrease in TNF-α during exercise as compared to rest and suggested that an exercise-induced elevation of IL-6 in the exercising muscles be released into the systemic circulation, therefore, may inhibit TNF-α production in the blood. Indirect evidence in animal studies supports that elevation of IL-6 is tightly linked to TNF-α appearance (Fischer, 2006).

Even though epinephrine was not measured in the present study, exercise-induced increase in epinephrine may suppress the expression of proinflammatory cytokines such as TNF-α and CRP by increasing IL-4 and IL-10, and decreasing IL-12 in the blood circulation (Agarwal and Marshall, 2000; Shaw et al., 2018). It corresponds to van der Poll et al. (1996) who found epinephrine infusions to healthy male subjects increased level of IL-10 and attenuated TNF-α secretion in response to endotoxin administration.

Evidence from animal studies indicates that exercise training may reduce expression of proinflammatory cytokines from adipose tissue independent of its effects of fat mass. It was found in animal studies that exercise training increased the capillary density in visceral adipose tissue (Czarkowska-Paczek et al., 2011; Hatano et al., 2011) and reduced vasoconstriction factors (Pereira et al., 2009), and elevated blood flow in adipose tissue consequently (Enevoldsen et al., 2000). Thereby, it is plausible that exercise training may reduce hypoxia and associated proinflammatory production in adipose tissue in the absence of fat loss, even though there is no human study conducted yet.

In the present study, CRP and adiponectin did not change following the 4 weeks of moderate-intensity exercise training. It is probable that changes in CRP and adiponectin may require a certain duration of exercise training or at least moderate amount of weight loss as shown in other studies (Marcell et al., 2005; Shephard, 2002) and increases in adiponectin (Bouassida et al., 2010; Marcell et al., 2005).

There are two potential limitations to this study that must be considered. Firstly, daily diet intake was not controlled in this study even though subjects were asked to maintain their lifestyle during the 4-week intervention period. Therefore, it is possible that unchanged body weight and % body fat in exercise group may be caused by an additional caloric intake due to an increased energy expenditure. Secondly, this study was conducted in a predominantly Hispanic area and focused on Hispanic female adults, therefore it cannot be fully concluded whether aerobic exercise trainings can independently contribute to changes in inflammatory cytokines and oxidative stress in other demographics under the condition in which body weight and % body fat were unaltered.

In conclusions, the present study found that that a positive improvement in inflammatory and oxidative status can be observed following a short term, 4-week aerobic exercise training at moderate intensity in middle-aged obese female before any significant changes in body weight or fat mass were occurred. This result suggests that regular aerobic exercise may be able to contribute, at least a part, to improvement in inflammation and oxidative stress independently from a change in fat mass. These findings provide a clinical evidence that exercise can be used as a potential therapeutic intervention for overweight and obese individuals to prevent the prevalence of chronic diseases. More practically, it is believed that results of the present study may increase adherence rate to regular physical activities in overweight and obese populations even they may not reduce body weight or % body fat from physical activities. In addition, the present study also confirmed that changes in CRP and adiponectin may need a longer duration of training or may require a significant change in fat mass. Further investigations should be conducted to investigate the potential mechanisms of exercise training associated with inflammatory cytokines and markers of oxidative stress to elucidate the independent role of aerobic exercise training in overweight and obese population.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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