Inflammatory and Adipocytokines Response to Moderate Versus Mild Aerobic Exercise Training in Obese Patients

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Abstract: Background: Obesity is a serious health issue by itself; it is also associated with other health problems. Currently, there is little information about the effects of aerobic exercise training on these biomarkers and the risk of metabolic complications in obese patients. However, some plasma biomarkers of inflammation have been recently recognized as important cardiovascular risk factors. Objective: The aim of this study was compare the impact of moderate versus mild aerobic exercise training on inflammatory and adipocytokines in obese patients. Material and Methods: Sixty obese patients of both sexes with body mass index (BMI) ranged from 31 to 35 Kg/m², non smokers, free from respiratory, kidney; liver, metabolic and neurological disorders were recorded in this study. Their age ranged from 42 to 56 years. The subjects were included into 2 equal groups; the first group (A) received moderate aerobic exercise training. The second group (B) received mild aerobic exercise training three times a week for 2 months. Results: The mean values of leptin, TNF-α, IL6 and C-reactive protein were significantly decreased in group (A) and group (B). Also; there was a significant difference between both groups after treatment. Conclusion: Moderate aerobic exercise training is more appropriately modulate inflammatory and adipocytokines levels than mild aerobic exercise training in obese patients.

Key words: Aerobic Exercise; Inflammatory Cytokine; adipocytokines and Obesity.

INTRODUCTION

Obesity is rising throughout Europe and at least 135 million European citizens are affected. More than half of European population is overweight (BMI greater than 25 kg/m2) and obese (BMI greater than 30 kg/m2) and almost a third are estimated to be obese. During the past 25 years, the incidence of obesity in Europe increased in different proportions from country to country. In several countries obesity is more common in women (Mastorakos, G., et al., 2010). Obesity must be considered as a disease in its own right but is also a risk factor for other diseases, as a result of overweight and the frequently associated metabolic disorders (Ghroubi, S., 2009).

Cardiovascular disease (CVD), the number one cause of mortality in the USA, is almost twice as common in obese diabetic individuals (Kelley, G.A. and K.S. Kelley, 2007). Morbidity and mortality in type 2 diabetes is mainly associated with atherosclerotic cardiovascular disease and late complications as a result of dysfunction of plasma biomarkers of inflammation including leptin, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). (Neto, J., et al., 2009). Tumor necrosis factor α (TNF-α) induced insulin resistance by interacting with insulin receptor signaling and through activation of lipolysis and inhibition of lipoprotein lipase. TNF-α was proposed to have preferentially paracrine effects and to be a regulator of insulin resistance at the tissue level (Ruan, H. and H. Lodish, 2003) (Tuomisto, K., et al., 2006). C-reactive protein (CRP) was known to be produced primarily by the liver in response to inflammatory cytokines including interleukin (IL)-6 and TNF-α (Calabro, P., et al., 2005).

Interleukin (IL)-6 and tumor necrosis factor α (TNF-α) are two major pro-inflammatory cytokines, are secreted in significant amounts from adipose tissue and consequently obese women (healthy and diabetic) have higher cytokine levels than healthy lean women. Furthermore, increased levels of IL-6 and TNF-α are associated with deterioration of glycemic control, increased IR and dyslipidemia, contributing to the dysfunctional metabolic status of obese and type 2 diabetic individuals (Pradhan, A. and L. Ridker 2002). Adipose tissue is an active endocrine tissue, which secretes hormones, such as adiponectin, resistin and leptin appear to contribute to inflammation, atherosclerosis and may be involved in the etiology of type 2 diabetes, possibly constituting the missing link between obesity and insulin resistance (Havel, P., 2002). Leptin alters metabolism by mediating appetite and energy expenditure via feedback mechanism on the hypothalamic satiety-regulating centers and has also been linked to obesity-related IR. Leptin resistance is associated with the development of insulin resistance in individuals with type 2 diabetes and in animals, administration of leptin reverses insulin resistance (Taylor, S., V. Barr and M. Reitman, 1996).
Aerobic exercise training prevents the development of chronic inflammation associated with diabetes by reducing the production of proinflammatory cytokines TNF-α and IL-6. The beneficial effects of regular physical activity in improving insulin resistance, dyslipidemia and levels of proinflammatory cytokines (Pedersen, B. and A. Toft, 2000). The potential mechanisms for the anti-inflammatory effect of exercise, including reduced percentage of body fat and macrophage accumulation in adipose tissue, muscle-released interleukin-6 inhibition of tumor necrosis factor-a and the cholinergic anti-inflammatory pathway (Woods, J., V. Vieira and K. Todd, 2009).

Circulating inflammatory biomarkers originate from multiple sources, particularly visceral adipose tissue, where excess fat promotes macrophage recruitment and both adipocytes and macrophages secrete numerous cytokines (adipokines), including IL-6, TNF-α and leptin (Calabro, P., et al., 2005). Skeletal muscle is another source of cytokines, called myokines, among which IL-6 is considered to play a dual role as anti-inflammatory and pro-inflammatory. High-intensity training of long duration may significantly influence myokine production, thus driving the anti-inflammatory effect of exercise (Wilund, R., 2007).

The aim of this study was to compare the impact of moderate versus mild aerobic exercise training on inflammatory and adipokines in type 2 diabetic patients.

**MATERIALS AND METHODS**

**Subjects:**

Sixty obese patients of both sexes with body mass index (BMI) ranged from 31 to 35 Kg/m², non smokers, free from respiratory, kidney; liver, metabolic and neurological disorders were recorded in this study. Their age ranged from 42 to 56 years. The subjects were included into 2 equal groups; the first group (A) received moderate aerobic exercise training. The second group (B) received mild aerobic exercise training three times a week for 2 months. Informed consent was obtained from all participants.

**Methods:**

**Evaluated Parameters:**

**Chemical analysis:**

Blood sample after fasting for 12 hours was taken from each patient in clean tubes containing few mg of K2EDTA, centrifuged and plasma was separated and stored frozen at -20° used for estimation of leptin, plasma TNF-α, C-reactive protein (CRP) and interleukin-6 (IL-6) using colorimetric method.

**The Aerobic Exercise Training Program:**

The aerobic treadmill-based training program (Track master 400E, gas fitness system, England) was at 65 to 70% of the maximum heart rate (HRmax) achieved according to a modified Bruce protocol for group (A) who received moderate intensity aerobic exercise training, where group (B) received mild intensity aerobic exercise training at 60 to 65% of the maximum heart rate (HRmax). After an initial, 5-minute warm-up phase performed on the treadmill at a low load, each endurance training session lasted 30 minutes and ended with 5-minute recovery and relaxation phase. All patients performed three sessions/week (i.e. a total of 24 sessions per patient over 2-months period).

**Statistical Analysis:**

The mean values of leptin, TNF-α, CRP and IL-6 obtained before and after two months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups (P<0.05).

**RESULTS AND DISCUSSION**

Sixty obese patients of both sexes with body mass index (BMI) ranged from 31 to 35 Kg/m². The subjects were included into 2 equal groups; the first group (A) received moderate aerobic exercise training. The second group (B) received mild aerobic exercise training three times a week for 2 months in order to compare the effect of moderate and mild intensity aerobic exercise training on leptin, TNF-α, CRP and IL-6 in obese patients. The mean values of leptin, TNF-α, CRP and IL-6 were significantly decreased in group (A) and group (B) (Table 1 and 2 and figure 1 and 2). Also; there was a significant difference between both groups after treatment (Table 3 and figure 3). So, moderate aerobic exercise training is more appropriate than mild aerobic exercise training in modulating inflammatory and adipokines levels than mild aerobic exercise training in obese patients.

**Discussion:**

A growing number of individuals are seeking obesity treatment and much attention has been directed towards improving treatment outcomes due to the extensive and expanding list of deleterious health outcomes.
associated with obesity. Aerobic exercise training has traditionally been advocated as an essential component in the medical management of obese patients in order to improve the cardiovascular health of these individuals (Stewart, K.J., 2004).

Table 1: Mean value and significance of Leptin, TNF- α, IL-6 and CRP in group (A) before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Mean ±SD</th>
<th>T-value</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Leptin (Ng/ml)</td>
<td>5.47 ± 41.21</td>
<td>7.85</td>
<td>&lt;0.05</td>
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<tr>
<td>TNF- α (pg/mL)</td>
<td>5.98 ± 1.65</td>
<td>5.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>8.55 ± 2.42</td>
<td>5.88</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>17.86 ± 3.17</td>
<td>9.45 ± 2.12</td>
<td>6.74</td>
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</tbody>
</table>

TNF- α = tumor necrosis factor – alpha. IL-6 = Interleukin-6  
CRP = C-reactive protein

Fig. 1: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA1c in group (A) before and after treatment.

Table 2: Mean value and significance of Leptin, TNF- α, IL-6 and CRP in group (B) before and after treatment.

<table>
<thead>
<tr>
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<th>Mean ±SD</th>
<th>T-value</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Leptin (Ng/ml)</td>
<td>41.56 ± 5.34</td>
<td>3.78</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TNF- α (pg/mL)</td>
<td>5.61 ± 1.77</td>
<td>3.35</td>
<td>&lt;0.05</td>
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<tr>
<td>IL-6 (pg/mL)</td>
<td>8.41 ± 2.32</td>
<td>3.51</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>18.11 ± 3.25</td>
<td>13.35 ± 2.31</td>
<td>4.12</td>
</tr>
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</table>

TNF- α = tumor necrosis factor – alpha. IL-6 = Interleukin-6  
CRP = C-reactive protein

Fig. 2: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA1c in group (B) before and after treatment.
Table 3: Mean value and significance of Leptin, TNF-α, IL-6 and CRP in group (A) and group (B) after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Mean ±SD</th>
<th>T-value</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group (A)</td>
<td>Group (B)</td>
<td></td>
</tr>
<tr>
<td>Leptin Ng/ml</td>
<td>± 33.985.76</td>
<td>37.87 ± 5.16</td>
<td>4.12</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>4.02 ± 1.43</td>
<td>5.06 ± 1.24</td>
<td>3.34</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>5.13 ± 1.17</td>
<td>6.92 ± 1.65</td>
<td>3.52</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>9.45 ± 2.12</td>
<td>13.35 ± 2.31</td>
<td>3.92</td>
</tr>
</tbody>
</table>

TNF-α = tumor necrosis factor – alpha. IL-6 = Interleukin-6
CRP = C-reactive protein

Fig. 3: Mean value and significance of Leptin, TNF-α, IL-2, IL-4, IL-6, HOMA-IR and HBA1c in group (A) and group (B) after treatment.

There is a controversy surrounding the beneficial effects of different aerobic exercise intensities on inflammatory cytokines in obese patients, so this study was to compare the impact of moderate versus mild aerobic exercise training on insulin resistance and inflammatory cytokines in obese patients. The mean values of leptin, TNF-α, CRP and IL-6 were significantly decreased in group (A) received moderate intensity aerobic exercise training and group (B) received mild intensity aerobic exercise training. Also, there was a significant difference between both groups after treatment, these findings are supported and agreed by several previous studies.

A twice-weekly, 6-month, moderate intensity aerobic-training program, without a concomitant weight loss diet, is associated with significant decreases in circulating P-selectin and ICAM-1 levels and with a less atherogenic lipid profile in overweight, non-smoking, older type 2 diabetic individuals (Zoppini, G., et al., 2006).

Eighty-two patients were randomized into 4 groups: sedentary control (A) received low-intensity aerobic exercise, group (B) performed high-intensity aerobic, group (C) performed aerobic and resistance exercises and group (D) performed exercise (with the same caloric expenditure) for 12 months. Physical exercise in type 2 diabetic patients with the metabolic syndrome is associated with a significant reduction of inflammatory and insulin resistance biomarkers, independent of weight loss. Long-term high-intensity (preferably mixed) training, in addition to daytime physical activity, is required to obtain a significant anti-inflammatory effect (Balducci, S., et al., 2010).

It is possible that aerobic exercise decreases subclinical, chronic inflammation and improves endothelial function simply as a result of reducing obesity (particularly visceral obesity) and improving insulin sensitivity (Hu, G., et al., 2005). Most published studies showing beneficial effects of moderate aerobic exercise on insulin sensitivity in obese patients have also constantly reported significant reductions in abdominal visceral fat, thus reinforcing the importance of diminished visceral adipose tissue in the treatment of insulin resistance (Rice, B., et al., 1999; Giannopoulou, I., et al., 2005).

During regular aerobic exercise, skeletal muscle fibres inhibit the production of the pro-inflammatory cytokine TNF-α and produce several anti-inflammatory cytokines (termed “myokines”) that may be involved in mediating the health-beneficial effects of exercise (Petersen, A.M. and B.K. Pedersen, 2005). Additionally, exercise training may reduce mononuclear cell production of pro-inflammatory cytokines by reducing chronic oxidative stress (Stewart, K.J., 2004). Exercise has the potential to lower the inflammatory status by the reduction of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor (TNF-α) and the enhancement of adiponectin (Mathur, N. and B.K. Pedersen, 2008) (Monzillo, L.U., et al., 2003).
Exercise suppresses the production of proinflammatory cytokines and enhances anti-inflammatory cytokines. Because proinflammatory cytokines, IL-6 and TNF-α, have cytotoxic actions, it can be proposed that regular exercise prevents further damage to insulin-producing β-cells by attenuating the production of these (Smith, J., et al., 1999). Aerobic exercise decreases subclinical, chronic inflammation and improves endothelial function simply as a result of reducing obesity (particularly visceral obesity) and improving insulin sensitivity (Stewart, K.J., 2004).

High-intensity exercise training program induced an improvement of biomarkers of inflammation and insulin resistance, with a reduction of IL-6, TNF-α and leptin (associated with decreased insulin, C-peptide and HOMA-IR) and an increase of IL-4 and IL-10 thus indicating that exercise has a full anti-inflammatory and insulin-sensitizing effect. These results suggest that the beneficial effect of physical activity on CVD morbidity and mortality may depend, at least partly, on the anti-inflammatory effect of exercise (Neto, J., et al., 2009).

**Conclusion:**
Moderate aerobic exercise training is more appropriately modulate insulin resistance, adipocytokines and inflammatory cytokine levels than mild aerobic exercise training in obese type 2 diabetic patients.

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**REFERENCES**


