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Adipokines Response to Continuous versus Interval Aerobic Training in Ischaemic Heart Disease Patients

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Abstract : background: Coronary artery disease (CAD) is the single most common cause of death in the developed world, responsible for about 1 in every 5 deaths and it is expected that the rate of CAD will accelerate in the next decade. **The aim:** of the current study was to find out adipokines response to continuous versus interval aerobic training in ischemic heart disease Patients. **Methods:** Forty men patients with an ischemic heart disease with age ranged from 50-60 years old participated in this study. Patients were assigned into two groups equal in number: **Group A** included 20 patients received high intensity interval aerobic training on treadmill 3 times per week for 12 week. **Group B** included 20 patients received moderate intensity continuous aerobic training on treadmill 3 times per week for 12 week. **Results:** The mean values of adiponectin, leptin and six minute walk distance were significantly improved from 8.46 ± 0.3 mg/ml, 38.83 ± 0.08 ng/ml and 433.72 ± 2.84 m to 10.85 ± 0.25 mg/ml, 35.26 ± 0.21 ng/ml and 505.52 ± 1.39 m respectively, in group A and from 8.44 ± 0.32 mg/ml, 38.95 ± 0.38 ng/ml and 434.02 ± 2.92 m to 9.65 ± 0.33 mg/ml, 37.13 ± 0.22 ng/ml and 479.05 ± 1.44 m respectively, in group B. Also, there was a significant difference between the groups after treatment on all measured variables. **Conclusion:** It is suggested that Interval are more effective than continuous aerobic training for the improvement fo adipokines, functional capacity in patients with ischemic heart disease.
Key words: Adipokines, High intensity interval aerobic training, Moderate intensity continuous aerobic training, Ischemic heart disease

Introduction

Stable coronary artery disease or classical angina refers to typical substernal discomfort related to ischemia or hypoxia triggered by effort or emotions or other stress, relieved with rest or nitroglycerin and reproducible but, which may also be occurring spontaneously[1]. Ischemic heart disease (IHD) considered the first leading cause of death. The prevalence of IHD increases with age; approximately 23% of men and 15% of women, majority of mortality and morbidity of cardiac disease caused by ischemic heart disease[2]. Adipokines (such as leptin and adiponectin), which released by adipose tissue ply important role in various physiological processes, including the regulation of arterial tone and they are related to cardiovascular risk factors[3].

Adiponectin is an important secreted serum protein. The human adiponectin gene is located on chromosome 3q27, and it codes for a 244 amino acid polypeptide with a signal sequence. It is present in human plasma and adipose tissue and is induced during adipogenesis[4]**.** Adiponectin is a collagen-like peptide, abundantly secreted by adipose tissue and has several biological activities, such as enhancement of insulin

sensitivity and stimulation of fatty-acid oxidation. Hypoadiponectinemia is associated with an increased risk of type 2 diabetes, hypertension and dyslipidemia, which are risk factors for atherosclerosis. There is an inverse association between adiponectin and coronary heart disease (CHD).These data suggest that high serum adiponectin levels might be related to a lower risk of coronary heart disease (CHD) [5].

Leptin is a product of ob gene, is an endocrine hormone produced by white adipose tissue. It is primarily involved in the regulation of food intake and energy expenditure**.** Hyperleptinemia is one of the novel risk factors contributing in many ways to CVD and it may be used as a maker for the diagnosis of CHD [6]**.**

Patients diagnosed ischemic heart disease; T2DM and hypertension often have low adiponectin concentrations in the blood, which is now a recognized risk factor for cardiovascular diseases. On the other hand, there is inversely relationship between leptin and adiponectin as leptin increases by obesity in contrast to adiponectin [7].

Aerobic (or cardiovascular exercise, a term attributed to this kind of exercise because of its various benefits in cardiovascular health) refers to exercise that involves or improves oxygen consumption by the body. Aerobic means "with oxygen", and refers to the use of oxygen in the body's metabolic or energy generating process. Many types of exercise are aerobic, and by definition are performed at moderate levels of intensity for extended periods of time. This intensity can vary from 50 - 80% of maximum heart rate [8]. High intensity interval training includes very high intensity exercise intervals and resting active recoveries with very low intensity, often performed with an "all out" effort. Depending on the training intensity, a single effort may last from a few seconds to several minutes [9]**.**

Exercise intensity was an important factor for improving aerobic capacity and reversing the risk factors of the metabolic syndrome. So high intensity exercise training is superior to moderate intensity training in increasing circulating adiponectin and improved insulin sensitivity and β-cell function. These findings may have important implications for exercise training in rehabilitation programs and future studies [10]**.**

High-intensity interval training three times per week for 15 weeks compared to the same frequency of steady-state exercise (SSE) was associated with significant reductions in total body fat and leptin concentrations [9]**.**

The six-minute walk test (6MWT) is a simple, easy-to-perform, commonly used test of functional exercise capacity. Its ability to predict outcomes has been established in patients with coronary artery disease, heart failure, pulmonary hypertension and pulmonary disease**[11].** The functional capacity, as expressed by distance walked during the 6MWT, is significantly reduced shortly after cardiac surgery and quickly improves after physical training[12].

Thus, the results of studies on the effects of aerobic training on adipokines are varied and on the other hand few studies applied on coronary artery disease patients. However, studies focusing on adiponectin and leptin response to high intensity interval training. Therefore the purpose of this study was to find out whether 12 weeks of high intensity interval aerobic training would affect adipokines and functional capacity in ischemic heart disease patients. The results were compared to a group performing moderate intensity continuous aerobic training.

Materials and Methods

Patient's characteristics and general experimental design

Patients:

Forty men patients with an ischemic heart disease with stenosis of one or two major epicardial coronary arteries with age ranged from 50-60 years old and body mass index (BMI) ranged from 30 to 34.9kg/m^2, free from any clinical events such as coronary artery syndrome and recent myocardial infarction at least 6 months prior to the study as well as free from neurological and orthopedic problems and association with another medical problem such as diabetes mellitus and uncontrolled hypertension.

Evaluated parameters

Blood Samples and Biochemical Markers:

5 ml blood was sampled from the patients after 12 hour fasting at 8:30 am which was taken from their hand antecubital vein while sitting and resting. Serum Adiponectin level was measured by ELISA method by using total adiponectin-specific kit and Leptin was measured by immunoassay of biosource leptin EASIA kit [13]**.**

Measurement of distance using 6 Minute walk test:

Patients were instructed to walk continuously on a hospital corridor 145.5 feet (44m) in length, covering as much ground as they could during six minutes. Total distance walked in six minutes was recorded [14].

Treatment procedures:

Patients were assigned randomly into two groups equal in number: Group A: high intensity interval aerobic training group, group B: moderate intensity continuous aerobic training group. They trained on treadmill three sessions / week (i.e. a total of 36 sessions per subject over a 3-month period). All sessions were supervised and participation assessed. All patients were free to withdraw from the study at any time. All participants provided their informed consent after receiving a detailed explanation of the study. If any adverse effects had occurred, the experiment would have been stopped and the Human Subjects Review Board would have been informed. However, no adverse effects occurred and so the data of all the patients were available for analysis. The detailed training regimen was as follows:

High intensity interval aerobic training:

Patients received instruction in walking on treadmill. Submaximal exercise test was used to determine maximum heart rate using modified Bruce protocol and all patients were encouraged to continue the exercise until their symptoms limits or until reaching the peak heart rate. Total duration of high intensity interval training session is 38 minutes 3 times per week for 12 week and including 8 minutes warming up at training heart rate from 50% to 60% of peak heart rate followed by 4 times of high intensity interval training at training heart rate from 80% to 85% of peak heart rate with active pause of 3 minutes of walking at 50% to 60% of peak heart rate. The session was terminated by 5 minute cool down at 50% to 60% of peak heart rate [15]**.**

Moderate intensity continuous aerobic training:

Received instruction in walking on treadmill. Each exercise training session included warm-up period, stimulus phase (moderate intensity continuous aerobic exercise) and the cool-down period. Warming up and cooling down included exercise at a low intensity for five to ten minutes in form of stretching exercise and range of motion exercises combined with breathing exercise. Intensity of the moderate continuous aerobic exercise was 50-60% of maximal heart rate (HR_{max}) that measured by stress test with duration 30 minutes 3 times per week for 12 week [16]**.**

Statistical analysis:

The mean values of serum adiponectin, serum leptin and six minute walk distance obtained before and after three month in both groups were compared using the paired ‘‘t’’ test. Unpaired ‘‘t’’ test was used for the comparison between the two groups ($P < 0.05$).

Results

The study involved forty men patients with ischemic heart disease. Their age ranged from 50 to 60 years. The patients were assigned into two groups equal in number: Group (A) received high intensity interval aerobic training on treadmill 3 times per week for 12 week. Group (B) received moderate intensity continuous aerobic training on treadmill 3 times per week for 12 week in order to compare between the effect of the two types of aerobic exercise on serum adiponectin, serum leptin, 6-minute walk distance in both groups. (Table 1) represented non significance difference between both groups. The mean values of adiponectin, leptin and six minute walk distance were significantly improved from 8.46 ± 0.3 mg/ml, 38.83 ± 0.08 ng/ml and 433.72 ±

2.84 m to 10.85 ± 0.25 mg/ml, 35.26 ± 0.21 ng/ml and 505.52 ± 1.39 m respectively, in group A and from 8.44 ± 0.32 mg/ml, 38.95 ± 0.38 ng/ml and 434.02 ± 2.92 m to 9.65 ± 0.33 mg/ml, 37.13 ± 0.22 ng/ml and 479.05 ± 1.44 m respectively, in group B (Tables 2 and 3). Also, there was a significant difference between the groups after treatment (Table 4). So, it can be concluded that both high intensity interval and moderate intensity continuous aerobic training have a positive effect on adipokines and six minute walk distance but high intensity interval aerobic training was more effective than moderate intensity continuous aerobic training.

Table 1: Descriptive statistics for comparing the mean age, weight, height, and BMI of group A and B

Groups	Group A N= 20	Group B N= 20	P-Value	Sig
Age (years)	53.55 ± 2.73	54 ± 3.09	0.62	NS
Weight (kg)	86 ± 3.04	85.55 ± 2.79	0.62	NS
Height (cm)	163.2 ± 2.33	162.65 ± 2.36	0.46	NS
BMI (kg/m²)	32.28 ± 0.75	32.33 ± 0.67	0.84	NS

Table 2: Mean value and significance of adiponectin, leptin and 6MWT in group A before and after high intensity interval aerobic training

	Pre- study	Post- study	T-value	P-value
Adiponectin mg/dl	8.46 ± 0.3	10.85 ± 0.25	-81.49	0.0001
Leptin ng/dl	38.83 ± 0.08	35.26 ± 0.21	64.31	0.0001
6 MWT m	433.72 ± 2.84	505.52 ± 1.39	-94	0.0001

Table 3: Mean value and significance of adiponectin, leptin and 6MWT in group B before and after moderate intensity continuous aerobic training

	Pre- study	Post- study	T-value	P-value
Adiponectin mg/dl	8.44 ± 0.32	9.65 ± 0.33	-45.24	0.0001
Leptin ng/ml	38.95 ± 0.38	37.13 ± 0.22	17.48	0.0001
6 MWT m	434.02 ± 2.92	479.05 ± 1.44	-65.55	0.0001

Table 4: Mean value and significance of adiponectin, leptin and 6MWT in group A and group B after treatment

Groups	Group A N= 20	Group B N= 20	T-value	P-value
Adiponectin mg/dl	10.85 ± 0.25	9.65 ± 0.33	12.83	0.0001
Leptin ng/dl	35.26 ± 0.21	37.13 ± 0.22	-26.93	0.0001
6 MWT m	505.52 ± 1.39	479.05 ± 1.44	59.12	0.0001

Discussion

The aim of this study was to compare changes in serum concentrations of adiponectin and leptin and also six minute walk distance after 12 weeks of high intensity interval versus moderate intensity continuous aerobic training in men patients with ischemic heart disease. The mean values of adiponectin and six minute walk distance were significantly increased in both group A and group B and mean values of leptin were significantly decreased in both group A and group B. Also, there was a significant difference between the groups after treatment. This means that in patients with ischemic artery disease, high intensity interval aerobic training is effective in improving adipokines and six minute walk distance as well as moderate intensity continuous aerobic training but high intensity interval aerobic training was more effective in improving adipokines and six minute walk distance than moderate intensity continuous aerobic training.

Abdelbar *et al.*[17] suggested that there was a strong negative correlation detected between serum adiponectin level and occurrence of the coronary lesions, meaning that patients with lower levels of serum adiponectin have more severe and prevalent coronary lesions. This might be attributed to the loss of protective functions of adiponectin on the vascular endothelium that may allow vascular inflammatory events to occur more rapidly.

Another cardiovascular disease hormone is leptin. Leptin peptide, which is secreted from adipose tissue. High levels of Leptin in obese subjects compared to thin ones can justify obesity issues and cardiovascular diseases with regard to leptin's role in regulating secretion of cytokines such as CRP, IL-6 and TNF- α. Higher levels of leptin in obese subjects compared with lean subjects could explain the inflammatory conditions associated with obesity and cardiovascular disease according to Iikuni *et al*. [18].

The current study was early supported by the study that investigated adiponectin and inflammatory cytokines secretion in epicardial adipose tissue in non-CAD and CAD patients. A low level of adiponectin was found in the latter, coupled with a high level of IL-6 and TNF- a and also found that decreased circulating adiponectin-induced coronary atherosclerosis might be independent of plasma levels of glucose and lipids, which suggests that high glucose and lipids concentrations are not necessary for disorders of epicardial adipose tissue biology or CAD according to Zhou *et al*. [19].

The current finding was supported also by many investigators such as Li *et al.* [5] indicated that plasma adiponectin concentration significantly decreased in CAD patients compared with matched control subjects, and positively correlated with the number of circulating endothelial progenitor cells (ECPs). The plasma adiponectin concentration was significantly lower in males, compared with females, in both CAD group and control group. In addition, this study also shows that adiponectin levels had significantly positive correlations with the functional activities of EPCs such as adhesive and migratory capacities. These findings indicate that lower circulating adiponectin level reflected the decreased number and impaired functional activities of EPCs in CAD patients. Therefore, therapeutic approaches, drug and/or non-drug, aiming at increasing circulating adiponectin levels could be used to treat patients with coronary artery disease.

Findings of current study are in line with the study that include total of 8 nested case-control studies consisting of 1,980 patients and 11,567 controls as meta-analysis and found that there was a significant association of leptin levels with incident CHD and stroke was demonstrated, and raised leptin levels could significantly increase the pathogenetic risk of CHD according to Zeng et al. [20].

The results of this study are coincided with results achieved by many investigators such as Vavruch and Nystrom [21] who found that high levels of leptin were positively related to increase the hazard ratio (HR) of ischemic heart disease in both men and women and this was independently of traditional risk factors (age, HbA_{1c}, BMI, systolic blood pressure and LDL-cholesterol / HDL -c cholesterol ratio).

The current finding was supported by the study that demonstrated the significant increase of plasma adiponectin due to 12 weeks of high intensity interval aerobic training in the experimental group compared with the control one. Moreover, a significant difference was observed in the plasma adiponectin of the experimental group from the pretest to posttest stages while this increase was not significant in the first 6 weeks of the training program from the pretest to the mid test. Increase of Adiponectin as a result of 12 weeks of aerobic training was probably a preventive factor for the diseases to adiponectin according to Akbarpour *et al.* [13].

Results of this study agreed with the result of by many investigators such as Racil *et al.* [22] who examined the effects of high-intensity interval training (HIIT at 100% MAS) versus moderate-intensity interval training (MIIT at 80% maximal aerobic speed: MAS) on cardiovascular fitness, leptin levels and ratings of perceived exertion (RPE) in forty-seven obese female adolescents and found that HIIT and MIIT positively changed cardio-metabolic determinants (i.e., VO2max, HR rest, blood pressures, blood glucose, blood insulin and RPP) and decreased blood leptin concentration, while HIIT (100% of MAS) induced better results compared to training at moderate intensity (80% of MAS).

The results of this study are coincided with results achieved by many investigators such as Sperandio *et al.* [23] who stated that the 6MWT represents a moderate-to-high intensity activity in middle-aged and older adults and proved to be useful for predicting cardiorespiratory fitness in the present study. The results suggested that the 6MWT may also be useful in asymptomatic individuals, and its use in walk-based conditioning programs

should be encouraged.

The results of this study are coincided with results achieved by who studied the acute cardiopulmonary responses of a 67-yr-old man with stable angina pectoris during a 34-min session of high-intensity aerobic interval training. Exercise was well tolerated with neither significant arrhythmia nor elevation of cardiac troponin-T and observed a complete disappearance of symptoms and signs of myocardial ischemia after 24 mins of exercise. This observation is similar to the warm-up angina phenomenon, an adaptation to myocardial ischemia that remains poorly understood according to Meyer *et al.* [24].

In contrast results achieved by some investigators such as Tsao *et al*, [25] who showed that there were no significant differences in leptin level in response different levels of exercise intensities (65%, 85% and 100% of VO2max) also there is no significant effect of aerobic exercise on adiponectin level and this is may be difference in age, sex and type of training according to Hara et al. [26].

From the current study, the mechanism by which the high intensity interval training may increase adiponectin include adiponectin in coronary artery disease patients due to the stimulation of adipocyte mitochondrial biogenesis which important for adiponectin synthesis and with impaired mitochondrial function reducing adiponectin synthesis so exercise help to release adiponectin from adipose tissue even in the absence of weight loss. Adiponectin level affected by intensity and volume of exercise so high intensity interval raining is more effective than low to moderate intensity aerobic training.

Therefore, it can be said that the intensity of workout is the most effective factor for adiponectin release from adipose tissue into the bloodstream. Adiponectin has anti-inflammatory effects on the vascular wall by its ability to inhibit the synthesis of endothelium-derived inflammatory cytokines and induces the production of the anti-inflammatory mediators IL-10 and IL-1RA in human inflammatory cells.

High intensity aerobic training may lead to a decrease in leptin concentrations in coronary artery disease patients may be due to weight reduction, fat loss, stimulate free fatty acid release in obese men and by increase in sensitivity of its hypothalamic cellular receptors that help to decrease leptin resistance that help to improve patients with coronary artery disease through two mechanisms, the first is decreased low grade chronic inflammation related to obesity and the second through improving its direct effect on the blood vessels that include decrease vascular resistance, vasodilatation, increase arterial elasticity and decrease oxidative stress.

Conclusion

In summary, it can be concluded that both interval and continuous aerobic training is effective for patients with ischemic heart disease but interval appears to be more effective than continuous aerobic training because high intensity aerobic interval training is safe mode of training that helping patients with stable coronary heart disease by decreasing leptin level and increasing adiponectin level which help to induce coronary artery vasodilatation and decrease inflammation related to arthrosclerosis and also improve patient's functional capacity and that has a positive reflect on overall quality of life of patients and decrease morbidity and mortality rate.

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