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Influence of exercise training on leptin levels in patients with stable coronary artery disease: A pilot study

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Abstract

Background: *This study was designed to examine the influence of exercise training on leptin levels in patients with stable coronary artery disease (CAD).*

Methods: *Sixty-four male patients, mean age 55.6 ± 6.0 years, were randomized either to six weeks of aerobic training, three times a week, at 60–80% of maximal heart rate (training group, Ex, n = 32) or to a control group (n = 32). Exercise stress test was performed and body mass index (BMI), waist-to-hip ratio (WHR), waist circumference and plasma leptin levels were measured at the beginning and end of the study.*

Results: *Physical capacity increased significantly only in Ex patients (max workload in METs from 7.7 ± 1.4 to 8.2 ± 1.4, p < 0.05). There were no significant differences between initial and final results in either group in terms of BMI, WHR or waist circumference. Although, at the end of the study, leptin levels did not change in Ex patients (6.7 ± 3.2* vs *6.9 ± 3.6 ng/mL, NS), they did increase significantly in the control group (8.0 ± 4.0* vs *9.3 ± ± 5.2 ng/mL, p < 0.02).*

Conclusions: *A short period of exercise training in CAD patients improved their physical capacity, but did not influence BMI, WHR and waist circumference. Exercise training prevented an increase in leptin levels during the study period.* (Cardiol J 2010; 17, 5: 477–481)

Key words: coronary artery disease, exercise training, leptin levels

Introduction

Adipose tissue, as an active endocrine organ, releases proteins termed adipokines, including a hormone known as leptin. It has been established that increased leptin levels are common in obese and diabetic patients and independently associated with insulin resistance [1], cardiovascular diseases [2, 3], and low-grade chronic inflammation in humans [4, 5].

To date, the influence of regular physical activity on leptin levels has been examined in healthy subjects as well as in obese and diabetic patients.

The effects of exercise training on leptin levels in patients with coronary artery disease (CAD) are unknown. Therefore, the aim of this pilot study was to assess the influence of six- weeks of exercise training on leptin levels in patients with stable coronary artery disease.

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Methods

We enrolled consecutive male patients < 65 years, with stable CAD, who had been referred for our exercise training program between 1 January and 31 December 2007. We excluded patients with heart failure, unstable angina, diabetes mellitus, uncontrolled arrhythmias, poorly controlled hypertension, hemodynamically significant valvular heart disease, those with chronic inflammatory, autoimmune, neoplastic, or other systemic diseases, chronic hepatic or kidney diseases. All the patients were clinically stable at least one month before their inclusion in the program, without any changes in medical treatment. The subjects received standard medications such as statin, aspirin, beta-blocker and angiotensin-converting enzyme inhibitor. The doses of medications were not changed during the study period. The study protocol was approved by the Local Ethics Committee. Afterwards, a written informed consent was obtained from each patient. The patients were randomized into two groups: training group (Ex) and control group. Ex patients agreed to participate in our training program. The baseline evaluation included clinical history and examination, resting electrocardiogram, chest X-ray, two-dimensional echocardiogram, blood chemistry (total and high- and low-density lipoprotein cholesterol, triglycerides, fasting and postprandial glucose levels, and liver and kidney function tests), We defined patients as non-smokers when they had not smoked tobacco for at least one year. All the patients were advised to follow a diet containing limited amounts of fat and high-carbohydrate foods, and not to change the diet during the study protocol.

Anthropometry

Fasting body weight and height were measured (B 150 L, Axis, Poland) in all participants wearing only underclothes, without shoes. Height was measured without shoes to within an accuracy of 1 cm. Waist-to-hip ratio (WHR) was measured as a ratio of the circumference of the waist [cm] to that of the hips [cm]. Body mass index (BMI) was calculated as [kg/m^2].

Blood sampling and laboratory measurements

All the participants were told to avoid vigorous exercise for four days before blood sampling. Blood samples were collected between 8 and 10am after an overnight fast. EDTA was added to whole blood for plasma preparation. The parameters of blood chemistry e.g. glucose, lipids, etc. were measured in fresh plasma by standard methods. Plasma samples for leptin measurement were immediately centrifuged (2,000 rpm for 10 min), decanted and frozen at temperature –70°C. Leptin concentration in plasma samples was quantified using Human Leptin RIA (RadioImmunoAssay) kit from Linco Research, Inc., St. Charles, Missouri, USA. Sensitivity of the assay was 0.5 ng/mL. Intra- and inter-assay coefficients of variation were 4.6% and 6.2%, respectively.

Exercise stress testing

Each subject performed a symptom-limited maximal exercise treadmill test according to the modified Bruce protocol. Blood pressure was monitored by using mercurial sphygnomanometer and a 12-lead ECG was recorded at rest, every minute during exercise and during recovery, until heart rate (HR) and ECG returned to the baseline values (using the modified Mason-Likar 12-lead system, Marquette Case 12; Marquette Electronics, Milwaukee, Wisconsin, USA). All treadmill tests were supervised by a cardiologist. The main reasons of stopping the tests were reaching the age-adjusted limit of HR and/or fatigue. None of the tests were discontinued because of signs of ischemia in ECG and/ /or angina. The following parameters were analyzed: duration and distance of exercise stress test, workload in metabolic equivalents (METs), HR at rest and at peak exercise (max HR).

Exercise training program

Ex group patients underwent a six-week controlled, standardized exercise training program on bicycle ergometer, three times a week. Each session included a ten-minute warm-up, 40 minutes of cycling with telemetry monitoring (the intensity set at 60% at the beginning of the exercise program was progressively increased to 80% of peak HR measured during exercise stress testing), and a ten-minute cool-down. The training was documented by a written protocol.

Cardiac rhythm was continuously monitored on a three-channel telemetry system in all trained patients and in all sessions throughout the study. No patient left the program at any point during the study.

Patients in the control group were advised to walk at least three times per week for 30 minutes during the study period.

Statistical analysis

Statistical analysis was performed using SAS statistical software (Version 9.2, Cary, North Carolina, USA). Values are expressed as mean ± standard deviation for normally distributed variables. Normal distribution was evaluated by the Shapiro-Wilk test. The difference in mean values was compared with Student's t-test, either the unpaired one to detect differences between groups, or the paired one to detect differences within each group over time.

Comparisons of non-normally distributed data were carried out using the Wilcoxon rank test. A p value of less than 0.05 was considered statistically significant.

Results

Baseline results

No significant differences were found between Ex and control groups regarding age, number of smokers, presence of hypertension, history of myocardial infarction or left ventricular ejection fraction (Table 1). There were no significant differences between the groups in terms of baseline metabolic parameters considered or BMI (Table 2). Similarly, HR at rest and at peak exercise as well as METs were comparable between the two groups at the beginning of the study (Table 3). Moreover, at the initial evaluation, leptin levels did not differ significantly between the two groups (Table 2).

Final results

Sixty-four patients completed the study. No adverse events occurred in either group during the study period. As shown in Table 2, no significant differences were found between the two groups in any of the analyzed metabolic parameters. Moreover, BMI, WHR and waist circumference were stable and did not change significantly in either study group during the study period. After six weeks, exercise duration and distance improved significantly in both study groups (Table 3). However, in the Ex group only, maximal workload in METs increased significantly (7.7 ± 1.4 *vs* 8.2 ±

Table 1. Study population.

Characteristic	Exercise group (n = 32)	Control group (n = 32)	P
Age (years)	54.0 ± 4.8	54.5 ± 5.6	NS
CAD (years)	3.9 ± 4.6	2.8 ± 3.7	NS
History MI	20 (62%)	19 (58%)	NS
Non-smokers	28 (87%)	27 (83%)	NS
Smokers	4 (13%)	5 (17%)	NS
Hypertension	25 (78%)	25 (78%)	NS
Coronary angiography:			
1 vessel	5 (16%)	5 (16%)	NS
2 vessels	11 (34%)	7 (22%)	NS
3 vessels	16 (50%)	20 (62%)	NS
Medication:			
Beta-blocker	32 (100%)	32 (100%)	NS
ACE-I	30 (94%)	30 (94%)	NS
AT II blocker	3 (9%)	2 (6%)	NS
Statins	32 (100%)	32 (100%)	NS
Aspirin	31 (98%)	31 (98%)	NS
Clopidogrel/ /ticlopidine	2 (6%)	2 (6%)	NS
LVEF (%)	60.0 ± 7.5	56.8 ± 8.9	NS

CAD — coronary artery disease; MI — myocardial infarction; ACE-I — angiotensin converting enzyme inhibitor; AT II blocker — angiotensin II receptor blocker; LVEF — left ventricular ejection fraction; NS — non significant

Table 2. Metabolic parameters at baseline and at the end of the study.

Variables	Exercise group (n = 32)		Control group (n = 32)	
	Baseline	Final	Baseline	Final
Body mass index [kg/m^2]	27.3 ± 2.8	27.4 ± 2.8	28.0 ± 3.2	28.4 ± 3.6
Waist circumference [cm]	95.8 ± 7.0	96.0 ± 8.4	99.6 ± 7.6	99.8 ± 7.5
Waist-to-hip ratio	1.02 ± 0.05	1.01 ± 0.05	1.03 ± 0.05	1.03 ± 0.06
Total cholesterol [mmol/L]	3.9 ± 0.7	3.8 ± 0.8	4.1 ± 0.6	4.2 ± 1.0
HDL cholesterol [mmol/L]	1.3 ± 0.4	1.3 ± 0.5	1.3 ± 0.4	1.3 ± 0.3
LDL cholesterol [mmol/L]	2.4 ± 0.8	2.3 ± 0.7	2.6 ± 0.8	2.6 ± 0.7
Triglycerides [mmol/L]	1.3 ± 0.6	1.4 ± 0.7	1.4 ± 0.7	1.5 ± 0.9
Fasting glucose [mmol/L]	5.1 ± 0.7	5.1 ± 0.7	5.2 ± 0.7	5.2 ± 0.6
Post-prandial glucose [mmol/L]	5.5 ± 1.5	5.6 ± 1.6	5.7 ± 1.8	5.6 ± 1.5
Leptin [ng/mL]	6.7 ± 3.2	6.9 ± 3.6	8.0 ± 4.0	9.3 ± 5.2*

All results are presented as mean ± SD; *p < 0.05

Table 3. Parameters during exercise stress test at baseline and at the end of the study.

Variables	Exercise group (n = 32)		Control group (n = 32)	
	Baseline	Final	Baseline	Final
Duration [s]	759.8 ± 96.8	830.1 ± 74.7*	750.5 ± 102.8	781.0 ± 136.5*
Distance [m]	672.7 ± 135.5	778.7 ± 117.8*	644.1 ± 152.3	717.6 ± 164.2*
Metabolic equivalents	7.7 ± 1.4	8.2 ± 1.4*	7.3 ± 1.8	7.7 ± 1.9
Heart rate at rest [bpm]	68.1 ± 11.3	62.9 ± 10.5*	65.1 ± 9.4	64.2 ± 8.2
Max heart rate [bpm]	125.9 ± 15.2	124.8 ± 15.6	121.2 ± 16.7	125.4 ± 15.3

All results are presented as mean ± SD; *p < 0.05

± 1.4, p < 0.03) compared to the control patients (7.3 ± 1.8 *vs* 7.7 ± 1.9, p = NS; Table 3).

Although, at the end of the study, leptin levels increased significantly only in the control patients (15% *vs* 2% in Ex group), there were no significant statistical differences between the two study groups (Table 2).

Discussion

This preliminary study aimed to investigate the effect of short-term exercise training on plasma leptin concentrations in stable CAD patients with preserved left ventricular function.

We found that our supervised exercise-training program improved physical capacity and did not affect leptin levels. On the contrary, in control patients, home-based activity e.g. walking did not change physical capacity measured in METs and caused an unfavorable increase in leptin levels.

Leptin is secreted by adipose tissue and its concentration in humans is known to correlate with weight, BMI [6] and body fat mass [7–9]. Moreover, leptin is thought to exert many potentially proatherogenic effects such as induction of endothelial cell dysfunction [10] and platelet aggregation [11], stimulation of inflammatory reactions [4, 5], propagation of oxidative stress [12], and proliferation of vascular smooth muscle cells [13].

To date, the influence of exercise training on leptin levels has been examined only in healthy, obese or diabetic patients. The majority of these studies have documented that short-term exercise training does not affect leptin levels.

However, Ishii et al. [14] showed that in type 2 diabetic patients, exercise training reduced plasma leptin levels, which was independent of changes in body fat mass.

Ours was the first study to show the influence of short aerobic training on leptin levels in patients with CAD. It should be emphasized that BMI, WHR and waist circumference did not change significantly in either of our study groups. Thus, we can conclude that an increase in plasma leptin concentration in the control patients was not associated with changes in weight or waist circumference. Since a significant increase of physical capacity measured in METs was observed only in the trained patients. We suggest that only a properly applied training program is able to prevent an increase in leptin level in optimally treated, clinically stable CAD patients.

Our findings, although promising, require confirmation on a larger number of patients to determine whether exercise training has a beneficial impact on leptin levels. In addition, the mechanism of favorable influence of exercise training on leptin levels deserves further investigation.

It might be of great importance, because several clinical studies have demonstrated that high leptin levels predicted the development of acute cardiovascular events, restenosis after coronary angioplasty and cerebral stroke, independently of traditional risk factors [2, 15, 16].

Limitations of the study

When interpreting our findings, one should take into account that this was a small, short-duration pilot study aimed only at determining whether exercise training had any impact on leptin levels. Our study did not assess the percentage of body fat. However, Flegal et al. [17] showed that it positively correlated with waist circumference in men, which was measured in our patients. We did not include women in this study because it is widely recognized that leptin levels are several times higher in women that in men, independently of fat mass content, suggesting that females have higher leptin levels per unit fat mass [18, 19].

Conclusions

1. A short period of exercise training in CAD patients improved physical capacity, but did not influence BMI, WHR or waist circumference.
2. Exercise training prevented an increase in leptin levels during the study period.

Acknowledgements

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