

# The relationship between leptin and obesity and cardiovascular risk factors in men with acute myocardial infarction

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## Abstract

**Background:** *Leptin, a hormone-like peptide secreted by adipose tissue, is a strong correlate of obesity. Conflicting data exist concerning leptin as an independent risk factor of coronary artery disease. The aim of the study was to assess the relationship between leptin and obesity and cardiovascular risk factors in men with acute myocardial infarction.*

**Methods:** *Two groups of patients who had experienced their first acute myocardial infarction were analysed: 40 obese and 40 non-obese men. Waist and hip circumferences, waist-to-hip ratio, C-reactive protein (CRP), uric acid, fasting glucose, lipid profile and leptin were measured.*

**Results:** *Mean leptin was significantly higher in obese than in non-obese patients (46.7 ng/ml ± ± 18.7 vs. 15.6 ng/ml ± 11.9;  $p < 0.01$ ). Leptin levels correlated positively with all anthropometric measurements, fasting glucose, triglyceride levels, CRP and uric acid and negatively with HDL-cholesterol.*

**Conclusions:** *In patients with acute myocardial infarction, obesity is related to increased leptin. The subcutaneous fat compartment seems to be an important determinant of plasma leptin concentration. Leptinemia is associated with several biochemical disorders, suggesting that leptin may be a pathogenetic factor in cardiovascular disease. (Cardiol J 2007; 14: 252–259)*

**Key words:** obesity, leptin, myocardial infarction

## Introduction

Obesity carries a cluster of traditional cardiovascular risk factors, such as hypertension, dyslipidemia and diabetes, and factors associated with

atherogenesis, namely elevated levels of uric acid and C-reactive protein (CRP) [1–6]. Leptin is a peptide produced by adipose tissue and is a strong correlate of obesity [7–11]. The amount of leptin synthesised and secreted is known to increase in proportion to the accumulation of body fat mass [9, 12, 13].

Recent studies on body weight regulation suggest a dual role of leptin in human physiology. Under conditions of steady-state energy balance leptin is an index of the amount of triglyceride stored in adipose tissue. In contrast, during fasting or overfeeding it is a sensor of energy balance. In this acute regulation leptin becomes an afferent component of a feedback loop to preserve the internal level of body fat content [14, 15].

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Because in the vast majority of cases human obesity is characterised by hyperleptinemia, it appears that obese individuals are insensitive to their endogenous leptin [16]. The possible explanations for the leptin resistance are impaired brain access to leptin, disorder of the leptin receptor, signalling cascade or a leptin transducer system. Conflicting data exist concerning leptin as an independent risk factor of coronary artery disease and cardiovascular events [7, 17–19]. Increased serum leptin concentrations have been observed in patients with angina pectoris and myocardial infarction [20, 21]. The mechanisms leading to its impact on cardiovascular dysfunction are complex. Leptin enhances sympathetic nervous tone, which increases vascular tone and blood pressure, but this action is counter-balanced by its direct and indirect peripheral vasorelaxation action [22, 23]. Evidence derived from experimental studies suggests that selective tissue resistance to the satiety and weight-reducing effects of leptin along with its preserved sympathoexcitatory actions is a possible deleterious pathophysiological factor [24]. Moreover, in vascular endothelial cells chronic hyperleptinemia induces intra-cellular signalling, which results in oxidative stress and may activate the atherogenic process [25]. Conflicting data exist on the widely studied association between high leptin concentration and metabolic complications.

The aim of the study was to assess the relationship of blood leptin concentration to the anthropometric parameters and cardiovascular risk factors in men with acute myocardial infarction (AMI) treated with primary coronary intervention (PCI).

## Methods

### Study population

From a cohort of patients who had experienced their first AMI and who had been successfully treated with PCI (TIMI flow grade 3, residual stenosis < 30%), 40 obese men aged  $\leq 65$  years, who admitted to having been obese for at least 5 years, were selected for the study group and 40 non-obese men, matched to the obese group for age and localisation of the AMI, were included in the study as a control group.

Insulin therapy before blood sampling for leptin measurement was considered an exclusion criterion. Additional exclusion criteria were applied owing to requirements for the acquisition of echocardiographic parameters which are unreported in this study. These conditions were atrial fibrillation, atrioventricular or bundle branch block,

temporary or permanent stimulation and significant valvular heart disease.

### Anthropometric measurement clinical definitions and treatment

Diagnosis of AMI was based on the clinical symptoms, electrocardiographic signs and elevation of myocardial necrotic markers. All patients received aspirin and those who underwent stenting were concomitantly treated with an additional antiplatelet agent. Heparin was infused during the procedure. Glycoprotein IIb/IIIa inhibitor was administered to a similar proportion of patients in each group. Pharmacological treatment with aspirin, clopidogrel, statins,  $\beta$ -blockers, angiotensin II inhibitors, nitrates and diuretics was similar in both groups.

A body mass index (BMI), calculated as the body weight divided by the square of the height ( $\text{kg}/\text{m}^2$ ), of 30 was used as a marker of obesity, while patients with a BMI below 25 were designated as non-obese. Weight and height were measured on the 3<sup>rd</sup> or 4<sup>th</sup> day after admission, while the subjects were fasting and wearing only their undergarments. Waist circumference (WC), a measure of subcutaneous plus visceral fat, was measured at the widest diameter between the xiphoid process of the sternum and the iliac crest. Hip circumference (HC), representing subcutaneous fat alone, was measured at the widest diameter over the greater trochanters. The waist-to-hip ratio (WHR) was then calculated. Systolic and diastolic blood pressure (SBP, DBP) was measured before blood sampling.

The study was approved by the Internal Ethics Committee of the Medical University of Łódź, and each patient gave his informed consent.

### Laboratory measurements

CRP and uric acid were assessed as part of a complex analysis of the samples of blood taken upon admission to the hospital. Fasting glucose, lipid profile and leptin levels were determined from the blood drawn the following day. Plasma triglycerides (TG) and total cholesterol (TCH) were measured by enzymatic analytical chemistry. HDL-cholesterol (HDL-CH) was precipitated using dextran-sulphate and measured enzymatically, while LDL-cholesterol (LDL-CH) was calculated using the Friedewald equation:  $\text{LDL-CH} = \text{TCH} - (\text{TG}/5) - \text{HDL-CH}$ . Impaired lipid metabolism was diagnosed if at least one of the following disorders was present: hypercholesterolemia ( $\text{TCH} > 200 \text{ mg}/\text{dl}$ ), hypertriglyceridemia ( $\text{TG} > 150 \text{ mg}/\text{dl}$ ), high LDL-CH ( $\text{LDL} > 100 \text{ mg}/\text{dl}$ ) or low HDL-CH ( $\text{HDL-CH} < 40 \text{ mg}/\text{dl}$ ). Plasma glucose concentrations were

measured with the oxidise method, uric acid with the colorimetric method and CRP concentrations with an immunotubidimetric assay.

Plasma samples for leptin concentration measurements were frozen at  $-70^{\circ}$  until analysis with a sandwich enzyme-linked immunosorbent assay (ELISA).

**Statistical analysis**

Descriptive statistics are expressed as mean  $\pm$   $\pm$  standard derivation. Variables were log-transformed before statistical analysis if necessary. Comparisons between the two groups were performed using the two-tailed, non-paired Student’s t-test or the Mann-Whitney test, as appropriate. Categorical variables are presented as numbers and percentages of patients and comparisons between groups were analysed with the  $\chi^2$  test. Associations between the parameters analysed were examined using Spearman’s correlation coefficient. A p value

of  $< 0.05$  was considered to be statistically significant. Statistical analysis was performed using Statistica software (version 5.0).

**Results**

The clinical characteristics and anthropometric measurements of the obese and non-obese patients are shown in Table 1. The occurrence of hypertension, diabetes, smoking and hypercholesterolemia was similar in the two groups. SBP, the proportion of patients with HDL-CH  $< 40$  mg/dl and TG  $< 150$  mg/dl and all the anthropometric measurements made (BMI, WC, HC, WHR) were significantly higher in the obese group than in the control group.

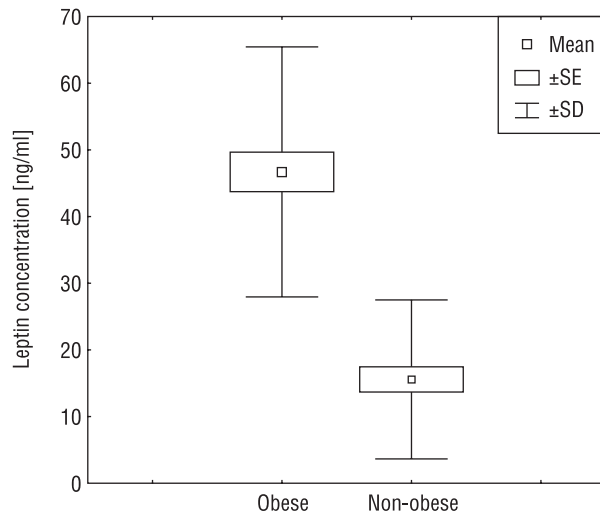
The mean values of the biochemical parameters are presented in Table 2. In the obese patients the values of TG, fasting glucose and CRP were significantly higher than in the non-obese patients, whereas HDL-CH levels were lower.

**Table 1.** Clinical characteristics and anthropometric measurements of the study groups.

	Obese (n = 40)	Non-obese (n = 40)	p
Age	53.6 $\pm$ 7.39	54.4 $\pm$ 6.62	NS
Hypertension	25 (62.5%)	18 (45%)	NS
Systolic blood pressure [mm Hg]	124.1 $\pm$ 9.32	119.0 $\pm$ 13.2	$< 0.05$
Diastolic blood pressure [mm Hg]	75.5 $\pm$ 6.18	73.1 $\pm$ 8.37	NS
Diabetes mellitus	11 (27.5%)	7 (17.5%)	NS
Total cholesterol $> 200$ mg/dl	27 (67.5%)	26 (65%)	NS
Triglicerydes $> 150$ mg/dl	24 (60%)	13 (32.5%)	$< 0.05$
LDL-cholesterol $> 100$ mg/dl	36 (90%)	34 (85%)	NS
HDL-cholesterol $< 40$ mg/dl	15 (37.5%)	5 (12.5%)	$< 0.01$
Smoking	25 (62.5%)	27 (67.5%)	NS
Body mass index [kg/m <sup>2</sup> ]	32.2 $\pm$ 1.96	23.8 $\pm$ 1.40	$< 0.0001$
Waist circumference [cm]	111.9 $\pm$ 7.52	88.1 $\pm$ 7.09	$< 0.0001$
Hip circumference [cm]	108.3 $\pm$ 6.73	91.4 $\pm$ 7.67	$< 0.0001$
Waist-to-hip ratio	1.03 $\pm$ 0.05	0.96 $\pm$ 0.30	$< 0.001$

**Table 2.** Biochemical parameters in the study groups.

	Obese (n = 40)	Non-obese (n = 40)	p
Fasting glucose [mg/dl]	110.1 $\pm$ 14.5	94.8 $\pm$ 10.3	$< 0.001$
Total cholesterol [mg/dl]	224.2 $\pm$ 44.0	216.7 $\pm$ 40.1	NS
LDL-cholesterol [mg/dl]	146.3 $\pm$ 43.1	138.4 $\pm$ 42.5	NS
Triglicerydes [mg/dl]	161.3 $\pm$ 59.8	132.9 $\pm$ 52.1	$< 0.01$
HDL-cholesterol [mg/dl]	45.6 $\pm$ 11.9	51.6 $\pm$ 12.3	$< 0.05$
C-reactive protein [mg/dl]	7.95 $\pm$ 7.29	4.25 $\pm$ 4.84	$< 0.01$
Uric acid [mg/dl]	6.11 $\pm$ 1.48	5.66 $\pm$ 1.47	NS



**Figure 1.** The mean value of plasma leptin concentration in the study groups.

The range of fasting plasma leptin concentrations in this population was 0.8 to 75.8 ng/ml. Obese patients had leptin levels approximately three times higher than non-obese subjects ( $46.7 \pm 18.7$  ng/ml *vs.*  $15.6 \pm 11.9$  ng/ml;  $p < 0.0001$ ) (Fig. 1).

In our study association between age and leptin concentration was not observed ( $r = 0.09$ , NS). In the study group as a whole a significant correlation was revealed between plasma leptin concentration and anthropometric parameters, the strongest correlation being with waist circumference (Fig. 2). A positive relationship was observed between leptin and fasting glucose, TG, CRP and uric acid and a negative relationship between leptin and HDL-CH. Similar relations were noted between the anthropometric measurements and the obesity related risk factors analysed (Table 3).

## Discussion

### Age and gender

In our group of patients aged under 65 years there was no independent relation between age and leptin. This observation is in agreement with some previous reports [18, 26, 27]. Ostlund et al. [13], in patients aged 18–80 years (mean  $52.8 \pm 15.8$  years), revealed a weak inverse relationship between leptin and age independently of body fat. They have also shown that subjects aged over 60 years had significantly lower plasma leptin concentrations than younger ones. These results could suggest a possible decrease in adipose tissue leptin production and/or increase in plasma leptin clearance in the elderly. In contrast with this a positive relation

of leptin with age has been revealed in other studies [12, 28–30]. It has been suggested that an age-related increase in fat mass can be a major confounding factor because adiposity is a strong determinant of leptin. Gender-specific differences in plasma leptin concentration with ageing have also been observed [31–33].

Our study was designed for males in order to avoid the impact of sex-related differences in the location of the adipose tissue, the number of fat cells, fat cell size and plasma leptin concentration [9, 34]. The molecular mechanisms underlying the regulation of adipose tissue mass distribution remains poorly understood, although this is likely to be regulated by hormonal factors, especially sex steroids, glucocorticoids and insulin [9, 35, 36].

### Obesity

The results of our study are in agreement with previous reports documenting the relationship between obesity, as reflected by BMI, and plasma leptin in various populations with different ranges of BMI and in both sexes [7–11, 13, 17, 18, 26, 28, 29, 37–39].

The independent relation of plasma leptin to fat distribution is controversial. Both negative [9, 11, 26] and positive [8, 27, 28, 40] relationships between leptin and WHR have been reported. A thorough analysis of the literature reveals that leptin is more likely to be positively related to WHR in men and negatively in particular groups of patients, including the majority of women. This gender-related difference could be explained by the presence of more abundant subcutaneous fat in women and of visceral fat in men. However, it has previously been established that leptin secretion rates are higher in subcutaneous than in visceral adipose tissue [41–43]. It has been reported that waist girth is likely to be a more convenient anthropometric correlate of visceral adipose tissue than WHR [44]. In our study to determine the predominant site of release of leptin we analysed correlations of leptin with WC representing both subcutaneous and visceral adipose tissue and with HC as a measure of subcutaneous fat alone. The significant positive correlation of leptin with WC ( $r = 0.76$ ,  $p < 0.0001$ ) and HC ( $r = 0.74$ ,  $p < 0.0001$ ) and suggests that secretion of leptin into the bloodstream might be regulated both by visceral and subcutaneous adipose tissue.

### Biochemical disorders

Hyperleptinemia may coexist with other proatherogenic factors typical for obesity. We found a significant difference in leptin concentrations as well as in TG, HDL-CH and fasting glucose between

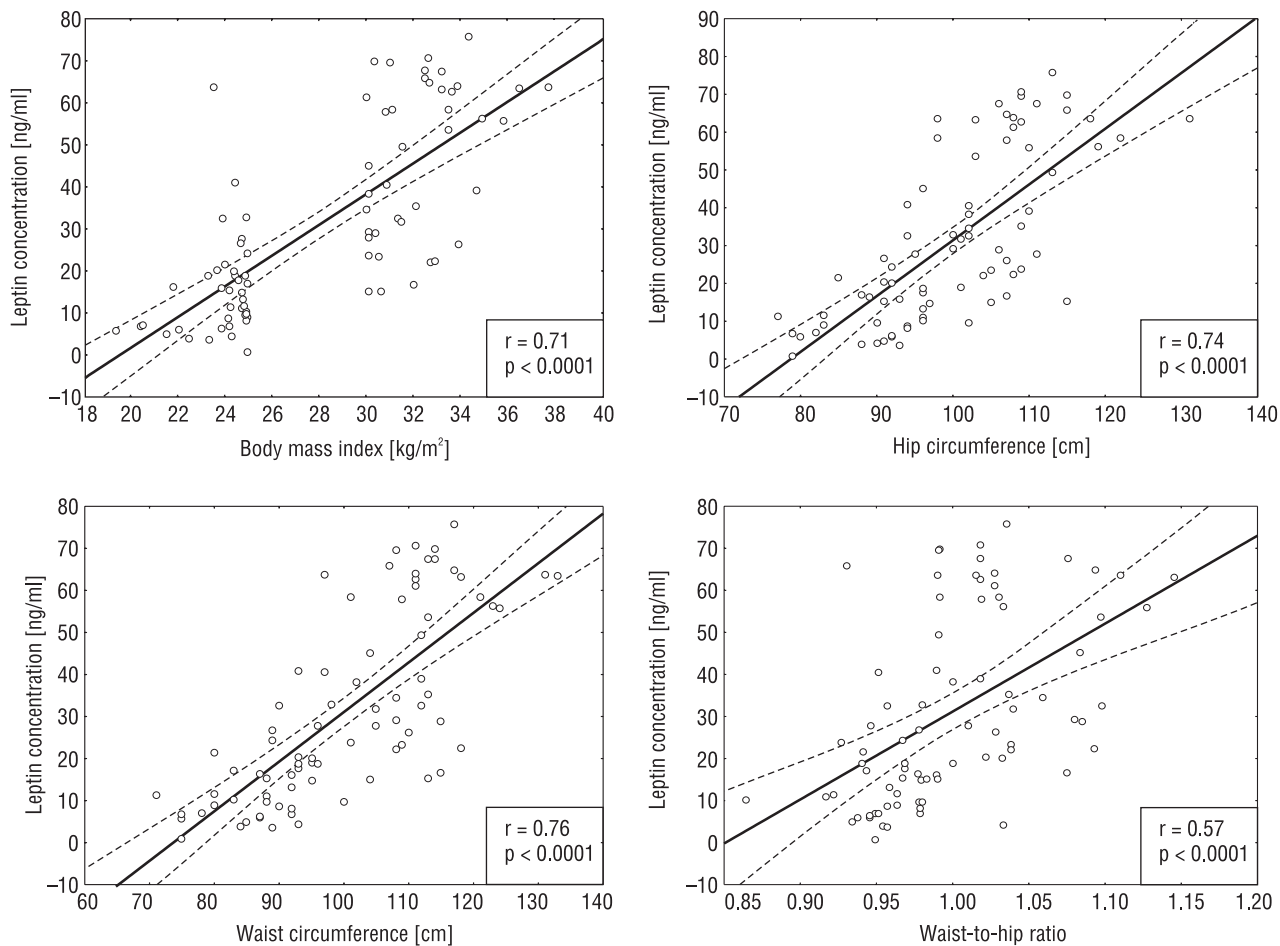


Figure 2. The relation of leptin with anthropometric measurements.

Table 3. The relationship of leptin and anthropometric measurements to obesity-related risk factors.

	Leptin	Body mass index	Waist circumference	Hip circumference	Waist-to-hip ratio
Systolic blood pressure	r = 0.17 NS	r = 0.29 p < 0.01	r = 0.23 p < 0.05	r = 0.21 NS	r = 0.23 p < 0.05
Diastolic blood pressure	r = 0.12 NS	r = 0.28 p < 0.05	r = 0.18 NS	r = 0.20 NS	r = 0.14 NS
Fasting glucose	r = 0.46 p < 0.0001	r = 0.47 p < 0.0001	r = 0.50 p < 0.0001	r = 0.45 p < 0.0001	r = 0.40 p < 0.001
Total cholesterol	r = 0.18 NS	r = 0.001 NS	r = 0.01 NS	r = -0.04 NS	r = 0.09 NS
HDL-cholesterol	r = -0.27 p = 0.05	r = -0.30 p < 0.01	r = -0.39 p < 0.001	r = -0.30 p < 0.05	r = -0.35 p < 0.01
LDL-cholesterol	r = 0.19 NS	r = 0.03 NS	r = 0.07 NS	r = 0.002 NS	r = 0.14 NS
Triglycerides	r = 0.31 p < 0.01	r = 0.18 NS	r = 0.22 p < 0.05	r = 0.20 NS	r = 0.16 NS
C-reactive protein	r = 0.35 p < 0.01	r = 0.40 p < 0.001	r = 0.39 p < 0.0001	r = 0.22 p < 0.05	r = 0.50 p < 0.0001
Uric acid	r = 0.28 p < 0.05	r = 0.18 NS	r = 0.23 p < 0.05	r = 0.19 NS	r = 0.18 NS
Leptin	— —	r = 0.71 p < 0.0001	r = 0.76 p < 0.0001	r = 0.74 p < 0.0001	r = 0.57 p < 0.0001



the group of obese and non-obese patients. In the present study, in agreement with most previous reports, a positive correlation between plasma leptin and TG [7, 8, 11, 18, 28, 45] and no correlation between leptin and LDL-CH [18, 26, 27] was revealed. There is disagreement among authors concerning the relationship between plasma leptin and HDL-CH. It is weak but negative in the group studied by us and some previously reported series of patients [8, 18, 45, 46], but no relationship was revealed in other studies [7, 9, 26]. Thus the role of plasma leptin as a good correlate of known lipid risk factors for coronary artery disease is in question. In our study, in consensus with other opinions, leptin is positively related to the other coronary risk factors namely fasting glucose [8, 11, 18, 28] and uric acid [8, 11, 28, 47].

Recent studies have established that inflammation plays a fundamental role in mediating all stages of atherosclerosis [48]. Adipose tissue secretes various bioactive substances, including leptin, CRP, IL-6, TNF- $\alpha$ , adiponectin and resistin [49, 50]. CRP is not only a marker of the chronic inflammatory process but also a molecule known to promote atherogenesis [51]. It has been suggested that leptin may be involved in the acute response to stress and that in patients with AMI leptin is an acute-phase reactant, facilitating metabolic adaptation to increased demands during stress [52]. This view may find support in the observation that leptin levels increase in the 24 hours following myocardial infarction [52, 53]. Moreover, pro-inflammatory cytokines increase serum leptin concentration [54], while, on the other hand, that leptin may produce inflammation at the site of injection [53]. The possible explanation of this interaction is the resemblance of the leptin receptor and IL-6 receptor [55]. A positive association between leptin and CRP was revealed in our group of patients and is in agreement with previous studies in obese and non-obese individuals, in groups of healthy subjects and in patients with coronary artery disease [18, 29, 39, 56, 57], although it is denied by Fujimaki [58].

Not all these discrepancies and examples of conflicting data can be explained by the simple impact of one additional factor. The groups analysed were different and inhomogeneous in terms of ethnicity, age, presence and degree of obesity, coexisting disease, the possible incidence of insulin and leptin resistance and other co-factors. It has been suggested that leptin in the physiological range may play a protective role against cardiovascular risk, whereas an elevated plasma leptin concentration may act as a trigger and/or marker for

cardiovascular risk, possibly because of leptin resistance [59, 60]. Future investigations, including basic scientific research into the mechanisms of leptin action and resistance, are called for to elucidate the pathophysiological impact of leptin on cardiac function.

Although the relationship between metabolic risk factors and leptin [7–9, 11, 18, 26–28, 45–47] and the relationship between metabolic risk factors and anthropometric parameters [1–6] have been widely documented, there has been no investigation of whether there is any advantage in assessing leptin over anthropometric parameters in terms of the prediction of obesity-related metabolic risk factors. In our study the correlation between metabolic risk factors and leptin did not achieve any higher significance than that for anthropometric parameters (Table 3). This suggests that in general practice blood sampling for leptin is not necessary, unless it is identified as an independent risk factor.

## Conclusions

1. In patients with acute myocardial infarction obesity is related to increased plasma leptin concentration.
2. Both subcutaneous and visceral fat compartment seems to be an important determinant of plasma leptin concentration.
3. Measurement of plasma leptin concentration has no advantage over simple anthropometric measurements in the prediction of obesity-related risk factors.

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