Research Article

Leptin Resistance and Insulin Resistance Go Hand In Hand, but Lipids are Left Behind

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Abstract

Leptin is a hormone secreted by adipose tissue in direct proportion to amount of body fat and it regulates energy homeostasis. Leptin resistance is often associated with insulin resistance and lipid metabolism disorders in obese persons. Study investigates correlation of leptinemia with insulin resistance, and lipid and lipoprotein metabolism parameters in obesity. Study included 60 obese patients. The most common endocrine causes of obesity (hypothyroidism, hyperprolactinemia, hypercortisolism and insulinoma) were eliminated. The patients didn't suffer from manifest cardiovascular diseases, metabolic or endocrine disorders (except hyperlipidemia and essential hypertension) and didn't take any anti-diabetic, anti-obesity or lipid lowering therapy. Analysis of leptinemia, fasting blood glucose and insulinemia, lipid and lipoprotein metabolism parameters was performed. In statistical analysis, we used mean values with standard deviations and linear regression. Mean fasting blood glucose was in higher quarter of normal values, while mean fasting insulinemia and mean HOMA-IRI indicated existence of hepatic insulin resistance. Mean total cholesterol, mean apolipoprotein B and mean triglycerides were in normal range, while mean HDL cholesterol was lower than normal. Mean leptinemia was triple higher than normal and it directly correlated with fasting insulinemia and HOMA-IRI, while there was no significant correlation of leptinemia with fasting blood glucose, lipid and lipoprotein metabolism parameters. Leptin has been reported to have effects on carbohydrate and lipid metabolism that are independent of its centrally mediated effects on energy balance. Study shows that leptin resistance is associated with insulin resistance, while leptinemia doesn't correlate with lipid metabolism parameters in our obese patients.

Keywords: Obesity; Leptin; Insulin Resistance; Lipid Disorders

Introduction

Obesity is defined as the enlargement of total fat mass in the body. It is associated with a variety of metabolic disorders, mainly insulin resistance, type 2 diabetes, dyslipidemia and cardiovascular diseases (CVD) [1].

Insulin resistance is defined as a failure of target organs to respond normally to the action of insulin. This causes incomplete suppression of hepatic glucose output and impaired insulin-mediated glucose uptake in the periphery leading to increased insulin requirements [2]. Insulin resistance is associated with central obesity, hypertension and dyslipidemia [3]. Obesity is the risk factor for the development of insulin resistance and the metabolic syndrome. Beside total amount of fat, distribution of adipose tissue is also important. Visceral depots of fat are connected with development of insulin resistance. The mechanisms by which accumulation and anatomic distribution of adipose tissue may be related to the development of insulin resistance are still unclear [2].

Adipose tissue has traditionally been considered an energy storage organ, but over the last decades, a novel role of the adipose tissue as an endocrine organ has been discovered [4]. Adipose tissue is currently known to secrete a large number of factors with diverse functions. These factors include free fatty acids (FFA) with well described physiological and pathophysiological effects on glucose homeostasis [5]. It also secretes proteins, termed adipocytokines, which act in an autocrine, paracrine or endocrine way and control various metabolic functions [2]. Some of these adipocytokines have been implicated in the development of insulin resistance [2]. They may act locally or distally to alter insulin sensitivity in insulin-targeted organs such as muscle and liver or may act through neuroendocrine, autonomic or immune pathways [2].

Obesity is the most common cause of secondary hyperlipidemia [6]. The most usual lipid disorder associated with obesity is combination of elevated triglycerides, low high density lipoprotein (HDL) cholesterol and increased low density lipoprotein (LDL) cholesterol [6]. Obesity may also be associated with isolated low HDL cholesterol or high triglycerides and postprandial hyperlipidemia [6].

Leptin is a hormone secreted by adipose tissue in direct proportion to amount of body fat, presumably to inform the brain regarding the quantity of stored fat [7]. The circulating leptin regulates energy homeostasis, neuroendocrine functions, metabolism, and also has a structural and functional relation to proinflammatory cytokines [8, 9]. Persons with congenital deficiency of leptin are obese, and their treatment with leptin results in dramatic weight loss through decreased food intake and possible increased energy expenditure [8]. However, the most obese persons are resistant to the weight reducing effects of leptin. Increased circulating leptin, a marker of leptin resistance, is common in obesity and it is independently associated with insulin resistance and CVD in humans [8, 10]. This phenomenon of leptin resistance may have several possible underlying mechanisms: genetic mutation, self-regulation, limited tissue access, action of cellular and circulating molecules [11]. Leptin resistance can be inherited, but this case is not common. Mutation of gene producing leptin leads to its ineffectiveness at signaling, which leads to hyperleptinemia and leptin resistance [11]. Similar results could be obtained through leptin receptor mutation [11]. Like other biological signaling pathways, leptin appears to regulate its own receptor and signaling. Receptor down-regulation may promote pathological leptin resistance [12]. Reduced hypothalamic leptin receptor expression and leptin signaling are observed in rodent models of age-related and diet-induced obesity. The reduction appears to be a direct byproduct of increased central leptin. Consequently, obesity promotes hyperleptinemia, which in turn self promotes leptin resistance and further obesity, making leptin resistance both a consequence and cause of obesity [13, 14]. Resistance to leptin`s action may occur via limited tissue access, such as at the blood-brain barrier. Saturation in Ob-Ra transport mechanism could lead to leptin resistance [11]. Perhaps this is why obese hyperleptinemic mice and humans have a decreased cerebrospinal fluid to serum leptin ratio. Leptin administration into the cerebrospinal fluid of hyperleptinemic obese mice results in short-term weight loss. The blood-brain barrier appears to be a site for leptin regulation and resistance, although such theories demand further testing [15, 16]. Action of cellular (suppressor of cytokine-signaling family members and tyrosine phosphatase 1B) and circulating (serum leptin-interacting proteins) molecules can inhibit leptin to cause resistance [11].

Aim of our study is assessment of correlation between leptinemia, insulin resistance level expressed through Homeostatic Model Assessment-Insulin Resistance Index (HOMA-IRI) value and lipid and lipoprotein metabolism parameters in obese patients.

Research Design and Methods

Cross sectional study included 60 obese patients examined at our clinic. Study has been approved by the local ethics committee and it is performed according to Helsinki Declaration. Participation was voluntary and written consent of all participants was provided. Hyperalimentation obesity was defined with values of body mass index (BMI) ≥ 30 kg/m2 and the previous elimination of the most common endocrine causes of obesity (hypothyroidism, hyperprolactinemia, hypercortisolism and insulinoma). The patients didn't suffer from manifest CVD, metabolic or endocrine disorders (except hyperlipidemia and essential hypertension) and didn't take any anti-diabetic, anti-obesity or lipid lowering therapy.

Patient's general information and medical history were noted and physical examination was conducted. After that, anthropometrical measurements were performed. Body height

was measured with Martin anthropometer with accuracy of 0.1 cm, while body weight was measured with professional medical body weight scale. BMI was calculated as a ratio of body weight and square value of body height expressed in meters.

Table 1. General and anthropometrical parameters.

	Age (years)	BMI (kg/m^2)	WC (cm)	FM (%)
Mean +/-SD	37.73 +/- 11.76	38.491 +/- 12.778	111.548 +/- 36.041	41.056 +/- 12.457

Abbreviations: BMI=body mass index; WC=waist circumference; FM=fat mass;

Table 2. Leptin, glucose, lipid and lipoprotein metabolism parameters

	FBG (mmol/l)	FI (mIU/l)	HOMA-IRI	TC (mmol/l)	HDL-C (mmol/l)	APO-B (g/l)	TG (mmol/l)	Leptin (ng/ml)
Mean +/- SD	5.373 +/- 1.803	18.644 +/- 11.368	4.576 +/- 3.002	4.969 +/- 1.628	1.006 +/- 0.392	0.936 +/- 0.324	1.472 +/- 0.679	52.188 +/- 21.373

Abbreviations: FBG=fasting blood glucose; FI=fasting insulin; HOMA-IRI=Homeostatic Model Assessment-Insulin Resistance Index; TC=total cholesterol; HDL-C=HDL cholesterol; APO-B=apolipoprotein B; TG=triglycerides;

Waist circumference was measured in the middle of the line connecting the anterior superior iliac crest bone and arch ribs with a centimeter tape with a precision of 0.1 cm. For the analysis of body composition, we used bioelectrical impedance analysis (BIA) apparatus produced by Tanita, Japan. BIA is based on measurement of tissue resistance to the passage of alternating current, and it can distinguish percentage of body fat mass, fat-free body mass and total body water. Blood was sampled for analysis of fasting blood glucose, fasting insulin, total cholesterol, HDL cholesterol, apolipoprotein B, triglycerides and leptin. Fasting blood glucose was determined with glucose oxidase-phenol+aminophenazone (GOD-PAP) method and its value was expressed in mmol per liter. For the quantitative analysis of fasting insulin, we used Institute for the application of nuclear energy-radio-immunoassay-insulin-polyethylene glycol (INEP-RIA-I-PEG) method and its value was expressed in mIU per liter. HOMA-IRI was calculated according to formula: fasting blood glucose (mmol/l) x fasting insulin level (mIU/l) / 22.5. Existence of hepatic insulin resistance was defined with value of HOMA-IRI ≥ 2.20. For determination of total cholesterol and triglycerides, we used standard enzyme procedure while HDL cholesterol was analyzed with method of precipitation with sodium-phospho-tungstate and their values were expressed in mmol per liter. Apolipoprotein B was analyzed with enzyme-linked immunosorbent assay (ELISA) method and its value was expressed in gram per liter. Determination of leptin level was performed with ELISA test and its value was expressed in ng per milliliter.

In statistical analysis, we used mean values with standard deviations and linear regression in Statistica 10.0 software.

Results

Eighty percent of patients were female. Analysis of age and anthropometric parameters is shown in Table 1. Results of anthropometric measurements pointed out high risk, second degree central obesity with high percentage of total body fat mass.

As it is shown in Table 2, mean fasting blood glucose was in higher quarter of normal values, while mean fasting insulinemia and mean HOMA-IRI indicated existence of hepatic insulin resistance.

Mean total cholesterol, mean apolipoprotein B and mean triglycerides were in normal range, while mean HDL cholesterol was lower than normal. Mean leptin was triple higher than normal.

As it is shown in Table 3, linear regression model shows that leptin level directly correlated with fasting insulinemia and HOMA-IRI value. There was no statistically significant correlation of leptin and fasting blood glucose. Linear regression model shows that there was no statically significant correlation of leptin and total cholesterol, HDL cholesterol, apolipoprotein B and triglycerides.

Table 3. Correlations of leptin with glucose, lipid and lipoprotein metabolism parameters

	Leptin	
Parameter	r	p
FBG	0.1183	0.3806
FI	0.3697	0.005[*]
HOMA-IRI	0.4078	0.0016[*]
TC	-0.1543	0.2519
HDL-C	-0.1181	0.3817
APO-B	-0.1314	0.3435
TG	0.2190	0.1017

*statistically significant (p<0.05)
Abbreviations: FBG=fasting blood glucose; FI=fasting insulin; HOMA-IRI=Homeostatic Model Assessment-Insulin Resistance Index; TC=total cholesterol; HDL-C=HDL cholesterol; APO-B=apolipoprotein B; TG=triglycerides;

Discussion

Leptin has been reported to have effects on carbohydrate and lipid metabolism that are independent of its centrally mediated effects on energy balance. There has been a wealth

of experiments attempting to discern the extent and nature of the direct effects of leptin on peripheral tissues. However, many of these studies have used in vitro or ex vivo preparations in a hormonal milieu somewhat removed from that seen in vivo, making it difficult to place the data within a proper physiological context.

As far as human studies are concerned, many of them tested correlation between leptin level and parameters of glucose metabolism, especially insulin resistance. The most of them concluded that there is strong positive correlation of leptin resistance and insulin resistance. Some of them brought the same results even independently of waist circumference [17-21]. Jazet et al. showed that there is a correlation between leptin level and insulin resistance even after adjustment for BMI and body fat mass, while Huang KC et al. showed positive correlation of leptin level and insulin resistance independent of age, gender, BMI, body fat mass, waist circumference, Tanner stage and triglycerides in nondiabetic adolescents [22, 23]. Results of these studies suggest that this connection might be independent of amount of body fat mass. A number of mechanisms may directly link leptin level to hyperinsulinaemia and insulin resistance [24, 25]. Firstly, leptin may influence insulin levels by a direct action on the islet β-cells [24]. Secondly, insulin may increase leptin secretion by adipocytes [24, 25].

Numerous studies analyzed relation of leptin level and lipid and lipoprotein metabolism parameters. Tamer L. et al. showed that leptin level positively correlates with total cholesterol, LDL cholesterol, lipoprotein (a) and apolipoprotein B while negatively correlates with HDL cholesterol in patients with developed CVD [26]. Jurimae et al. didn't find correlation between leptin level and lipids in physically active postmenopausal women [27].

Major limitations of this study are modest number of enrolled subjects and lack of data on other parameters which have an influence on leptin and insulin secretion, and on the lipid and lipoprotein metabolism parameters.

Our study shows that leptin resistance is associated with insulin resistance, while leptinemia doesn't significantly correlate with lipid and lipoprotein metabolism parameters in our obese patients.

Acknowledgements

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