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Serum Leptin Concentrations in Patients with Combined Hyperlipidemia: Relationship to Serum Lipids and Lipoproteins

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Summary

Leptin is a protein hormone produced predominantly by adipocytes. Serum leptin concentrations in healthy individuals positively correlate with the body fat content and body mass index, i.e. they are higher in obese than in lean subjects. The relations between serum leptin concentration and serum lipids and lipoproteins is not yet clear. The aim of our study was to compare serum leptin concentrations in 22 randomly selected patients with untreated combined hyperlipidemia and 19 healthy control subjects matched for age and the body mass index. The relationship was studied between serum leptin concentrations and serum lipids (total, HDL, LDL cholesterol and triglycerides) and lipoproteins (lipoprotein (a), apolipoprotein B). It was found that serum leptin levels in patients with combined hyperlipidemia did not significantly differ from those of control subjects (6.69±4.3 vs 5.78±3.2 ng.ml^{-1}). Serum leptin concentrations in both groups correlated positively with the body mass index. The relationship between leptin concentrations and lipid or lipoprotein levels found in any of the studied groups was not statistically significant. We conclude that serum leptin concentrations in patients with combined hyperlipidemia as well as in healthy control subjects reflect the body fat content and have no significant relation to serum lipids or lipoproteins.

Key words

Leptin • Cholesterol • Triglycerides • HDL • LDL • Body mass index

Introduction

Leptin is a protein hormone produced by adipocytes, placental and Graafian follicle cells (Mise *et al.* 1998). It was identified by cloning of mouse *ob* gene (Zhang *et al.* 1994). It has been reported that serum leptin levels in healthy subjects positively correlate with the body fat content and body mass index (Ostlund *et al.* 1996, Maffei *et al.* 1995, Haluzík *et al.* 1998). Serum leptin concentrations in obese subjects are higher in comparison with lean individuals and the degree of its increase usually reflects the degree of obesity. However, the loss of positive correlation between serum leptin concentrations and the body fat content and body mass index, respectively, was found in some serious malnutrition states. These include patients with short bowel syndrome (Cederholm *et al.* 1997) and with

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anorexia nervosa before or after realimentation (Eckert *et al.* 1997, Haluzík *et al.* 1999).

The relationship between serum leptin concentrations and serum lipids or lipoproteins has not so far been extensively studied. Moreover, to our best knowledge, no study concerning this topic in patients with disorders of lipid metabolism has yet been published.

Leyva *et al.* (1998) studied the relationship between serum leptin concentrations and the concentrations of serum lipids in middle-aged men with metabolic syndrome X. Serum leptin concentrations in this study correlated positively with the body mass index, systolic and diastolic pressure, serum triglycerides, uric acid, blood glucose and insulin concentrations. Al-Shoumer *et al.* (1997) followed similar parameters in patients with growth hormone deficiency. These authors reported that serum leptin concentrations in patients with growth hormone deficiency were significantly higher than in healthy controls matched for age and the body mass. A positive correlation was only found between serum leptin concentrations and the body mass index and body fat content. No significant relationship was found between serum leptin concentrations and serum concentrations of IGF-I, blood glucose, insulin, total, HDL and LDL cholesterol and triglycerides.

The relation of serum leptin concentrations and different HDL phenotype moieties was investigated by Rainwater *et al.* (1997) who found that only two of the nine studied moieties positively correlate with serum leptin concentrations. Couillard *et al.* (1998) compared serum leptin concentrations and metabolic profiles in men with or without coronary heart disease. No significant differences in serum leptin concentrations were found between these two studied groups. Serum leptin concentrations correlated positively only with serum triglyceride concentrations in both groups studied. Chapman *et al.* (1997) investigated the relationship of serum leptin concentrations and serum lipids in patients with the polycystic ovary syndrome and healthy controls. Serum leptin concentrations in patients with this syndrome did not significantly differ from those of healthy controls. No statistically significant relation was found between serum leptin and lipid concentration with the exception of a significant positive correlation between serum leptin and serum HDL cholesterol concentrations in both groups.

As was demonstrated above, the relationship between serum leptin concentrations and serum lipids and lipoproteins has not been well established so far. Moreover, to our best knowledge, this topic has not yet been investigated in patients with disorders of lipid metabolism. We have therefore decided to compare serum leptin concentrations in a randomly selected sample of patients with combined hyperlipidemia and in an age- and body mass index-matched control group without a disorder of lipid metabolism. The relations between serum leptin concentrations and serum total, HDL, LDL cholesterol, triglycerides and lipoprotein (a) and B (only in the combined hyperlipidemia group) were also studied.

Subjects and Methods

Twenty-two untreated randomly selected men with combined hyperlipidemia (serum cholesterol concentrations above 5.6 mmol/l and serum triglycerides concentration above 2.0 mmol/l) and 19 healthy control subjects without lipid metabolism disorder were included in the study. The two groups were matched for age and the body mass index. None of the subjects suffered from diabetes mellitus, acute infectious disease and none were treated by hypolipidemic medication or drugs known to affect lipid metabolism or food intake. All subjects included in the study were informed about the purpose of the study and gave their informed consent to participate.

All subjects were measured and weighed. Blood was withdrawn after an overnight fast (14 hours) between 07:00 and 08:00 h. Serum leptin concentrations were assessed by a commercial ELISA kit (Biovendor, CR). Serum total, HDL cholesterol and triglycerides were measured by standard laboratory methods in the Department of Clinical Biochemistry of the General Faculty Hospital in Prague. Serum lipoprotein (a) and apolipoprotein B were measured by Laurent's rocket method using Behring and Sevac antisera (Češka *et al.* 1989). Serum LDL concentrations were computed using Friewald's formula.

The statistical analysis was performed on SigmaStat software (Jandel Scientific, USA). The results were expressed as means ± standard deviations. The significance of differences between the studied groups was assessed by the unpaired T-test. The correlations between studied parameters were computed by linear regression analysis and Pearson's correlation test.

Results

Serum leptin values in combined hyperlipidemia and the controls did not differ significantly (Table 1).

Serum total, LDL and triglycerides concentrations were significantly higher in the combined hyperlipidemia group (Table 1). No significant difference was found in HDL cholesterol concentrations.

Table 1. Age, body mass index (BMI), serum leptin, total, HDL, LDL cholesterol and triglyceride concentrations in control and combined hyperlipidemia group as well as apolipoprotein (a) and B concentrations in combined hyperlipidemia group.

Control group	Combined hyperlipidemia	
n	19	22
age	51.63±11.70	54.70±12.53
BMI ($kg.(m^2)^{-1}$)	27.01±3.43$^+$	26.8±3.19$^+$
leptin ($ng.ml^{-1}$)	5.78±3.20	6.69±4.31
cholesterol ($mmol.l^{-1}$)	5.23±0.61	7.03±1.14*
triglycerides ($mmol.l^{-1}$)	1.49±0.53	3.05±0.59*
LDL cholesterol ($mmo.l^{-1}$)	3.21±0.56	4.53±1.16*
HDL cholesterol ($mmol.l^{-1}$)	1.32±0.38	1.17±0.46
lipoprotein (a)	–	0.29±0.25
apolipoprotein B	–	1.24±0.37

*The values are means ± S.D. * statistically significant difference in comparison with control group ($p<0.01$, T-test).*
$^+$ statistically significant positive correlation with serum leptin levels ($p<0.01$, Pearson correlation test).

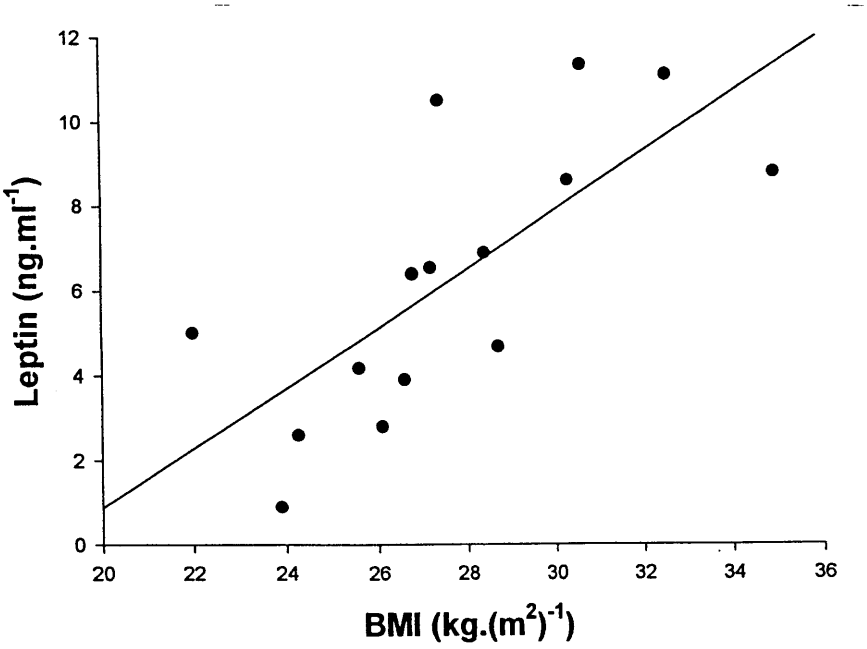

Fig. 1. *Correlation of serum leptin concentrations and body mass index in the control group ($r=0.72$, $p< 0.01$, linear regression analysis).*

Serum leptin concentrations positively correlated with the body mass index in both studied groups (Table 1, Figs 1 and 2). No significant relationship was found between leptin and total, LDL, HDL cholesterol concentrations in any of the studied groups. No significant relation was found between leptin and apolipoprotein (a) and B concentrations in the combined hyperlipidemia group.

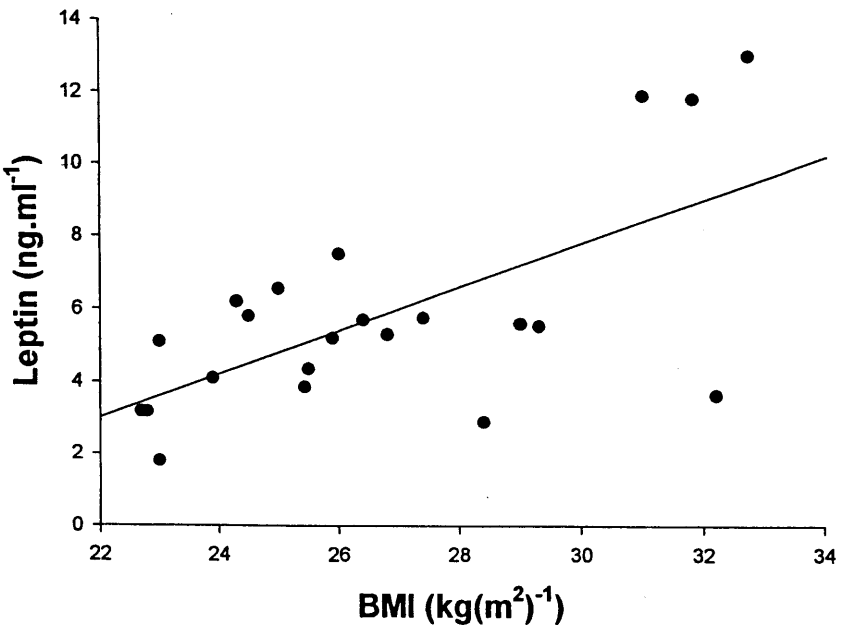

Fig. 2. *The correlation of serum leptin concentrations and body mass index in combined hyperlipidemia group (r=0.64, p<0.01, linear regression analysis).*

Discussion

The aim of this study was to compare serum leptin concentrations in patients with combined hyperlipidemia and in age- and body mass index-matched controls as well as to study the relationship between leptin and selected serum lipids and lipoproteins concentrations. No statistically significant difference was found in serum leptin concentrations between the combined hyperlipidemia and control group. No significant relationship was found between serum leptin and total, HDL, LDL cholesterol and triglyceride concentrations in any of the studied groups. Moreover, no significant relation was found between serum leptin and apolipoprotein (a) and B concentrations in the group with combined hyperlipidemia.

Leptin is a protein hormone produced by adipocytes and locally also by placental and Graafian folicle cells (Zhang *et al.* 1994, Mise *et al.* 1998). Serum leptin concentrations correlate in most healthy individuals with the body fat content and body mass index, i.e. they are higher in obese than in lean subjects (Maffei *et al.* 1995, Ostlund *et al.* 1996, Haluzík *et al.* 1998). The loss of correlation between leptin and body fat content is described in some patients with extremely decreased body fat, i.e. in severely malnourished patients with anorexia nervosa (Eckert *et al.* 1997, Haluzík *et al.* 1999) and elderly patients with malnutrition caused by benign afflictions of the digestive tract (Cederholm *et al.* 1997). Serum leptin concentrations in females are two or three times higher than in age- and body mass index-matched males (Maffei *et al.* 1995, Ostlund *et al.* 1996). The production of leptin has a circadian rhythmicity (Licinio *et al.* 1997) and vary throughout the menstrual cycle (Hardie *et al.* 1997).

Serum leptin concentrations provide the peripheral signal from the adipose tissue that probably affects the appetite and food intake through the hypothalamic satiety center. The relationship between serum leptin concentrations and resting energy expenditure in humans is not definitely clear. The resting energy expenditure in leptin-deficient *ob/ob* mice is significantly decreased. Recombinant leptin treatment significantly increases resting energy expenditure in these animals. The mechanisms by which leptin influences food intake regulation and energy storage in the form of subcutaneous fat are complex. We therefore suggested the possibility of direct or indirect influence of leptin on the synthesis and metabolism of triglycerides and other lipids or lipoproteins. The aim of our study was to clarify whether alteration of serum lipids and lipoproteins levels in patients with combined hyperlipidemia is accompanied by changes of serum leptin levels.

As has been demonstrated above, there is probably no clear relationship between serum leptin and total and LDL cholesterol concentrations in healthy individuals as well as in patients with growth hormone deficiency. In some studies (Leyva *et al.* 1997, Chapman *et al.* 1997, Rainwater *et al.* 1997, Couillard *et al.* 1998) significant positive correlation between leptin and HDL

cholesterol or leptin and triglycerides was found.

We did not find a significant difference in serum leptin concentrations between the group of randomly selected patients with combined hyperlipidemia and healthy age- and body mass index- matched healthy controls in our study. Moreover, no significant relation was found between serum leptin and total, LDL, HDL cholesterol or triglyceride concentrations either in the combined hyperlipidemia group or the controls. No significant relationship was found between serum leptin concentrations and the levels of apolipoprotein (a) and apolipoprotein B in the combined hyperlipidemia group. Serum leptin concentrations in both studied groups correlated positively with the body mass index. We thus suggest that leptin changes do not probably play a causal role in the increase of serum lipids and lipoprotein concentrations in patients with combined hyperlipidemia.

We conclude that serum leptin concentrations in patients with combined hyperlipidemia do not significantly differ from those of age- and body mass index matched control group. Moreover, no significant relationship between serum leptin concentrations and serum lipids and lipoprotein levels was found in our study.

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References

AL-SHOUMER KAS, ANYAOKU V, RICHMOND W, JOHNSTON DG: Elevated leptin concentration in growth hormone-deficient hypopituitary adult. *Clin Endocrinol* **47:** 153-159, 1997.

CEDERHOLM T, ARNER T, PALMBLAD J: Low circulating leptin levels in protein energy malnourished chronically ill elderly patients. *J Intern Med* **242:** 377-382, 1997.

ČEŠKA R, KVASILOVÁ M, PROCHÁZKOVÁ R, ŠOBRA J: Our experience with apo B determination using Sevac serum (in Czech) *Sborník Lék* **91:** 334-338, 1989.

COUILLARD C, LAMARCHE B, MAURIEGE P, CANTIN B, DAGENAIS GR, MOORJANI S, LUPIEN PJ, DESPRES JP: Leptinemia is not a risk factor for ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Diab Care* **21:** 782-786, 1998.

ECKERT ED, POMEROY C, RAYMOND N, KOHLER PF, THURAS P, BOWERS CY: Leptin in anorexia nervosa *J Clin Endocrinol Metab* **83:** 791-798, 1997.

HALUZÍK M,. BOUDOVÁ L, NEDVÍDKOVÁ J, HALUZÍKOVÁ D,. NOVOTNÝ A, BARÁČKOVÁ M, BRANDEJSKÝ P, VILIKUS Z: Serum leptin concentrations in rugby players, correlation with anthropometric and biochemical parameters (in Czech). *Medicina Sportiva Bohemica et Slovaca* **7:** 44-47, 1998.

HALUZÍK M,. PAPEŽOVÁ H, NEDVÍDKOVÁ J, KÁBRT J: Serum leptin levels in patients with anorexia nervosa before and after partial refeeding, relationships to serum lipids and biochemical nutritional parameters. *Physiol Res* **48:** 197-202, 1999.

HARDIE L, TRAYHURN P, ABRAMOVICH D, FOWLER P: Circulating leptin in women: a longitudinal study in the menstrual cycle and during pregnancy. *Clin Endocrinol* **47:** 101-106, 1997.

CHAPMAN IM, WITTERT GA, NORMAN RJ: Circulating leptin concentrations in polycystic ovary syndrome: relation to anthropometric and metabolic parameters. *Clin Endocrinol* **46:** 175-181, 1997.

LEYVA F, GODSLAND IF, GHATEI M, PROUDLER AJ, ALDIS S, WALTON C, BLOOM S, STEVENSON JC: Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. *Arterioscl Thromb Vasc Biol* **18:** 928-933, 1998.

LICINIO J, MANTZOROS CH, NEGRAO AB, CIZZA G, WONG M, BONGIORNO PB, CHROUSOS GP, KARP B, ALLEN CH, FLIER JS, GOLD PW: Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. *Nat Med* **3:** 575-579, 1997.

MAFFEI M, HALAAS J, RAVUSSIN E, PRATLEY RE, LEE GH, ZHANG Y, FEI H, KIM S, LALLONE R, RANGANATHAN S: Leptin levels in human and rodent: measurement of plasma leptin and of RNA in obese and weight-reduced subjects. *Nat Med* **1:** 1155-1161, 1995.

MISE H, SAGAWA N, MATSUMOTO T, YURA S, NANNO H, ITOH H, MORI T, MASUZAKI H, HOSODA K, OGAWA Y, NAKAO K: Augmented placental production of leptin in preeclampsia: possible involvement of

placental hypoxia. *J Clin Endocrinol Metab* **83:** 3225-3229, 1998.

OSTLUND RE, YANG JW, KLEIN S, GINGERICH R: Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab* **81:** 3909-3913, 1996.

RAINWATER DL, COMUZZIE AG, VANDEBERG JL, MANAHEY MC, BLANGERO J: Serum leptin levels are independently correlated with two measures of HDL. *Atherosclerosis* **132:** 237-243, 1997.

ZHANG Y, PROENCA R, MAFFEI M, BARONE M, LEOPOLD L, FRIEDMAN JM: Positional cloning of the mouse obese gene and its human homologue. *Nature* **372:** 425-432, 1994.

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