Relationship Between Leptin Levels and Body Indexes in Patients with Haematologic Malignancy

Rafet METE*, Ýmdat DÝLEK**, Ekrem ALGÜN***, Reha ERKOÇ****, Hayati AYAKTA****, Cevat TOPAL****, Haluk DÜLGER*****, Halis AKSOY****

* Department of Internal Medicine, Medical Faculty, Yüzüncü Yýl University,
** Department of Haematology, Medical Faculty, Yüzüncü Yýl University,
*** Department of Endocrinology, Medical Faculty, Yüzüncü Yýl University,
**** Department of Nephrology, Medical Faculty, Yüzüncü Yýl University,
***** Department of Biochemistry, Medical Faculty, Yüzüncü Yýl University, Van, TURKEY

ABSTRACT

Leptin is a recently found hormone regulating body weight. In human obesity, this weight-regulating hormone level is in a positive correlation with FMI (fat mass index) and BMI (body mass index). In this study, we aimed to investigate the relation between serum leptin levels and BMI, PF (percentage fat), LMI (lean mass ýndex), FMI and some other parameters of patients with haematologic malignant diseases. Fourty-four patients with haematologic malignant diseases and 25 healthy control group were taken into the study. In the comparison, there were no significant difference between the PF and FMI values of both groups, while the mean BMI and LMI values of the control group were significantly higher than that of the patient group. There was a positive correlation between leptin levels and BMI and FMI among parameters studied in our control group, whereas we couldn't demostrate any such correlation in patient group. We estimate that the alteration may be due to disturbances in the feed back mechanism developing in patient with haematologic malignancy.

Key Words: Leptin levels, Body indexes, Haematologic malignant diseases.

Turk J Haematol 2001;18(3):185-189.

Received: *01.12.2000* ***Accepted:*** *20.02.2001*

INTRODUCTION

Leptin is a recently discovered adipocyte derived hormone that acts primarily on hypothalamus to regulate body weight[1]. Recently, a related man and woman with congenital leptin deficiency have been described[2]. Both showed hypogonadism of hypothalamic origin, suggesting that, leptin not only controls body mass but may also be necessary to initiate human puberty[1,2]. The 16-kd protein is the ob-gene product synthesized and secreted by adipocytes[3]. In human obesity, this weight-regulating hormone level is in a positive correlation with FMI (fat mass index) and BMI

(body mass index), suggesting that most obese subjects may be resistant to leptin[4]. Weight loss and cachexia is a dominant feature of malignant disease and this is usually attributed to cytokines such as TNF-a[5]. However the possible role of leptin in the weight loss of malignant diseases have not been investigated yet. In this study, we aimed to investigate the relation between serum leptin levels and BMI, FMI, LMI (lean mass index), PF (percentage fat), serum glucose and BUN concentrations of patients with haematologic malignant diseases.

MATERIALS and METHODS

The study group consisted of 44 patients (mean age 44.5 ± 18, 26 men and 18 women) with a haematologic malignancy who were admitted to our haematology department between 1997-1998 and 25 healthy individuals (mean age 32.7 ± 12, 15 men and 10 women) as a control group. Determination of diseases, regarding to standart criterias, were established by means of histopathologic, morphologic, immunophenotypic, cytochemical, protein electrophoretic and immunoglobulin characteristic properties. The diagnoses of the patient group are shown in Table 1. All of the patients were newly diagnosed and not only given chemotherapy yet, but also have taken any routine continious drug. In both groups serum samples were taken after an overnight fast. The biochemical parameters were determined with a commercial kit (Biotrol) by Technicon RA-XT auto-analyzer. Serum leptin levels were determined by Radioimmunoassay (RIA) with Isocomp I gamma counter using a commercial kit (Linco-research). BMI was calculated with the ratio of weight (kg)/square of height (m^2). Body skin fold-thickness were measured with a caliper (Holtain). Using these skin fold measures total body PF were calculated by the Data of Durnin and Womersley Scala 1974. Using these PF, FMI = BMI x PF and LMI = BMI - FMI were calculated. Statistical analysis were done with "student's-t test" and p values less than 0.05 is taken as significant.

RESULTS

Mean age, BMI, PF, LMI, FMI, leptin, BUN, creatinine and glucose levels of the patient and control groups are shown on Table 2 and the correlation between leptin and these parameters are shown on Table 3.

DISCUSSION

In humans serum leptin concentrations reflect the amount of adipose tissue in the body. The

Table 1. Characteristic and number of diseases in patient group

Diagnose	Patient counts
Hodgkin disease	11
Nonhodgkin lymphoma	13
Chronic lymphocytic leukemia	6
Acute lymphoblastic leukemia	2
Chronic myeloid leukemia	3
Acute myeloid leukemia	6
Waldenström macroglobulinemia	1
Multiple myeloma	2

Table 2. Correlation between leptin and glucose, BUN and body index parameters in patient and control groups

	Patient group		Control group	
Parameters	p	r	p	r
BMI	-0.025	0.872	0.431	0.031
FMI	0.118	0.443	0.834	0.001
LMI	-0.100	0.515	-0.229	0.271
Glucose	-0.004	0.975	0.044	0.834
BUN	-0.115	0.457	-0.379	0.061

Table 3. Comparison of parameters in patient and control groups

Parameters	Patient group	Control group	p value
Age	44.5 ± 17.94	32.7 ± 12.46	0.005
Lepton	2.14 ± 2.07	3.48 ± 2.42	0.024
BUN	15.6 ± 4.58	14.9 ± 4.59	0.572
Creatinin	0.76 ± 0.75	0.65 ± 0.11	0.385
Glucose	95.9 ± 9.2	87.6 ± 13.2	0.008
BMI	21.68 ± 2.92	24.36 ± 4.44	0.004
PF	0.21 ± 0.45	0.22 ± 0.98	0.488
LMI	17.02 ± 2.2	18.52 ± 3.0	0.023
FMI	4.6 ± 1.3	5.6 ± 3.0	0.075

BMI: Body mass index. LMI: Lean mass index. FMI: Fat mass index, PF: Percentage fat

mechanism by which the increase in body fat is translated into an increase in serum leptin appears to involve induction of the ob gene. Although several factors may contribute to the elevation of serum leptin concentrations in obesity, the values were most closely correlated with the percentage of body fat. It therefore appears that, in humans, serum leptin concentrations reflect the amount of adipose tissue in the body. In a study a 10% reduction of the body weight resulted in a 53% of decline in serum leptin concentrations[6]. The large fluctuations in serum leptin concentrations in the presence of relatively small changes in body weight suggest that leptin secretion is regulated by other factors in addition to the size of the adipose-tissue depot.

In our study, although the patient and the control groups ages were different significantly, we know that serum leptin concentration are not only effected with age[7], but also altered by the presence of an inflammatory response[8]. In patients with a negative calorie balance, there were a decrease in leptin levels and the patients had increased appetite. Besides weight loss, decreases in serum glucose and insulin levels also resulted in a reduction of serum leptin concentrations. But, in our study group, renal functions and serum glucose concentrations were within normal limits. As weight loss values were up to history which's taken from patients and relatives, so that were not objective, excluded from the evaluated parameters.

Comparing the body fat compositions of the patient and control groups, there were no significant difference between the PF and FMI values. When we compare the mean BMI and LMI values, the mean BMI and LMI values of the control group were significantly higher than that of the patient group. In the patient group, there were no significant relationship between leptin and BMI, FMI, LMI and serum glucose and BUN concentrations, whereas the relationship between leptin and BMI and FMI values were statistically significant in control group. As seen in this data, the relationship between leptin and body index parameters disappeared in patient group. In addition, only 44 patient (26 male and 18 female) addmitted over 2 years period and only 13 was the highest number of patient with a sort of haematological malignancy, so we didn't evaluate subgroups seperately upon gender and type of disease to establish proper analyse (Table 1).

Although the mean weight of the patient group were less than the control group, this difference is largely attributable to the decrease in the LMI rather than a decrease in body fat stores, similar to our results, as there was not a significant difference in PF and FMI values between groups. In a study evaluating leptin levels in thalassaemic patients, 162 patient with Cooley's anaemia and 138 normal subjects were matched and leptin concentration was appeared to be significantly lower ($p < 0.05$) than in controls[9].

In patients with a malignant disease, increased cytokine production leads to a decrease in appetite, weight loss and finally cachexia[10]. Cachexia is a leading feature in more than half of the cancer patients. This cachexia is characterized with the loss of the adipose tissue and skeletal muscle mass. These patients also usually have decreased calorie intake and increased basal energy expenditure[3]. This increase is mostly attribute to the increased activity of the Cori cycle and hepatic gluconeogenesis[11] and a number of cytokines including tumor necrosis factor-alpha, interleukins 1 and 6, IFN-a, leukemia inhibitory factor and ciliary neurotrophic factor which have been proposed as mediators of cachectic process, may play a pivotal role in long-term inhibition of feeding by mimicking hypothalamic effect of excessive negative feedback signaling from leptin[12]. Among these cytokines, interleukin-1 and TNF were shown to increase the leptin gene expression in rats[13]. As cytokines (IL-1, tumor necrosis factor-alpha etc.) were not involved in this study, the relation between leptin and other cytokines weren't discussed.

In a study which is performed on 21 patients with lung cancer of Simons et al, leptin concentrations were shown as non-detectable in 15 of the patients conversely to our data for there were not any undetectable leptin level. The other six patients who had detectable leptin levels, there were less weight loss and a higher fat mass, so the authors have suggested that the afferent part of the leptin feedback mechanism functions normally and, in particular, elevated leptin levels are not involved in the development of cachexia. Since the absence of plasma leptin was not associated with an increased appetite and decreased energy expenditure, disturbances in the hypothalamic part of the feedback mechanism are hypothesized[14].

By the datas from literature[6] and our study, we suggest that there's an inappropriate positive correlation between leptin level and FMI. But, it is imposible to determine cachexia only by means of FMI and leptins. We suppose that, cachexia is a result of complex mechanism led by multifactorial events including a number of cytokines.

As there were no significant reduction in the fat mass of our patient group, and we know that cytokines increase the leptin concentrations of the cancer patients; then why did we find decreased leptin levels in our patient group? We can explain this controversy in 3 ways. First, although statistically not significant, low reductions in the fat mass can lead to higher reductions in serum leptin concentrations by unknown mechanisms. Second, there may be some acquired mutations of the leptin gene in cancer patients. And last, there may be other factors or cytokines for defensive goal against progressive wasting leading to early death, regulating leptin metabolism in patients with haematologic malignancies.

The interrelation between leptin and neuroendocrine, reproductive, haemopoietic and metabolic control pathways is quite important[12,15]. In healthy bone marrow CD-34 (+) hemopoetic stem cells and almost all human leukemia cells contain leptin receptors and the expression of the leptin receptor were shown to decrease in vitro during leukaemic blastic differentiation. However any effect of leptin on leukemia cells have not been demonstrated yet[16]. We found decreased leptin concentrations in our patient group, though they had normal fat tissue. Based on this data, we suggest that, the patient with haematological malignant disease might have decreased the leptin levels as a defense mechanism in order to keep appetite up to gain weight and to avoid weight loss. As seen in other studies[6-8], there was a positive correlation between leptin levels and BMI and FMI in our control group. But we couldn't demonstrate any such correlation in our patient group. This may be due to disregulation in the feedback mechanisms developing in patient with haematologic malignancy. The mechanism of these disregulation and the precise role of leptin on body indexes of patient with haematological malignancy needs further investigation in homogenous groups.

REFERENCES

1. Flier JS, Maratos-Flier E. Obesity and the hypothalamus: novel peptides for new pathways. Cell 1998; 92:437-40.
2. Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. A leptin missense mutation associated with

hypogonadism and morbid obesity. Nature Genetics 1998;18:213-5.

3. Caro JF, Sinha MK, Kolaczynski LW, Zhang PL, Considine PL. Leptin: The tale of an obesity gene. Diabetes 1996;45:1455-62.
4. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal weight and obese humans. N Eng J Med 1990;334: 292-6.
5. Tisdale MJ. Biology of cashexia. J Natl Cancer Inst Dec.1997;3:89:1763.
6. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425-31.
7. Martin LJ, Jones PJ. Serum leptin levels and energy expenditure in normal weight women. Can J Physiol Pharmacol 1998;76:237-41.
8. Wallace AM, Sattare N, Mc Millan DC. Effect of weight loss and the inflammatory response on leptin concentration in gastrointestinal cancer patients. Clin Cancer Res 1998;4:2977-9.
9. Del Giudice EM, Carbone MT, De Rosa C, et al. Evaluation of leptin protein levels in patients with Cooley's anaemia. Br J Haematol 1999;105:839-40
10. Matthys P, Billiau A. Cytokines and cachexia. Nutrition 1997;13:763-70.
11. Bai Y, Zhang S, Kim KS. Obese gene expression alters the ability of 30A5 preadipocytes ta respond to lipogenic hormones. J Biol Chem 1996;271: 13939-42.
12. Inui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? Cancer Res 1999;15;59: 4493-501.
13. Janic JE, Curti BD, Considine RV, et al. Interleukin 1 alpha increases serum leptin concentrations in humans. J Clin Endocrinol Metab 1997;82:3084-6.
14. Simons JP, Schols AM, Campfiel LA. Plasma concentration of total leptin and human lung-cancer-associated cachexia. Clin Sci 1997;93:273-77.
15. Auwerx J, Staels B. Leptin. The Lancet 1998;351: 737-42.
16. Nakao T, Hino M, Yamane T. Expression of the leptin receptor in human leukaemic blast cells. Br J Haematol 1998;102:740-5.

Address for Correspondence:

Ýmdat DÝLEK, MD

Týp Fakültesi Hastanesi

Maraþ Cad. 65200 Van, TURKEY