Leptin levels in children with insulin dependent diabetes mellitus

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Leptin, a product of the *ob* gene, is a polypeptide hormone produced in adipose tissue that informs the brain about the amount of energy storage of body fat. It has very important effects on neuroendocrine functions and energy expenditure. The aim of our study was to determine leptin levels of children with insulin dependent diabetes mellitus (IDDM), which is known to affect body metabolism, and to investigate the relationship between duration of the disease, insulin dosage, HbA1c levels, body mass index (BMI), serum lipids and IGF-1 levels. Sixteen patients with IDDM (chronological age 13.8 ± 2.6 years) whose HbA1c levels were 10.2 ± 1.9 %, BMI 21.2. ± 2.7 kg/m^2, insulin dosage 0.9 ± 0.4 U/kg/day and duration of the disease 6.7 ± 2.6 years, and 12 healthy controls (13.4 ± 2.6 years) were included in the study. Fasting plasma leptin levels were measured by radioimmunoassay method. The mean plasma leptin levels of the patient and the control groups were 19.1 ± 7.6 ng/ml and 6.1 ± 2.9 ng/ml, respectively, and significant difference was found between the two groups ($p<0.05$). No correlation was found between leptin values and IGF-1, cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride levels, atherogenic index, insulin dosage or HbA1c levels in the patient group. A weak statistical correlation was determined between BMI and leptin levels in the IDDM group ($r=0.28$, $p<0.05$). A positive correlation was also found between leptin levels and the duration of the disease ($r=49$, $p<0.05$). As a result, it seems that leptin levels of children with IDDM differed from the levels of the control group significantly, and that the duration of insulin therapy was responsible for this difference.

Key words: leptin, insulin dependent diabetes mellitus, children.

Leptin, a satiety factor and the product of the *ob* gene, is produced in the adipose tissue and its expression is stimulated by insulin[1-3]. Serum leptin concentrations in humans are shown to be positively correlated with body fat ratio, body mass index (BMI) and serum insulin and cortisol levels[2-5]. Leptin as a satiety factor is thought to reduce food intake, stimulate energy expenditure, inhibit insulin secretion from the pancreas, increase glucose utilization, induce lipolysis and affect triglyceride synthesis[3,5].

We planned to investigate leptin levels and the possible relation with disease duration, insulin dose, HbA1c levels, serum lipids and IGF-1 levels in children with insulin dependent diabetes mellitus (IDDM).

Material and Methods

The local ethics committee approved the study, and informed consent was taken from all parents and the patients.

Sixteen children (8 girls, 8 boys) with IDDM whose ages were between 8-16 years were involved in the study. The control group consisted of 20 age-matched, healthy children. All the cases with IDDM had received mixture insulin (consists of regular and NPH insulins) two times a day and a diabetic diet. In all subjects duration of diabetes, insulin doses and HbA1c levels were measured. The characteristics of the cases are shown in Table I. None of the patients had an acute or chronic illness apart from IDDM, high blood pressure or

Table I. Anthropometric measurements of patient and control groups

	IDDM group	Control group
Chronological age (years)	13.8 ± 2.6	13.4 ± 1.9
Height (cm)	144.9 ± 10.9	151.2 ± 11.3
Weight (kg)	39.6 ± 11.3	41.3 ± 9.8
BMI (kg/m^2)	21.2 ± 2.7	22.3 ± 2.2
Insulin dosage (U/kg/day)	0.9 ± 0.4	-
Duration of disease (years)	6.7 ± 2.6	-
HbA1c levels (%)	10.2 ± 1.9	-

IDDM: insulin dependent diabetes mellitus; BMI: body mass index.

microalbuminuria, and none had been taking medication other than insulin. Neyzi's growth and developmental norms for children were used for the evaluation of heights and weights[6]. Genital examination and pubertal staging were performed according to the staging system of Tanner[7,8]. Bone ages were determined using the atlas of Greulich and Pyle[9].

Serum leptin levels were measured after an overnight fast, between 07:30 and 08:00, before the first insulin administration of the morning. When blood samples were taken, plasma glucose levels were determined by glucose-oxidase method using a glucose analyzer. Leptin concentrations were determined in plasma using a commercially available kit (Rinco Research IM). IGF-1 levels were determined by radioimmunoassay method.

HbA1c levels were measured using a spectrophotometer. Serum levels of total cholesterol, triglycerides and HDL-cholesterol (HDL-C) were measured by Technicon ra-xt device through colorimetric method. LDL-cholesterol (LDL-C) levels were found with Friedewaled's formula. Atherogenic index was calculated by the formula [(Total cholesterol-HDL-cholesterol)/HDL-cholesterol].

Anthropometric data of the study population are given as mean ± SD. Data was analyzed using Student's test, Mann-Whitney U and Pearson's correlation method. A p value below 0.05 was accepted as significant. All analyses were two-tailed and performed with the SPSS Software Version 7.0 Windows.

Results

The mean plasma leptin levels of the patient and control groups were 19.1 ± 7.6 ng/ml and 6.1 ± 2.9 ng/ml, respectively, and significant difference was found between the two groups ($p<0.05$). There was no difference between the two groups for IGF-1 levels ($p>0.05$). Nor was a significant difference found between the two groups regarding total cholesterol, triglycerides, HDL-C and LDL-C levels and atherogenic index (Table II). No correlation was found between leptin values and IGF-1, total cholesterol, triglycerides, HDL-C and LDL-C levels, atherogenic index, insulin dose or HbA1c levels in the patient group. A weak statistical correlation was determined between BMI and leptin levels in the IDDM group ($r=0.28$, $p<0.05$). A positive correlation was found between leptin levels and the duration of the diseases ($r=0.49$, $p<0.01$).

Discussion

The recent isolation and characterization of the obese (*ob*) gene and its gene product leptin has made a great contribution to the pathophysiology of obesity and weight homeostasis[2,3]. Leptin is thought to signal satiety and filling of peripheral fat stores to the brain, acting through specific receptors in the hypothalamus[2-4]. Serum leptin concentrations in humans are known to be positively associated with body fat percentage, BMI and serum insulin concentration[5,10]. In addition, leptin production by adipose tissue seems to be under neuroendocrine control[2]. In humans and animals, factors involved in glucose metabolism are glucose itself, insulin and glucocorticoids, and a variety of cytokines have been found to be potent regulators of leptin expression[4,5]. Especially in the newly diagnosed IDDM patients leptin levels were found to be lower, a finding related to low insulin levels[10-13]. Streptozocin-treated diabetic mice have reduced leptin mRNA levels which are partially restored

Table II. Lipid profile and IGF-1 levels of patient and control groups

	IDDM group	Control group	p values
IGF-1 (ng/ml)	200.1 ± 41.3	224.3 ± 29.2	>0.05
Cholesterol (mg/dl)	191.4 ± 32.1	164.2 ± 37.7	>0.05
LDL-Cholesterol (mg/dl)	105.4 ± 16.4	98.7 ± 20.3	>0.05
HDL-Cholesterol (mg/dl)	50.1 ± 12.6	51.9 ± 10.7	>0.05
Triglycerides (mg/dl)	114.3 ± 21.6	118.0 ± 23.4	>0.05
Atherogenic index	2.8 ± 1.0	2.3 ± 0.98	>0.05

IDDM: insulin dependent diabetes mellitus.

by insulin treatment[11]. Tuominen et al.[13] found fasting plasma leptin levels to be higher in patients with IDDM than in controls. These authors suggested that this difference may be due to chronically high insulin concentrations in diabetic patients. In our study, a positive correlation was found between disease duration and leptin levels. This finding was related to the long duration of insulin treatment. The relation between poor metabolic control and leptin levels has been stated in previous studies[10,12-14], however, leptin levels in patients with IDDM have given contradictory results. The higher leptin levels in patients with IDDM were related to the relatively higher insulin doses given and the subsequent large amount of adipose tissue[11]. However, in our study the higher leptin levels in IDDM patients seems to have been related to the duration of the disease rather than BMIs, as there was no significant difference in terms of BMI between the two groups. In addition, this difference could not be attributed to insulin doses, as our IDDM patients were receiving injections only two times daily rather than intensive therapy. The higher leptin levels could somehow be related to the relatively higher plasma glucose levels in our IDDM patients, due to their poor control of their diabetes. In previous studies in patients with IDDM, a low and deteriorated growth hormone-IGF axis was shown[15-17]. We did not find any difference between the IDDM and control groups in terms of IGF-I levels in our study. The possible correlation between leptin and IGF-1 levels was investigated, as the relation between insulin resistance and IGF-1 levels was known; however, we were unable to show any correlation. Although there are some studies in the literature showing a correlation between serum leptin levels and lipids, we were not able to show such a correlation.

As a result, it seems that leptin levels of children with IDDM differ from the levels of the control group significantly, and that the duration of insulin therapy rather than the amount of adipose tissue creates this difference.

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