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SERUM LEPTIN LEVELS DURING CHILDHOOD AND ADOLESCENCE: RELATIONSHIP WITH AGE, SEX, ADIPOSITY AND PUBERTY*

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SUMMARY: Kırel B, Doğruel N, Akgün N, Kılıç FS, Tekin N, Uçar B. (Department of Pediatrics, Osmangazi University Faculty of Medicine, Eskişehir, Turkey). Serum leptin levels during childhood and adolescence: relationship with age, sex, adiposity and puberty. Turk J Pediatr 1999; 41: 447-455.

We studied serum leptin levels in 189 healthy children to evaluate related factors during childhood and adolescence. Leptin corrrelated with body mass index (BMI), triceps skinfold thickness ($p<0.001$) and body weight ($p<0.01$). Obese children and girls had higher leptin levels than non-obese children and boys, respectively ($p<0.001$). In girls, leptin correlated positively with age, skinfold thickness and BMI ($p<0.001$). In boys, leptin correlated negatively with age ($p<0.001$) and positively with skinfold thickness ($p<0.05$). Prepubertal boys had higher leptin levels than prepubertal girls and pubertal boys ($p<0.05$). Pubertal girls had higher leptin levels than prepubertal girls and pubertal boys ($p<0.001$). Leptin levels in girls were higher at Tanner stages 4 and 5 than at stage 1 ($p<0.001$). In conclusion, serum leptin levels are related with adiposity, have obviously age-related gender differences during childhood and adolescence, and may be involved in the maturation of reproductive capacity. *Key words: childhood, leptin, obesity, puberty.*

In 1994, Zhang et al.[1] identified an obesity gene (ob) exclusively expressed in adipose tissue. Its protein product, leptin, acts as a satiety signal and regulates body-fat mass by affecting energy intake and expenditure at the hypothalamic level[2-7]. Little is known about leptin metabolism. Studies in animals and humans have demonstrated a direct relationship between leptin and adiposity. Obese humans have both higher serum leptin concentrations and higher leptin mRNA levels in adipose tissue than found in normal-weight adults and children. There is a strong positive correlation between serum leptin concentrations and percentage of body fat and body mass index (BMI)[7-13]. Females have higher serum leptin concentrations than males[11-18]. Reproduction and puberty appears to be affected by leptin[19,20]. Leptin is proposed to signal the onset of puberty. In some studies, leptin levels increased in parallel with age during prepubertal

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years and varied at different stages of puberty in both sexes, independent of adiposity, whereas in others, leptin levels did not change during the prepubertal or pubertal period[15,16,21-26]. There is limited data on leptin levels during childhood and adolescence and related factors, or on the role of leptin in growth and development. We therefore studied serum leptin levels, and also evaluated the relationship between leptin and adiposity, sex and puberty in children.

Material and Methods

This study included 189 (94 girls, 95 boys) healthy children admitted to our hospital for a hepatitis B vaccination. Ages ranged from six months to 19.5 years, with a mean of 12.56 ± 0.3 years. No children had clinical evidence of any diseases and were receiving no medication at the time of the study. Children and parents consented to participate in the study. Physical examinations were normal. Pubertal development was classified as defined by Tanner[27].

Body weight (BW), height, triceps skinfold thickness, and waist and hip circumference were measured by the same examiner. Height and BW measurements were compared with standard physical development tables for sex and age[27]. Percentage expected weight (PEW) was calculated as BW/ expected weight for height at 50th percentile x 100. Obesity was defined as weight above 120 percent. Body mass index (BMI) was calculated as BW/height^2. Triceps skinfold thickness was measured at the midarm using skinfold calipers.

Waist circumference was measured at umbilicus and hip circumference at widest horizontal distance around the buttocks. Waist/hip ratio (WHR) was calculated for estimating body fat distribution.

Fasting blood samples were obtained and serums were stored at –70°C until analysis. Serum leptin levels were determined by a commercially available radioimmunoassay (RIA) kit (Linco Research Inc.).

Relationships between leptin levels and anthropometric data were assessed by Pearson Product Moment Coefficient. One-way ANOVA and independent samples t test were used for comparing data of both sexes, of prepubertal (Tanner 1: breast development in girls, genital development in boys) and pubertal Tanner 2-5) children and of different Tanner stages. Data are presented as mean ± SEM.

Results

Clinical data of the children are presented in Table I. For the entire study group, leptin levels strongly correlated with BMI, triceps skinfold thickness and BW ($r=0.34$, $r=0.45$, $p<0.001$ and $r=0.19$, $p<0.01$, respectively), and did not correlate with age, waist and hip circumference or WHR ($p>0.05$).

Table I: Clinical Data of the Children

	Girls	Boys
Age (yr)	12.95 ± 0.43 (n=94)	12.17 ± 0.45 (n=95)
Body weight (kg)	47.8 ± 1.8 (n=90)	47.7 ± 2.0 (n=95)
Height (cm)	148 ± 2.2 (n=92)	148.5 ± 3.0 (n=95)
BMI (kg/m²)	20.85 ± 0.5 (n=89)	20.3 ± 0.44 (n=94)
Skinfold thickness (cm)	1.3 ± 0.06* (n=57)	0.92 ± 0.43 (n=50)
Waist (cm)	64 ± 1.1 (n=60)	65.96 ± 1.3 (n=62)
Hip (cm)	87.4 ± 1.86 (n=60)	83.05 ± 2.0 (n=62)
WHR	0.74 ± 0.01** (n=60)	0.84 ± 0.03 (n=62)
Leptin (ng/ml)	3.95 ± 0.3*** (n=94)	2.43 ± 0.22 (n=94)

Values are expressed as mean ± SEM.

*p<0.05, **p<0.01, ***p<0.001, girls versus boys.

BMI: body mass index; WHR: waist/hip ratio.

Leptin levels were higher in obese children than in non-obese children (4.8 ± 0.5 and 2.8 ± 0.2 ng/ml, respectively) (p<0.001).

Girls had higher leptin levels than boys (p<0.001) (Table I). There was no difference in BMI for girls and boys (p>0.05). Skinfold thickness (p<0.001) and WHR (p<0.01) were significantly different for girls and boys (Table I). In girls, leptin levels positively correlated with age (Fig. 1), skinfold thickness and BMI (r=0.45, r=0.56, r=0.5, p<0.001, respectively) and negatively correlated with WHR (r=–0.26, p<0.05). In boys, leptin negatively correlated with age (r=–0.4, p<0.001) (Fig. 1) and positively correlated with WHR and skinfold thickness (r=0.49, p<0.001 and r=0.33, p<0.05, respectively).

When the effects of puberty were investigated, leptin levels were higher in boys than in girls in prepubertal children (3.16 ± 0.42, 2.02 ± 0.31, p<0.05, respectively). In prepubertal girls, leptin did not correlate with age, BMI, or WHR (p>0.05) but did with skinfold thickness (r=0.98, p<0.001). In prepubertal boys, leptin negatively corelated with age (r=–0.38, p<0.05) but did not correlate with the other anthropometric data (p>0.05).

Pubertal girls had higher leptin levels than prepubertal girls and pubertal boys (4.5 ± 0.3, 2.02 ± 0.3, p<0.001, respectively). Pubertal boys had lower leptin levels than prepubertal boys (1.97 ± 0.24, 3.16 ± 0.42, p<0.05, respectively).

Leptin levels were significantly higher in girls than in boys in pubertal children (4.5 ± 0.3, 1.97 ± 0.24, p<0.001, respectively). When girls and boys in the pubertal group were compared, skinfold thickness (1.47 ± 0.07, 0.96 ± 0.06,

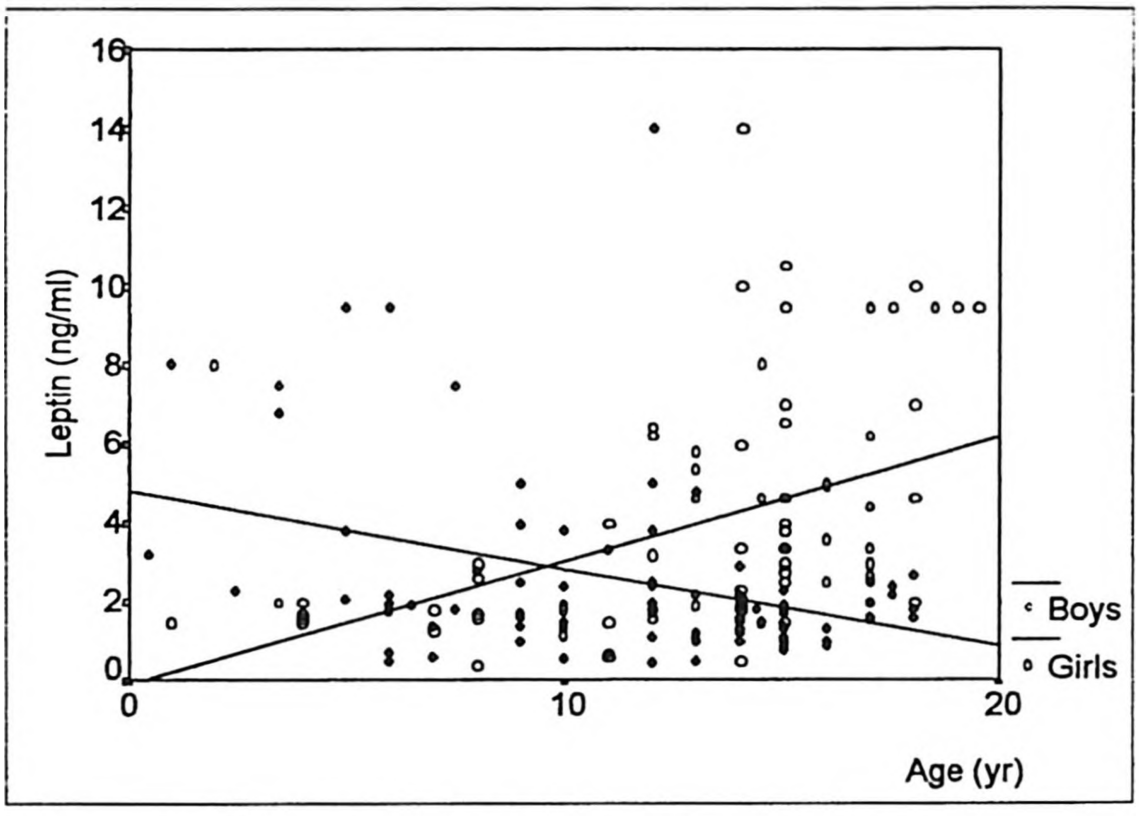

Fig. 1: Relation between age and leptin levels in both sexes.

p<0.05, respectively) and WHR (0.72 ± 0.01, 0.78 ± 0.01, p<0.001, respectively) were different. In pubertal girls, leptin correlated with age, BMI, BW (r=0.42, r=0.42, r=0.48, p<0.001, respectively) and skinfold thickness (r=0.49, p<0.01). In pubertal boys, leptin correlated with BMI (r=0.35, p<0.01), skinfold thickness (r=0.47, p<0.05) and WHR (r=0.54, p<0.001).

For the entire study group, there was no difference in at different Tanner stages (p>0.05). The findings at different Tanner stages for both sexes are shown in Table II. When an analysis was done according to sexes, BMI in girls was significantly different at Tanner stages 3, 4 and 5 than at stage 1 (p<0.0001). Both leptin and skinfold thickness were higher at stages 4 and 5 than at stage 1 (p<0.001) (Fig. 2). BMI in boys was higher at Tanner stage 5 than at stage 1 (p<0.05), but leptin levels and other measurements did not change at different Tanner stages (p>0.05). Although leptin levels at Tanner 5 in boys were slightly higher, as seen in Figure 2, they were not statistically different than in previous stages, and were still lower than at stage 5 in girls (p<0.001).

Discussion

We found serum leptin levels higher in obese children than in those normal-weighted. Leptin also strongly correlated with BMI, skinfold thickness and BW, as described previously in adults and adolescents[7-13]. We attributed the negative

Table II: Adiposity Parameters and Leptin Levels in Different Puberty Stages

Tanner Stage		BMI (kg/m²)	Skinfold thickness (cm)	WHR	Leptin (ng/ml)
1	Girls	16.6 ± 0.4 (n=20)	0.9 ± 0.0 (n=16)	0.8 ± 0.0 (n=15)	2.02 ± 0.3 (n=20)
	Boys	18.7 ± 0.7 (n=36)	0.9 ± 0.0 (n=20)	0.9 ± 0.0 (n=23)	3.2 ± 0.4 (n=36)
2	Girls	20.9 ± 2.3 (n=10)	1.1 ± 0.3 (n=4)	0.8 ± 0.0 (n=4)	2.7 ± 0.6 (n=10)
	Boys	20.3 ± 1.2 (n=15)	1.1 ± 0.6 (n=5)	0.7 ± 0.0 (n=6)	2.4 ± 0.8 (n=15)
3	Girls	20.3 ± 1** (n=14)	1.3 ± 0.3 (n=9)	0.7 ± 0.0 (n=9)	3.7 ± 0.6 (n=14)
	Boys	19.9 ± 1.4 (n=11)	0.8 ± 0.1 (n=7)	0.7 ± 0.0 (n=7)	1.7 ± 0.3 (n=19)
4	Girls	21.3 ± 0.6** (n=25)	1.5 ± 0.4† (n=18)	0.7 ± 0.3 (n=18)	4.6 ± 0.6† (n=27)
	Boys	19.1 ± 0.5 (n=13)	0.7 ± 0.1 (n=11)	0.7 ± 0.1 (n=13)	1.4 ± 0.1 (n=13)
5	Girls	24.2 ± 0.9** (n=20)	1.6 ± 0.4† (n=10)	0.7 ± 0.0 (n=14)	5.5 ± 0.6† (n=23)
	Boys	22.5 ± 0.8* (n=20)	0.9 ± 0.1 (n=7)	0.8 ± 0.0 (n=15)	2 ± 0.1 (n=20)

Values are expressed as mean ± SEM. *p<0.05, Tanner 5 versus Tanner 1 in boys, **p<0.0001, Tanner 3, 4, 5 versus Tanner 1 in girls, †p<0.001, Tanner 4-5 versus Tanner 1 in girls.
BMI: body mass index; WHR: waist/hip ratio.

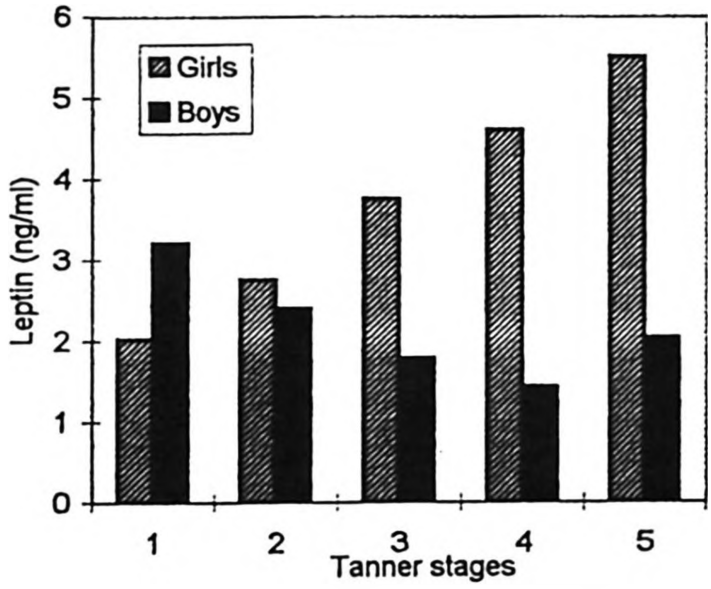

Fig. 2: Leptin levels at different puberty stages in both sexes.

correlation in girls and the positive correlation in boys between leptin and WHR to the existence of different distributions of body-fat stores. This finding also suggests a relationship between serum leptin levels and body-fat content.

The role of leptin in the pathophysiology of human obesity is not yet understood. The ob/ob mouse, which has a genetic leptin deficiency, has obesity and diabetes. Administration of exogenous leptin to these mice caused a decrease in food intake, weight loss, increased caloric expenditure and reversed insulin resistance[1-4]. In contrast, obese humans have higher leptin levels in spite of much more body-fat mass. This finding indicates that they have a decreased

sensivity or resistance to the satiety action of leptin in the brain, possibly at the hypothalamic level via appetite-stimulating hypothalamic neuropeptide Y, which is found to be inhibited by leptin in obese animals[6,8]. It was hypothesized that leptin is delivered to the brain by a saturable transport system. A decreased capacity to transport leptin to the brain via cerebrospinal fluid has already been shown in obese humans despite their having higher leptin concentrations than found in lean individuals. This is another mechanism that may provide an explanation for leptin resistance in obese individuals[28].

In our study, leptin increased with age in girls and decreased with age in boys, as reported by Garcia-Mayor et al.[15], and Blum et al.[29]. These results suggest that leptin metabolism has age-related sexual differences during childhood. Although leptin levels correlated with adiposity parameters in both sexes, we found that girls had higher body fatness in regard to skinfold thickness than boys and higher leptin levels, which may be related to their high body-fat percentage. On the other hand, leptin levels were still found to be higher in women when compared to men with similar body composition. Gender differences in leptin, independent of body fatness, suggest that females have genetic leptin resistance or that there are sex-related differences in leptin metabolism[14,18].

Studies on the reproductive system and puberty in both animals and humans have provided some explanation on gender differences in leptin levels that seem to be related with sex steroids[14,18,30]. Lower leptin levels were found in postmenopausal women than in premenopausal women, indicating that leptin metabolism is related to estrogen and/or progesterone. But postmenopausal women had higher leptin levels than males who were similar in body-fat mass to postmenopausal women[18]. It was also found that testosterone substitution normalized leptin levels in hypogonadal men whose leptin levels were found to be 3-fold higher than normal males with a similar BMI[30]. These results suggest that gender differences in leptin seem to be caused by suppressive effects of androgens on leptin metabolism[18,30].

The onset of puberty requires adequate nutrition and critical body fat stores and BW. Both pathological obesity and malnutrition are associated with delayed puberty[31]. A metabolic signal between adequate energy stores and the neuroendocrine axis is also necessary for the onset of puberty. Recently, in view of that known about the relationship between leptin and adiposity[7-18] and neuroendocrine function[32], it was hypothesized that leptin may be a metabolic signal triggering puberty. Treatment of ob/ob mice, with a genetic leptin deficiency and infertility, with leptin resulted in increased LH levels and ovarian weight in females and increased FSH levels and testicular mass in males, in spite of more weight loss than in pair fed controls. There were stimulation findings of gonadal

function on histologic examination[19]. Chehab et al.[20] gave leptin to normal prepubertal female mice and observed earlier maturation of the reproductive tract and earlier reproduction than controls, indicating that leptin regulates the neuroendocrine system in the hypothalamus, pituitary and ovary.

In prepubertal children, we found that boys had higher leptin levels than girls. Leptin was not related with age in girls. It was negatively correlated with age in boys, and it was only correlated with skinfold thickness in girls, whereas there was no correlation between leptin and anthropometric data in boys. Previously, either higher leptin levels in girls than in boys or similar leptin levels in both sexes in prepubertal children have been reported[13,15,22,29]. The etiology or importance of gender differences in leptin levels is unclear during this period when the effects of sex steroids are absent.

We found that pubertal boys had lower leptin levels than prepubertal boys. But, pubertal girls had higher leptin levels than both prepubertal girls and pubertal boys. These results confirmed the results of previous studies[15,22,29]. In the study Garcia-Mayor et al.[15], leptin levels rose in parallel with BW until 10 years of age, then a striking difference was observed in both sexes. While leptin levels decreased in boys after this age and testesterone, FSH and LH rose, leptin levels progressively rose, followed a rise in FSH and later LH and estradiol in girls during puberty. In another study, leptin levels in boys rose just before the onset of puberty and decreased to approximately baseline values and remained stable for more than two years, while testosterone progressively rose after the initiation of puberty[24]. Clayton et al.[22] reported an inverse relationship between leptin and testosterone levels and testicular volume. These clinical studies suggest that leptin plays a role in the initiation of puberty and also confirm that gender differences may be due to a negative effect of testosterone on leptin metabolism.

In this study, leptin levels in boys did not change at different Tanner stages whereas BMI increased. However, pubertal girls had higher leptin levels at stages 4 and 5 than at stage 1, as reported by Carlsson et al.[21]. The importance of the increase of leptin levels at this stage remains to be determined. Increased leptin levels at this stage may be related with the onset of the menarche, which occurs at midpuberty. During puberty, high leptin levels were found to be associated with a decline in age at menarche. An increase of 1 ng/ml in serum leptin lowered the age at menarche by one month. Similarly, an increase of body fat content wis inversely related to the age at menarche in human females[25], suggesting that leptin is a mediator between gonads and adipose tissue in women.

In conclusion, serum leptin levels are mainly related with adiposity, and there are obvious age-related gender differences during childhood and adolescence.

Leptin may be involved in the maturation of reproductive capacity. Further prospective studies are needed to understand the role of leptin in growth and development during childhood and adolescence and in the reproductive function.

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