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Odwrócenie związanych z płcią różnic w stężeniu leptyny u otyłych dzieci z zaburzoną tolerancją glukozy

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Streszczenie

Wstęp: Stężenia leptyny korelują z wieloma wskaźnikami otyłości, jak również z insulinoopornością. Dotychczas niewiele natomiast wiadomo o regulacji poziomu leptyny u otyłych dzieci z początkowymi fazami zaburzeń metabolizmu glukozy.

Celem pracy było ustalenie wpływu zaburzeń tolerancji glukozy na poziom leptyny u dzieci z otyłością prostą, w zależności od płci.

Materiał i metody: Badania przeprowadzono u 70 otyłych dzieci z zaburzeniami tolerancji glukozy (IGT) i odpowiednio dobranej grupie 70 dzieci z otyłością i prawidłową tolerancją glukozy (NGT). Oznaczono stężenia w surowicy krwi leptyny oraz glukozy i insuliny na czczo i w 120 minucie testu doustnego obciążenia glukozą (OGTT). U badanych dzieci oceniono wybrane parametry antropometryczne.

Wyniki: Stężenie leptyny w surowicy krwi dziewcząt z IGT było znamiennie niższe niż dziewcząt z NGT (odpowiednio: 17,7±6,5 µg/L i 23,1±7,7 µg/L; $p<0.001$). Nie stwierdzono podobnej zależności u chłopców. Analiza statystyczna metodą regresji wielowymiarowej, z uwzględnieniem wieku i stopnia otyłości, wykazała, że u dziewcząt poziom leptyny korelował z poziomem glukozy i insuliny w 120 minucie OGTT (odpowiednio: $r = -0,49$; $p<0,005$ oraz $r = 0,34$; $p<0,05$). U chłopców stwierdzono korelację pomiędzy poziomem leptyny i insuliny w 120 minucie OGTT ($r = 0,36$; $p<0,05$)

Wnioski: Wykazano różnice w regulacji syntezy leptyny u dziewcząt i chłopców z otyłością prostą. U dziewcząt stymulujący efekt działania insuliny na syntezę leptyny jest większy w stanach normoglikemii niż przy występowaniu zaburzeń tolerancji glukozy.

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Słowa kluczowe: *leptyna, zaburzenia tolerancji glukozy, otyłość prosta*

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Reversal of the sex difference in plasma leptin levels in obese children with impaired glucose tolerance

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Abstract

Introduction: Basal leptin level has been demonstrated to correlate positively with many indices of obesity, as well as insulin resistance. However, to date, little is known about regulation of leptin in obese children with incipient glucose metabolic disorders.

Objective: The aim of this study was to define the precise influence of the glucose tolerance status on plasma leptin in obese boys and girls separately.

Material and methods: 70 obese children with impaired glucose tolerance (IGT) and well-matched 70 normal glucose-tolerant (NGT) subjects were examined. Fasting and 2-h post glucose load plasma glucose and insulin levels as well as fasting leptin levels were determined, apart from anthropometric measurements.

Results: Leptin levels were significantly lower in girls with IGT compared to NGT girl (17.7±6.5 μg/L vs. 23.1±7.7 μg/L; p<.001). No such difference was observed in boys. In a multiple regression analysis adjusting for age and adiposity, in the female group plasma glucose and insulin levels 2-h after glucose load were the best predictors of fasting plasma leptin (r = -0.49, p<.005 and r = 0.34, p<.05; respectively). In boys, plasma insulin level 2-h after glucose load was the independent determinant of leptin (r = 0.36, p<.05).

Conclusion: The differences between regulation of leptin synthesis in girls and boys with simple obesity were found. The stimulatory effect of insulin on leptin synthesis was greater in girls with normoglycemia than in girls with impaired glucose tolerance.

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Key words: *leptin, impaired glucose tolerance, simple obesity*

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Introduction

Leptin, the peptide product of the ob gene, was cloned in 1994, but its exact physiological role is still a matter of discussion [1]. It is well-known that for a given body weight, leptin levels are higher in women than in men. Basal leptin level has been demonstrated to correlate positively with many indices of obesity, as well as insulin resistance [2, 3]. It has also been shown that plasma leptin and insulin correlate with each other, possibly because insulin stimulates leptin synthesis and release [4]. A number of epidemiological studies have examined serum leptin concentration in diabetic and non-diabetic subjects [1, 5]. The majority of researchers have found no differences in plasma leptin levels between normal and diabetic adult patients [5]. Most of these studies were not performed in newly diagnosed diabetics, and other variables (such as gender) could have confounded the results. However, to date, little is known about regulation of leptin in obese children with incipient glucose metabolic disorders. Therefore, the aim of this study was to define the precise influence of the glucose tolerance status on plasma leptin in obese boys and girls separately.

Subjects and methods

The study group consisted of 70 obese children and adolescents (body mass index-BMI>97th percentile for age and sex) [6], aged 6-18 y., with impaired glucose tolerance (IGT). The control group comprised 70 obese children with normal glucose tolerance (NGT). The classification was based on World Health Organization criteria using a standard 2-h 1.75 g glucose/kg "ideal" body weight, tolerance test (OGTT). None of the subject was previously diagnosed as having any medical problems other than obesity. Tanner stage was determined by physical examination. Patients were subjected to anthropometric measurements of their height, body weight, waist and hip circumferences, using the standardized technique and devices [6].

BMI, and waist to hip ratio (WHR) were calculated. Since BMI changes with age, the BMI-SD score was also calculated [6]. The study group and controls were well-matched for age, body weight and height, as well as BMI and BMI-SD score. Measurement of body composition was performed by means of bioelectrical impedance (Bioelectrical Impedance Analyzer Tanita, Japan).

Plasma insulin levels were measured using a human insulin-specific radioimmunoassay (Linco Research, St.-Louis, MO, USA). Glucose levels were assessed by automated enzymatic methods (Hitachi 937; Roche). Plasma leptin was determined by using a specific radioimmunoassay (Human Leptin Specific RIA Kit, Linco Research, St.-Louis, MO., USA).

Data that not normally distributed were log-transformed. Comparisons of variables were performed using the Mann-Whitney U- test. Relationships between plasma leptin and independent variables were assessed using the Spearman rank correlation coefficient (r). Multiple linear regression analyses were performed using the log-transformed leptin level as the dependent variable. Differences were considered significant at a p value <0.05.

Results

The clinical and metabolic characteristics of the studied children are summarized in Table 1 according to gender and glucose tolerance status. There was no significant difference in pubertal development between boys and girls of different glucose tolerance status, although girls, on average, were more advanced in pubertal development (data not shown).

The leptin level was significantly higher in NGT girls compared to NGT boys (p<.01). Obese girls with IGT had significantly lower plasma leptin levels than control girls. No such between-group differences were observed in boys.

Spearman rank correlation coefficients between leptin level and selected clinical and biochemical parameters are presented in Table 2.

Table 2. *Spearman rank correlation coefficients between leptin and selected parameters*

Leptin / Parameter	Entire group	Boys	Girls
	r	r	r
Age	0.15	-0.04	0.42***
BMI	0.32***	0.25*	0.43***
Fat mass	0.39***	0.39***	0.42***
Fasting glucose	0.12	0.09	0.15
2-h glucose	0.16	0.21	0.30**
Fasting insulin	0.18*	0.24*	0.27*
2-h insulin	0.19*	0.27*	0.29*

**.01<p<.05 **.001<p<.01 ***p<.001*

Table 3 shows the linear regression analysis controlled for age, gender, Tanner stage, BMI and fat mass. A significant association between female gender and plasma leptin was found: the fat mass, 2-hour OGTT glucose, and 2-hour OGTT insulin were all independent determinants of leptin level. In boys, only the 2-hour OGTT insulin was a significant predictor of plasma leptin.

Discussion

In the present study we investigated the relationship between serum leptin and metabolic parameters such as plasma glucose and insulin across genders in children with impaired glucose tolerance. To the best of our knowledge, this study is the first to investigate such association in obese children.
As expected girls had higher serum leptin levels

Table 1. *Comparison of subjects by gender and glucose tolerance status*

Variable	Boys (n=62)			Girls (n=78)		
	NGT (n=31)	p	IGT (n=31)	NGT (n=39)	p	IGT (n=39)
Age (y)	12.8±2.2	NS	12.8±2.2	11.9±2.5	NS	12.0±2.6
BMI (kg/m^2)	28.4±1.7	NS	28.6±3.5	28.9±4.0	NS	29.1±4.5
SD-BMI	3.1±0.9	NS	3.2±1.4	3.7±1.3	NS	4.0±1.7
% body fat	31.5±6.7	<.05	34.1±6.9	36.0±4.6	NS	37.4±4.9
Fat mass (kg)	23.0±5.7	<.05	25.3±5.8	25.2±8.4	NS	26.6±9.7
WHR	0.97±0.06	NS	0.99±0.06	0.93±0.05	<.05	0.96±0.07
Fasting glucose (mmol/L)	4.9±0.5	NS	4.9±0.6	4.7±0.6	<.01	5.1±0.7
2-h glucose (mmol/L)	6.4±0.8	<.001	8.8±1.3	6.1±0.8	<.001	8.8±1.3
Fasting insulin (pmol/L)*	120.2 (54-291)	NS	111.4 (28- 807)	108.6 (40.5-216)	<.05	157.5 (40-411)
2-h insulin (pmol/L)	456.2 (43-1072)	<.001	695.1 (58-6162)	427.2 (116 -1246)	<.001	1013.7 (159-3259)
Leptin (µg/L)	15.2±7.5	NS	15.8±8.3	23.3±7.7	<.01	17.7±6.5

*The results are expressed as means ± S.D.; * Data are expressed as median and range.*

Table 3 *Regression models with serum leptin (log-transformed) as the dependent variable*

Leptin	Entire group (n=140)	Boys (n=62)	Girls (n=78)						
Parameter	beta	t	p	beta	t	p	beta	t	p
Gender	0.246	3.248	.001	—			—		
Fat mass	0.381	4.891	<.001	0.191	1.469	.147	0.517	5.023	<.001
2-h glucose*	-0.180	-1.993	.048	-0.107	-0.756	.452	-0.489	-3.437	.004
2-h insulin*	0.219	2.391	.018	0.359	2.388	.020	0.342	2.015	.022

**log-transformed variables*

than boys and leptin levels were positively correlated with BMI and fat mass, confirming that the study sample was comparable to other cohorts [2, 3]. According to several previous reports, our data confirm a significant relationship between plasma leptin and insulin levels [2, 7]. It has been recently shown that despite high levels of circulating leptin according to the increased fat mass, leptin seems to fail exerting its effect in both hypothalamus and the pancreatic β-cells [4]. Leptin resistance at the level of pancreatic β-cell may promote hyperinsulinemia in obese patients prone to developing type 2 diabetes. Elevated insulin level facilitates both insulin resistance and further stimulation of leptin production and secretion, which may in turn enhance leptin resistance of the endocrine pancreas by further desensitizing leptin signal transduction pathways and constituting a vicious circle, leading to clinical manifestation of type 2 diabetes [4].

However, in this study statistically significant difference in leptin level was revealed in girls between the IGT group and the NGT group. Moreover, plasma glucose level 2-h post glucose load correlated inversely with leptin level in girls only. Only few studies demonstrated an independent association between plasma leptin and glucose levels in adults [8, 9]. Panarotto et al. [9] found lower leptin level in IGT and type 2-diabetic women, but not in men. It has been suggested that postprandial hyperglycemia such as that observed in IGT state or in the early phase of type 2 diabetes may restrain the stimulatory effect of insulin on leptin synthesis by adipocytes [9]. Lack of this association in males suggests that adipose tissue in girls is more susceptible to in vivo regulation by glucose and insulin than in boys.

Further studies are needed to confirm our findings in a longitudinal prospective and to gain insight into the pathophysiologic mechanism of leptin regulation in both genders.

Conclusion:

The differences between regulation of leptin synthesis in girls and boys with simple obesity were found. The stimulatory effect of insulin on leptin synthesis was greater in girls with normoglycemia than in girls with impaired glucose tolerance.

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