LEPTIN IN CHILDHOOD OBESITY

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Keywords: *obesity, child, leptin*

Abstract: *The latest theories suggest that resistance to leptin is the first link of the metabolic changes in obesity. In adults, leptin levels predict the onset of the metabolic syndrome (MS) and its components, and in those with metabolic syndrome the worsening of the MS. The objectives of the study was to determine the leptin levels in overweight children and establish correlation of the leptin with changes in glucidic and lipid metabolism present in child obesity, with metabolic syndrome and the influence of lifestyle on leptinemia. The study was performed on 33 subjects, overweight and obese children aged between 5-16 years. The nutritional status was assessed by BMI and laboratory test needed to diagnose MS according to IDF criteria. Fasting leptin levels were determined. Leptin levels in obese were 82,74 ng/ml, in overweight 48,81ng/ml. No statistical significant correlations were found with glucidic and lipidic metabolism changes or with MS. Negative correlation r=-0,58 were between leptin level and physical activity in boys. Leptinemia positively correlates with the degree of the obesity (BMI) , with the degree of abdominal obesity (WC) and negatively with regular physical activity in boys.*

Cuvinte cheie: *obezitate, copil, leptină*

Rezumat: *Cele mai recente teorii sugerează rezistenţa la leptină ca fiind prima verigă a modificărilor metabolice din obezitate. La adulţi, nivelul leptinei prezice apariţia sindromului metabolic şi a componentelor sale, iar la cei cu sindrom metabolic agravarea ei. Obiectivele studiului au fost determinarea nivelului leptinei la copiii supraponderali şi obezi şi stabilirea unor corelaţii ale leptinei cu modificări ale metabolismului glucidic şi lipidic prezente în obezitatea copilului, cu sindromul metabolic şi stabilirea influenţei stilului de viaţă asupra leptinemiei. Studiul a cuprins 33 subiecţi, copii supraponderali şi obezi cu vârsta între 5-16 ani. Statusul nutriţional a fost apreciat pe baza indicelui de masă corporală. Au fost efectuate examinări paraclinice necesare diagnosticului sindromului metabolic, pe baza criteriilor IDF. Leptinemia a jeun a fost de asemenea determinată. Nivelul leptinemiei a fost 82,74 ng/ml la obezi şi 48,81ng/ml la supraponderali. Nu au fost corelaţii semnificative ale leptinemiei cu parametrii metabolismului glucidic, lipidic sau sindromul metabolic. Corelaţie negativă r=-0,58 a fost cu activitatea fizică la băieţi. Leptinemia s-a corelat pozitiv cu gradul obezităţii (IMC), cu gradul obezităţii abdominale (CA) şi negativ cu activitatea fizică regulată la băieţi.*

INTRODUCTION

The accidental discovery of leptin in 1994 gave researchers great hope that they could elucidate the complex mechanisms underlying the pathophysiology of obesity and its treatment. This discovery has led to the reconsideration of the concept of body fat: no longer an energy storage organ, but an active endocrine organ.(1) The level of the leptin secreted by the adipose tissue and other tissues is influenced by gender, age, Tanner stage, the intensity of regular physical activity.

The latest theories suggest that resistance to leptin is the first link of the metabolic changes in obesity, due to fat accumulation in various tissues, fatty acids oxidation reduction, insulin resistance being a response to these changes. Epidemiological studies suggest a close association of hyperleptinemia with the metabolic syndrome and an increased risk of cardiovascular morbidity and mortality.(2) Hypertriglyceridemia contributes to leptin resistance by inhibiting leptin transport through the hematoencephalic barrier.(3) Chronic hyperleptinemia results in high blood pressure through "selective leptin resistance" at the level of the CNS and through the changes of the leptin action in the kidney.(2)

In adults, leptin levels predict the onset of the metabolic syndrome and its components (obesity, glucose intolerance, insulin resistance, hypertension), and in those with metabolic syndrome the worsening of the MS.(4,5)

PURPOSE

The objectives of the study was to determine the leptin levels based on the nutritional status, age, gender, to establish the influence of overweight and abdominal obesity on the level of leptinemia, to establish correlations between leptinemia and changes in glucidic and lipid metabolism present in child obesity and the influence of lifestyle (physical activity, inactivity, sleep) on leptinemia.

METHODS

We performed a cross sectional study in a group of 33 subjects, children aged 5-16 years. The study was performed during the period 2005-2010. The parents of the children gave their informed consent to use the data in this study. We obtained the approval of the medical ethics committee of the Pediatric Emergency County Hospital.

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The children were measured: weight, height, waist circumference (WC) and blood pressure (BP). We calculated the body mass index (BMI). The laboratory tests performed were: fasting glucose, fasting insulin, oral glucose tolerance test, total cholesterol, HDL cholesterol, triglycerides (TG) and fasting leptin levels. Only those with idiopathic obesity were included in this study, we excluded the children with obesity due to other causes and children with diseases which may influence the laboratory tests.

We defined the metabolic syndrome based on IDF criteria (6) (mentioned in table).We considered a MS diagnosis if at least 3 of 5 criteria were present.(7)

Table no. 1. Metabolic syndrome in children-definition criteria

Metabolic syndrome in children-definition criteria					
Age	WC	TG	HDL	BP	glucose
<10 years	>p90	>p90 and/or ≥150mg/dl	<p10 and/or <40 mg/dl	>p90	gl ≥100mg/dl* and/or OGTT≥200mg/dl* and/or HOMA-IR>2,5**
10-16 years	>p90	≥150mg/dl	<40mg/dl	BPs≥130mm Hg BPd≥85mmHg	gl≥100mg/dl and/or OGTT≥200mg/dl and/or HOMA-IR>2,5
>16 years	Girls≥80cm Boys≥94 cm	≥150mg/dl	Girls<50mg/dl Boys<40mg/dl	BPs≥130mm Hg BPd≥85mmHg	gl ≥100mg/dl
WC: waist circumference; HDL: high-density lipoprotein cholesterol; BP: blood pressure BPs systolic BPd diastolic; gl: fasting glucose; OGTT: oral glucose tolerance test *(8) **(9)					

RESULTS

In the study group, there were no significant differences between the ages of the subjects with different nutritional statuses and between the two genders. Groups aged below 10 years old, 10-16 years old, were similar in terms of BMI/BMIp50 and CA/CAp50uk. There were significant differences between overweight and obese patients in terms of BMI and BMI compared against BMI corresponding to the 50th percentile, but not in terms of CA and CA compared against CA corresponding to the 50th percentile, as there was only one subject without abdominal obesity. Gender subgroups within the age groups were similar in terms of BMI/BMIp50, CA/CAp50uk. There were no significant differences in terms of fasting insulinemia and HOMA IR in overweight patients when compared to obese patients. The differences between groups of girls and boys in the age group 10-16 years were in terms of fasting insulinemia and HOMA IR.

Table no. 2. The mean values, the standard deviation, the minimum and maximum values of leptin on BMI groups, abdominal obesity, MS and gender

	n	Leptin level
Overweight (OW)	13	48,81±29,05 (23,30-112,90)
Obese (OB)	20	82,74±64,31 (6,4-277)
OW+OB	33	70,70±56,33 (6,4-277)
OW vs OB p=0,05		
Girls	15	76,68±17,05 (6,4-277)
Boys	18	63,25±10,82 (14,5-190,4)
G vs B p=0,51		
WC<90	1	-
WC≥90	32	71,73±52,34 (14,50-277)
MS present	17	80,92±61,19 (14,5-277)
MS absent	16	58,46±48,77 (6,4-190,4)
p=0,16		

The average level of leptin was significantly higher in obese patients compared to overweight patients, with no significant differences between girls and boys or between patients with MS and those without MS. With only one subject without abdominal obesity, we could not compare the mean values of leptinemia in patients with and in patients without abdominal obesity.

Table no. 3. Mean leptin values and the Spearman correlation coefficient between leptin with age, by age and gender groups

	<10 years n=15	10-16 years n=18
Leptin	70,38±44,61 (14,5-190,4)	75,16±65,29 (14,8-277)
	<10 years vs 10-16 years p=0,81	
correlation coefficient r=-0,14 p=0,42		
Girls	<10 years n=5	10-16 years n=10
Leptin	78,14±39,72 (21,5-120,2)	91,15±80,51 (14,8-277)
	G < 10 years vs 10-16 years p=0,70	
correlation coefficient leptin-age in girls r=-0,14 p=0,60		
Boys	<10 years n=10	10-16 years n=8
Leptin	66,5±48,42 (14,5-190,4)	59,18±45,49 (23,3-145,9)
	B <10 years vs 10-16 years p=0,74	
correlation coefficient leptin-age in boys r=-0,18 p=0,45		
	<10 years	10-16 years
Leptin	G vs B p=0,63	G vs B p=0,35

We found no correlations between leptinemia and age, in neither boys nor girls, as the mean values of leptinemia in the age group 10-16 years was higher in girls and lower in boys than those in the age group below 10 years old, but with no statistically significant differences.

Table no. 4. The mean values, the standard deviation, the minimum and maximum values of leptin on BMI and gender groups

OW		OB	
48,81±29,05 (23,30-112,90)		82,74±64,31 (6,40-277)	
p=0,05			
Girls n=6	Boys n=7	Girls n=8	Boys n=12
62,40±34,43 (23,9-122,9)	37,5±20,04 (23,3-76,7)	92,66±84,03 (6,4-277)	76,12±50,31 (14,5-190,4)
p=0,20		p=0,62	
Girls OW vs OB p=0,38		Boys OW vs OB p=0,03	

There were significant differences between the mean values of leptin in overweight and obese patients, and these differences were notable in boys, but not in girls. In overweight and obese patients there were no leptinemia differences between the two genders.

Figure no. 1. Correlation between leptin and BMI

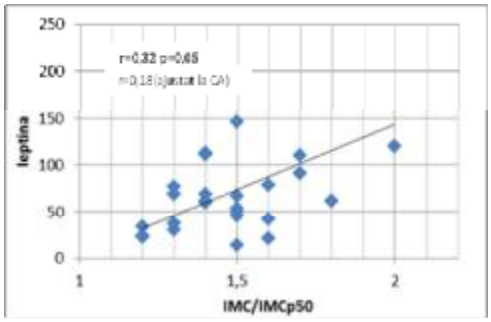
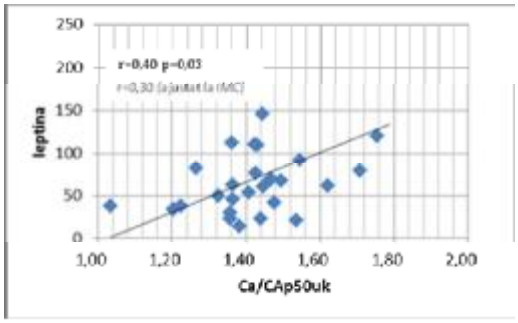


Figure no. 2. Correlation between leptin and WC



Leptin correlated with BMI and waist circumference, both compared against the appropriate 50th percentile.

Table no. 5. The mean values, the standard deviation, the minimum and maximum values of leptin between the BMI, gender groups in those with and those without MS

MS present n=17		MS absent n=16	
81,46±64,03(6,4-277)		56,48±42,94 (14,8-190,4)	
p=0,16			
Girls n=11	Boys n=6	Girls n=4	Boys n=12
80,31±74,52 (6,4-277)	83,56±44,75 (14,5-145,9)	66,67±40,87 (14,8-112,9)	53,09±44,12 (23,3-190,4)
Girls p=0,89		Boys p=0,09	
OW n=5	OB n=11	OW n=6	OB n=9
55,16±23,09 (23,9-76,7)	93,36±76,45 (6,4-277)	43,53±34,46 (23,3-112,9)	69,75±46,62 (42,1-190,4)
OW MS present vs MS absent p=0,52		OB MS present vs MS absent p=0,46	

Leptinemia in those with MS was higher than in those without MS, but there were no statistically significant differences, valid differences within the gender groups.

Table no. 6. The Spearman correlation coefficient between leptin with glucose and lipid metabolism parameters

	fasting insulin	HOMA IR	TG	HDL colesterol	LDL colesterol
leptin	0,06	0,05	-0,10	-0,02	0,21
p	NS	NS	NS	NS	NS
		NS=no statistical significant			

Leptin did not correlate with fasting insulinemia, HOMA IR, TG, HDL cholesterol or LDL cholesterol.

There were no statistically significant differences between the mean values of leptin in those with and those without elements of MS. Leptinemia did not correlate with the number of MS elements present.

Table no. 7. The mean values, the standard deviation, the minimum value, the maximum value of leptin in the presence / absence of the MS elements

component of the MS	**present**	**n**	**Leptin** mean±SD (min-max)	
Fasting glycemia>100mg/dl	yes	11	85,09±74,38(14,5-277)	p=0,49
	no	22	61,48±43,08(6,4-190,4)	
HOMA IR ≥2,5	yes	16	68,93±37,95(21,5-145,9)	p=0,53
	no	17	73,60±67,98(14,5-277)	
Glucidic metabolism*	yes	19	77,36±61,35(14,5-277)	p=0,30
	no	14	58,48±46,22(6,4-190,4)	
TG**	yes	14	62,88±51,34(6,4-190,4)	p=0,48
	no	19	74,12±51,21(23,3-277)	
HDL cholesterol***	yes	9	47,73±25,31(6,4-68,9)	p=0,34
	no	24	76,63±62,45(14,5-277)	
BP****	yes	10	91,27±75,95(6,4-277)	p=0,29
	no	23	59,43±32,66(14,80-112,9)	
correlation coefficient leptin-number of MS elements				r=0,22 p=0,22

*subjects that fulfil MS glucidic metabolism criteria
**TG<10 years >p75 or ≥150mg/dl, ≥10 years ≥150mg/dl
***HDL<10 years under p10, ≥10 years <40mg/dl
****BP <10 years over p90, ≥10 years SBP≥130 and/or DBP≥85mmHg

Table no. 7. Spearman correlation coefficient between leptin and physical activity, sedentary activities and hours of sleep per night

		Physical activity	Sedentary activities	Screen hours	Hours of sleep per night
Leptin	r	-0,165	-0,054	-0,038	0,043
	p	0,368	0,767	0,835	0,815
	n	33	33	33	33
correlation coefficient leptin-physical activity by gender boys r=0,30 p=0,26 Girls r=-0,58 p=0,01					

Leptin correlated with physical activity only in boys; sedentary activities, screen hours or the hours of sleep per night did not correlate with leptin.

DISCUSSIONS

Leptin levels correlated moderately with the degree of obesity, but the intensity of the correlation decreases if we take into account waist circumference; mean values were significantly higher in obese patients than in overweight patients, and the relevant studies in the field show a correlation between leptin, body mass index and the amount of adipose tissue.(10-12)

The intensity of the correlation between leptin and abdominal circumference varies from weak to moderate /good in different studies; in our group, the correlation was good, r = 0.40, and statistically significant, better than the correlation with the degree of obesity; the intensity of the correlation was also maintained after the body mass index adjustment.(11,13)

Leptin levels correlate with changes in body weight, but the increase of leptin with age, especially before puberty, leads to a significant increase of leptin in overweight patients who maintain their overweight level, and an insignificant decrease of leptin in overweight patients who experience a significant weight loss, explained by the onset of puberty.(10)

Serum concentrations of leptin in adults were found to be higher in women than in men, in children they are dependent on age and Tanner stage, and play a part in the onset of puberty. Within our group, we did not find any correlations with age, or significant differences of leptin levels between girls and boys in the complete group, nor on age groups, although most studies have shown these differences.(12,14,15) The large age range and lack of consideration of the Tanner stage, lack of information on changes in previous body weight could account for our failure to find such correlations. Correlations with age appear to be better in the case of girls, while in boys the correlations appear to be better with the Tanner stage; Koebenick found differences in leptin levels between the two genders only after adjusting it to age, Tanner stage, and the percentage of adipose tissue.(16)

There is a distinct trend of leptinemia in girls compared to boys depending on the Tanner; in girls it increases steadily in parallel with the increase of physiological adiposity, in boys it initially increases until it reaches Tanner stage 2 (median age 12 years), and then it decreases.(17) These differences of leptinemia evolution between the two genders could explain the higher mean values in girls in the age group 10-16 years as compared to those in girls in the age group below 10 years, and the lower values in boys of the same two age groups.

Positive weak / moderate correlation was also described between leptin, insulinemia and HOMA IR (11-14;16); overweight and obese patients in our study group showed no correlation between leptin, insulinemia and HOMA IR. Leptin correlates better with HOMA IR in girls compared to boys.(14) Within our study group, although there were statistically significant differences between BMI in overweight and obese patients, the degree of obesity was not as high as in other studies and there were no significant differences between insulinemia and HOMA IR between the two subgroups. The subgroups were not significantly statistically different from the point of view of insulin resistance, which may account for our failure to detect any differences in terms of leptin.

Changes in leptin correlate with IR and insulin changes (but not with acute changes of insulinemia (16))when obesity decreases, but after adjustment to age, gender, pubertal stage, and BMI, the only correlation that remains is with insulinemia (11)

Regarding the correlation of leptin with lipid metabolism parameters, the results are not consistent in the literature, as some authors show a correlation with TG, LDL and HDL cholesterol, and others only with LDL cholesterol, while all these correlations are weak correlations. In our study group leptin did not correlate with any lipid metabolism parameters, as well as in the case of Reinhr after adjustment to age, sex, Tanner stage, BMI.(11-13)

Mean leptin levels were higher in patients with MS, in both girls and boys, in obese and overweight patients, but were not statistically significantly different. The number of MS components present did not correlate with leptin levels either. The presence of no MS element determined a significant increase of leptinemia. Studies in children are limited, and epidemiological studies in adults have shown a close link between hyperleptimenia and MS, as leptinemia level predicts the worsening of the MS.(2,4)

The level of regular physical activity in adults may be an important determinant of leptin levels, independently of the individual's body fat percentage. In children, the studies had mixed results, reporting positive correlation, negative or zero correlation, or differentiated by gender. In girls, physical activity correlates with leptin, independently of the pubertal status and adiposity, but this is not the case in boys(17). Surprisingly, we found a good negative correlation between physical activity and leptimenia in boys, but not in girls, nor in the group as a whole. Sedentary life, the number of hours of sleep per night, the habit of feeding in front of the television did not correlate with leptin.

The large number of variables that are supposed to influence or that correlate with leptinemia, the relatively small size of the study group, which did not allow us to divide it on different subgroups depending on a larger number of variables (age, gender, Tanner stage, nutritional status) that would still be statistically interpretable, have greatly limited our study.

CONCLUSIONS

Leptinemia positively correlates with the degree of the obesity (BMI), with the degree of abdominal obesity (WC) and negatively with regular physical activity in boys. There are no differences in leptinimia between the two genders. Leptin did not correlate with insulinemia, HOMA IR, triglyceridemia, HDL cholesterol, LDL cholesterol. Leptin did not correlate with the metabolic syndrome in children, or with its elements.

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