Metabolic Syndrome and Serum Leptin Levels in Erbil Population

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ABSTRACT

Background and Objectives: Metabolic syndrome is a potent risk factor for cardiovascular diseases (CVDs), has not been adequately explored in Erbil individuals and its relation to leptin hormone. The present study aim to evaluate such a relationship between serum leptin and metabolic syndrome in Erbil individuals.

Methods: Samples collection were carried out in Razgary teaching hospital, 45 cases with metabolic syndrome and 30 healthy control subjects, anthropometric variables measurements (blood pressure, body weight, body height, body mass index) and biochemical tests: fasting, serum glucose, serum triglycerides, high-density lipoprotein cholesterol and serum leptin were obtained from the study samples.

Results: Serum leptin levels were significantly higher in females in comparison to the males in metabolic syndromes group (with median 53.6 Vs 23.8 ng/dl with P value < 0.05) with also present statistical significant difference in leptin between metabolic syndrome group and control group in both males and females. No important association between serum leptin and each of selected criteria of metabolic syndrome. The observed case-control difference in serum leptin is mainly attributed to gender and body mass index (BMI) differences and not a function of metabolic syndrome itself.

Conclusions: Among subjects with metabolic syndrome, only age , gender and body mass index were important in determining the magnitude of serum leptin among cases groups.

Key words: Leptin ; Metabolic syndrome; body mass index.

INTRODUCTION:

Metabolic syndrome is characterized by a clustering of metabolic abnormalities which lead to increased cardiovascular disease and all-causes mortality.The five generally accepted features of metabolic syndrome are obesity, insulin resistance ,dyslipidemia (including increased triglycerides ,and decreased high density lipoprotein cholesterol (HDL-cholesterol), impaired glucose tolerance, and hypertention[1]. Obesity has a central role in metabolic syndrome[2].Recent studies suggest that this syndrome may also occur in children[3]. Leptin is a peptide produced by differentiated adipocyte [4].It is thought to be a key hormone in the regulation of body fat stores. This peptide controls energy metabolism at the level of hypothalamus by supporting food intake and stimulating energy expenditure[4] .The relationship between serum leptin and body mass index (BMI) has been well established [5].Leptin is also proposed to be associated with insulin resistance and diabetes in human [6].However, potential relationship between metabolic syndrome and leptin has not been sufficiently addressed in previous studies.

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SUBJECTS AND METHODS:

Two groups of subjects were studied (metabolic syndrome group and healthy control group) and their clinical and biochemical characteristics are indicated in Table(1).All subjects were seen in Razgary teaching hospital after overnight fasting, blood samples were obtained for determination of serum, leptin (was measured by a commercial ELISA Kit Diagnostics Biochem Canada Inc.),glucose and lipid profile (were measured through enzymetic colorimetric assays. Anthropometric variables includes body weight, body height, body mass index was calculated as the ratio of body weight to body height sequer expressed as K/ m^2 , waist circumference was measured, blood pressure also was measured. Diagnosis of metabolic syndrome was established when three or more of the following was presented: fasting serum, glucose level equal or greater then 110 mg/dl, triglycerides level more than 150 mg/dl, HDL-cholesterol less than 40 mg/dl for males and less than 50 mg/dl for females, blood pressure equal or more than 130 / 85 mm Hg, males waist circumference more than 102 cm and for female more than 88 cm.[7]

Statistical analysis: Data were analyzed using SPSS13 computer software. An expert statistical advice was sought for. The difference in median serum leptin (quantitative non-normally distributed variable) between 2 groups was assessed by non-parametric test (Mann-Whitney). The statistical significance, strength and direction of linear correlation between 2 quantitative variables (one of which being non-normally distributed variable) was assessed by Spearman rank linear correlation coefficient. P value less than 0.05 was considered statistically significant. Multiple linear regression model was used to study the independent and net effect of selected explanatory (independent) variables on serum leptin as a response (outcome) variable. The area under the Receiver Operating Characteristics (ROC) curve gives an idea about the usefulness of the test and helps in comparing it to other tests. The closer the area to one (ideal test) the more valid it is and them more useful it is in differentiating between cases and non-cases[8].

RESULT:

The results were based on the analysis of 30 healthy controls and 45 cases with metabolic syndrome. Males constituted 50% of healthy controls and 13.3% of case group, (Table 1). The mean age was obviously lower among healthy controls (32.6+/-8.4 years) compared to case group (51+/-10.9 years), the mean BMI was also obviously lower among healthy controls (23.8+/-1.4 Kg/m^2) than that of case group (35.1+/-6 Kg/m^2), the systolic and diastolic blood pressure, fasting plasma glucose and selected blood lipid measurements were also recorded for both study groups, (Table 2). As shown in (Table 3), five criteria of metabolic syndrome were analyzed, these include low Serum HDL-C (<50 mg/dl in females and <40 mg/dl in males), high fasting plasma glucose (≥110 mg/dl),BMI (≥ 30 Kg/m^2), high blood pressure and high Serum TG (≥ 150 mg/dl), low serum HDL-C was the most frequently prevalent criteria in both study groups, while high serum TG was the least prevalent criterion, being positive in 26.7% of case group. About three quarters of healthy controls (73.3%) had only one positive criterion of metabolic syndrome. The highest proportion of case group (60%) had 4 positive criteria, (Table 4). The ROC analysis showed that BMI was the strongest variable in the context of differentiating cases with metabolic syndrome and healthy controls in both males and females group. Fasting serum plasma glucose and, both systolic and diastolic blood pressure ranked second in importance. Serum leptin ranked third in importance in the context of case-control comparison. The remaining blood lipid parameters were of less importance, (Table 5). The median serum leptin was obviously

higher in females (17 ng/ml) compared to males (10 ng/ml) in healthy controls, but the difference failed to reach the level of statistical significance, a similar and statistically significant difference was also observed in cases with metabolic syndrome, (Table 6). The median serum leptin was consistently and significantly higher among cases with metabolic syndrome than control group in both males and females , (Table 7). When adjusting for gender and BMI the case-control differences in serum leptin were almost cancelled as revealed by the small and statistically insignificant partial regression coefficient. The BMI was the most important independent variable in deciding serum leptin after adjusting for gender and cases-control group membership. For each one Kg/m^2 increase in BMI the serum leptin is significantly increased by a mean of 3.9 ng/ml. Being a male is associated with a significantly lower serum leptin by 19.2 ng/ml compared to females after adjusting for BMI and group membership. The regression model was statistically significant and able to explain 46% of observed variation in serum leptin, (Table 8). Among cases with metabolic syndrome there were no important or statistically significant association between serum leptin and each of selected criteria of metabolic syndrome, (Table 9). Only BMI had a moderately strong and statistically significant linear correlation with serum leptin. The remaining variables had either a weak or statistically nonsignificant linear correlation with serum, (Table 10). Among subjects with metabolic syndrome, The age, gender and BMI were the most important independent variables in explaining the magnitude of serum leptin after adjusting for the variables related to metabolic syndrome included in regression model. The model was statistically significant and able to explain 40% of observed variation in serum leptin, (Table 11).

Table 1: Case-control comparison according to sex.

	Healthy controls		Cases (Metabolic syndrome)	
Gender	**N**	**%**	**N**	**%**
Females	15	50	39	86.7
Males	15	50	6	13.3
Total	30	100	45	100

Table 2: Description of the 2 study samples by selected variables.

	Healthy controls (n=30)	Cases (Metabolic syndrome) (n=45)
Age in years		
Range	(21 - 51)	(28 - 70)
Mean+/-SD	32.6+/-8.4	51+/-10.9
BMI (Kg/m^2)		
Range	(19 - 26)	(26.8 - 53.3)
Mean+/-SD	23.8+/-1.4	35.1+/-6
Fasting serum glucose (mg/dl)		
Range	(75 - 110)	(85 - 327)
Mean+/-SD	94.2+/-10.5	159.2+/-57.2
Serum total cholesterol (mg/dl)		
Range	(110 - 210)	(99 - 217)
Mean+/-SD	166.1+/-29.4	169.9+/-26.4
Serum TG (mg/dl)		
Range	(64 - 170)	(40 - 243)
Mean+/-SD	106.5+/-26.4	116+/-54.4
Serum HDL (mg/dl)		
Range	(30 - 55)	(19 - 47)
Mean+/-SD	38.9+/-7	31+/-6.6
Serum LDL (mg/dl)		
Range	(50 - 144)	(39 - 171)
Mean+/-SD	111.8+/-24.1	114.7+/-27.6
Systolic blood pressure (mmHg)		
Range	(110 - 120)	(120 - 180)
Mean+/-SD	116.8+/-4.3	143.8+/-17
Diastolic blood pressure (mmHg)		
Range	(70 - 80)	(80 - 110)
Mean+/-SD	77.7+/-3.7	90.7+/-9.1

Table 3: The case-control difference in positivity rate of selected criteria of metabolic syndrome.

	Healthy controls (n=30)		Cases (Metabolic syndrome) (n=45)	
Positive criteria for metabolic syndrome	**N**	**%**	**N**	**%**
Low Serum HDL (<50 mg/dl in females and <40 mg/dl in males)	18	60	44	97.8
High Fasting serum glucose (≥110 mg/dl)	2	6.7	41	91.1
Obese BMI (≥ 30 Kg/m^2)	0	0	41	91.1
High blood pressure	0	0	38	84.4
High Serum TG (≥ 150 mg/dl)	2	6.7	12	26.7

Table 4: The case-control difference in count of positive criteria for metabolic syndrome.

Count of positive criteria for metabolic syndrome	Healthy controls		Cases (Metabolic syndrome)	
	N	**%**	**N**	**%**
0	8	26.7	0	0
1	22	73.3	0	0
3	0	0	11	24.4
4	0	0	27	60
5	0	0	7	15.6
Total	30	100	45	100

Table 5: The ROC analysis comparing the area under the curve for selected variables when used to differentiate between metabolic syndrome and healthy controls stratified by gender.

	Female		Male	
	ROC area	**P**	**ROC area**	**P**
BMI (Kg/m^2)	1	<0.001	1	<0.001
Fasting serum glucose (mg/dl)	0.936	<0.001	1	<0.001
Systolic blood pressure (mmHg)	0.954	<0.001	0.9	0.005
Diastolic blood pressure (mmHg)	0.887	<0.001	0.9	0.005
Serum Leptin (ng/ml)	0.8	0.001	0.933	0.002
Serum total cholesterol (mg/dl)	0.536	0.69[NS]	0.444	0.7[NS]
Serum TG (mg/dl)	0.421	0.37[NS]	0.811	0.029
Serum LDL (mg/dl)	0.537	0.68[NS]	0.406	0.51[NS]
Serum HDL (mg/dl)	0.787	0.001	0.8	0.036

Table 6: The gender difference in median serum leptin stratified by study group.

	Serum Leptin (ng/ml)		P (Mann-Whitney)
	Female	Male	
Healthy controls			**0.15[NS]**
Range	(2.5 - 55.3)	(4.8 - 18.5)	
Median	17	10	
Interquartile range	(6 - 48.5)	(6.9 - 17.5)	
N	15	15	
			0.042
Cases (Metabolic syndrome)			
Range	(12.1 - 175.7)	(12.3 - 65)	
Median	53.6	23.8	
Interquartile range	(32.1 - 133)	(18.2 - 49.9)	
N	39	6	

Table 7: The case-control difference in median serum leptin stratified by gender.

	Serum Leptin (ng/ml)		P (Mann-Whitney)
	Healthy controls	Cases (Metabolic syndrome)	
Female			**0.001**
Range	(2.5 - 55.3)	(12.1 - 175.7)	
Median	17	53.6	
Interquartile range	(6 - 48.5)	(32.1 - 133)	
N	15	39	
Male			**0.002**
Range	(4.8 - 18.5)	(12.3 - 65)	
Median	10	23.8	
Interquartile range	(6.9 - 17.5)	(18.2 - 49.9)	
N	15	6	

Table 8: Multiple linear regression model with serum leptin as the dependent (response) variable and gender, BMI and group membership as the explanatory (independent) variables.

	Serum Leptin (ng/ml)		
	Unstandardized partial regression coefficient	P	Standardized partial regression coefficient
Cases with metabolic syndrome compared to healthy controls	-0.9	0.95[NS]	-0.009
Male gender compared to female	-19.2	0.07[NS]	-0.179
BMI (Kg/m^2)	3.9	<0.001	0.593

P (Model)<0.001
R^2=0.46

Table 9: The median serum leptin by selected variables among subjects with metabolic syndrome.

	Serum Leptin (ng/ml)				P (Mann-Whitney)
	Range	Median	Interquar-tile range	N	
High blood pressure (systolic ≥130 and/or diastolic≥85 mmHg)					
Negative	(12.3 - 175.7)	23.2	(22 - 57.1)	7	0.19[NS]
Positive	(12.1 - 170)	53.4	(30.3 - 115.8)	38	
High Fasting serum glucose (≥110 mg/dl)					
Negative	(38.5 - 160.2)	104.5	(42.3 - 159)	4	0.23[NS]
Positive	(12.1 - 175.7)	52.3	(23.5 - 104)	41	
High Serum TG (≥ 150 mg/dl)					
Negative	(12.3 - 175.7)	52.3	(24.1 - 134)	33	0.77[NS]
Positive	(12.1 - 160.7)	53.7	(24 - 96.3)	12	
Low Serum HDL-C (<50 mg/dl in females and <40 mg/dl in males)					
Negative	(65 - 65)	65	(65 - 65)	1	0.64[NS]
Positive	(12.1 - 175.7)	52.8	(24 - 108.9)	44	
Obese BMI (≥ 30 Kg/m^2)					
Negative	(23.8 - 53.2)	34.7	(24 - 51.1)	4	0.27[NS]
Positive	(12.1 - 175.7)	53.6	(24.1 - 121.5)	41	

Table 10: The linear correlation coefficient between serum leptin and selected variables among cases group with metabolic syndrome.

	Serum Leptin
BMI	r=0.618 P<0.001
Age in years	r=0.3 P=0.045
Serum LDL-C	r=0.311 P=0.038
Serum TG	r=-0.256 P=0.09[NS]
Serum total cholesterol	r=0.114 P=0.46[NS]
Fasting serum glucose	r=-0.113 P=0.46[NS]
Systolic blood pressure	r=0.084 P=0.58[NS]
Diastolic blood pressure	r=-0.013 P=0.93[NS]
Serum HDL-C	r=-0.09 P=0.56[NS]

Table 11: Multiple linear regression model with serum leptin as the dependent (response) variable and gender, BMI, age and selected variables related to metabolic syndrome as the explanatory (independent) variables among cases group.

	Serum Leptin (ng/ml)		
	Unstandardized partial regression coefficient	P	Standardized partial regression coefficient
(Constant)	-40.939	0.67[NS]	
Age in years	1.905	0.019	0.397
Male gender compared to female	-54.064	0.037	-0.356
BMI (Kg/m^2)	2.367	0.12[NS]	0.271
Systolic blood pressure (mmHg)	-0.594	0.32[NS]	-0.194
Serum TG (mg/dl)	-0.158	0.26[NS]	-0.165
Serum LDL-C (mg/dl)	0.297	0.33[NS]	0.157
Fasting serum glucose (mg/dl)	0.097	0.47[NS]	0.107
Diastolic blood pressure (mmHg)	-0.036	0.97[NS]	-0.006
Serum HDL-C (mg/dl)	-0.154	0.89[NS]	-0.019

P (Model)=0.021
R^2=0.4

DISCUSSION:

Leptin is a product of Ob gene and is expressed only in adipose tissue[9] .It circulates in plasma in a free or bound to leptin-binding proteins [9]. Leptin levels reflect not only the amount of fat stored in the adipose tissues but also energy imbalance, prolonged fasting, for instance, substantially decrease leptin levels, whereas overfeeding greatly increases it [9]. Our results show that the male had lower plasma leptin levels comparing to the females, obviously lower but not significantly in male in healthy control group while significantly lower in males compared to females in case of metabolic syndrome group (Table 7), with (p=0.001,0.02),which similar to previous studies [10,11], this finding is in line with the hypothesis, that there are gender differences in leptin synthesis, transport or clearance rates [12],this may be due to an-androgen-induced reduction in leptin production [13,14], for this reasone in our study, the case –control comparison in median serum leptin was stratified by gender to adjust for the confounding effect of gender. Development of metabolic syndrome is suggested to be a consequence of hyperleptinemia in obese subject [9 ,15] ,in our study , we found higher concentration of plasma leptin in patient with metabolic syndrome, however ,this association disappeared after adjustment for BMI and sex in regression analysis (Table 8). Although some studies have proposed leptin an independent predictor of insulin resistance and metabolic syndrome [2],our results showed case-control difference in serum leptin is mainly attributed to age, gender and BMI difference and able to explain 40% of observed variation in serum leptin (Table 11) not a function of metabolic syndrome itself, as in (Table 9) no important association between leptin and each of selected criteria of metabolic syndrome ,this agree with previous studies[11,14,16], that

showed that leptin has no major role in linking various components of the metabolic syndrome. However, in our study only BMI had moderately strong and statistically significant linear correlation with serum leptin (Table 10) this finding suggests that BMI is the main determinants for the variations of leptin.

CONCLUSION:

Among subjects with metabolic syndrome, the measurements used in the criteria of metabolic syndrome had no important contribution to the magnitute of serum leptin, only age ,gender and body mass index were important in determining the magnitude of serum leptin among case group.

REFERENCES:

1.Moreno LA, Pineda I , Rodriguez G. Leptin and metabolic syndrome in obese and non- obese children .Horm Metab Res 2002;34:394-9.
2.Chu NF, Wang DJ, Shieh SM. Plasma leptin concentrations and obesity in relation to insulin resistance syndrome components among school children in Taiwan. The Taipi Children Heart Study. Int J Obesity 2000;24:1265-71
3.Weiss R, Dziura J, Burget TS. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004;350:2362-74.
4.Steinberger J, Steffen L, Jacobs DR. Relation of leptin insulin resistance syndrome in children.Obes Res 2003;11:1124-30.
5.Erturk E, Kuru N, Savci V.Serum leptin levels correlate with obesity parameters but not with hyperinsulinism in womem with polycystic overy syndrome. Fertil Steril 2004 ;82:1364-8.
6.Christors S, Mantzoros.The role of leptin in human obesity and disease: A review of current evidence. Ann Intern Med 1999;130:671-80.
7. Crook MA.Clinical chemistry and metabolic medicine, 7th ed.Hodder Arnold 2006; 174-97.
8.Sorlie DE (ed). Medical biostatistics and epidemiology: Examination and Board review. First ed, 1995, Norwalk, Connecticut, Appleton and Lange: 47-88.
9.Remesar X, Rafecas I, Fernandez-Lopez JA.. Is leptin an insulin counter-regulatory hormone? FEBS letters 1997;402:9-11.
10.Zimmet P, Hodge A, Nicolson M. Serum leptin concentration, obesity, and insulin resistance in western samoas :cross sectional study. BMJ 1996;13:965-9.
11.Roemmich JN, Clark PA, Berr VM, Mantazoros CS , Flier JS. Gender differences in leptin levels during puberty are related to the subcutaneous fat depot and sex steroids. Am J Physiol Endocrinol Metab 1998;275:E543-E51.
12.Blum WF, Englaro SH, Juul NT, Muller NE, Heiman MB. Plasma leptin levels in healty children and adolescents :dependence on body mass index, body fat mass,gender, pubertal stage, and testosterone.J Clin Endocrinol Metab 1997;82:2904-10.
13.Wabitsch MW, Blum WF, Muche R, Braun M, Rascher HW, Hauner H. Contribution of androgens to the gender difference in leptin production in obese children and adolescents.J Clin Invest 1997;100:808-13.
14.Ruhl CE, Harris TB,Ding J, Goodpaster BH, Kanaya AM .Body mass index and serum leptin concentration independently estimate percentage body fat in older adults .Am J Clin Nutr 2007;85,4:1121-6.
15.Nishina M,Kikuchi T, Yamazaki H. Relationship among systolic blood pressure, serum insulin and leptin, and visceral fat accumulation in obese children. Hypertens Res 2003;26:281-8.
16.Park HS, Lee MS, Park JY.Leptin and metabolic syndrome in Korean adolescents: Factor analysis. Ped Int 2004;46:697-703.