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Research Article

Hyperleptinemia - an independent predictor of metabolic syndrome in the adult population in Kerala, India

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ABSTRACT

Background: Hyperleptinemia, associated with obesity which is a major risk factor for metabolic syndrome. Kerala has the highest prevalence of most of the cardio metabolic disorders and risk factors. So we analysed the ability of serum leptin level to predict the risk of developing metabolic syndrome among the adult population in Kerala, India.
Methods: The study included 149 men and 155 women in the age group of 20-60years. Anthropometric measurements and Blood pressure were recorded. BMI and WHR were calculated. Fasting blood sample was used to measure serum leptin, insulin, lipid profile and glucose. HOMA-IR and HOMA-β were calculated. Baseline characterestics (means ± SEM) of men and women were examined by quartiles of serum leptin levels using ANOVA. The strength of association between leptin and components of metabolic syndrome was expressed as Odds Ratio (OR) using logistic regression analysis. p values <0.05 were considered significant.
Results: In men and women, participants in the upper leptin quartiles were more likely to have factors associated with metabolic syndrome including waist circumference, systolic BP, decreased HDL cholesterol etc. Furthermore, those with metabolic syndrome were more likely to be in the upper leptin quartiles. On multivariate binary logistic regression analysis of leptin, the OR was: BMI (OR=3.51), waist circumference (OR=3.14), insulin (OR=4.43), and HOMA-IR (OR=2.4) in men, while in women the association of leptin was strong with abdominal obesity (OR=7.6), insulin (OR=2.8) and Insulin resistance (OR=4.1).
Conclusions: Serum leptin levels had a strong association with components of metabolic syndrome, especially abdominal obesity and insulin resistance. Elevated leptin level should be taken as a warning sign of metabolic syndrome.

Keywords: Metabolic syndrome, Leptin, Kerala, Abdominal obesity, Insulin resistance

INTRODUCTION

Leptin, a 16kDa cytokine hormone secreted by adipocytes in proportion to body fat acts as sensor of the energy balance by influencing appetite.[1] Leptin was first identified as the product of a gene designated *ob* (obese) in laboratory mice.[2] Obese humans present with hyperleptinemia as an indicator of leptin resistance which plays a major role in the pathogenesis of obesity.[3] Obesity has a central role in the incidence of metabolic syndrome, characterized by a clustering of metabolic abnormalities which leads to increased cardiovascular diseases all-causes morbidity and mortality. The prevalence of metabolic syndrome is greater in obese individuals, but not all obese subjects suffer from metabolic syndrome and non-obese subjects may also be

affected.[4] South Indians have a high tendancy to develop metabolic syndrome, which may be due to an increase in the body fat, in particular abdominal fat.[5,6] Considine et al reported elevated leptin levels in obese humans which was most closely correlated with body fat percentage.[3] Obesity is known to be associated with insulin resistance, hypertension and dyslipidemia.[7-9] Recent studies have reported a positive correlation of insulin resistance with leptin.[10]

The five generally accepted features of metabolic syndrome are obesity, insulin resistance, dyslipidemia, impaired glucose tolerance and hypertension. Specifically, a three- fold increase in the prevalence of metabolic syndrome is associated with a two- fold increased risk of cardiovascular disease fatality, 150% increase in total mortality, and a five-fold increased risk of diabetes mellitus.[11] Because metabolic syndrome is associated with increased risk for CVD and diabetes mellitus, early diagnosis of metabolic syndrome and resultant intervention strategies may help to reduce the incidence of these associated diseases.[12]

Many studies reported the association of leptin with obesity, insulin resistance, hypertension etc. All of these elements influence the atherogenic process and need to be prevented or treated, in order to reduce the already high prevalence of cardio vascular diseases and type 2 diabetes in Kerala. So we analysed the ability of serum leptin to predict the risk of developing metabolic syndrome in the adult population in Kerala, India.

METHODS

The study conducted was a cross-sectional analytical study. The study population consisted of 149 men and 155 women aged 20-60 years, selected from Obesity clinic, Government Medical College, Trivandrum and Sree Gokulam Medical College and Research Foundation (SGMC&RF), Venjaramoodu, Trivandrum, India. Mean age was 39years with no significant difference between genders. Those subjects with a history of medication for diabetes, hypertension, dyslipidemia etc. and those with liver diseases, renal diseases or thyroid dysfunction were excluded from the study.

Anthropometric measurements and blood pressure were recorded. BMI and WHR were calculated. Fasting blood sample was used to measure serum leptin, insulin, lipid profile and glucose. An informed consent and a detailed proforma including socio economic details, life style habits, family history of diseases etc. was obtained from each participant.

Analytical methods

Fasting blood samples were obtained and the biochemical parameters such as glucose, total cholesterol, triglycerides, HDL cholesterol were estimated by colorimetric enzymatic methods in 'Siemens Dimension' fully auto-analyzer using Flex reagent cartridges. LDL cholesterol was calculated by Friedewal's formular.[13] Sandwich ELISA kits were used to measure serum leptin (BioVendor, Czech Republic, EU) and insulin (DRG, USA).[2,14]

The inter-assay and intra –assay coefficients of variation (CV) for leptin were 8.6% and 6.9% respectively with a sensitivity of 1ng/ml and that for insulin were 6% and 1.8% respectively with a sensitivity of 1.76µIU/ml. Homeostatic Model Assessment of Insulin Resistance (HOMA –IR) score and HOMA-β cell function were calculated using the formula proposed by Matthews et al.[15]

HOMA-IR=[(fasting serum insulin concentration in micro U/l X fasting blood glucose in mg/dl) /405]

HOMA-β=[360X insulin (mU/ml)/ (glucose(mg/dl)-63)].

Definitions and reference values

Metabolic syndrome was defined according to the National Cholesterol Education Program, adult treatment panel III (NCEP ATP III), with modifications for Asian Indians as the presence of 3 or more of the 5 risk components as follows: 1) waist circumference >90cm for men and >80cm for women; 2) Triglycerides≥ 150mg/dl; 3) HDL-Cholesterol <40mg/dl for men and <50mg/dl for women; Blood Pressure ≥130/85mmHg; 5) Fasting Plasma Glucose ≥100mg/dl.[16,17]

Statistical analysis

Statistical analysis was performed using SPSS windows version 17. Baseline characteristics (means ± SEM) of men and women were examined by quartiles of serum leptin levels using ANOVA to study the predictive power of leptin in the incidence of metabolic syndrome. The strength of association between leptin and components of metabolic syndrome was expressed as Odds Ratio (OR) using logistic regression analysis. Variables showing a statistically significant association with elevated leptin levels on univariate binary logistic regression were analysed by multivariate logistic regression. p value <0.05 was considered statistically significant for all analyses.

RESULTS

The characterestics (means±SEM) of male and female participants stratified by leptin quartiles are shown in Table 1 and 2 respectively. In men and women, participants in the upper leptin quartiles were more likely to have factors associated with metabolic syndrome. No significant difference in fasting plasma glucose, HOMA –β and lipoproteins were observed in males. Among females, no difference was observed in HOMA- β only. On multivariate binary logistic regression analysis, the variables associated with high leptin levels were BMI

(OR=3.51), hyperinsulinemia (OR=4.43) in men (Table 3), while in women, abdominal obesity (OR=7.6), body fat percentage (OR=5.92), Insulin resistance (OR=4.1), cholesterol (OR=3.24) (Table 4).

Table 1: Characteristics of study population according to leptin levels for males.

Study variables	Q1 (n=37)	Q2 (n=38)	Q3 (n=37)	Q4 (n=37)	P value
BMI (kg/m^2)	22.0±0.5	23.5 ± 0.4	25.9 ±0.4	29.1 ±0.6	0.000
Waist circumference (cm)	84.8±1.4	88.8 ± 1.2	94.9 ±1.2	101.9 ± 1.6	0.000
Hip circumference (cm)	92.1±1.2	95.9 ± 1	99.8 ± 1.4	105.1 ± 1.6	0.000
WHR	0.9±0.0	0.9 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.000
Systolic BP (mmHg)	116.8±1.8	121.2 ±2.4	124.5 ±2.6	125.7 ± 2.1	0.026
Diastolic BP (mmHg)	77.3±1.4	79.8 ±1.5	82.3 ±1.7	82.9±1.8	0.062
Insulin (µIU/ml)	16.8±2.7	17.8 ±2.1	27.8 ±4.1	43.2 ±4.6	0.000
HOMA-IR	4.1±0.7	4.5±0.6	7.7 ±1.4	11.6±1.6	0.000
HOMA (%)	276.5±71.5	259.3±34	355.2±75	439±49	0.130
FBS (mg/dl)	97.2 ±4.1	102.9±6.4	102.7±5.2	104.1±3.6	0.765
Total cholesterol (mg/dl)	200.9±7.6	212±7.1	223.1±7	205.9±6.3	0.143
Triglycerides (mg/dl)	113.1±10.2	149.4±15.9	143.6±8.7	145.4±16	0.190
HDL cholesterol (mg/dl)	47.5±1.8	48.1±1.7	47.6±2.2	44.9±2.1	0.668
LDL cholesterol (mg/dl)	131.7±7	134.7±44.5	146.2±41.7	128.6±6.3	0.291
HDL/LDL ratio	0.4 ±0.0	0.4 ±0.0	0.4 ±0.0	0.4 ±0.0	0.744

Data expressed as mean±SEM. Study subjects were grouped in to quartiles (Q1-Q4), according to leptin levels(Q1 <3.59, Q2 is 3.59 - 7.98, Q3 is 7.98 -19.02 and Q4 >19.02) for males. Analysis was done by ANOVA.

Table 2: Characteristics of study population according to leptin levels for females.

Study variables	Q1(n=39)	Q2 (n=39)	Q3 (n=39)	Q4 (n=38)	P value
BMI (kg/m^2)	20.8±0.7	23.9±0.5	26.9±0.6	29.5±0.6	0.000
Waist circumference (cm)	77.6±1.7	85.8±1.6	91.9±1.8	100.8±1.3	0.000
Hip circumference (cm)	87.5±1.5	94.8±1.6	100.3±1.6	107.4±1.1	0.000
WHR	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.016
Systolic BP (mmHg)	113±2.4	117±1.7	120.3±1.8	123.7±2.9	0.010
Diastolic BP (mmHg)	72.6±1.4	76.8±1.2	79.4±1.4	79.1±2.0	0.006
Insulin (µIU/ml)	11.9±1.4	18.7±1.9	32.4±4	37.9±3.2	0.000
HOMA-IR	2.6±0.3	4.3±0.5	9.5±1.6	10.3±1.0	0.000
HOMA-β (%)	331.4±97.9	239.4±34.5	377.5±71.8	384.9±44	0.396
FPG (mg/dl)	85±1.8	90.4±2.1	108.9±6.1	110.2±5.9	0.000
Total cholesterol (mg/dl)	190.4±5.7	207.5±6.6	108.9±6.1	110.2±5.9	0.028
Triglycerides (mg/dl)	75.3±5.7	80.6±6	108.4±8.3	100.9±6.8	0.001
HDL cholesterol (mg/dl)	60.6±2.2	57.3±2.2	50.7±2	52.1±2	0.003
LDL cholesterol (mg/dl)	114.3±5.5.0	133.9±6.0	134.6±4.8	143.9±6.5	0.004
HDL/LDL ratio	0.6 ±0.0	0.5 ±0.0	0.4 ±0.0	0.4 ±0.0	0.000

Data expressed as mean±SEM. Study subjects were categorized in to quartiles (Q1-Q4), according to leptin levels(Q1 <11.31, Q2 is 11.31 – 28.01, Q3 is 28.01 -84.49 and Q4 > 84.49) for females. Analysis was done by ANOVA.

Table 3: Binary logistic regression analysis of leptin levels with study variables in males.

Study variables	OR univariate analysis	OR multivariate analysis
BMI	13.1	3.51
Waist circumference (cm)	8.9	1.21
Insulin (µIU/ml)	5.2	4.4
HOMA-IR	3.4	2.4
Systolic BP(mmHg)	3.3	1.32

Table 4: Binary logistic regression analysis of leptin levels with study variables in females.

Study variables	OR univariate analysis	OR multivariate analysis
BMI	10.95	0.463
Waist circumference (cm)	20.6	7.6
Insulin (µIU/ml)	18.9	2.83
HOMA-IR	13.6	4.1

DISCUSSION

Recent Studies in Kerala reported that the prevalence of metabolic syndrome is higher among obese patients than non-obese subjects.[18] Studies reported that hyper-leptinemia is usually associated with human obesity and should be considered to be a biomarker of obesity.[18,19]

The present study also supports this finding as evidenced by the significant increase in BMI with serum leptin. Leptin is secreted in response to body fat, thus acts as a regulator of body weight.[20] High levels of serum leptin leads to reduced appetite with increased energy expenditure, while low levels of leptin reflecting weight loss increase appetite and reduce energy expenditure. But in obese subjects, this mechanism is impaired due to leptin resistance.[21]

The present study is different in that it studied the association of serum leptin with components of metabolic syndrome in the adult population at different levels of leptin. In contrast, many studies have investigated these relationships in obese and normal individuals.[22]

In the present study the increase in BMI from the first to forth quartile of leptin levels was statistically significant ($p<0.000$), indicating the role of leptin as a biomarker of obesity. With the exception of HDL-cholesterol, the study variables showed a statistically significant increase from the first to the forth quartile of leptin levels. In women the lipoproteins show a statistically significant difference among the different quartiles of leptin levels but such a difference was not seen in men.

Hyperinsulinemia and insulin resistance showed a statistically significant increase with increase in serum leptin levels in both men and women. But there was no statistically significant difference in the rate of secretion of insulin, expressed as HOMA-β with different leptin levels in men and women. This is in agreement with recent studies reporting the strong association of leptin with insulin resistance.[23] In adipocytes, leptin inhibits glucose uptake, impairs lipogenesis, and inhibits lipolysis.[24] But in hepatocytes, leptin triggers insulin-like effects through regulating insulin signalling pathways; thus making the hepatocytes more sensitive to insulin.[25] On logistic regression analysis of the data, hyperinsulinemia and insulin resistance are found to be the components of metabolic syndrome having strong association with leptin. Present results demonstrate that as the concentration of serum leptin increases the number of determinants of metabolic syndrome increases. So it is clear that serum leptin can be considered an additional component of metabolic syndrome.

CONCLUSION

Human obesity is associated with hyperleptinemia.Leptin levels were significantly associated with metabolic syndrome especially, abdominal obesity and insulin resistance. Serum leptin levels could predict metabolic syndrome; therefore, analysis of leptin as part of routine physical examination could be beneficial in the early diagnosis of metabolic syndrome. Moreover, the reduction of serum leptin levels may confer cardiovascular and metabolic protective effects.

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