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Correlation of Insulin Resistance and Serum Leptin in Metabolic Syndrome

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ABSTRACT

The metabolic syndrome mostly represented by obesity, hypertriglyceridemia and reduced level of HDL-C. Obesity and hyperinsulinemia connected with insulin resistance, present the main mechanism in the pathogenesis of CVD. The present study was designed to compare the fasting leptin level with the insulin and insulin resistance between metabolic syndrome patients and healthy subjects. The present study included 140 metabolic syndrome cases (81 men and 59 women) and 100 healthy controls. Metabolic syndrome cases were diagnosed by (NCEP ATP III) criteria. Serum leptin, insulin, glucose and lipid profile measured and insulin resistance and BMI were calculated. All the parameters were significantly (P<0.0001) high in metabolic cases excepts HDL-C which was significantly (P<0.0001) low. Serum leptin level was significantly (P<0.0001) high in metabolic women compare to metabolic men. The correlation of leptin with insulin, and BMI were strong in both sexes. Increased leptin level shows positive correlation with regards to the metabolic component except the HDL which was decreased. The present study concluded that increased leptin level observed in metabolic cases, more in women compare to men and level increased with the obesity increases. So leptin can be sign of hyperinsulinemia, insulin resistance and disturbance in lipid metabolism that are associated with CVD and type 2 DM.

Keywords: *Metabolic Syndrome, Insulin resistance, Type 2 diabetes Mellitus, Cardio Vascular Disease, Leptin, Hypertriglyceridemia*

INTRODUCTION

Metabolic syndrome is a disorder of energy utilization and storage. The prevalence of the metabolic syndrome is high varying between 10 and 40% depending on the age and sex. This prevalence will increase in the years to come due to the increased prevalence of overweight/obesity. [1] Obesity, insulin resistance and type 2 diabetes mellitus have been characterized as chronic inflammatory states that are associated with abnormal concentrations of cytokines, acute phase reactants and other inflammatory signalling markers. [2] Furthermore, it plays an important role in the development of IR that triggers the associated comorbidities of metabolic syndrome such as atherosclerosis, dyslipidemia, hypertension, prothombotic state and hyperglycemia.[3] Leptin is a protein hormone mainly produced in adipose tissue, the mass of which it regulates through its effects on food intake and energy metabolism. Because leptin has a certain degree of influences on appetite, energy consumption, adipose synthesis, and insulin function. Elevated serum leptin are common in human obesity. The higher the body mass index (BMI) on the waist circumference, the higher the serum leptin level. [4] The elevated concentration of circulating leptin has been consistently associated with the cardiometabolic risk factors such as, hypertension, insulin resistance and type 2 DM. [5] In mice, mutation of the Ob gene on chromosomes 7, which encodes the leptin protein, results in obesity and type 2 DM. [6] However few studies have analyzed the association of leptin with metabolic syndrome so in the present study we measured the circulating leptin, insulin level, glucose and lipid profile and assessed the relationship with metabolic syndrome.

MATERIAL & METHODS

The study was carried out at MGM Medical College. Total 140 patients of MetS included, who attended OPD of MY Hospital. MetS cases were identify by using the ATP III (Adult Treatment Panel III) criteria and 100 normal healthy subjects were included as control. Patients who had liver disease, renal disorder, thyroid disorder, hormonal disorder and other diseases excluded from the study. At the patients visit a standard questionnaire was asked with patients.

Clinical measurements

After 12 hours fast, venous blood sample was obtained and stored at -20^{o}C. Biochemical parameters were quantified by colorimetric enzymatic methods using ERBA diagnostics. Plasma glucose measured by GOD-POD method, [7] triglyceride by GPO/PAP method [8] total cholesterol by CHOD/PAP method [9] and HDL-C measured by direct enzymatic method [10] LDL and VLDL calculated by frieldwal equation. Serum leptin levels were determined by enzyme linked immunosorbent assay (ELISA) using human leptin ELISA kit [11] and serum insulin measured by using insulin ELISA kit.[12]

BMI was calculated by weight in Kg divided by height in m^2. The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated using the formula : (fasting insulin

conc. In μU/ml * fasting blood glucose in mmol/L) / 22.5

The following criteria were used for the diagnosis of metabolic syndrome, as described by NCEP-ATP III committee.

1. Elevated triglycerides (>150mg/dl or >1.7mmol/l)
2. Reduced HDL-C (<40 mg/dl or <1.036mmo/l) in males and (<50 mg/dl or <1.295 mmol/l) in females.
3. High blood pressure (>130/85 mmHg)
4. Raised fasting blood glucose (>100 mg/dl or 5.6 mmol/L)
5. Obesity measured as WC>35 inches in women and >40 inches in men or BMI 25-30 Kg/m^2 (obesity or overweight)

If three of the above mentioned five criteria were present in the patient, he/she was considered as the case of metabolic syndrome.

STATISTICAL ANALYSIS

Statistical analysis was performed by using the IBM SPSS version 20 and MedCalc version 14. A p value <0.05 was considered statistical significant. Comparision of two groups was done by student 't' test and values are presented as Mean ± SD. Correlation coefficient (r) between data sets were calculated by Pearson's correlation coefficient. Linear regression analysis was applied for coefficient determination factor (R^2) of leptin with metabolic factors.

RESULTS

Table 1 shows the general anthropometric and biochemical data of 140 metabolic and 100 control subjects. MetS cases have highly significantly (P<0.0001) elevated mean TC, LDL, VLDL, and TG while the HDL-C is significantly (P<0.0001) decrease as compare to control. The mean value of glucose, insulin and HOMA are also significantly (P<0.0001) increased in metabolic cases and leptin concentration is also high in metabolic cases as compare to control (P<0.0001). The characteristics of male and female MetS participants are compared, the mean leptin level of women is significantly high (P<0.0001) as compared to metabolic male mean leptin level. As shown in Table 2, Pearson's correlation coefficient (r) analysis of leptin level with metabolic risk factors for men and women are undertaken. In both men and women, leptin levels are positively correlated with BMI, WC, FBG, TG, Cholesterol, VLDL, Insulin and HOMA but negatively correlated with HDL-C. It has seen that correlations between leptin levels with insulin, BMI and VLDL are very strong (P<0.0001) in male while association is less strong for triglycerides in women. Linear regression (R^2) is also performed between leptin level and metabolic factors, the strong relation is obtained with BMI and insulin level (Table 3).

Table 1. Anthropometric measurements, fasting biochemical variables of MetS and Control group.

Variables	Units	Control n=100	MetS n=140	t-value
Age	Years	42.63±12.21	52.20±11.92	6.073
Weight	Kg	58.87±9.45	65.87±11.97	4.853
WC	cms	84.30±10.15	89.51±14.22	3.138
BMI	Kg/m2	22.59±4.45	25.13±5.07	4.019
Systolic	mmHg	118.46±5.77	141.06±21.67	10.169
Dystolic	mmHg	81.81±5.85	87.80±9.49	5.595
Glucose	mmol/L	5.10±0.67	10.35±4.99	10.432
Insulin	µU/ml	9.28±1.21	13.93±1.25	28.735
HOMA	-	2.10±0.36	6.47±3.55	12.893
TC	mmol/l	3.94±0.62	5.33±1.26	10.105
TG	mmol/l	1.58±0.71	2.40±1.16	6.248
HDL-C	mmol/l	1.26±0.37	0.88±0.19	-10.322
LDL	mmol/l	2.56±0.59	3.99±1.22	12.351
VLDL	mmol/l	0.31±0.14	0.45±0.18	6.256
Leptin	ng/ml	5.96±.75	10.04±1.69	8.001

MetS= Metabolic Syndrome, WC=Waist Circumferences, BMI= Body Mass Index, TC=Total Cholesterol, TG=Triglyceride, HDL-C=High Density Lipoprotein, LDL=Low Density Lipoprotein, VLDL=Very Low Density Lipoprotein, HOMA=Homeostasis Model Assessment

Table 2: Pearson's Correlation Coefficient (r) between leptin levels and study variables by gender

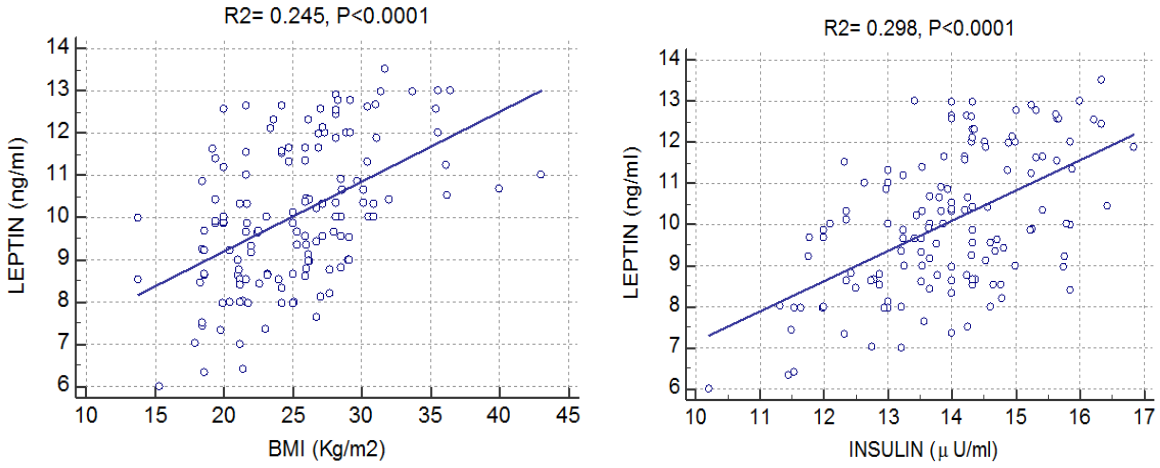
Variables	MetS n=140	Men n=81	Women n=59
WC	0.167	0.241	0.318
BMI	0.495*	0.681*	0.642*
Glucose	0.028	0.102	0.182
TG	0.225**	0.360**	0.199**
HDL	-0.155	-0.150	-0.123
VLDL	-	0.451*	0.231
Insulin	0.542*	0.456*	0.410*
HOMA	0.059***	0.156***	0.094***

(P<0.0001)=* , (P<0.01)=**, (P=0.05)=***

Table 3: Linear regression of leptin with metabolic factors

Parameters	95% CI	Coefficient of determination (R2)	p-value
WC	6.45 to 10.04	0.028	=0.047
BMI	4.62 to 7.13	0.245	<0.0001
Glucose	9.48 to 10.79	0.0008	=0.735
TG	8.61 to 9.88	0.050	=0.007
Insulin	-2.89 to 2.46	0.298	<0.0001
HOMA	9.23 to 10.46	0.003	=0.488

Figure 1: Linear regression graph of MetS patients Leptin level with BMI and Insulin



(ii)

Figure1: Linear regression graph of MetS patients showing significant positive correlations of leptin with (i) BMI (r=0.245, p<0.0001) and with (ii) insulin (r=0.298, p<0.0001).

DISCUSSION

Leptin is an adipokines that regulates energy balance. It plays a major role in the control of body fat stores through coordinated regulation of feeding behaviours metabolism, the autonomic nervous system and body energy balance. Insulin resistance and changes in lipid parameters are typical for early signs of the MetS. Increased triglycerides and decreased HDL-C were the main strong criteria for the selection of metabolic cases.

In present study we compare the biochemical values of control with metabolic cases. All the parameters were significantly high in metabolic cases while HDL-C was low. We observed that serum leptin level was significantly (P<0.0001) high in MetS cases compare to control (Table 1). Insulin and IR which plays a important role in this cases also significantly high in MetS. Present study shows that hyperinsulinemia and IR strongly influence leptin levels. There was a

strong correlation between leptin levels and insulinemia (Table 2). Hyperinsulinemia and IR are major elements of MetS, reflecting the strong interconnection between metabolic risk factors for CVD, type 2 DM, and hypertension, when present together, these risk factors have multiplicative rather than additive effects, greatly increasing the morbidity and mortality caused by these conditions. [13] Even a small but chronically problem to come into existence between energy intake and consumption may be resulted in obesity. Obesity, DM, CAD and hypertension are closely related to increased mortality.[14] High level of leptin is an important marker of MetS in obese patients. This inter relation can be seen in Table 1 which shows that with the exception of HDL-C, the other study variables (which are in fact MetS components) all rose in a statistically significant fashion. The relationship between leptin, hyperinsulinemia and other MetS components is so clear that serum leptin could be considered as an additional component of MetS and a new CVD factor. [15] Hyperleptinemia increases CVD risk in obesity and T2DM.

In present study mean serum leptin levels 9.08±1.22 (95%CI interval 8.87 to 9.35) in men and mean leptin 11.35 ± 1.33 (95% CI interval 11.01 to 11.70) (P<0.0001) for women thus we found. As many authors, presented that serum leptin levels in females are significantly (P<0.0001) higher compare to males. [16] Other authors reported that leptin level in females are approximately three times higher than that in males, a ratio that is found in children and adolscents, pre and post menopausal women, and in the elderly. [17, 18, 19] In present study overweight and obesity defined by BMI was the strongest predictor of high leptin levels (Table 1) Leptin level in obese and overweight persons have a positive and strong correlation with BMI. [20] In the present study significant positive correlation (P<0.0001) between leptin and BMI (Table 2) was obtained. High level of leptin is an important marker of MetS in obese patients. In some studies, it has been shown that obesity, MetS and CVD factors are closely associated with increase in leptin level. [21] Some authors relate this gender difference in fat distribution to difference in lipid profile and glucose insulin homeostasis that are more favourable in women, which was also found in our study. Since for similar BMI values, women had lower levels of lipids, glucose and insulin, which would make them less vulnerable to the effects of obesity. [21]

CONCLUSION

In present study it concluded that serum leptin concentration was higher in metabolic cases and it has a direct association with obesity which measured by BMI, Leptin levels were strongly associated with hyperinsulinemia with small differences between the sexes, and also has correlation with the components of MetS. In our work women had higher leptin level than men. Increase concentration of leptin, in obese subject may act as a sign of insulin resistance, hyperinsulinemia and imbalance of lipid metabolism and these symptoms are linked with the onset of CVD and type 2 diabetes. Serum leptin level may also predict metabolic syndrome; therefore estimation

of serum leptin level in routine examination may be helpful in the early diagnosis of metabolic syndrome.

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