Correlation of Adiponectin and Leptin with Insulin Resistance: A Pilot Study in Healthy North Indian Population

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Abstract The increasing incidence of obesity, leading to metabolic complications is now recognized as a major public-health problem. Insulin resistance is a central abnormality of the metabolic syndrome, or syndrome X, originally hypothesized by Reaven. Insulin resistance is more strongly linked to intra abdominal fat than to fat in other depots. Adipose tissue secretes numerous factors (adipokines) known to markedly influence lipid and glucose/insulin metabolism, oxidative stress, and cardiovascular integrity. Some of these adipokines have been shown to directly or indirectly affect insulin sensitivity through modulation of insulin signaling and the molecules involved in glucose and lipid metabolism. A pilot study was conducted with 80 healthy subjects who were non diabetic, non hypertensive and having no family history of hypertension, the aim was to evaluate the correlation of adiponectin and leptin levels with obesity and insulin resistance markers in healthy north Indian adult population. Serum leptin, adiponectin and insulin was estimated by sandwich ELISA method. In our study, Leptin correlated significantly with BMI (P value of 0.0000), WC (P value = 0.007), and HC (P value = 0.000). leptin showed significant positive correlation with fasting insulin (P value 0.002), post prandial insulin (P value = 0.000) and HOMA-IR (P value = 0.002). Adiponectin showed significant positive correlation with triglycerides (P value = 0.038), strong negative correlation with HDL-cholesterol (P value = 0.017). Serum concentrations of

leptin are associated with central body fat distribution. Insulin resistance and adiponectin is associated with dyslipidemia and these all disorders may ultimately lead to metabolic syndrome.

Keywords Adiponectin · Leptin · Insulin resistance · Cytokines

Introduction

Insulin resistance is a pathological state in which insulin action is impaired in target tissues including liver, skeletal muscle, and adipose tissue. Thus, any defects in the insulin signaling cascade can cause insulin resistance. Insulin resistance is a central abnormality of the Metabolic syndrome, or syndrome X originally hypothesized by Reaven [1] to describe a constellation of metabolic abnormalities, including hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia with increased triglycerides, and decreased HDL.

Insulin resistance is more strongly linked to intra abdominal fat than to fat in other depots. Adipose tissue besides being a source of energy for body is now well recognized as an endocrine organ, playing an important role in modulating insulin activity, inflammation and vascular thrombosis [2, 3]. Regulated by multiple hormonal signals, nuclear hormone receptors Adipose tissue secretes numerous factors (adipokines) known to markedly influence lipid and glucose/insulin metabolism, oxidative stress, and cardiovascular integrity [4]. Adiponectin an antiinflammatory adipokine appears to have a role in regulation of energy balance and peripheral tissue lipid metabolism [5]. The molecular mechanism by which it mediates enhanced insulin sensitivity appears to be linked mainly to increase fatty acid oxidation and glucose uptake via activation of AMPK and PPAR-alpha [6, 7] thereby directly

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regulating glucose metabolism and insulin sensitivity. Leptin, a product of the *ob* gene [8] is almost exclusively expressed and produced by white adipose tissue specifically, by differentiated adipocytes [9]. It regulates body weight, modulates insulin activity and sensitivity, metabolism and reproductive function [10].

Not much data is available on the Indian population. So, with this background the present study was conducted in north Indian population with an aim to overview the role of obesity, adiponectin, leptin and insulin resistance which lead to the metabolic syndrome.

Materials and Methods

A pilot study was conducted in healthy adult population to evaluate correlation of adiponectin and leptin levels with lipid parameters, anthropometrics indices of obesity and insulin resistance markers. Total 80 healthy subjects who were non diabetic, non hypertensive and having no family history of hypertension were enrolled in our study. Permission from Institutional Ethics Committee was obtained for this study.

Sample Collection

Venous blood sample was collected in a plain vial under sterile conditions. Serum routine investigations were done on the same day. The serum for adiponectin, leptin and insulin was then stored at -20°C till serum insulin was batch analyzed on automated analyzer.

Lipid Parameters

Total cholesterol, LDL cholesterol, HDL cholesterol, Triglyceride, VLDL cholesterol. All these parameters were done on fully automated analyzer.

Anthropometrics Indices of Obesity

The following parameters were taken as anthropometric indices: Waist circumference in centimeters, Hip circumference in centimeters, Waist hip ratio, and Body mass index in kg/m^2 .

Markers of Insulin Resistance

Fasting insulin, Post prandial insulin, Fasting blood glucose (FBS), post prandial blood glucose (PPBS), HOMA insulin resistance (HOMA-IR).

Insulin Estimation

Serum insulin was estimated by sandwich ELISA method using Bioline insulin assay kit for research purpose only.

Adiponectin Estimation

Measured using Bio Vendor's Human ELISA (sandwich) commercial kit for research use only.

Leptin Estimation

It was measured using DRG kit (sandwich ELISA) for research use only.

Results

In our study conducted in 80 healthy north Indian populations, 46 were males and 34 were females in the age group of 19–57 years. 1 male and 2 female were obese when defined by $\text{BMI} > 30 \text{ kg}/\text{m}^2$ number of subjects with $\text{BMI} > 25 \text{ kg}/\text{m}^2$ was 16 of whom 9 were males and 6 were females. In Asian Indian population $\text{BMI} > 23 \text{ kg}/\text{m}^2$ is considered obese. In the study we found non-significant but negative correlations of adiponectin with BMI, WHR, WC and HC. A strong negative correlation was found between adiponectin and WHR with statistically significant P value of 0.002 in our study. The other parameters did not show any statistically significant correlation. Adiponectin value in cases was $7.56 \pm 0.497 \text{ } \mu\text{g}/\text{ml}$ (Table 1) however it shows a negative (nonsignificant) relation with fasting insulin, post-prandial insulin, post-prandial blood sugar and HOMA-IR. We found significant positive correlation between adiponectin and HDL-cholesterol (P value 0.014) in total study group (Table 2); however, it did not show significant correlation with other parameters of lipid profile although no significant negative correlation is present.

In our study, leptin $6.18 \pm 1.075 \text{ ng}/\text{ml}$ (Table 1) correlated significantly with BMI having a P value of 0.0000, WC (P value = 0.007), and HC (P value = 0.000) (Table 2). With parameters of insulin resistance leptin showed significant positive correlation with fasting insulin (P value 0.002), post prandial insulin (P value = 0.000) HOMA-IR (P value = 0.002). Our study shows significant positive correlation with triglycerides (P value = 0.038), strong negative correlation with HDL-cholesterol (P value = 0.017) (Table 2) however it does not show any correlation with other parameters.

Discussion

Central body fat consists of abdominal subcutaneous and intra-abdominal visceral adipose tissue. To determine predominant sites of release, we analyzed correlations with waist circumference, representing both subcutaneous and visceral adipose tissue, and hip circumference as a measure

Table 1 Adiponectin and leptin with anthropometric indices, markers of insulin resistance and lipid profile in normal adult population (North Indian)

	<i>n</i> = 80 (mean ± SEM)	Males <i>n</i> = 46	Females <i>n</i> = 34
BMI (kg/m ²)	21.8 ± 0.52	21.19 ± 0.62	22.62 ± 0.88
WHR	0.84 ± 0.00	0.86 ± 0.01	0.80 ± 0.01
WC	77.85 ± 1.530	79.11 ± 1.99	76.14 ± 2.39
HC	92.31 ± 1.157	90.74 ± 1.36	94.42 ± 1.97
Fasting insulin (IU/l)	6.26 ± 0.420	6.17 ± 0.536	6.38 ± 0.68
Post prandial insulin (IU/l)	47.90 ± 5.160	44.3 ± 5.35	52.74 ± 9.79
FBS (mg/dl)	96.74 ± 1.16	94.89 ± 1.66	99.24 ± 1.49
PPBS (mg/dl)	119.21 ± 1.89	116.8 ± 2.32	122.47 ± 3.13
Homa-IR	1.49 ± 0.10	1.45 ± 0.13	1.56 ± 0.16
Total cholesterol	146.99 ± 3.87	143.96 ± 5.75	151.09 ± 4.742
Triglycerides	110.07 ± 8.64	115.20 ± 12.75	103.15 ± 10.86
HDL cholesterol	42.59 ± 0.99	40.54 ± 1.19	45.35 ± 1.58
LDL cholesterol	82.79 ± 3.11	80.78 ± 4.51	85.50 ± 4.07
Ratio (HDL/LDL)	0.566 ± 1.72	0.57 ± 0.03	0.57 ± 0.03
Adiponectin (μg/ml)	7.56 ± 0.497	6.36 ± 0.522	9.19 ± 0.86
Leptin (ng/ml)	6.18 ± 1.075	4.24 ± 0.690	8.79 ± 2.29

Table 2 Correlation of adiponectin and leptin with anthropometric indices markers of insulin resistance and lipid profile

<i>N</i> = 80	Adiponectin		Leptin	
	<i>r</i> value	<i>P</i> value	<i>r</i> value	<i>P</i> value
BMI	−0.111	0.326	0.415	0.000
WHR	−0.337	0.002	0.005	0.962
WC	−0.197	0.079	0.299	0.007
HC	−0.027	0.813	0.451	0.000
Fasting insulin	−0.100	0.376	0.336	0.002
Postprandial insulin	−0.050	0.659	0.518	0.000
FBS	0.035	0.755	0.102	0.367
PPBS	−0.010	0.931	0.119	0.293
Homa-IR	−0.099	0.381	0.347	0.002
Total cholesterol	0.012	0.918	0.029	0.799
Triglycerides	−0.060	0.600	0.233	0.038
HDL cholesterol	0.275	0.014	−0.267	0.017
LDL cholesterol	−0.023	0.840	−0.017	0.879
Ratio (HDL/LDL)	0.171	0.130	−0.121	0.284

Values in bold are the significant findings of the study

of subcutaneous fat alone. Our findings are consistent with studies by Indian researchers [11] who found that adiponectin levels correlate (inversely) strongly with anthropometric parameters in Asian-Indians though unlike their study, our study does not show a strong correlation. Adiponectin concentrations were negatively correlated with WHR, independent of gender and overall adiposity. Our findings were consistent with those of the findings of Berg [5]. Possible explanation for such (negative but nonsignificant) findings in our study could be that the majority subjects included in this study were non-obese

causing selection bias. One might speculate that serum concentrations of adiponectin positively correlate with adiposity e.g., the fat depot around the hip, resulting in this negative correlation with WHR. In agreement with the hypothesis that the levels of adiponectin are down-regulated in hypertrophic adipose tissue by a negative feedback mechanism [5, 12] we conclude that serum adiponectin concentrations are an inverse function of central body fat mass. Serum adiponectin levels showed no correlation with hip circumference. This strongly suggests that secretion of adiponectin into the bloodstream is not regulated by subcutaneous, but rather by visceral, adipose tissue. This is in agreement with in vitro findings showing lower adiponectin mRNA levels in omental versus subcutaneous adipose tissue from type 2 diabetics [13]. This provides further, indirect evidence, that adiponectin secretion in humans is a function of visceral fat mass.

Adiponectin however shows a nonsignificant negative relation insulin resistance parameters, Our findings are in consistent to the findings of Matsubara [14], Weyer and Funahashi [15] who after a multivariate analysis demonstrated that hypoadiponectinemia was more intensively related to the degree of insulin resistance and hyperinsulinemia. Our study failed to support the same probably because the subjects (majority non obese, healthy, no risk factor) included in the study were actually not the representative of insulin resistant population. We found significant positive correlation between adiponectin and HDL-cholesterol in total study group consistent with the findings of Yamamota [16] and Hotta [17].

It is well established that leptin mRNA levels and secretion rates are higher in subcutaneous than in visceral adipose tissue [18]. The positive correlation between leptin and

waist circumference may, therefore, reflect the contribution of subcutaneous abdominal fat mass and may link leptin with central obesity. Leptin significantly correlated with BMI, WC and HC and this is also in consistent with the findings of De Courten [19]. Leptin showed significant positive correlation with parameters of insulin resistance. Our findings were consistent with other studies [20] done by Walder and coworker. The serum leptin concentration significantly correlates with HOMA-IR which reflects the degree of insulin resistance and with the concentration of serum insulin in both control and test groups of men and women respectively. We can place our results along the large group of studies, which declare an important role of leptin in pathogenesis of insulin resistance. Our study shows significant positive correlation of leptin with triglycerides and, strong negative correlation with HDL-cholesterol however it does not show any correlation with other parameters. This finding is consistent with previous studies [21]. Insulin resistance and changes in lipid parameters are typical for early signs of the metabolic syndrome. Hypertriacylglycerolaemia together with decreased of HDL cholesterol were pivotal criteria in the selection of the groups.

Conclusion

From our study we can establish significant positive correlation between leptin and anthropometric indices, insulin resistance parameters and triglycerides. There was significant direct correlation between circulating leptin levels and insulin resistance markers. Leptin showed positive correlation that was significant statistically with BMI in total study population. We also established significant negative correlation of leptin with HDL-cholesterol, while adiponectin correlated positively with HDL-CH. Body Mass Index (BMI) correlated negatively with adiponectin though not significant in study population. Negative correlation of adiponectin was also found with insulin resistance markers though it was not significant statistically. In conclusion, our data suggest that serum concentrations of both adipocytokines are associated with central body fat distribution that serum adiponectin concentrations are determined predominantly by the visceral fat compartment, and that serum leptin concentrations are determined mainly by subcutaneous adipose tissue, although a role of visceral fat cannot be excluded.

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