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RESEARCH ARTICLE

The Relationship of Adiponectin/Leptin Ratio with Insulin Resistance and obesity in north Indian population

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Abstract

Adiponectin and leptin both react in a reciprocal approach with increasing obesity, leptin increases while adiponectin decreases with the obesity. Therefore, in the present study we investigate the relationships of A/L ratio with insulin resistance measured by HOMA-IR. This study was a population-based cross-sectional study, only 642 (BMI 29.14±2.54 kg/m^2) individual were participated. Commercial kits were used for determining lipid profile. Insulin, leptin were determined by enzyme-linked immunosorbent assay. Adiponectin was assayed with ELISA method. Spearman's correlation, multiple regression and one-way analysis of variance (ANOVA) were conducted. Mean leptin and Homeostasis model assessment-insulin resistance (HOMA-IR) levels were significantly higher, while Adiponectin /Leptin ratio (A/L ratio) and adiponectin were significantly lower in obese subjects in comparison to overweight and lean subjects. In multiple regression analysis, HOMA-IR was significantly correlated with fasting glucose, insulin and A/L ratio, while A/L ratio were significantly correlated with weight, body mass index, percent body fat, leptin, adiponectin and HOMA-IR. HOMA-IR and A/L ratio were significant predictors for each other after adjustment for other factors. The decreased A/L ratio in obese subjects, suggests its property as the predictive marker for insulin resistance in the north Indian population.

Introduction

Obesity is rapidly increasing in prevalence and closely associated with type 2 diabetes, cardiovascular diseases and hypertension. Obesity is commonly associated with insulin resistance, hyperinsulinemia and is often linked with high blood pressure and various metabolic abnormalities, such as dyslipidaemia and elevated plasma glucose

(Thomas et al, 2004). Due to its association with various complex diseases, increased mortality (Calle et al, 1999) and morbidity (Eckel et al, 1998) obesity has emerged as a major public health issue for the 21st century.

A higher percentage of abdominal visceral adiposity in comparison to subcutaneous adiposity among Asians than Caucasians (Lear et al, 2007, Tanaka et al, 2003) may be responsible for insulin resistance and other metabolic disorder related to obesity (Hayashi et al, 2008, Fox et al, 2007). Obesity-induced insulin resistance is a most important etiological feature in the pathogenesis of type 2 diabetes mellitus. Adiponectin and leptin, adipocyte-derived hormones, are probable principal biological mechanisms under ethnic differences in disease risk. Adiponectin and leptin both respond in a reciprocal manner with increasing adiposity, leptin increases while adiponectin decreases with adiposity (Badman et al, 2007), and the plasma leptin to adiponectin ratio may be a possible measure of insulin resistance (Finucane et al, 2009). In various studies, leptin and adiponectin have been associated with the regulation of metabolic homeostasis (Ahima et al, 2000; Berg et al, 2002; Baskin et al, 2001). It is also reported that decreased plasma adiponectin concentration is associated with increased adiposity (BMI- Body Mass Index) and it negatively correlates with insulin resistance (Arita et al, 1999; Weyer et al, 2001).

In previous studies, leptin has been suggested as a sensitive biomarker for the diagnosis of obesity and obesity-related phenotypes and positively correlated with increased BMI and insulin resistance (Zhang et al, 1994; Considine et al, 1996). In another study, leptin level positively correlated with visceral fat while adiponectin level negatively correlated with the visceral fat (Chan-Hee et al, 2010). In several studies the ratio of plasma adiponectin/leptin (A/L) ratio has been suggested as a useful measure for assessment of insulin resistance (Finucane et al, 2009; Inoue et al, 2005; Inoue et al, 2006; Zaletel et al, 2010). Various recent published studies have also supported the important role of the A/L ratio in the prediction of insulin resistance in subjects with or without metabolic syndrome and diabetes (Zhuo et al, 2009; Lee et al, 2009). We hypothesized that the A/L ratio might be a useful measure of insulin sensitivity, given: the fundamental role of adipose tissue in insulin resistance, adipose tissue have a capacity to produce well-recognized hormones (adipocytokines) that involved in the regulation of energy balance and insulin action and this is also a fact that the two best characterized adipocytokines (adiponectin and leptin) react in a reciprocal manner with increasing adiposity (Badman et al, 2007).

In this study, we investigated the relationships of the A/L ratio with insulin resistance measured by homeostasis model assessment- insulin resistance HOMA-IR in Indian populations. We also analyzed whether the A/L ratio would have a more predictable role in the assessment of insulin resistance than HOMA-IR.

Methods

This study is a population-based cross-sectional study, designed to evaluate the effects of adiponectin on obesity and obesity related phenotypes. All individuals were of north Indian origin and the population was homogeneous with regard to ethnic background. A total of 845 subjects (volunteers) enrolled initially from general population of the different part of Lucknow city, Lucknow, Utter Pradesh, India (North India). Out of these, only 642 (BMI 29.14±5.54 kg/m^2) individual were selected after taking informed consent.

In all subjects' body height, body weight, waist circumferences and hip circumferences were measured for calculation of BMI and WHR (waist to hip ratio). Body weight was measured to the nearest 0.1 kg, and height was measured to the nearest 0.01 m (Bray et al, 2009). The waist circumference was measured half way between the lower rib and iliac crest, the hip circumference was measured over the widest part in the gluteal region, and the WHR was calculated (Pouliot et al, 1994). Subjects with established diabetes mellitus, coronary artery disease, hyperthyroidism, pituitary disease, hypogonadism, chronic liver disease, or chronic renal disease and pregnant women were excluded. Diabetes was diagnosed when a subject provided history of previously diagnosed diabetes or the fasting blood glucose was ≥126 mg/dL. Hypertension was diagnosed when the systolic or diastolic BP was ≥140/≥90 mm Hg on repeated single-day measurements. The study was carried out in accordance with the institutional ethics committee.

All study participants were subjected to a thorough screening program that included assessment of a detailed personal and family history, physical examination, determination of anthropometric indices and measurement of various biochemical parameters.

Estimation of body fat composition

The Body fat analyzer (Bioelectrical impedance was obtained using a device, Tanita–TBF–310, Tanita, Tokyo, Japan; calibrated to suit Indian population) was used for assessing the parcentage body fat and fat mass (FM).

Biochemical Parameters

Venous blood was collected after an overnight fast, and plasma and serum samples were either used immediately for analysis or were stored frozen at -80^{0}C. Commercial enzymatic test kits were used for determining HDL-

cholesterol, triglyceride concentrations and total serum cholesterol, LDL cholesterol was calculated by the formula of Friedewald (LDL-cholesterol = total cholesterol – HDL cholesterol – triglyceride/ 5 mg/dl). The inter assay coefficient of variation was less than 5.0% for HDL-cholesterol, less than 2.5% for triglycerides.
Insulin level was determined by enzyme-linked immunosorbent assay RIA (Linco Research, Inc.USA). The intra- and the inter assay coefficients of variation for the insulin assay were 5.7 and 9%, respectively. The lowest detection limit of insulin assay was 0.5 μU/ml. Laboratory measurements. The degree of insulin sensitivity/ resistance was calculated according to the homeostasis model assessment (HOMA) which is a good index for assessing insulin sensitivity/resistance. Insulin resistance (IR) was calculated as follows: IR = FI x g/22.5; where FI = fasting insulin (μu/ml) and g = fasting glucose (mmol/1) (Matthews et al, 1985).
Serum leptin level was measured using radioimmunoassay (Linco Research, Inc.USA). The intra-assay coefficient of variation of leptin was 4.5 to 9%, and the inter-assay coefficient of variation was 4.0 to 7%. Adiponectin was assayed with ELISA method. The intra-assay coefficient of variation of was 4.1 to 5%, and the inter-assay coefficient of variation was 3.3 to 6.9%. The fasting glucose concentration was measured by Glucose oxidase-Peroxidase (GOD-POD) method (Young et al, 1997) systolic (SBP) and diastolic (DBP) blood pressure were measured twice on the right arm, after a 15-min rest, using a mercury sphygmomanometer (Parker et al, 1988).

Statistical analysis
Quantitative variables are expressed as mean ± standard deviation (S.D.). Spearman's correlation analyses were used to analyze the relationships between variables and HOMA-IR, leptin, adiponectin, and A/L ratio. Multiple regression analyses were conducted to determine the predictor for A/L ratio and HOMA-IR after adjusting for the confounding variables like age and sex. A P-value less than 0.05 were considered statistically significant. Groups were also compared by one-way analysis of variance (ANOVA). A two-tailed probability value of $p < 0.05$ was considered statistically significant. All statistical analysis was performed with SPSS 15.0 software.

Results

The general characteristics of the participants
The general characteristics of the study participants are presented in Table 1. The mean age of the participants was 43.60±2.26 years, and the mean BMI of the participants was 29.14±5.54 kg/m^2. The mean value of leptin, adiponectin, and A/L ratio was (17.84±3.63), (7.19±1.86) and (1.50±1.11) respectively. (Table 1)

Table 1 The general characteristics of the study subjects (n = 642)

	Mean±SD
Age, yr	43.60±2.26
Weight, kg	73.79±14.52
BMI, kg/m^2	29.14±5.54
WC, cm	98.80±12.29
PBF, %	32.39±7.73
FM, kg	25.41±9.64
SBP, mm Hg	124.30±4.04
DBP, mm Hg	83.39±3.32
Fasting glucose, mg/dL	109.42±3.27
Insulin, μIU/mL	12.54±2.35
TC, mg/dL	186.66±18.16
TG, mg/dL	118.27±7.08
HDL-C, mg/dL	44.63±3.99
LDL-C, mg/dL	124.52±12.69
HOMA-IR	3.47±1.47
Leptin, ng/mL	17.84±3.63
Adiponectin, μg/mL	7.19±1.86
A/L ratio	1.50±1.11

Data are presented as mean ± standard deviation (SD), BMI, body mass index; WC, waist circumference; PBF, percent body fat; FM , fat mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol;

TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; A/L ratio, adiponectin/ leptin ratio.

Bivariate correlation analyses between HOMA-IR, adiponectin, leptin or A/L ratio, and various parameters

Serum adiponectin level showed significant negative correlations with body weight (r = -0.559, P < 0.001), BMI (r = -0.378, P < 0.001),WHR(r = -0.301, P < 0.001), PBF%(r = -0.372, P < 0.001), FM(r = -0.435, P < 0.001), insulin(r = -0.475, P < 0.001), leptin (r = -0.606, P < 0.001), SBP (r = -0.326, P < 0.001), DBP (r = -0.303, P < 0.001) and HOMA-IR (r = -0.466, P < 0.001) (Table 2). However, serum leptin level exhibited significant positive correlations with BMI (r = 0.456, P < 0.001), body weight (r=0.670, P < 0.001), PBF (r = 0.511, P < 0.001), FM (r = 0.599, P < 0.001), insulin (r = 0.413, P <0.001), and HOMA-IR (r = 0.403, P < 0.001) adiponectin (r =.572, P < 0.001 (Table 3).

The A/L ratio was significantly correlated with the same parameters as was leptin, with the exception of HDL-C and TC (Table 3). In HDL-C, significant correlation was shown with serum adiponectin level but not with serum leptin level or the A/L ratio. In the case of TC, significant correlation was apparent with serum leptin level but not with adiponectin level or the A/L ratio. HOMA-IR level correlated significantly with BMI (r = 0.296, P < 0.001), PBF (r =0.284, P < 0.001), FM (r = 0.314, P = 0.001), FBG (r = 0.443, P < 0.001), adiponectin (r = 0-.466, P =0.001), and insulin (r = 0.960, P < 0.001) (Table 3).

Table 2 Bivariate correlation analyses between HOMA-IR, adiponectin, and the variables

	HOMA-IR		**Adiponectin**	
	r	p-value	r	p-value
Age, yr	0.073	0.066	-0.029	0.463
Weight, kg	0.359	<0.001	-0.559	<0.001
BMI, kg/m^2	0.296	<0.001	-0.378	<0.001
WHR	0.147	<0.001	-0.301	<0.001
PBF, %	0.284	<0.001	-0.372	<0.001
FM, kg	0.314	<0.001	-0.435	<0.001
SBP, mm Hg	0.194	<0.001	-0.326	<0.001
DBP, mm Hg	0.191	<0.001	-0.303	<0.001
Fasting glucose, mg/dL	0.443	<0.001	-0.115	0.004
Insulin, µIU/mL	0.960	<0.001	-0.475	<0.001
TC, mg/dL	0.101	0.011	-0.146	<0.001
TG, mg/dL	0.083	0.034	-0.128	<0.001
HDL-C, mg/dL	-0.027	0.488	-0.005	0.908
LDL-C, mg/dL	0.084	0.033	-0.132	0.001
HOMA-IR	-	-	-0.466	<0.001
Leptin, ng/mL	0.403	<0.001	-0.572	<0.001
Adiponectin, µg/mL	-0.466	<0.001	-	-
A/L ratio	-0.456	<0.001	0.713	<0.001

Table 3 Bivariate correlation analyses between leptin, A/L ratio, and the variables

	Leptin		A/L ratio	
	r	p-value	r	p-value
Age, yr	0.060	0.127	-0.054	0.169
Weight, kg	0.670	0.001	-0.731	0.001
BMI, kg/m^2	0.456	0.001	-0.371	0.001
WHR	0.177	0.001	-0.262	0.001
PBF, %	0.511	0.001	-0.480	0.001
FM, kg	0.599	0.001	-0.517	0.001
SBP, mm Hg	0.298	0.001	-0.344	0.001
DBP, mm Hg	0.276	0.001	-0.301	0.001
Fasting glucose, mg/dL	0.099	0.012	-0.109	0.006
Insulin, µIU/mL	0.413	0.001	-0.467	0.001
TC, mg/dL	0.140	0.001	-0.109	0.006
TG, mg/dL	0.182	0.001	-0.165	0.001
HDL-C, mg/dL	-0.023	0.564	-0.014	0.727
LDL-C, mg/dL	0.138	0.001	-0.093	0.019
HOMA-IR	0.403	0.001	-0.456	0.001
Leptin, ng/mL	-	-	-0.853	0.001
Adiponectin, µg/mL	-0.572	0.001	0.713	0.001
A/L ratio	-0.853	0.001	-	-

The comparison of mean adipokine level and A/L ratio according to the status of obesity:

The mean levels of adiponectin were lower in lean, overweight subjects compared with the obese subjects, and this difference was statistically significant between the groups (8.18 µg/mL vs. 7.56 µg/mL vs. 6.52, P = <0.001). The mean levels of leptin and HOMA-IR in lean, overweight subjects were significantly higher than in obese subjects. In addition, obese subjects showed a significantly lower the A/L ratio compared with that of overweight and lean subjects (0.39 vs. 0.57 vs. 0.78, P = <0.001).

The participants were divided into two groups according to the insulin resistance status, with an insulin resistance status, the mean levels of leptin and HOMA-IR increased (P = 0.002, P = <0.001) and the A/L ratio decreased significantly (P = <0.001). However, the level of adiponectin showed a tendency to decrease with the insulin resistance status, although this tendency was not statistically significant (P = 0.229) (Table 4).

Table 4 The comparison of mean adipokine levels and A/L ratios according to the obesity and insulin resistance status

	Adiponectin, µg/mL	Leptin, ng/mL	HOMA-IR	A/L ratio
According to the obesity status				
Lean (n=136)	8.18	12.70	2.37	0.78
Over-weight (n=197)	7.56	16.17	3.15	0.57
Obese (n=309)	6.52	21.13	4.15	0.39
p-value	<0.001	<0.001	<0.001	<0.001
According to the insulin resistance status				
Insulin sensitive (n=421)	7.69	15.98	2.03	0.63
Insulin resistance (221)	6.24	21.32	6.21	0.34
p-value	0.229	0 .002	<0.001	<0.001

Multiple regression analyses with HOMA-IR or A/L ratio as the dependent variable:

Multiple linear regression models with HOMA-IR or the A/L ratio as the dependent in separate models are presented in Table 5. Fasting glucose and insulin were significant determinants for HOMA-IR (R2= 0.978), and weight, BMI, insulin, leptin and adiponectin were the significant determinants for the A/L ratio (R2 = 0.832) (Table 5). Also, we carried out multiple linear regression analyses with HOMA-IR or the A/L ratio as the dependent variable, including each variable in the opposite model. When the analysis was performed with HOMA-IR as the dependent variable including the other variable in the model, BMI, fasting glucose, insulin and the A/L ratio were the significant

determinants, with a correlation coefficient for the A/L ratio of -0.254 (R2 = 0.978). When the analysis was performed with the A/L ratio as the dependent variable including the other variable in the model, weight, BMI, leptin, adiponectin and HOMA-IR were the significant determinants, with a correlation coefficient for HOMA-IR of (R2 = 0.832) (Table 6).

Table 5 Multiple regression analysis with HOMA-IR or A/L ratio as the dependent variable

Independent variable	HOMA-IR		A/L ratio	
	beta	P value	beta	P value
Weight, kg	0.008	0.337	-0.204	<0.001
BMI, kg/m^2	-0.015	0.044	0.116	<0.001
PBF, %	0.013	0.085	-0.066	0.002
Fasting glucose, mg/dL	0.244	<0.001	0.0001	0.984
Insulin, µIU/mL	0.902	<0.001	-0.048	0.014
Leptin, ng/mL	-0.001	0.924	-0.558	<0.001
Adiponectin, µg/mL	-0.008	-0.950	0.277	<0.001
R^2	0.978		0.832	

β (beta) standard regression coefficient.

Table 6 Multiple regression analysis with HOMA-IR or A/L ratio as the dependent variable including the other variable in the model

Independent variable	HOMA-IR		A/L ratio	
	beta	P value	beta	P value
Weight, kg	0.006	0.467	-0.204	<0.001
BMI, kg/m^2	-0.015	0.043	0.117	<0.001
PBF, %	0.013	0.079	-0.066	0.002
Fasting glucose, mg/dL	0.244	<0.001	-0.011	0.720
Insulin, µIU/mL	0.902	<0.001	-0.088	.381
Leptin, ng/mL	0.002	0.840	-0.558	<0.001
Adiponectin, µg/mL	-0.009	0.302	0.277	<0.001
HOMA-IR	-	-	-0.435	<0.001
A/L ratio	-0.254	0.032	-	-
R^2	0.978		0.832	

Discussion

The result of the present study showed that A/L ratio showed negatively significant correlations with BMI, Body weight, PBF, lipid profile, insulin, leptin and HOMA-IR. Mean leptin and HOMA-IR levels were significantly higher and the A/L ratio was significantly lower in participants with obesity and status of insulin resistance. Norata et al., (2007) also reported that L/A ratio were significantly correlated to BMI, and the homeostasis model of insulin resistance.

In multiple regression analysis, HOMA-IR and the A/L ratio affected each other and were significant predictors for each other, suggesting that the A/L ratio might be used as an insulin resistance marker. However, models including the A/L ratio as the dependent variable showed significantly higher correlations with other metabolic parameters compared with model with HOMA-IR as the dependent variable, suggesting that the A/L ratio is the stronger marker for insulin resistance than is the HOMA-IR. Adiponectin and leptin, has a critical roles in Metabolic Syndrome especially their ratio have been recommended as a useful serum markers for identification of Metabolic Syndrome by previous studies (Zhuo et al, 2009; Jung et al, 2010).

Mirza et al., (2011) observed the remarkable sensitivity and specificity of A/L ratio for diagnosis of metabolic syndrome. On the other hand the A/L ratio and the K-means classification of metabolic syndrome are two autonomous analytical systems, showed considerably association with each other. This association showed the fundamental role of the A/L ratio in diagnosis of metabolic syndrome. Computer Aided Diagnosis (CAD) of metabolic syndrome and the A/L ratio showed the strong association, it also recommended that IDF and ATPIII guidelines lack the sensitivity necessary to diagnose metabolic syndrome.

Our data indicate that the A/L ratio is an independent predictor of insulin resistance. Of note, when the predictive power on insulin resistance of leptin and adiponectin per se was assessed by multiple regression analysis, none of the 2 adipokines appeared to be an independent predictor of insulin resistance. It is realistic that the obesity status could influence the levels of adipokines; however, our data suggest that the assessment of the A/L ratio could be a powerful predictor of insulin resistance independent of BMI not only in subjects with obesity, but also in healthy subjects. Finucane et al., (2009) reported that the ratio of adiponectin and leptin was negatively correlated with insulin sensitivity indexes, and Labruna et al., (2009) previously confirmed that this ratio contributed to the metabolic syndrome.

Our results in agreement with Inoue et al., (2006), who suggested the use of the A/L ratio might be more useful than HOMA-IR to assess insulin resistance in subjects without hyperglycemia and Satoh et al., (2004) also suggested the use of the A/L ratio may serve as an atherogenic index in obese type 2 diabetes subjects.

A few recent previous studies have reported that the A/L ratio was significantly associated with clamp-derived insulin sensitivity index (Zaletel et al, 2010; Oda et al, 2008), on the other hand Zaletel et al., (2010) suggested that the A/L ratio is an stronger predictor for insulin sensitivity in comparison to other insulin sensitivity indices, such as HOMA and QUICKI (Quantitative Insulin Sensitivity Check Index). However, in the present study, the A/L ratio showed better correlation with other parameters related to insulin resistance, such as PBF, FM, BMI, WHR or Lipid profile, compared with HOMA-IR that is in agreement with other previous studies (Finucane et al, 2009; Zaletel et al, 2010).

In this study, the A/L ratio was significantly higher in those with the status of obesity and insulin resistance status. In a study performed on Chinese adults, suggesting that the A/L ratio has better ability for correctly classifying subjects with and without MS than adiponectin or leptin alone (Zhuo et al, 2009). Our study results showed that the presence of obesity and insulin resistance lead to decreased the A/L ratio and include more supportive data on the correlation of the A/L ratio with insulin resistance in that the A/L ratio showed significantly decreased mean values according to status of insulin resistance. Aging is a significant biological factor for metabolic problems like insulin resistance and has been shown to be associated with a pro-inflammatory state and subsequent alterations in levels of metabolic markers, together with adiponectin and leptin. As the age was independently associated with levels of metabolic markers like adiponectin or leptin, suggests the role of age as confounder, when any marker is used alone. As the ratio of the two markers is independent of age it can serve as a better diagnostic marker of insulin resistance, than the two adipokines separately.

In fact, the numbers of the participants enrolled in most published studies were in the range of 100 to 220, compared with the 642 in our study. Second, participants in the present study included both females and males. Furthermore, previous studies were mainly performed with Caucasians, while our study focused on Asians (north Indian). The levels of Adipokine are known to be different with the gender and ethnicity (Norata et al, 2007; Mente et al, 2010). However, our result is meaningful in that this was the first study in north Indian adults for the evaluation of the A/L ratio with insulin resistance, and in that we showed that the A/L ratio varied according to the status of obesity. So these data support the association of this novel ratio as the prediction marker for insulin resistance in north Indian.

The ratio of plasma adiponectin to leptin (A/L) might be a useful measure of insulin resistance due to the following reason: (1) the insulin resistance controlled by excess adipose tissue; (2) the regulation of energy balance and insulin action done by adipocytokines (hormones) produced by the adipose tissue; and (3) the fact that the leptin and adiponectin respond in a reciprocal manner with the increasing adiposity (Badman et al, 2007).

In summary, the A/L ratio correlated well with % body fat, fat mass, lipid profile, several metabolic parameters of insulin resistance in north Indian population, although HOMA-IR showed stronger correlation with metabolic parameters. Furthermore, these data suggest that the A/L ratio decreased in subjects with obesity, suggesting the A/L ratio as the predictive marker for insulin resistance in the north Indian population. Further research is needed on the confirmation of the A/L ratio as the marker for insulin resistance index in various ethnic groups before application to clinical practice.

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