Research Article

Association of insulin resistance and adiponectin in metabolic syndrome

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Abstract

Background: Metabolic syndrome (MetS) and decreased adiponectin level have been reported to be clinically associated with type 2 diabetes mellitus and coronary artery disease (CAD). Serum level of adiponectin has been shown to be reduced in several disease states like obesity and diabetes. The clinical relationship between serum adiponectin level and MetS and its association with insulin resistance has been investigated.

Objective: The present study was designed to compare the fasting adiponectin level with the insulin and insulin resistance between metabolic syndrome patients and healthy subjects.

Materials and Methods: 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 adiponectin, leptin , insulin, glucose and lipid profile measured and insulin resistance, leptin and adiponectin ratio and BMI were calculated.

Result: All the parameters were significantly ($p < 0.0001$) high in metabolic cases excepts HDL-C and adiponectin which were significantly ($p < 0.0001$) low. In both men and women, adiponectin levels are negatively correlated with triglycerides, VLDL, insulin, LAR, and leptin while positively with HDL-C. Pearson's correlation coefficient (r) is also performed between LAR level and metabolic factors, the strong positive relation of LAR is obtained with TG, VLDL, and leptin while strong negative relation with adiponectin ($p < 0.0001$).

Conclusion: The present study concluded that decreased adiponectin level observed in metabolic cases, which was low in men compare to women. The finding indicate that adiponectin may have a wide role in metabolism of lipoprotein. It may act as an anti atherosclerotic factor through improving insulin resistance and lipid profile.

KEYWORDS: Metabolic syndrome, insulin resistance, type 2 diabetes mellitus, cardio vascular disease, hypoadiponectinemia

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic risk factors associated with at least a twofold increase in risk of developing cardiovascular disease and a fivefold increase in risk for type 2 diabetes mellitus.[1–3] 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.[4] Furthermore, adipokine 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.[5] The dysregulation of adipokines has been implicated in obesity, type 2 diabetes, and cardiovascular disease. Recently, inflammatory responses in adipose tissue have been shown as a major mechanism to induce peripheral tissue insulin resistance. Adipose tissues produce leptin and adiponectin to regulate feeding behaviour and also generate pro- and anti-inflammatory adipokines to modulate inflammatory responses.[6] Adiponectin has been found to have vasoprotective andanti-inflammatory effects and therefore could be viewed as a potential link between MetS and its cardiovascular consequences. Adiponectin has multidirectional biological

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action. It inhibits hepatic gluconeogenesis, reduces hepatic glucose output and decreases the level of free fatty acids as a result of their oxidation.[7] Moreover, it was shown that this adipokine has complex anti-atherogenic and anti-inflammatory activity. Unlike other adipokines, plasma adiponectin concentration is inversely correlated with body mass.[7]

However, few studies have analyzed the association of adiponectin with metabolic syndrome so in the present study the circulating adiponectin, insulin level, glucose and lipid profile were measured and assessed the relationship with MetS.

Materials and Methods

The study was carried out at MGM Medical College. Total 140 patients of MetS included, who attended OPD of the hospital. MetS cases were identified by using the Adult Treatment Panel III (ATP III) criteria[8] and 100 normal healthy subjects were included as control. Patients who had liver disease, renal disorder, thyroid disorder, hormonal disorder, and other diseases were excluded from the study. At the patients visit a standard questionnaire was asked with patients.

Clinical measurements

After 12 h fast, venous blood sample was obtained and stored at -20° C. Biochemical parameters were quantified by colorimetric enzymatic methods using ERBA diagnostics. Plasma glucose measured by GOD-POD method,[9] triglyceride by GPO/PAP method,[10] total cholesterol by CHOD/PAP method,[11] and HDL-C measured by direct enzymatic method,[12] LDL and VLDL calculated by frieldwal equation. Serum adiponectin levels,[13,14] serum leptin levels[15] and serum insulin levels[16] were determined by enzyme linked immunosorbent assay (ELISA). LAR (leptin adiponectin ratio) was calculated by formula: (leptin/adiponectin) and 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 concentration 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/m2 (obesity or overweight)

If 3 of the above mentioned 5 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 statistically significant. Comparison 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 adiponectin with LAR.

Result

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 ($p < 0.0001$) decreased as compare to control. The mean value of glucose, insulin and HOMA, leptin and LAR are also significantly ($p < 0.0001$) increased in MetS cases while adiponectin concentration is decreased in metabolic cases compare to control ($p < 0.0001$). The characteristics of male and female MetS participants are compared, the mean adiponectin level of male is significantly low ($p < 0.0001$) as compared to metabolic female mean adiponectin level. As shown in Table 2, Pearson's correlation coefficient (r) analysis of adiponectin level with metabolic risk factors for men and women are undertaken. In both men and women, adiponectin levels are negatively correlated with triglycerides, VLDL, insulin, LAR, and leptin while positively with HDL-C. It has seen that correlations between adiponectin levels with TG, VLDL, LAR are very strong ($p < 0.0001$) in male while association is very strong for LAR but less strong

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	93.51 ± 14.22	5.324
BMI	Kg/m^2	22.59 ± 4.45	26.13 ± 5.07	6.013
Systolic	mmHg	118.46 ± 5.77	141.06 ± 21.67	11.76
Dystolic	mmHg	81.81 ± 5.85	87.80 ± 9.49	6.033
Glucose	mmol/L	5.10 ± 0.67	10.35 ± 4.99	12.22
Insulin	µU/ml	9.23 ± 1.21	14.68 ± 1.28	32.818
HOMA	–	2.10 ± 0.36	6.77 ± 3.35	16.321
TC	mmol/l	3.94 ± 0.62	5.33 ± 1.26	11.194
TG	mmol/l	1.58 ± 0.71	2.40 ± 1.16	6.74
HDL-C	mmol/l	1.26 ± 0.37	0.88 ± 0.19	–9.369
LDL	mmol/l	2.36 ± 0.59	3.99 ± 1.22	13.710
VLDL	mmol/l	0.31 ± 0.14	0.45 ± 0.18	6.556
Adiponectin	µg/ml	20.73 ± 2.39	8.10 ± 2.02	–44.138
Leptin	ng/ml	5.96 ± .75	10.04 ± 1.69	8.001
LAR		0.29 ± 0.22	14.68 ± 1.28	24.246

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 adiponectin levels and study variables by gender

Variables	MetS, *n* = 140	Men, *n* = 81	Women, *n* = 59
WC	–0.076	–0.150	0.188
BMI	0.009	0.020	–0.008
Glucose	–0.082	–0.143	0.107
TG	–0.319	–0.655*	–0.302***
HDL	0.133	–0.061	–0.020
VLDL	–0.360*	–0.702*	–0.360***
Insulin	0.041	0.202	0.010
HOMA	–0.064	–0.095	0.100
Leptin	0.300	–0.402	–0.415
LAR	–0.751*	–0.840*	–0.820*

($p < 0.0001$)=*, ($p < 0.001$)=**, ($p < 0.05$)=***

Table 3: Pearson's correlation coefficient (r) of LAR with metabolic factors

Variables	Metabolic syndrome, *n* = 140
BMI	0.0036
WC	0.0848
Glucose	0.1477
TG	0.5584*
HDL-C	–0.0608
VLDL	0.5921*
Adiponectin	–0.7512*
Leptin	0.3440*
Insulin	0.195
HOMA-IR	0.096

($p < 0.0001$)=*

for VLDL and TG in women. Pearson's correlation coefficient (*r*) is also performed between LAR level and metabolic factors, the strong positive relation of LAR is obtained with TG, VLDL, and leptin while strong negative relation with adiponectin ($p < 0.0001$) (Table 3).

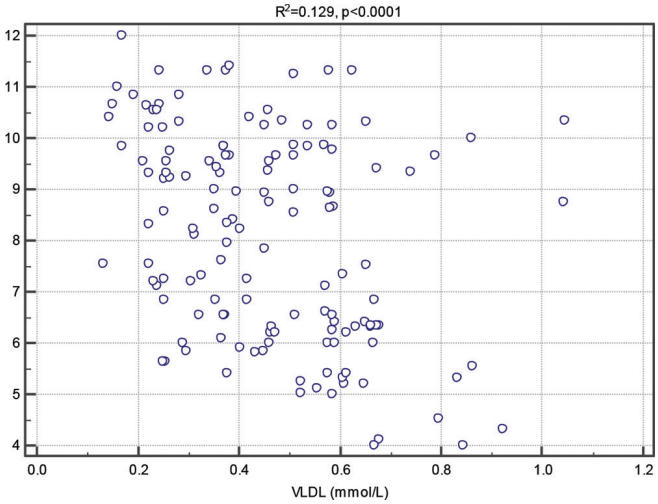

Figure 1: Pearson's correlation of adiponectin with VLDL.

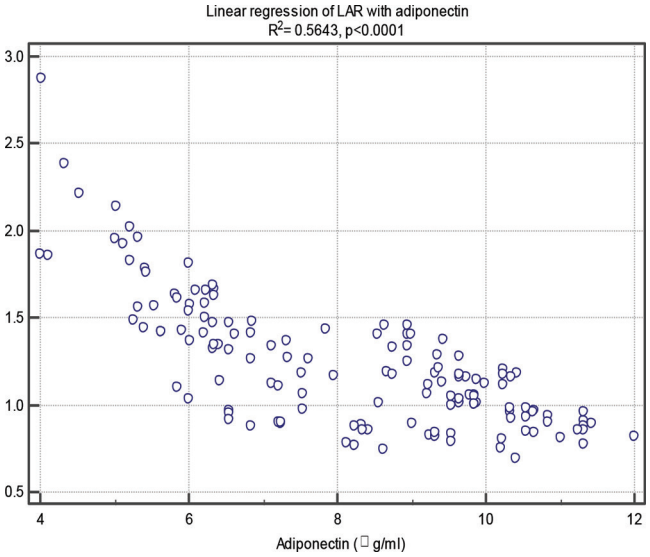

Figure 2: Linear regression of LAR with adiponectin.

Discussion

Adipokines function as classic circulating hormones to communicate with other organs including brain, liver, muscle, the immune system, and adipose tissue itself. The dysregulation of adipokines has been implicated in obesity, type 2 diabetes, and cardiovascular disease. Recently, inflammatory responses in adipose tissue have been shown as a major mechanism to induce peripheral tissue insulin resistance. Although leptin and adiponectin regulate feeding behaviour and energy expenditure, these adipokines are also involved in the regulation of inflammatory responses. Adiponectin is a plasma protein that is secreted specifically by adipocytes, and its function as an antiatherosclerotic factor is being clarified.[17,18] 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, the biochemical values of control with metabolic cases were compared. All the parameters were significantly high in metabolic cases while HDL-C was low. It has been observed that leptin and LAR were significantly ($p < 0.0001$) high while adiponectin was significantly ($p < 0.0001$) low in metabolic cases compare to control (Table 1). Insulin and HOMA-IR which plays an important role in these cases also significantly high in metabolic syndrome. Serum adiponectin was inversely correlated with waist circumference, BMI, plasma glucose, serum TG, VLDL, serum insulin, HOMA-IR, leptin, and LAR while

positive association with HDL-C were observed (Table 2). The relationship of the adiponectin with various metabolic factors reflects the classical association between low adiponectin and MetS.[19] Pham et al.[20] also investigated the association of total plasma adiponectin, antheropometric, and metabolic parameters and found an inverse association of total plasma adiponectin and fasting glucose levels as well as BMI.[20] Decreased adiponectin concentration have been linked to higher LDL-C and TG concentration probably due to adiponectin directly affecting lipoprotein lipase.[21,22] Data from two large cross sectional studies indicate that circulating adiponectin concentration are negatively correlated with TG concentration and strongly positively correlated with plasma HDL concentration.[22,23] In previous studies reported the adiponectin levels was low in patients with MetS and those with type 2 diabetes mellitus, suggesting the hypoadiponectinaemia contributes to the atherogenesis of these conditions.[24,25] Insulin resistance is a major risk factor for the development of atherosclerosis and it also affects adiponectin levels, which become gradually decreased with increasing insulin resistance.[26] Insulin regulates the secretion of various proteins from adipose tissue. Elevated plasma insulin in the metabolic subjects in present study may be responsible for the decreased adiponectin concentrations.

Evaluation of the leptin/adiponectin ratio (LAR) has been suggested as a useful parameters for assessing insulin resistance in patients with and without DM.[27,28] Inoue et al.[27] reported that the LAR was a more effective measure of insulin resistance than either adiponectin or leptin alone, and it was a more sensitive and reliable marker of insulin resistance than the HOMA-IR in subjects without hyperglycemia, as well as in type 2 DM. The utility and potential benefits of determining the correlation between the LAR and HOMA-IR is a measure of insulin resistance in metabolic syndrome cases. The correlation between LAR and other metabolic variables showed positive correlation with all variables except HDL-C and adiponectin these two showed the inverse relation with LAR. Similar finding indicated by Finucane et al.[29] Moreover, some studies have reported that the LAR was a more effective indicator of insulin resistance than adiponectin, leptin or the HOMA-IR in non diabetic healthy Korean males[30] and type 2 diabetic patients. Recently Kotani and Sakane reported that the LAR could serve as a clinically useful marker for detecting metabolic syndrome in the general Japanese population. Present results showed that the LAR had a highly significant positive correlation with glucose, TC, LDL, and insulin and a highly significant negative correlation with HDL and adiponectin (Table 3) (graph 2). These findings were in agreement with those of Yoon et al.,[31] who reported that LAR had more predictive power than the HOMA-IR for the lipid components of MetS such as TG and HDL because the LAR is based on the presence of leptin and adiponectin. Both of these adipokines are closely linked to fat metabolism and indicate an enhancement of insulin resistance and obesity. Therefore, lipid metabolism linked to the LAR could provide a different explanation than insulin resistance for the pathophysiology of MetS.[31] Its concluded from the present study that hypoadiponectinemia was associated with metabolic syndrome. It was found that metabolic males have significantly lower levels of adiponectin than females. It was observed that the serum adiponectin level was negatively correlated with HOMA-IR and positively correlated with HDL-C. The finding indicate that adiponectin may have a wide role in metabolism of lipoprotein. It may act as an anti atherosclerotic factor through improving insulin resistance and lipid profile.

Conclusion

The present study concluded that decreased adiponectin level observed in metabolic cases, which was low in men compare to women. The finding indicate that adiponectin may have a wide role in metabolism of lipoprotein. It may act as an anti atherosclerotic factor through improving insulin resistance and lipid profile.

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