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Original Research Article

Hypoadiponectinemia is associated with increased insulin resistance, dyslipidemia and presence of type 2 diabetes in non obese central Indian population

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ABSTRACT

Background: Accumulating evidence suggests that adiponectin, a major adipocyte secretory protein, has insulin-sensitizing and anti-atherogenic properties and protects against later development of type 2 diabetes. We investigated the association of adiponectin with insulin resistance, blood lipids and type 2 diabetes in non obese central Indian population.
Methods: Anthropometric and biochemical parameters were measured in 149 (81 male and 68 female) newly diagnosed non obese type 2 diabetic patients and 157 (85 male and 72 female) age and body mass index (BMI) matched controls.
Results: Adiponectin level ($p<0.0001$) was significantly lower in the diabetic group than in non diabetic control. In an age, gender and BMI adjusted model, adiponectin level was significantly negatively correlated with waist circumference, waist to hip ratio, systolic blood pressure, fasting insulin, homeostasis model assessment-insulin resistance (HOMA-IR) ($p= 0.0034$), HbA1C, total cholesterol, LDL-cholesterol, and triglycerides ($p<0.0001$) and positively correlated with HDL-cholesterol ($p =0.0014$) in non obese type 2 diabetic group. However, there was no significant correlation between adiponectin and glucose in this study. In stepwise linear regression analysis, adjusted for potential confounder, significant inverse association was observed between serum adiponectin level and HOMA-IR ($p = 0.0001$). In multivariate logistic regression model, adjusted for age, gender, BMI, waist circumference, and waist-hip ratio, lower adiponectin was independently associated with the presence of type 2 diabetes ($p<0.0001$).
Conclusions: Lower adiponectin levels in non obese type 2 diabetic patients were significantly related to the increased insulin resistance, dyslipidemia, and presence of type 2 diabetes, independently of overall and abdominal adiposity, thereby suggesting a direct link between adiponectin and carbohydrate and lipid metabolism in human.

Keywords: Adiponectin, Dyslipidemia, HDL-cholesterol, Insulin resistance, Triglycerides, Type 2 diabetes

INTRODUCTION

The prevalence of type 2 diabetes has been increasing day by day in the world.[1] According to International Diabetes Federation estimates, around 415 million people had diabetes mellitus in 2015 and this number is expected to rise to 642 million by 2040.[2] Furthermore, Asian Indians are known to be at a high risk for type 2 diabetes, cardio-vascular disease (CVD), and metabolic syndrome.[3] India is home to 69.1 million people with diabetes mellitus and

is estimated to have the second highest number of cases of diabetes mellitus in the world after China in 2015.[2] Type 2 Diabetes mellitus constitutes up to 95% of all diabetes and is characterized by chronic hyperglycemia, impaired insulin secretion from pancreatic beta cells and insulin resistance of the peripheral target tissue.[4] Insulin resistance is significantly associated with obesity, especially with abdominal and visceral obesity with an abnormally increased waist to hip ratio, dyslipidemia, hypertension and other metabolic disorders, the most likely underlying cause being the increased free fatty acid flux secondary to insulin resistance.[5] Both type 2 diabetes and the insulin resistance syndrome are associated with a marked increase in the risk for CVD.[6]

Accumulated evidence suggests that increased cytokines secreted from adipose tissue, known as adipokines, may be responsible for initiation of proinflammatory status that percolates the development of both insulin resistance (IR) and endothelial dysfunction. Adiponectin, also known as adipocyte complement-related protein of 30 kDa (Acrp30), a 244 amino acid protein, consisting of four domains, an amino-terminal signal sequence, a variable region, a collagenous domain (cAd), and a carboxy-terminal globular domain (gAd), is the gene product of the adipose most abundant gene transcript 1(apM1).[7,8] It is a collagen-like protein that is exclusively synthesized in white adipose tissue, and circulates at relatively high (microgram/millilitre) concentrations in the serum. Whereas adiponectin is expressed largely in adipose tissue, circulating levels of adiponectin are significantly decreased in obesity, diabetes, metabolic syndrome, and coronary artery disease and can be increased upon administration of the insulin-sensitizing thiazolidinedione (TZD) class of compounds.[9-12] Adiponectin knockout mice exhibits diet-induced insulin resistance.[13] Furthermore, adiponectin decreases insulin resistance in mouse models of obesity and lipoatrophy.[14] Basic scientific studies have demonstrated that adiponectin has insulin-sensitizing, anti-atherogenic, and anti-inflammatory properties.[14-16] Plasma adiponectin levels were shown to be negatively correlated with fasting plasma glucose, serum insulin, serum triglycerides, and body mass index, and positively correlated with HDL-cholesterol.[10,16,17] Several previous studies have shown that increased adiponectin level protects against later development of type 2 diabetes.[10,16,18]

Despite having lower body weight and obesity rates, because of genetic predisposition, India has a higher prevalence of diabetes compared to western countries, suggesting that diabetes may occur at a much lower body mass index (BMI) in Indians compared with Europeans.[19] Therefore, relatively lean Indian adults with a lower BMI may be at equal risk as those who are obese.[20] To the best of our knowledge, although some studies have been done in Indian population regarding association between adiponectin and carbohydrate and lipid metabolism, similar studies, in central Indian population, specifically, in non obese newly diagnosed type 2 diabetic patients, are scanty. Therefore, the present study was designed to evaluate serum adiponectin levels in central Indian non obese newly diagnosed type 2 diabetic patient and study the association of adiponectin with insulin resistance, atherogenic lipid profile and presence of type 2 diabetes in that population.

METHODS

Participant selection

This study was conducted in the Department of Biochemistry, Peoples College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh and approved by the Institutional Ethics Committee. One hundred forty nine (81 male and 68 female) non obese newly diagnosed type 2 diabetic patients (Age: mean±SD; 51.77±9.19 years) were recruited from the out patient department of Peoples Hospital. One hundred fifty seven age and BMI matched healthy subjects (85 male and 72 female; age: mean±SD; 52.22±8.88 years) who had come for routine health check-up in our hospital, were taken as control. Diabetes mellitus was confirmed according to the 1999 World Health Organization (WHO) criteria.[21] To select the non-diabetic control individuals, the following criteria were used: 1) No diabetes in their first degree relatives. 2) Fasting plasma glucose concentration less than 110mg/dL. 3) Hemoglobin A1c concentration less than 5.5%. Non-obese (BMI<25kg/m^2) was selected based on the World Health Organization Asia Pacific Guidelines.[22] Brief clinical history of present and past illness and medical therapy were recorded from all participants. Written informed consent was obtained from the study group and controls before entry into the study. The exclusion criteria in the study group were:

- Suffering from or history of any systemic disease other than type 2 diabetes,
- Under hypoglycaemic, hypolipidemic drug or insulin treatment,
- Smokers or alcohol abuser.

Procedure

Body mass index (BMI) was calculated for all subjects by using the formula weight in kilograms divided by the square of heights in metres. Waist (WC) and hip circumference were measured in the standing position using standard techniques and waist to hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Seated systolic (SBP) and diastolic blood pressure (DBP) were measured by manual sphygmomanometer.

Laboratory analyses

Venous blood samples were collected after an overnight fasting in the morning in an aseptic condition from ante-cubital vein. Blood samples were centrifuged at -4°

centigrade and stored immediately at -80° centigrade until they were analysed. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were estimated by a standard laboratory kit (Biosystem) method using fully automated biochemistry analyser (Biosystem A25; BioSystems S.A., Barcelona, Spain). Low density lipoprotein-cholesterol (LDL-C) was calculated according to Friedewald's formula (TC [mg/dL]-HDL-C [mg/dL]-TG [mg/dL]/5).[23] Serum adiponectin was measured by ELISA method (Ray Biotech Inc, Norcross, GA, USA). Fasting insulin was measured by commercially available ELISA kit (LDN, Nordhorn). Insulin resistance was calculated by homeostasis model assessment (HOMA) based on the formula:[24]

HOMA-IR = fasting glucose (mmol/L)×fasting insulin (µU/ml)/22.5.

Statistical analyses

The Kolmogorov-Smirnov statistical test was used to test the normality of the distribution. Variables with a skewed distribution were log-transformed before performing statistical analyses. Data were shown as the mean±standard deviation. Comparison of baseline anthropometric and biochemical parameters between groups was done by unpaired Student's t-test. All correlations were analysed with Pearson's correlation coefficient. To adjust for confounding variables in the correlation analyses, partial correlation coefficients were calculated. Stepwise Linear regression analyses were done to study the association between HOMA-IR and adiponectin after multivariate adjustment for potential confounders. Multivariate logistic regression models were used to assess the association between serum adiponectin and type 2 diabetes with age, gender, BMI, WC and WHR as covariates. All tests were two-tailed and p value less than 0.05 were considered to be statistically significant. All data were analysed using statistical software SPSS version 20 (SPSS Inc., Chicago, IL, USA).

RESULTS

The baseline anthropometric and biochemical characteristics of 157 control (male: 85, female: 72, Mean age±SD; 52.22±8.88years) and 149 non obese type 2 diabetic patients group (Male: 81, female: 68, Mean age±SD; 51.77±9.19years) are presented in Table 1. The diabetic group had significantly higher BMI (21.84±1.78 Kg/m^2; vs. 21.65±1.98Kg/m^2; p = 0.0001), waist circumference (93.20±12.31cm vs.88.08±10.41 cm; p<0.0001), waist to hip ratio (1.01±0.14 vs.0.89±0.08; p <0.0001), fasting blood glucose (9.74±1.08mmol/L vs.4.69±0.97mmol/L; p<0.0001), fasting insulin(16.47±7.56µIU/ml vs.7.93±4.30µIU/ml; p <0.0001), HOMA-IR (7.15±3.47vs.1.64±0.94; p <0.0001), HbA1c (7.98±1.58% vs.5.41±0.93%; p <0.0001), and triglycerides levels (138.27±21.95mg/dl vs.101.46±14.32mg/dl; p<0.0001) than the control group, whereas HDL-cholesterol (47.96±11.97mg/dl vs.55.35±9.15mg/dl; p<0.0001) and adiponectin level (10.47 ± 4.66 µg/ml vs. 19.14±6.64µg/ml; p<0.0001) was significantly lower in the diabetic group (Table 1). However, there were no significant differences in diastolic and systolic blood pressure, total cholesterol and LDL-cholesterol levels between groups. Serum adiponectin levels were significantly lower among male when compared with female in both control (17.68±5.84µg/ml vs.20.85±7.15µg/ml; p=0.0031) and diabetic groups (9.45±4.85µg/ml vs.11.69±4.14; p=0.0027) (Table 2).

Table 1: Anthropometric and biochemical characteristics of control and non obese type 2 diabetic patients.

Parameters	Control	Non obese type 2 diabetic patients	p
N (Male/Female)	157(85/72)	149(81/68)	0.6579
Age (Years)	52.22±8.88	51.77±9.19	0.3832
BMI (Kg/m^2)	21.65±1.98	21.84±1.78	0.0001
Waist circumference (cm)	88.08±10.41	93.20±12.31	<0.0001
Waist to Hip ratio	0.89±0.08	1.01±0.14	<0.0001
DBP (mmHg)	81.55±5.36	82.44±5.48	0.1524
SBP (mmHg)	121.84±8.83	122.10±7.05	0.2042
Fasting blood glucose (mmol/L)	4.69±0.97	9.74±1.08	<0.0001
Fasting insulin (µIU/ml)	7.93±4.30	16.47±7.56	<0.0001
HOMA IR	1.64±0.94	7.15±3.47	<0.0001
HbA1c (%)	5.41±0.93	7.98±1.58	<0.0001
Total cholesterol (mg/dl)	174.09±19.08	179.19±39.31	0.1532
LDL-C (mg/dl)	103.45±20.78	103.59±39.64	0.9706
HDL-C (mg/dl)	55.35±9.15	47.96±11.97	<0.0001
Triglycerides (mg/dl)	101.46±14.32	138.27±21.95	<0.0001
Adiponectin (µg/ml)	19.14±6.64	10.47±4.66	<0.0001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol

Table 2: Comparison of serum adiponectin levels in male and female non obese type 2 diabetic patients.

Adiponectin levels (µg/ml)			
Groups	**Male**	**Female**	**p**
Non obese type 2 diabetic patients	9.45±4.85	11.69±4.14	0.0027
control	17.68±5.84	20.85±7.15	0.0031

Table 3: Pearson and partial correlation coefficients for associations between adiponectin and anthropometric and biochemical parameters in non obese type 2 diabetic patients.

Parameters	r	p	r_a*	P_a*
Age (Years)	0.277	0.0006	-	-
BMI(Kg/m^2)	-0.292	0.0003	-	-
Waist circumference (cm)	-0.380	<0.0001	-0.357	<0.0001
Waist to Hip ratio	-0.223	0.0063	-0.177	0.0323
DBP (mmHg)	-0.115	NS	-0.053	NS
SBP (mmHg)	-0.271	0.0008	-0.260	0.0015
Fasting blood glucose (mmol/L)	-0.151	NS	-0.109	NS
Fasting insulin (µIU/ml)	-0.296	0.0003	-0.233	0.0046
HOMA IR	-0.308	0.0001	-0.241	0.0034
HbA1c (%)	-0.228	0.0051	-0.188	0.0232
Total cholesterol (mg/dl)	-0.227	0.0053	-0.197	0.0172
LDL-C (mg/dl)	-0.285	0.0004	-0.236	0.0041
HDL-C (mg/dl)	0.354	<0.0001	0.262	0.0014
Triglycerides (mg/dl)	-0.424	<0.0001	-0.355	<0.0001

p<0.05 is significant. NS, not significant. *Adjusted for age, gender, and BMI (body mass index). HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein-cholesterol

Table 3 showed Pearson and partial correlation coefficients for associations between adiponectin and anthropometric and biochemical parameters in non obese type 2 diabetic patients. In diabetic group, significant inverse correlations between adiponectin and waist circumference (r= -0.380; p<0.0001), waist to hip ratio (r = -0.223; p= 0.0063), SBP (r = -0.271; p = 0.0008), fasting insulin (r= -0.296; p =0.0003), HOMA-IR (r = -0.308; p =0.0001), HbA1C (r = -0.228; p =0.0051), total cholesterol (r = -0.227; p =0.0053), LDL-cholesterol (r = -0.285; p=0.0004), and positive correlation between adiponectin and HDL-cholesterol (r = 0.354; p<0.0001), was attenuated but remained statistically significant even after additional adjustment for age, gender and BMI.

Further, the strength of inverse relationship of adiponectin and triglycerides remained same in both unadjusted and adjusted model (p<0.0001). Although, adiponectin levels tended to be negatively correlated with the fasting blood glucose (r = -0.151; p= NS), this did not reach statistical significance (Table 3).

Furthermore, we looked for associations of adiponectin with HOMA-IR in type 2 diabetic group using stepwise linear regression analysis. After adjustment for age, gender, BMI, waist circumference and waist to hip ratio, SBP, total cholesterol, HDL-cholesterol, and triglycerides, significant inverse association was observed between serum adiponectin level and HOMA IR (β = -0.229; p = 0.0001) (Table 4).

Table 4: Stepwise linear regression analyses of the relationship between HOMA-IR and adiponectin levels.

Independent variables	β	SE	Standardized β	p
Adiponectin*	-0.229	0.058	-0.308	0.0001

*Age, gender, BMI, waist circumference and waist to hip ratio, SBP, total cholesterol, HDL-C, and TG were also entered into the model and were excluded in the final step

When multivariate logistic regression analyses were performed with the presence of diabetes as dependent variable and serum adiponectin as independent variable, higher adiponectin levels were associated with lower odds of type 2 diabetes in unadjusted model (odds ratio = 0.788; p<0.0001; 95% CI=0.735-0.823), age, gender and BMI adjusted model (odds ratio = 0.763; p<0.0001; 95% CI = 0.719-0.809) as well as age, gender, BMI, waist circumference, and waist to hip ratio adjusted model (Odds ratio = 0.744; p<0.0001; 95% CI= 0.690-0.803) (Table 5).

Table 5: Association between adiponectin levels and type 2 diabetes among central Indian non obese population.

	β	Standard error	p	Odds ratio	95% confidence interval
Model 1: Unadjusted	-0.251	0.029	<0.0001	0.788	0.735-0.823
Model 2: Adjusted for age, gender and BMI	-0.271	0.030	<0.0001	0.763	0.719-0.809
Model 3: Adjusted for age, gender, BMI, Waist circumference and waist to hip ratio	-0.295	0.039	<0.0001	0.744	0.690-0.803

DISCUSSION

Adiponectin, an adipose tissue specific cytokine, is known to have a regulatory effect on the metabolism of glucose and lipid and seems to protect against the development of insulin resistance and diabetes. In light of alarming rise in diabetes among Indians, research on levels of serum adiponectin and its association with other risk factors for the development of type 2 diabetes in this population, is of great interest. In the present study, non obese type 2 diabetic patients group was characterized by significant hyperglycemia, hyperinsulinemia, and increased insulin resistance. In line with the previous studies, we have also demonstrated significantly lower levels of plasma adiponectin in those with type 2 diabetes than non diabetic group.[9,10,16] Experimental study has showed that secretion of adiponectin by 3T3-L1 adipocytes requires phosphatidyl inositol-3-kinase (PI-3K), a major intermediate of insulin signalling activity.[25] Insulin stimulated insulin receptor substrate 1(IRS-1)-associated PI-3K activity has been shown to be suppressed in adipocytes of type 2 diabetic subjects.[26] Thus, it is possible that the decreased adipocyte PI-3K activity in type 2 diabetic patients may contribute to the decreased adiponectin levels and in a negative feedback loop, adiponectin may regulate glucose metabolism, modulating both beta cell insulin secretion and peripheral insulin resistance. Additional investigations to test this hypothesis are warranted.

Our findings of significant inverse association between adiponectin levels and presence of type 2 diabetes among central Indian population, independent of overall and abdominal adiposity, are in line with recent animal study reported a decline in adiponectin before the onset of obesity, insulin resistance and diabetes, and AdipoR agonist ameliorated diabetes of obese rodent model db/db mice.[27,28] The close connection between adiponectin and diabetes is further supported through genetic study which has mapped a susceptibility locus for the diabetes to chromosome 3q27, where the adiponectin gene is located.[29] However, the results from previous studies on the adiponectin-type 2 diabetes relationship in human have not been entirely consistent. Using the adiponectin gene summary statistics genetic risk scores, Yaghootkar H et al found no evidence of an association between adiponectin lowering alleles and insulin sensitivity, which do not support a causal role for reduced circulating adiponectin levels in insulin resistance and type 2 diabetes.[30] In the study of Davis SK et al, adiponectin level was inversely associated with type 2 diabetes only among women but not in men.[31] Our finding is in agreement with previous studies consistently reported a lower risk of type 2 diabetes in individuals with higher circulating adiponectin levels.[10,16,18,32] Given these observations, combined with our result, it is logical to speculate that decreased adiponectin is a risk factor for type 2 diabetes independent of other risk factors including BMI, even in non obese population.

Our analysis revealed significant negative correlations of serum adiponectin levels with fasting insulin and HOMA-IR in a model adjusted for age, gender, and BMI. Inverse association of adiponectin with HOMA-IR remained significant even after adjustment for age, gender, BMI, waist circumference, waist to hip ratio and other potential confounder suggesting that adiponectin mediated insulin action may not be fully dependent on adiposity. Our observations are in accordance with several previous studies, but contradict some other study which showed no significant correlation of adiponectin with fasting insulin and HOMA-IR in diabetic patients.[10,14,16,33] Our findings were also highly consistent with animal study showed that adiponectin knockout mice displayed impaired insulin signalling in the liver to cause hepatic insulin resistance, and administration of recombinant adiponectin increased insulin sensitivity in mouse models of obesity and lipoatrophy.[13,14] Further, the findings that adiponectin level improves in the thiazolidinedione treated subject, support the thought that adiponectin may play a role in the thiazolidinedione effect of improving insulin sensitivity.[12]

A beneficial effect of adiponectin on blood glucose has been confirmed in previous studies.[10,12,16] However, we did not find statistically significant correlation between adiponectin and glucose in this study. This contradictory finding may be attributed to several factors including difference in adiponectin concentration among different ethnic groups, and overall study design. Also, altered insulin secretion or difference in body fat distribution may play a role. However, prospective studies with large number of sample in different population are needed to confirm our finding.

Although it is unclear how adiponectin affects insulin resistance, some evidence indicates that adiponectin regulates glucose metabolism and insulin sensitivity by activating 5'AMP activated protein kinase (AMPK) mediated phosphorylation of acetyl coenzyme A carboxylase, modulating insulin induced tyrosine phosphorylation of insulin receptor in skeletal muscle to improve glucose tolerance and fatty acid oxidation in myocytes and hepatocytes.[14,34] It is also speculated that adiponectin facilitates glucose uptake by increasing glucose transporter-4 expression and its translocation. It also stimulates glucose utilization and fatty acid oxidation in skeletal muscles and simultaneously suppresses gluconeogenesis in the liver, by inhibiting the hepatic enzyme phosphoenolpyruvate carboxylase, inhibits the synthesis of fatty acids and stimulates their oxidation.[35]

In our study, adiponectin levels showed significant negative correlation with triglycerides and positive correlation with HDL-cholesterol in non obese type 2 diabetic patients group. Further, these correlations remained strongly significant, even after adjustment for age, gender, and BMI, thereby suggesting a potential direct link between adiponectin and lipid metabolism.

The result of our study is confirmed by previous authors.[11,17,36] On the other hand, some studies found no significant association between adiponectin levels and HDL-cholesterol.[37] The exact mechanisms mediating the relationship between adiponectin and lipid metabolism are largely unknown. In experimental study, hypertriglyceridemia has been reported in adiponectin-deficient mice.[38] Furthermore, administration of adiponectin normalized high-fat diet-induced hyper triglyceridemia in mice.[14] It is unclear, however, whether adiponectin improves both insulin resistance and lipid profile or whether low insulin resistance and or a good lipid profile increases the plasma adiponectin level. Effects of adiponectin on hepatic lipase activity, increased in central obesity, may play a role.[36] Some other studies demonstrated that adiponectin could decrease plasma triglyceride levels by increasing the triglycerides and VLDL-TG catabolism by the way to increase skeletal muscle lipoprotein lipase and VLDL receptor expression.[39] The possible mechanisms underlying association of adiponectin with HDL cholesterol metabolism may partially be explained with the peroxisome proliferator-activated receptor- α (PPAR-α), which affects the gene associated with HDL-cholesterol metabolism. Adiponectin stimulated PPR-α ligand activates in liver and skeletal muscles, which results in the increased synthesis of HDL-cholesterol. Adiponectin has also been shown to reduce the release of ApoB and ApoE from hepatocytes, resulting in reduced release of TG-rich lipoproteins from the liver thus preventing the formation of TG-rich HDL and leading to elevated systemic HDL-cholesterol.[14] Increased insulin resistance and or hyperinsulinemia in type-2 diabetes may play a role in the association of adiponectin with dyslipidemia.[14,16] Taken together these data, our results confirm the protective role of adiponectin in lipid metabolism. In the present study, female subjects had significantly higher adiponectin levels than male subjects irrespective of diabetic status. Similar reports have been published by some authors.[11,36] The reason for the sex difference in adiponectin concentration has not yet been understood. It is believed that sex hormones may influence the plasma adiponectin levels.[40] Another explanation might be due to the different body fat distribution between males and females as the number of fat cells and their size are possible determinants of adiponectin levels in blood since it is mainly synthesized from adipocytes.

There were several limitations to this study. First, the experimental group consisted of only subjects who visited peoples hospital, a tertiary care centre, for the evaluation of type 2 diabetes mellitus, which may have resulted in a biased selection. Therefore, our findings need to be confirmed in a large number of subjects in different population through random selection. Secondly, sample size was not large enough. Third, authors must emphasize the cross-sectional nature of our study and therefore, no inferences of causality can be made.

CONCLUSION

In conclusion, in the present study, adiponectin levels were significantly decreased in central Indian non obese type 2 diabetic patients compared to non diabetic control group. Furthermore, lower adiponectin levels in this population were significantly related to the increased insulin resistance, atherogenic lipid profile, and presence of type 2 diabetes, even after adjustment for other potential confounders. It appears that the insulin-sensitizing and anti atherogenic effect of adiponectin may not be mediated by changes in the adiposity level, thereby suggesting a direct link between adiponectin and carbohydrate and lipid metabolism in human. However, we found no significant relationship between adiponectin levels and fasting blood glucose in non obese patients with type 2 diabetes. Nevertheless, our results support the concept of a disturbed adipose tissue metabolism in the pathophysiology of type 2 diabetes. Further prospective studies are warranted to generalize our results.

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