



Serum Adiponectin Levels and Insulin Resistance in Obesity Associated with Type 2 Diabetes Mellitus

Mansi Jha^{*1}, S.K. Vardey¹, Jyoti Jain¹, Sachdev Yadav²

Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan, India.

Department of Pharmacy, Banasthali University, Rajasthan, India.

*Corresponding author's E-mail: writetomansi@rediffmail.com

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ABSTRACT

The anti-inflammatory and insulin-sensitizing properties of adiponectin make this adipose tissue secreted adipokine a very promising target for therapeutic intervention. Adiponectin concentrations are decreased in many disorders such as obesity, type 2 diabetes (T2DM) and adiposopathy. Asian Indians are known to have an unfavorable adipokine profile and findings from metabolic studies have suggested several mechanisms through which it may decrease the risk of T2DM and obesity including suppression of hepatic gluconeogenesis and stimulation of insulin secretion. Limited studies exist on the role of adiponectin in T2DM and obesity in our population since ethnic differences have previously been reported, we determined the levels of serum adiponectin levels in T2DM patients with and without obesity. Total of 100 T2DM patients (mean age 44.93±9.08; 63 male and 37 female) were enrolled for the study. The Diabetic non obese group comprised of 39 patients (27 male and 12 female), 61 patients were included in the Diabetic obese group (36 male and 25 female). Body mass indexes (BMI), waist to hip ratio (WHR) were determined. Plasma concentrations of adiponectin, glucose, insulin, cholesterol, triglycerides, HDL and LDL were measured at fasting. HOMA-IR was calculated. Plasma adiponectin levels were lower in the diabetic obese group (3.86±1.05) than the diabetic non-obese group (5.00±1.81) and the difference was statistically significant (p=.000) and the percentage of obesity associated with T2DM was more in females (67.56%) than males (57.14%). Hypoadiponectinemia is related to both obesity and diabetes and the prevalence % of obesity is more pronounced in diabetic women than diabetic men.

Keywords: Adiponectin, adipokine, insulin resistance, type 2 diabetes, obesity.

INTRODUCTION

Many recent epidemiological studies have documented the rapid increase in the prevalence of obesity. The metabolic complications of obesity, often referred to as metabolic syndrome a term that consists of insulin resistance, often culminating in β -cell failure, impaired glucose tolerance and type 2 diabetes, dyslipidemia, hypertension, and premature heart disease.¹ Adipokines contribute to the pathophysiology of obesity-linked disorders through their abilities to modulate inflammatory and metabolic processes.² Diabetes mellitus (DM) is a hereditary, chronic and endocrine metabolic disorder which causes deaths world wide.³ India, a developing Asian country with fast industrialization and a modern lifestyle is facing a grave problem in having the largest number of people with diabetes^{4,5} which is estimated to reach 80 million by the year 2030.^{6,7} The literature on Indian studies showed a threefold rise in the diabetic prevalence in rural as well as urban areas.^{8,9} Recently, considerable concern has been caused by the increasing prevalence of diabetes in India,¹⁰ particularly in the urban population.¹¹ Diabetes is associated with a greater risk of mortality from cardiovascular disease (CVD) which is well known; due to an increased prevalence of insulin resistance and T2DM due to excess body weight and sedentary lifestyle.¹² Insulin resistance plays a key role in the development of the metabolic risk factors, including hyperinsulinemia, hypertension, glucose intolerance, and dyslipidemia that

dramatically heightens cardiovascular risk.^{13, 14} In terms of pathogenesis and pathophysiology DM and obesity are closely interrelated. The prevention and control of these diseases has become prime health concern.¹⁵⁻¹⁷ The susceptibility to the metabolic disorders like type 2 diabetes mellitus (T2DM), insulin resistance (IR) and cardiovascular disease (CVD) is higher in Asian Indians compared to the Western population due to greater prevalence of high body fat (%) and abdominal obesity despite low BMI.^{18,19}

The recent focus on adipose tissue as an endocrine organ secreting signalling proteins, collectively termed adipokines, has prompted current interests in associations of adipokines with insulin resistance and diabetes.²⁰ This has led to growing scientific interest in the biology of adipokines. Although underlying mechanisms have not been completely explained, adipokines have been linked with obesity induced inflammation and signalling pathways that contribute to type 2 diabetes.²¹ Prospectively, adiponectin, an anti-inflammatory, anti-atherogenic, and insulin-sensitizing adipokine²², Adiponectin is an adipokine whose biosynthesis is deranged in obesity and diabetes mellitus, predisposing to atherosclerosis. Clinical and experimental studies also suggest that low adiponectin levels contribute to the development of obesity-linked illness including cardiovascular disease, insulin resistance and inflammation.²³ Therefore it is perhaps the most interesting and promising compound for the clinician



since it has profound protective actions in the pathogenesis of diabetes and cardiovascular disease.²⁴ It is exclusively expressed in white adipose tissue and is located on chromosome 3q27 that has a mapped susceptibility locus for T2DM and metabolic syndrome.^{25,26} It is a hormone produced solely by adipocytes and is regulator of glucose and energy homeostasis^{27,28} and is collagen – like protein synthesized by adipocytes that circulates in human plasma as approximately 0.01 percent of total plasma protein it increases insulin sensitivity and tissue fat oxidation, resulting in reduced circulating fatty acid levels.^{29,30} Adiponectin has become an important object for physiological and pathophysiological studies with the aim of potential therapeutic applications because of its anti – inflammatory properties and the ability to stimulate insulin sensitivity.³¹

MATERIALS AND METHODS

We studied a total number of 100 T2DM (aged 44.93 ± 9.08; 63 male and 37 female; fasting blood glucose 169 ± 61.08) patients visiting the SMS endocrinology OPD. This group was divided into two groups on the basis of obesity. Patients with BMI ≤ 25 Kg/m² were included in the non obese T2DM group and patients with ≥25 Kg/m² were included in obese T2DM group.³² The study was performed in SMS Medical College and Hospital, Jaipur. Signed informed consent was obtained from all participants, and the study was approved by the hospital ethics committee.

All study patients were subjected to investigations and physical examination which were recorded on a performa. Height and weight were measured to the nearest 0.1 kg and 0.5 cm, respectively. Waist circumference was measured at the horizontal circumference between the lowest rib margin and the iliac crest and hip circumference was measured at the maximum circumference over the buttocks. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Waist to hip ratio (WHR) was calculated as waist circumference divided by hip circumference. The insulin resistance index was assessed by homoeostasis model assessment (HOMA-IR) using the formula (HOMA-IR) = fasting plasma glucose (mg/dl) x insulin (μU/ml)/405.³³

Blood samples were obtained by venipuncture after overnight fasting (minimum 12 hours fasting) to estimate the following : Serum insulin was estimated by chemiluminescent immunometric assay using Immulite 2000 machine, Fasting Blood glucose, Serum lipid profile (Total cholesterol, Triglycerides, HDL,) were measured using (Recombigen, Anamol, Beacon, Logotech kits as per manufacturers instructions) on fully automated analyzer (AU400/Kopran). LDL was calculated by friedwald formula. Serum was stored at -20° C in aliquots for analysis of adiponectin. Adiponectin was measured using Biovendor's Human Elisa (sandwich) commercial kit for research use only.

The presentation of the results is in the form of mean ± standard deviation. SPSS for windows (version 19, Chicago, IL, USA) was used for the analysis of data collected. The Group means were compared using independent *t* test. For all statistical assessment a value of *p* < 0.05 was accepted to be significant.

RESULTS

Anthropometric and metabolic characteristics of the study population along with adiponectin concentrations are summarized in Table 1. The mean age of T2DM non-obese group was 43.18±11.29 years and that T2DM obese group was 46.05±7.19 years. The BMI for diabetic non-obese group and diabetic obese group was 22.07±1.89 (Kg/m²) and 29.28±3.01 (Kg/m²), respectively (*p*</0.00). BMI, WC and HC were significantly higher in the diabetic obese group (*p*<0.000). When we compared the two groups with respect to lipid profile parameters there was no statistically significant difference between the two groups. The markers of insulin resistance i.e. fasting blood glucose, insulin were significantly greater in the diabetic obese group. (*p*<0.05) when compared with the diabetic non-obese group.

Plasma adiponectin levels were lower in the diabetic obese group (3.86±1.05) than the diabetic non-obese group (5.00±1.81) and the difference was statistically significant (*p*=.000).

Table 2 shows the distribution of gender and obesity in relation to T2DM. Among the total 100 patients (63 male and 37 female) studied, the percentage of obesity was more in females (67.56%) than males (57.14%). Fig. 1 and Fig 2 illustrate the same findings.

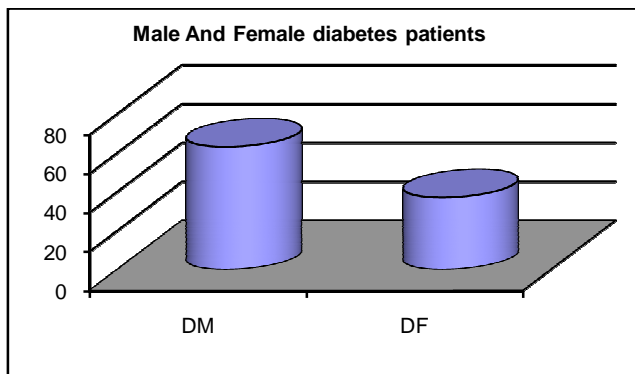
Table 1: Anthropometric and metabolic characteristics of the diabetic population (mean ± SD)

Variables	Diabetic non-obese	Diabetic obese	P
N	39	61	
(Male/Female)	27/12	36/25	
Age(yrs.)	43.18±11.29	46.05±7.19	NS
BMI(Kg/m ²)	22.07±1.89	29.28±3.01	0.0
WC(Cm)	87.17±8.40	97.70±9.53	0.0
HC(Cm)	91.70±9.37	101.88±10.45	0.0
WHR	0.95±.07	0.96±.08	NS
TG (mg/dl)	143.64±69.23	164.92±62.55	NS
Cholesterol (mg/dl)	187.31±49.52	191.30±33.33	NS
HDL(mg/dl)	44.19±4.79	44.66±6.27	NS
LDL(mg/dl)	114.20±44.83	113.31±31.17	NS
HOMAIR	2.31±2.02	3.02±2.38	NS
Insulin(μU/ml)	5.00±4.41	7.88±6.07	0.012
Glucose(mg/dl)	158.80±57.57	185.35±63.59	0.033
Adiponectin(μg/ml)	5.00±1.81	3.86±1.05	0.000

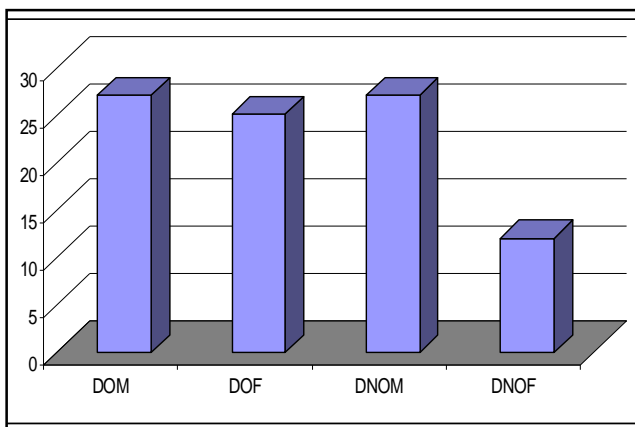
NS = Not significant, *p* < .05 is taken as statistically significant.

Table 2: Prevalence of obesity in the overall diabetic population

Variables	Men	Women
Total Diabetic	63	37
Diabetic non obese	27	12
Diabetic obese	36	25
% diabetic obesity	57.14%	67.56%

Figure 1: Diabetes in Men and Women

DM = Diabetic Males (63) , DF = Diabetic females (37)

Figure 2: Obesity in association with type 2 diabetes mellitusDOM = Diabetic obese male (36), DOF = Diabetic obese female (25)
DNOM = Diabetic non- obese male (27), DNOF = Diabetic non-obese female (12)

DISCUSSION

In the present study, comprehensive relationships between adiponectin and insulin resistance index, lipids and anthropometric parameters, which are important risk factors for the development of atherosclerosis, were evaluated in T2DM patients with and without obesity. Plasma adiponectin levels were lower in the diabetic obese group (3.86 ± 1.05) than the diabetic non-obese group (5.00 ± 1.81) and the difference was statistically significant ($p = .000$). Al Kayatt et al. studied the association between plasma adiponectin level with lipid profile in type-2 diabetic obese patients and found that decreased serum adiponectin level was associated with obesity and type-2 diabetes mellitus and that adiponectin as a hormone plays an important role in the prevention of hyperlipidemia, and consequently atherosclerosis and its

complications.³⁴ Kim C et al. (2006) reported that the homeostasis model assessment of the insulin resistance score was similar in non diabetic obese and diabetic obese groups, whereas serum adiponectin was lower in the diabetic obese group.³⁵ Rizk N et al. (2008) provided the first evidence that adiponectin is reduced in Qatari obese subjects with and without diabetes.³⁶ Izadi M et al. (2011) demonstrated that the concentration of adiponectin, an anti-inflammatory and antidiabetic marker, is a precise insulin resistance predictor in obese patients with type 2 diabetes.³⁷

Previous study performed by Weyer et al. (2001) also demonstrated hypo-adiponectinemia in obesity and type-2 diabetes mellitus and a close association with insulin resistance and hyperinsulinemia confirming that adiponectin is the only adipose-specific protein known to date that, despite its exclusive production in white adipose tissue, is negatively regulated in obesity.³⁸ Hotta et al. also reported that subjects with type 2 diabetes mellitus showed significantly decreased plasma adiponectin concentrations.³⁹ Lower adiponectin levels in diabetic patients have also been observed in an indian study conducted by Lele, Joshi et al.⁴⁰ Earlier studies have also reported hypoadiponectinemia in Asian Indians compared to Caucasians.^{41,42} Our study confirmed previous findings that type 2 diabetes and obesity are associated with low plasma adiponectin concentrations and that adiponectin is further decreased in T2DM patients with obesity. The hypoadiponectinemia in people with type 2 diabetes is in large part attributable to insulin resistance and/or hyperinsulinemia. Adiponectin is the most abundant adipokine and has insulin-sensitizing^{43,44} and anti-inflammatory properties.^{45,46} Levels of adiponectin are significantly reduced in obese subjects compared to non-obese subjects, such that a significant negative correlation is found between body mass index (BMI) and plasma adiponectin levels. The reason for this reduction in adiponectin in obese subjects remains unclear but it may be due to either transcriptional suppression or decreased secretion caused by inflammatory cytokines. For example, pro-inflammatory cytokines (such as IL-6) are upregulated in the obese state and cause both a decrease in adiponectin mRNA and a reduction in adiponectin secretion from 3T3-L1 adipocytes.⁴⁷ It was demonstrated in several experimental studies that both adipose adiponectin mRNA expression and plasma adiponectin levels are decreased in most rodent models of obesity.⁴⁸ Because adiponectin is thought to have an anti-atherogenic action, the presence of hypoadiponectinemia may predispose subjects to atherosclerosis, and may progress the atherogenesis in insulin resistance.⁴⁹ We also found that in our study group obesity was more prevalent in the T2DM women obesity was more in females (67.56%) than males (57.14%). Gupta et al reported that % of obesity was higher in women (50.7 %) than men (46.2%) in normal urban middle class population of Jaipur.⁵⁰

CONCLUSION

Lower concentrations of adiponectin were found in type 2 diabetes with obesity. An interesting finding of our study is that adiponectin was lower in both groups than reported by other previous studies putting our local population to a further cardiometabolic risk and also that obesity is more pronounced in diabetic women than diabetic men.

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