

Adiponectin: Role in Glucose Homeostasis in Relation to BMI in Type 2 Diabetics

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ABSTRACT

Introduction: Amongst the many adipocytokines discovered in recent times, Adiponectin has drawn much attention for its insulin sensitising, anti-atherogenic and anti-inflammatory actions. Though, Adiponectin is secreted by adipose tissue, its decreased levels are associated with obesity and Type 2 Diabetes Mellitus (T2DM).

Aim: The present investigation was conducted to study the role of Adiponectin in glucose homeostasis in T2DM subjects in relation to Body Mass Index (BMI).

Materials and Methods: Seventy five T2DM patients visiting the Endocrinology OPD of a tertiary care hospital were selected for the study. Patients on thiazolidinediones were not included. They were divided into three groups of 25 each based on BMI. Group A: <25 kg/m² Group B: 25-29.99 kg/m² Group C: ≥30 kg/m². Waist Hip Ratio (WHR) was recorded. Serum Adiponectin levels were estimated by ELISA, FBS, CRP, HbA1c, insulin and lipid profile was analysed on Cobas 6000 (Roche). Insulin

resistance was measured by Homeostasis Model Assessment (HOMA-IR).

Results: A 56% patients had low Adiponectin levels (<10 µg/mL), only 10.8% patients had >25 µg/mL. Group B patients had lowest levels of Adiponectin (11.86±8.79 µg/mL). FBS, HbA1c, insulin levels and HOMA-IR showed a negative correlation with Adiponectin in all the groups but was significant in group B only (r=-0.555, -0.611, -0.477 and -0.528 respectively). CRP and all the fractions of lipid profile (except HDL) showed negative correlation with Adiponectin in all the groups but it was not significant. HDL levels increased with increase in Adiponectin levels in all the groups.

Conclusion: This study reaffirms the significant role that adipose tissue hormones play in pathophysiology of T2DM. Significant negative correlation of glucose, HbA1c, insulin resistance with Adiponectin noted in overweight diabetics supports the hypothesis that these patients can be potential therapeutic target for drugs increasing Adiponectin levels.

Keywords: Adipocytokines, HOMA-IR, Insulin levels, Waist hip ratio

INTRODUCTION

A cluster of biochemical and physiological changes characterised by increased body weight, WHR and the incidence of impaired glucose tolerance, dyslipidaemia and hypertension is defined as metabolic syndrome. This has been recognised as the main cause of global epidemic of diabetes and cardiovascular disease. T2DM seems to be closely related to obesity and endocrine activity of adipose tissue [1]. However, the effect of adipose tissue on glucose metabolism still needs to be evaluated.

Diabesity is new term describing diabetes in the context of obesity [2]. It is an acknowledgement of the intricate relationship that exists between the pathophysiology of obesity and T2DM. While the association between these two has long been apparent, the endocrine role of adipose tissue has been only recently acknowledged. Hormones secreted by adipose tissue referred to as "adipocytokines" include Adiponectin, Leptin, Resistin, TNF-α etc., [3-5].

Adiponectin is a unique and essential adipocytokine synthesized in white adipocytes and secreted as trimer, tetramer and High Molecular Weight (HMW) form. In obesity, its levels are lower in spite of the fact that adipose tissue is the only source of adiponectin, suggesting a negative feedback inhibition on its synthesis. Exact mechanisms of body weight regulating adiponectin levels are still not clear [6-8].

Adiponectin levels are found to be low in T2DM patients whereas high adiponectin levels were found to decrease its incidence. Various studies have shown the analogy between low levels of adiponectin and insulin resistance [5,6]. Adiponectin (especially HMW oligomers) has been reported to sensitise the body tissues towards action of insulin. It mediates insulin sensitivity by increasing

fatty acid oxidation and glucose uptake by activation of Adenosine Monophosphate Dependent Kinase (AMPK), PPAR-α, thereby regulating glucose metabolism [8-10]. Low adiponectin levels often reported in T2DM patients may be the cause of insulin resistance in these patients. Apart from glucose, it also regulates peripheral tissue lipid metabolism and inflammation [5,6].

In obese individuals adiponectin levels have been shown to be more tightly linked with insulin resistance than with degree of obesity [11]. The ever increasing incidence of obesity and T2DM is compelling us to look for newer approaches to understand the complex pathophysiology underlying these conditions and search for new markers and therapeutic targets. With this aim, the present study was conducted on obese T2DM patients to study correlation of adiponectin with HOMA-IR, lipid profile and C-Reactive Protein (CRP). Correlation of central obesity with adiponectin levels was also studied.

MATERIALS AND METHODS

In a prospective observational study seventy-five T2DM patients (age >40 years, both gender) visiting the Endocrinology OPD of Dayanand Medical College and Hospital, Ludhiana were selected. Patients with liver disease, kidney disease, infections, malignancy and on thiazolidinediones were excluded. Study patients were divided into three groups of 25 each based on BMI: Group A: <25 kg/m², Group B: 25-29.99 kg/m², Group C: ≥30 kg/m². WHR was recorded. Fasting blood sample was taken for biochemistry analysis. Serum adiponectin levels were estimated by Enzyme-Linked Immunosorbent Assay (ELISA) using Human Adiponectin ELISA kit, fasting blood sugar and lipid profile (enzymatic method) [12-16], glycated haemoglobin (HbA1c, immunoturbidometrically) [17],

CRP (turbidometrically) [18], and insulin (electrochemiluminescence method) [19] were analysed on Cobas 6000 (Roche). Insulin resistance was estimated by HOMA-IR.

Study protocol was approved by ethical committee of the institution. Informed and written consent was taken from all the patients.

Mean and standard deviation was computed and comparison between three groups done using t-test. Pearson's correlation coefficient was used to assess the relationship of adiponectin with WHR, FBS, HbA1c, insulin, CRP and lipid profile. A p-value <0.05 was considered as statistically significant.

RESULTS

In the present study, adiponectin levels ranged from 2.1-35 µg/mL. Majority of the patients (56%) had low adiponectin levels <10 µg/mL, only 10.8 % patients had >25 µg/mL [Table/Fig-1].

Adiponectin levels	<10 µg/mL n=42	10-25 µg/mL n=25	>25 µg/mL n=8	r-value
FBS	220.57±83.48	167.56±55.36	155.50±48.53	FBS vs. Adipo -0.378**
HbA1c	10.25±2.20	8.88±2.07	8.18±1.45	HbA1 vs. Adipo -0.394***
Insulin	30.89±23.55	27.65±24.67	19.40±9.86	Insulin vs. Adipo -0.228*
HOMA-IR	16.5±12.9	12.5±11.2	7.9±5.6	HOMA-IR vs. Adipo -0.286**
WHR	1.05±0.12	0.97±0.11	0.91±0.07	WHR vs. Adipo -0.311**

[Table/Fig-1]: Mean Levels of glucose metabolism markers and its correlation with adiponectin in total subjects. [n=75]
Significance, p-value *<0.05, **<0.01, ***<0.001.

FBS, HbA1c, insulin levels, HOMA-IR and WHR decreased with increase in adiponectin levels (patients were grouped in 3 levels of adiponectin), showing significant negative correlation with adiponectin when taken in all the subjects (-0.378, -0.394, -0.228, -0.286 and -0.311 respectively) [Table/Fig-1]. All the lipid fractions (except HDL) and CRP correlate negatively with adiponectin although not statistically significant. HDL levels increased with increase in adiponectin from 37.18±6.60 to 42.63±12.91 mg/dL [Table/Fig-2] Mean adiponectin levels were lowest and WHR was highest in group B patients (11.86±8.79 µg/m, 1.03±0.15) but were not significantly different from other two groups [Table/Fig-3]. No significant difference was observed between males (14.2±9.9 µg/mL) and females (13.1±9 µg/mL) adiponectin levels.

Adiponectin levels	<10 µg/mi n=42	10-25 µg/mL n=25	>25 µg/mL n=8	r-value n=75
Cholesterol	196.52±47.45	193.32±40.48	182.50±38.57	Chol vs. Adipo -0.108
Triglyceride	230.43±95.15	179.64±63.13	229.25±95.23	TG vs. Adipo -0.162
HDL	37.18±6.60	38.35±6.18	42.63±12.91	HDL vs. Adipo 0.153
LDL	119.05±33.33	121.84±27.84	108.88±38.87	LDL vs. Adipo -0.047
CRP	7.35±6.96	4.43±5.25	3.73±2.47	CRP vs. Adipo -0.192

[Table/Fig-2]: Mean Levels of lipid profile, CRP and its correlation with adiponectin in total subjects.

Investigation	Group A	Group B	Group C
Adiponectin (µg/mL)	14.6±10.31	11.86±8.79	13.2±9.18
WHR	0.90±0.11	1.03±0.15	0.98±0.12

[Table/Fig-3]: Mean levels of adiponectin and WHR in groups (n=75)

On analysing the subjects on the basis of BMI, all the glucose homeostasis parameters including insulin resistance correlated negatively with adiponectin in all the three groups. In group B

(overweight diabetics) all the correlation values were significant but in other two groups values were not significant except HbA1c in group A which is significant [Table/Fig-4]. Lipid profile (except HDL) and CRP correlated negatively with adiponectin in the groups though not significantly [Table/Fig-5].

Biochemical Parameters	r-value		
	Group A	Group B	Group C
FBS	-0.372*	-0.555**	-0.063
HbA1c	-0.427*	-0.611***	-0.054
Insulin	-0.267	-0.447*	-0.311*
HOMA-IR	-0.303*	-0.528**	-0.278*

[Table/Fig-4]: Correlation of adiponectin with glucose metabolism markers in relation to BMI.
Significance, p-value *<0.05, **<0.01, ***<0.001

Biochemical Parameters	r-value		
	Group A	Group B	Group C
Cholesterol	-0.254*	0.139	-0.234
Triglyceride	-0.228	-0.084	-0.182
HDL	0.214	0.142	0.008
LDL	-0.172	0.371	-0.215
CRP	-0.187	-0.303*	-0.098

[Table/Fig-5]: Correlation of adiponectin with lipid profile and CRP in Groups.

DISCUSSION

Due to complex interactions between genetic and environmental factors, incidence of T2DM is increasing worldwide. The link between obesity and insulin resistance indicates the important secretory role of adipose tissue. Proinflammatory factors (cytokines, adipokines) secreted by adipose tissue are related to impaired glucose metabolism. Hence, we studied the role of adiponectin, in pathophysiology of diabetes [20].

No significant difference was observed in adiponectin levels in both the genders, although in some studies higher levels have been reported in females [21]. It has been shown that sexual dimorphism of adiponectin is mainly due to the difference in its High Molecular Weight (HMW) form [22]. Since it is the HMW fraction that is predominantly decreased in diabetics, it may explain the absence of sexual dimorphism in the present study of diabetic patients.

There was marked variation in the adiponectin levels in our patients, ranging from 2.1-35 µg/mL, similar trend has been reported by other workers also [23,24]. Plasma adiponectin levels are affected by multiple factors like genetic, ageing, lifestyle, diet, glycaemic control and duration of diabetes; this may be the reason for wide range of levels observed in our study [5,25-27].

When the patients were classified on the basis of adiponectin levels, a significant negative correlation was noted in all the glucose homeostasis markers and WHR [Table/Fig-1] Mean FBS and HbA1c were consistently high in subjects having adiponectin <10 µg/mL and significant negative correlation of adiponectin with FBS and HbA1c was observed. Other workers have also reported similar findings [28-30]. Adiponectin enhances glucose uptake by skeletal muscles and adipocytes, actions mediated by both insulin dependent and insulin independent pathways. Insulin dependent actions are mediated by stimulation of tyrosine phosphorylation of insulin receptor. Insulin independent actions being mediated by AMP activated protein kinase pathway. Studies have shown that adiponectin increases GLUT4 gene expression and their recruitment to the plasma membrane. Thereby, it increases insulin's ability to maximally stimulate glucose uptake [31-33]. Another mechanism by which adiponectin is known to regulate glucose homeostasis is by inhibiting expression of hepatic gluconeogenesis as well as rate of endogenous glucose production [34]. It is consistent with our findings of strong negative correlation of adiponectin with FBS and HbA1c.

Insulin levels and HOMA-IR correlated negatively and significantly with adiponectin in our patients. Similar findings of negative correlation have also been reported by other workers [11,27,35]. Insulin and adiponectin are antagonistic hormones reciprocally regulated. Low levels of adiponectin would decrease insulin's interaction with hepatic and skeletal muscle receptors. Also, it would contribute to the down-regulation of insulin transduction signal cascade. This would result in activation of hepatic gluconeogenesis, decrease glucose uptake and reduce fatty acid oxidation [11,28].

WHR showed strong negative correlation with adiponectin levels in T2DM patients. In our study overweight patients were centrally obese having higher WHR compared to obese group. Adiponectin levels had a stronger correlation with WHR compared to BMI in our study as its release is regulated by waist adipose tissue. It has been reported that adiponectin levels are inverse function of central body fat mass [35]. There was negative correlation between insulin resistance and adiponectin in all the BMI groups but was significant only in centrally obese overweight patients in our study, since insulin resistance is more strongly linked to intra-abdominal fat than to fat in other depots. In the literature also, it has been reported that adiponectin is more closely related to differences in insulin-mediated glucose disposal than obesity [36]. This shows that patient especially with central obesity rather than overall obesity is more at risk.

The negative correlation of adiponectin with FBS and HbA1c, CRP was strongest and significant in group B but lost its strength in group C. This may simply imply that 'body weight factors' may play a more important role in modulating adiponectin levels in this specific group because of central obesity, as has been earlier suggested by another study [37].

In the present study CRP, systemic marker for inflammation, correlated negatively with adiponectin in all the groups although not significantly, proving its anti-inflammatory role as already reported in the literature [38,39].

Even though adiponectin is a hormone secreted by adipose tissue, but its correlation with glucose homeostasis parameters was much stronger than with lipid profile in our study. All the lipid fractions (except HDL) showed non-significant negative correlation with adiponectin in all the three BMI groups. Similar findings have been reported by other workers also [37,40,41]. We found positive correlation between adiponectin and HDL but it was not significant although other studies in normal subjects have reported significant positive correlation [39]. We have studied T2DM patients, which are expected to have lower HDL levels than normal subjects [42].

LIMITATION

The main limitation of our study is the relatively small sample size, which may have led to lack of power to detect significant association between certain parameters especially lipids. Patient's medication may have influenced adiponectin levels so all the groups should be compared with normal controls.

CONCLUSION

Adiponectin plays an important role in the pathophysiology of T2DM, as its levels were negatively and significantly correlated with glucose homeostasis markers. Although, all the three BMI groups showed negative correlation between glucose homeostasis parameters and adiponectin but it was significant only in overweight centrally obese patients. So these patients can be potential therapeutic targets for drugs increasing adiponectin levels.

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Date of Submission: **Jul 06, 2017**
Date of Peer Review: **Sep 28, 2017**
Date of Acceptance: **Apr 14, 2018**
Date of Publishing: **Jul 01, 2018**

FINANCIAL OR OTHER COMPETING INTERESTS: None.