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Association of Serum Adiponectin in the Development of Type 2 Diabetes Mellitus in Bangladesh

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Abstract: Adiponectin appears as a molecular tool for the prediction of the development of type 2 diabetes mellitus (T2DM). A reduced level of serum adiponectin has been shown negatively correlated with the risk of developing T2DM. The role of adiponectin in developing T2DM in Bangladeshi population is not clearly understood. The present study aims to investigate how serum adiponectin influences in the development of T2DM in this population. A total of 74 healthy controls and 66 T2DM subjects were recruited in this study. Fasting serum glucose (FSG) levels were found significantly higher (p=0.001) in T2DM patients than the healthy controls. Significantly lower levels of serum adiponectin (p=0.001) and insulin secretory capacity, HOMA%B (p=0.001) were observed in T2DM patients compared to the healthy controls. These findings apparently show a positive correlation between serum adiponectin levels and insulin secretory dysfunction in T2DM patients. Bivariate Spearman's correlation analyses showed a significant negative association between HOMA%B and fasting serum glucose (FSG) in both control group (r = -0.271; p=0.020) and T2DM group (r= -0.813; p=0.0001). However, the Bivariate Spearman's correlation analyses showed no significant correlation between serum adiponectin level and insulin secretory capacity (HOMA%B). Multiple regression analysis also did not show any significant positive association of HOMA%B with serum adiponectin. This study suggests that low serum adiponectin is associated with T2DM in Bangladeshi population and the association is not accounted predominantly for insulin secretory dysfunction.

Key words: Adiponectin · Insulin Resistance · Insulin Secretory Capacity · Type 2 Diabetes Mellitus

INTRODUCTION

Adiponectin (also referred to as Acrp30, GBP28, apM1 or AdipoQ), the product of *apM1* gene (adipose most abundant gene transcript 1), is a highly abundant protein secreted exclusively by adipocytes (white adipose cells/fat cells) that regulates glucose and lipids metabolism [1-4]. It also acts as a hormone with anti-inflammatory and insulin sensitizing properties [5, 6]. Adiponectin has been found to influence the body's response to insulin thereby modulates insulin action and resistance [7]. A reduced adiponectin level in plasma or serum has been shown associated in developing type 2 diabetes mellitus (T2DM) and insulin resistance [5, 8]. Prospective and longitudinal studies indicate that lower adiponectin levels and higher incidences of T2DM are positively correlated [9-11]. Serum adiponectin levels were also shown inversely correlated with insulin resistance in patients with T2DM [12].

In a previous study, it has been shown that 44% of patients diagnosed with impaired fasting glucose (IFG) subsequently developed diabetes and these subjects had lower adiponectin levels compared to those who have not developed diabetes [13]. Moreover, a low adiponectin level at baseline was shown to be associated with a decrease in insulin sensitivity [14]. In a longitudinal

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case-control study in Pima Indian population, low concentrations of plasma adiponectin were shown to contribute in developing T2DM and the incidences of T2DM were less in individuals with higher concentrations of plasma adiponectin [15]. Low levels of adiponectin were also shown to be associated with increasing risk of subsequently developing T2DM and the concentrations of serum adiponectin were 22% lower in adults who subsequently develop diabetes than the individuals who do not [9, 11]. Recently Jee *et al.* [16] also reported a strong negative association between serum adiponectin levels and risk of developing T2DM. The authors also showed that women had higher adiponectin levels than men. A reduced level of serum adiponectin was suggested as a risk factor for the progression of T2DM in the Japanese population [10]. Longitudinal studies suggest that low concentration of serum adiponectin is a risk factor as well as a predictor for the onset of T2DM [9, 11, 16, 17]. An inverse relationship was also found between family history of diabetes (FHD) and adiponectin levels in Korean cohort [18]. Human genetics, as for example, single nucleotide polymorphisms in adiponectin gene also contribute to the genetic risk of developing T2DM, hypoadiponectinemia and obesity [19, 20].

However, controversies also remain parallel over these findings. Annuzzi *et al.* [21] reported that adiponectin levels do not significantly differ between T2DM patients and healthy subjects. Expression of adiponectin gene and fasting plasma adiponectin levels were found similar in both diabetic and non-diabetic subjects and the adiponectin gene expression was shown independent of the degree of obesity and insulin sensitivity [21]. Yamamoto *et al.* [22] also found no significant relationship between fasting glucose and adiponectin levels. Adiponectin was also shown to exert no effect on the efficacy of pancreatic beta cells to secrete insulin [23]. Moreover, it was suggested that low level of serum adiponectin is not conclusive for the prediction of insulin resistance [24].

A good number of studies have explored the role of adiponectin in insulin sensitivity and insulin resistance in T2DM and its complications in various populations across the world. In Bangladesh, a few studies have been pursued to evaluate the association of serum adiponectin in impaired glucose tolerance (IGT) or IFG patients or in the development of T2DM [25-28]. Data from this population suggest that incidences of insulin secretory defect as well as insulin resistance are present in T2DM subjects, whereas insulin secretory defect appears as the major contributor [25, 26]. In case of prediabetes, IFG and IGT seem to be separate disorders where β-cell dysfunction is predominant in IFG and insulin resistance has a major role in IGT. Patients with combined IFG-IGT group have both insulin secretory defect and insulin resistance [27]. Though adiponection was shown to be associated in developing T2DM, there still needs further studies to examine whether serum adiponectin is associated with insulin secretory defect in T2DM in Bangladeshi population. Therefore, the present study was undertaken to investigate the association of serum adiponectin in developing T2DM in Bangladeshi population.

MATERIALS AND METHODS

Subjects: The study was conducted in the laboratory of Biomedical Research Group, Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh. A total number of 140 subjects were recruited in the study irrespectively of race, religion and socioeconomic status. Of the total, 74 subjects were non-diabetic healthy controls and 66 subjects were confirmed as T2DM patients. Subjects were collected from the Out-Patient Department (OPD) of BIRDEM who came for checking their glycemic status. Healthy control subjects were recruited through personal communication from the community and from relatives of recruited patients. The purpose of the study was explained to all the subjects before taking their consent for recruitment in the study. A predesigned case record form was used to record relevant clinical, medical, demographic and socio-economic data such as age, sex, educational status and occupational status from the consenting subjects. Anthropometric indices, like, height, weight, waist circumference and hip circumference of the subjects were measured by standard procedures.

Laboratory Methods: Serum glucose was estimated by Glucose-Oxidase (GOD-PAP) method. Serum triglyceride (TG), serum cholesterol and serum high-density lipoprotein (HDL) were measured by enzymatic colorimetric (GPO-PAP) method using an automatic analyzer (Hitachi 704, Hitachi Ltd., Tokyo, Japan) according to manufacturer's protocol. LDL cholesterol was calculated using the standard formula. Serum insulin level was measured by chemiluminescence based enzyme linked immunosorbent assay (ELISA) using Immulite, DPC, USA. Serum adiponectin was measured by ELISA using AssayMax Human Adiponectin ELISA Kit, UK. Insulin secretory capacity (HOMA% B) was calculated from fasting glucose and fasting insulin values using HOMA-CIGMA software.

Statistical Analysis: Statistical analysis was performed using SPSS (Statistical Package for Social Science) software for Windows version 11.5 (SPSS Inc., Chicago, Illinois, USA). All the data were expressed as mean ± SD and/or median (range) as appropriate. The statistical significance of differences among the groups was assessed by unpaired Student's 't' test or Mann-Whitney U test (as appropriate). A two-tailed p value of <0.05 was considered statistically significant. Multiple linear regression analysis of HOMA% B was done for adiponectin adjusted by BMI and waist hip-ratio (WHR).

RESULTS

Out of 140 subjects, 74 were healthy controls and 66 were T2DM subjects. T2DM patients had significantly higher WHR (p=0.0001) compared to healthy controls (Table 1). The clinical characteristics of the controls and patients are presented in Table 2 which indicate that T2DM patients had significantly higher levels of serum fasting glucose (p=0.001) and serum glutamate pyruvate transaminase (SGPT) (p=0.003) but significantly lower levels of HOMA%B (p=0.001) and serum adiponectin (p=0.001) compared to the healthy controls. These findings apparently indicate that a reduced level of serum adiponectin is involved in reduced insulin secretion in T2DM patients.

Bivariate Spearman's correlation analyses were performed for insulin secretory capacity (HOMA%B) with various parameters in the control and T2DM groups (Table 3). HOMA%B showed significant positive correlation with BMI (r=0.269; p=0.022) in control group but not in T2DM group. Significant positive association was also shown between HOMA%B and fasting insulin (F Insulin) in both control group (r = 0.899; p=0.0001) and T2DM group (r= 0.508; p=0.0001). In contrast, HOMA%B showed significant negative association with fasting serum glucose (FSG) in both control group (r = -0.271; p=0.020) and T2DM group (r= -0.813; p=0.0001).

Bivariate Spearman's correlation analyses for serum adiponectin level with various parameters (Table 4) in the control and T2DM groups showed that serum adiponectin level had significant negative association with triglycerides (TG) in both control group (r = -0.408; p=0.0001) and T2DM group (r= -0.266; p=0.030) and also showed significant positive association with total cholesterol (r = 0.239; p=0.052) in T2DM group but not in control group. It also showed significant positive association with HDL cholesterol in both control group (r = 0.428; p=0.0001) and T2DM group (r = 0.294; p=0.016). There is no significant correlation of serum adiponectin level with LDL cholesterol in either control or T2DM groups. Serum adiponectin level showed significant negative association with SGPT in T2DM group

Table 1: Anthropometric measurements of the study subjects.

Variables	Control (n=74)	T2DM (n=66)	*t/p values* ---------- Control vs T2DM
Age (years)	42.46±9.24	48.49±8.09	4.114/0.0001
BMI (kg/m^2)	25.02±3.55	25.85±3.62	1.372/0.172
MUAC (cm)	28.96±3.07	29.22±4.28	0.418/0.677
WHR	0.90±0.07	0.95±0.07	3.583/0.0001
SBP (mmHg)	117.09±15	118.21±10	0.526/0.600
DBP (mmHg)	70.76±9.07	70.78±7.67	0.014/0.989

Results were expressed as mean± SD. Comparison between groups was performed using unpaired Student's 't' test. T2DM, type 2 diabetes mellitus; BMI, body mass index; MUAC, mid upper arm circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2: Clinical characteristics of healthy controls and T2DM patients.

Variables	Control (n=74)	T2DM (n=66)	*z/p values* ---------- Control vs T2DM
TG (mg/dL)	147 (68-877)	171.5 (53-633)	1.770/0.077
T Chol (mg/dL)	190 (130-419)	192 (127-267)	0.167/0.867
HDL-c (mg/dL)	38 (25-56)	34.5 (24-58)	1.442/0.149
LDL-c (mg/dL)	125.5 (31.8-285)	115 (56-824)	1.753/0.080
SGPT (U/L)	23.50 (12-116)	30.50 (12-92)	2.986/0.003
S Creatinine(mg/dL)	0.90 (0.70-1.20)	1.0 (0.70-1.30)	1.637/0.102
FSG (mmol/L)	5.3 (4.2-6)	7 (4.3-15.4)	7.583/0.0001
F Insulin (picomol/L)	101.99(12.93-526.40)	125.8(28.49-297.16)	1.242/0.214
HOMA%B	160.10(33.40-493.40)	100.45(17.70-349.30)	4.714/0.0001
S Adiponectin (ng/mL)	17.73(1.52-31.93)	12.394(2.27-44.75)	3.557/0.0001

Results were expressed as median (range). Comparison between groups was performed using Mann–Whitney U test. T2DM, type 2 diabetes mellitus; TG, triglycerides; T Chol, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SGPT, serum glutamate pyruvate transaminase; S Creatinine, Serum Creatinine; FSG, fasting serum glucose; F Insulin, fasting insulin; HOMA%B, pancreatic B cell function assessed by homeostatic model assessment determined by HOMA CIGMA software; S Adiponectin, serum adiponectin.

Table 3: Spearman's correlation of HOMA%B with various parameters.

	Control n=74		T2DM n=66	
Variables	r	p	r	p
Age (years)	-0.055	0.643	-0.135	0.276
BMI (kg/m^2)	0.269	0.022	0.078	0.533
MUAC (cm)	0.170	0.150	0.185	0.133
WHR	-0.200	0.090	0.070	0.572
SBP (mm/Hg)	0.005	0.968	-0.188	0.127
DBP (mm/Hg)	-0.007	0.951	-0.082	0.508
TG (mg/dl)	-0.004	0.976	-0.167	0.178
T chol(mg/dl)	-0.115	0.333	-0.098	0.432
HDL-c (mg/dl)	-0.076	0.525	0.041	0.743
LDL-c (mg/dl)	-0.125	0.290	0.038	0.761
SGPT (U/L)	-0.085	0.474	-0.146	0.237
S Creatinine(mg/dL)	-0.028	0.814	-0.093	0.454
FSG (mmol/L)	-0.271	0.020	-0.813	0.0001
F Insulin (picomol/L)	0.899	0.0001	0.508	0.0001
S Adiponectin(ng/mL)	0.093	0.432	0.108	0.384

Results were expressed as Spearman's correlation coefficient r and statistical significance p. T2DM, type 2 diabetes mellitus; BMI, body mass index; MUAC, mid upper arm circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP; diastolic blood pressure; TG, triglycerides; T Chol, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SGPT, serum glutamate pyruvate transaminase; S Creatinine, serum creatinine; FSG, fasting serum glucose; F Insulin, fasting insulin; S Adiponectin, serum adiponectin.

Table 4: Spearman's correlation of serum adiponectin with various parameters.

Variables	Control n=74		T2DM n=66	
	r	p	r	p
Age (years)	0.078	0.511	0.177	0.151
BMI (kg/m^2)	0.181	0.123	0.067	0.590
MUAC (cm)	0.159	0.177	0.013	0.916
WHR	-0.113	0.339	-0.011	0.932
SBP (mm/Hg)	-0.072	0.542	-0.014	0.910
DBP (mm/Hg)	-0.049	0.678	-0.026	0.834
TG (mg/dl)	-0.408	0.0001	-0.266	0.030
T chol(mg/dl)	0.147	0.211	0.239	0.052
HDL-c (mg/dl)	0.428	0.0001	0.294	0.016
LDL-c (mg/dl)	0.170	0.147	0.222	0.071
SGPT (U/L)	-0.056	0.636	-0.239	0.051
S Creatinine(mg/dL)	-0.252	0.030	0.178	0.150
FSG (mmol/l)	0.153	0.192	-0.107	0.389
F Insulin (picomol/L)	0.156	0.187	0.219	0.075
HOMA%B	0.093	0.432	0.108	0.384

Results were expressed as Spearman's correlation coefficient r and statistical significance p. T2DM, type 2 diabetes mellitus; BMI, body mass index; MUAC, mid upper arm circumference ; WHR, waist hip ratio; SBP, systolic blood pressure; DBP; diastolic blood pressure; TG, triglycerides; T Chol, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SGPT, serum glutamate pyruvate transaminase; S Creatinine, serum creatinine; FSG, fasting serum glucose; F Insulin, fasting insulin; HOMA%B, insulin secretory capacity.

Table 5: Multiple regression analysis taking HOMA%B as dependent variable and Age, BMI, Group &Adiponectin as independent variables.

Variables	β Value	p Value
Age (years)	-0.088	0.309
BMI(kg/m^2)	0.149	0.070
GROUP	0.297	0.001
S Adiponectin (ng/mL)	-0.007	0.929

β for standardized regression coefficient, $p<0.05$ are considered as statistically significant. HOMA%B, insulin secretory capacity.

(r = -0.239; p=0.051) but not in control group. It also showed significant negative association with serum creatinine (r = -0.252; p=0.030) in control group but not in T2DM group. Serum adiponectin level did not show any significant association with Age, BMI, MUAC, WHR, SBP and DBP, glycemic and insulinemic status and also with insulin secretory capacity (HOMA%B) (Table 4).

Multiple regression analysis considering HOMA%B as dependent variable and Age, BMI, Group and serum adiponectin as independent variables indicated that HOMA%B showed significant positive association with Group (β=0.297, p=0.001) but not with serum adiponectin (Table 5).

DISSCUSSION

Bangladesh has one of the largest diabetic populations in the world. The basic defects that cause diabetes include insulin secretory defect and insulin resistance. A number of studies have been conducted to explore the basic defects of T2DM in Bangladeshi population.

In the present study, the value of serum adiponectin level was found 17.73(1.52-31.93) ng/ml in healthy populations whereas the range of serum adiponectin in T2DM subjects was 12.394 (2.27-44.75) ng/ml. Reduced level of serum adiponectin is associated with the risk of developing T2DM and this study found that the serum adiponectin level is lower in T2DM patients compared to the healthy counterparts in Bangladeshi populations. Both from group difference correlation data and regression analysis, it is evident that low adiponectin has an association with T2DM in Bangladeshi population. Therefore, this study is in agreement with the majority of findings and it does not support the contradictory claim. The association of adiponectin with the predominant basic defect (pancreatic β-cell dysfunction) was further explored both by correlation and regression analysis. In neither case there was any significant association of adiponectin with insulin secretory defect (HOMA%B). Since on regression analysis association of adiponectin with β-cell and groups (healthy vs T2DM) are found, it seems plausible that the adiponectin is linked with the development of these conditions through the alternate basic defects i.e. insulin resistance. Although an association of adiponectin in developing T2DM is postulated, it is noteworthy that this study has several limitations. In this study, insulin resistance (HOMA%S) and its correlation with other parameters were not studied. Thus the association of adiponectin with insulin sensitivity in the development of T2DM in this population cannot be firmly established. Furthermore, as it was a cross-sectional study, therefore no causal relationship can be understood.

CONCLUSION

Low serum adiponectin is associated with T2DM in Bangladeshi population and the association is mediated probably through insulin resistance rather than insulin secretory dysfunction.

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