

## Association of Circulating Fasting TNF- $\alpha$ with Hyperglycemia is Stronger than with Body Mass Index in Newly Diagnosed Bangladeshi Type 2 Diabetic Subjects

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### Abstract

**Background and aim:** Insulin resistance and hypo-insulinemia are the major problems in Type 2 Diabetes Mellitus (T2DM). Epidemiological evidences suggest that obesity is linked with insulin resistance. Inflammatory cytokines such as TNF- $\alpha$  has also been associated with obesity and insulin resistance. The present study aims to evaluate fasting serum TNF- $\alpha$  in newly diagnosed type 2 diabetic subjects in different BMI group to observe its association with insulin sensitivity and obesity.

**Methods:** A total number of 145 newly diagnosed T2DM subjects were recruited in this study. On a prescheduled morning fasting and postprandial (2hrs after 75g glucose load) blood was drawn. Serum glucose was measured by glucose-oxidase method, lipid profile by enzymatic end-point method, insulin and TNF- $\alpha$  by ELISA methods. Insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were calculated using fasting glucose and insulin by HOMA-CIGMA software. SPSS for Windows was used for statistical analysis.

**Results and conclusion:** The subjects were divided into three groups on the basis of BMI cut-off points suggested by WHO for the Asian population (Gr1: BMI  $\leq$  23, Gr2: BMI 23.1-27.5, Gr3: BMI >27.5). The fasting serum insulin and TNF- $\alpha$  levels were significantly ( $p < 0.005$ ) higher in group 3 than the other groups. HOMA%B was significantly higher in Gr 3 and HOMA%S was significantly lower in group 3 compared to group 1 and group 2. From multiple linear regression analysis it can be concluded that both BMI and postprandial serum glucose had potential effects on serum TNF- $\alpha$  level but the later one had stronger.

**Keywords:** TNF- $\alpha$ ; Body mass index; Type 2 diabetes

### Introduction

Reduced insulin-mediated glucose disposal is a dominant metabolic feature of obesity and type 2 diabetes mellitus and the basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues [1,2]. This phenomenon is due to peripheral cells being either completely or partially resistant to the effects of insulin [3]. Many clinicians point to certain habits, such as sedentary lifestyle and high calorie and fat intake, as the main culprit of diabetes [4]. Interventions focusing on weight loss, diet modifications, and regular physical exercise of at least 150 minutes per week reduce the incidence of diabetes in at-risk patients. These activities also reduce hemoglobin A<sub>1c</sub> levels in type 2 diabetes [5]. Genetic links have likewise been recognized. Researchers discovered at least 36 genes associated with diabetes [6]. A high concordance level among identical twins shows that type 2 diabetes is heritable [7]. It is uncertain at this point whether inflammation occurs prior to or after the onset of diabetes. Specific cytokines such as TNF- $\alpha$ , IL-6, and C-Reactive Protein (CRP) are elevated in type 2 diabetic patients in comparison to non-diabetic controls [8]. The role of inflammation in diabetes is still under investigation, it is important to consider which pathways may be targeted therapeutically. For example, TNF- $\alpha$  induces pathways that lead to increased insulin resistance throughout the body [9]. Tumor necrosis factor- $\alpha$  is the pre-inflammatory cytokine secreted by several types of cells such as macrophages, monocytes, neutrophils and T-cells. TNF- $\alpha$  is directly implicated in the destruction of  $\beta$ -cells from in vitro studies on isolated islets and profound inflammatory effects in vivo by acting directly on T lymphocytes [10,11]. Type 2 diabetes, particularly when poorly controlled, involves disease of the innate immune system

and manifest as chronic low-grade inflammation [12]. Consistent with this hypothesis, high levels of circulating acute phase proteins in particular IL-6, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), other mediators of inflammation such as serum-amyloid A (S-AA) and hs-CRP and their association with obesity and insulin resistance have been previously documented [13-17]. Additionally several studies have demonstrated elevated levels of IL6 and TNF- $\alpha$  among individuals with insulin resistance and diabetes. It has been examined the effects of TNF- $\alpha$  on proximal steps in the insulin-signaling pathway [18]. An important factor that could potentially contribute to inflammation is chronic hyperglycemia [19]. Inadequate glucose control and its associated inflammation in diabetes have been implicated in the pathogenesis of atherosclerosis, impaired lung function and cardiovascular disease [20]. Since TNF- $\alpha$  is associated with both insulin sensitivity and obesity therefore, this study was designed to explore the serum level of TNF- $\alpha$

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in relation to insulin sensitivity and with the different degrees of BMI (Body Mass Index) of the study subjects.

## Materials and Methods

In this cross-sectional-observational study 145 newly diagnosed type 2 diabetic subjects were recruited purposively from the Out-Patient-Department (OPD) of Bangladesh Institute of Health Sciences, Dhaka, Bangladesh. Subjects were considered as T2DM using WHO guidelines [21]. On a prescheduled morning, subjects were requested to come after overnight fast (eight to ten hours) for fasting blood sample. Informed written consent was taken and subjects were then given 75g glucose dissolved in 250 ml water. Blood was taken by venepuncture in fasting condition and two hours after glucose load. After 10-15 minutes of collection blood samples were centrifuged for 10-15 minutes at 3000 rpm to obtain serum and were kept frozen at -30°C until analysis.

Anthropometric and clinical parameters were also recorded using a pre-designed questionnaire by standard techniques. Serum glucose was measured by Glucose-oxidase (GOD-PAP) method, serum lipid profile and creatinine by enzymatic colorimetric method and serum SGPT by UV method using ALT (GPT) opt.kit (Randox Laboratories Ltd, UK). Serum insulin and TNF- $\alpha$  by Enzyme Linked Immunosorbent Assay (ELISA) method (Linco Research Inc, and Assaypro, USA respectively).

Insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were estimated using fasting glucose and fasting insulin levels by HOMA - CIGMA software [22].

Parameters	Mean $\pm$ SD
Age (yrs)	45 $\pm$ 10
BMI (kg/m <sup>2</sup> )	25.7 $\pm$ 4.3
WHR	0.97 $\pm$ 0.02
SBP (mm-Hg)	121 $\pm$ 15
DBP (mm-Hg)	79 $\pm$ 9
FSG (mmol/L)	10.5 $\pm$ 4.6
PPSG (mmol/L)	18.2 $\pm$ 5.5
Insulin ( $\mu$ IU/ml)	12.2 $\pm$ 7.2
Triglyceride (TG, mg/dl)	230 $\pm$ 139
Total Cholesterol (mg/dl)	172 $\pm$ 41
HDL-Cholesterol (mg/dl)	36 $\pm$ 10
LDL-Cholesterol (mg/dl)	94 $\pm$ 36
HOMA %B	56 $\pm$ 43
HOMA %S	67 $\pm$ 74
TNF- $\alpha$ (pg/ml)	24.16 $\pm$ 12.02

Results are expressed as mean  $\pm$  SD, BMI: Body Mass Index; WHR: Waist-Hip ratio; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FSG: Fasting Serum Glucose; PPSG: Postprandial Serum Glucose; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HOMA%B, Insulin Secretory Capacity; HOMA%S, Insulin Sensitivity, TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

**Table 1:** Clinical and biochemical characteristics of the study subjects (n=145).

Parameters	Gr1 n=48	Gr2 n=70	Gr3 n=35	t/p values		
				Gr1 vs. Gr2	Gr1 vs. Gr3	Gr2 vs. Gr3
Insulin ( $\mu$ IU/ml)	9.8 $\pm$ 5.5	11.4 $\pm$ 6.6	16.6 $\pm$ 7.6	-1.29/ 0.199	-4.82/ 0.0001	-3.75/ 0.001
TNF- $\alpha$ (ng/ml)	20.1 $\pm$ 10.9	22.2 $\pm$ 10.7	29.1 $\pm$ 12.9	-1.006/ 0.317	-3.58/ 0.001	-2.91/ 0.004
HOMA% B	52 $\pm$ 40	50 $\pm$ 36	70 $\pm$ 53	0.205/ 0.791	-1.7/ 0.08	-2.11/ 0.039
HOMA% S	86 $\pm$ 105	69 $\pm$ 62	39 $\pm$ 18	1.03/ 0.303	2.87/ 0.006	3.64/ 0.001

Gr1, BMI  $\leq$  23 Kg/m<sup>2</sup>; Gr2, BMI 23.1-27.5; Gr3, BMI>27.5

**Table 2:** Biochemical characteristics of the study subjects according to BMI.

## Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Science) version 11.5 for Windows (SPSS Inc., Chicago, Illinois, USA). All data were expressed as mean  $\pm$  SD (standard deviation) and/or percentage (%) as appropriate. The statistical significance of differences between the values was assessed by independent student's t test (as appropriate). Correlation was also observed among the parameters using Pearson's correlation and multiple linear regression analysis. A two-tailed p value of <0.05 was considered statistically significant.

## Results

### Clinical and biochemical characteristics of the study subjects (Table 1)

Age (Mean  $\pm$  SD) of the study subjects was 45  $\pm$  10 years. BMI, Waist to hip ratio (WHR), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were presented in Table 1.

Fasting and postprandial (after 75g glucose load) blood glucose (mmol/l) of the study subjects were 10.5  $\pm$  4.6 and 18.2  $\pm$  5.6. Mean  $\pm$  SD serum insulin ( $\mu$ IU/ml) level of the study subjects was 12.2  $\pm$  7.2. Mean triglyceride (mg/dl) level of the study subjects was higher than the reference range, cholesterol, HDL and LDL levels were within normal range. Insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were calculated using fasting glucose and fasting insulin values using HOMA-CIGMA software and the values were 56  $\pm$  43 and 67  $\pm$  74 respectively. Mean  $\pm$  SD serum TNF- $\alpha$  (pg/ml) level among the study subjects was 24.16  $\pm$  12.02 (Table 1).

The study subjects were categorized according to BMI cut-off-points suggested by WHO for Asian population (Gr1: BMI  $\leq$  23, Gr2: BMI 23.1-27.5, Gr3: BMI>27.5), fasting serum insulin levels in Gr 3 has been found to be significantly higher compared to Gr 1 and Gr 2. Similarly serum TNF- $\alpha$  level was significantly higher in Gr 3 compared to Gr 1 and Gr 2 (Table 2). Accordingly HOMA B was significantly increased in Gr3 compared to Gr2, on the other hand HOMA%S was significantly decreased in Gr 3 compared to Gr 1 and Gr 2 (Table 2).

Fasting serum TNF- $\alpha$  concentrations were reanalyzed on the basis of fasting and postprandial glucose concentrations and it has been found that TNF- $\alpha$  was significantly (p<0.05) increased when fasting glucose was more than 16mmol/l and postprandial glucose was more than 24mmol/l (Table 3).

In regression analysis (Figure 1) it has been found that TNF- $\alpha$  was positively associated with BMI and postprandial serum glucose and negatively associated with insulin sensitivity. In multiple linear regression analysis, positive association of TNF- $\alpha$  with BMI ( $\beta$ =0.252, p=0.003) and postprandial glucose ( $\beta$ =0.615, p=0.001) still preserved when the effects of age and blood pressure were adjusted (Table 4).

Groups		Serum TNF- $\alpha$	t/p Values
Fasting Glucose Category	Gr1, Upto 8mmol/l (n=53)	24.4 $\pm$ 12.7	Gr1 vs Gr2 : 1.455/0.148; Gr1 vs Gr3 : -2.039/0.045; Gr2 vs Gr3 : -2.382/0.028
	Gr2, 8.01-16mmol/l (n=73)	21.7 $\pm$ 7.8	
	Gr 3, >16mmol/l (n=19)	32.4 $\pm$ 18.7	
Postprandial Glucose Category	Gr1, Upto 16mmol/l (n=65)	23.1 $\pm$ 11.6	Gr1 vs Gr2 :-0.089/0.93; Gr1 vs Gr3 : -2.08/0.041; Gr2 vs Gr3 : -2.23/0.028
	Gr2, 16.01-24mmol/l (n=59)	23.2 $\pm$ 9.1	
	Gr3, >24mmol/l (n=21)	30.1 $\pm$ 17.9	

Table 3: Serum TNF- $\alpha$  concentrations according to fasting and postprandial glucose concentrations.

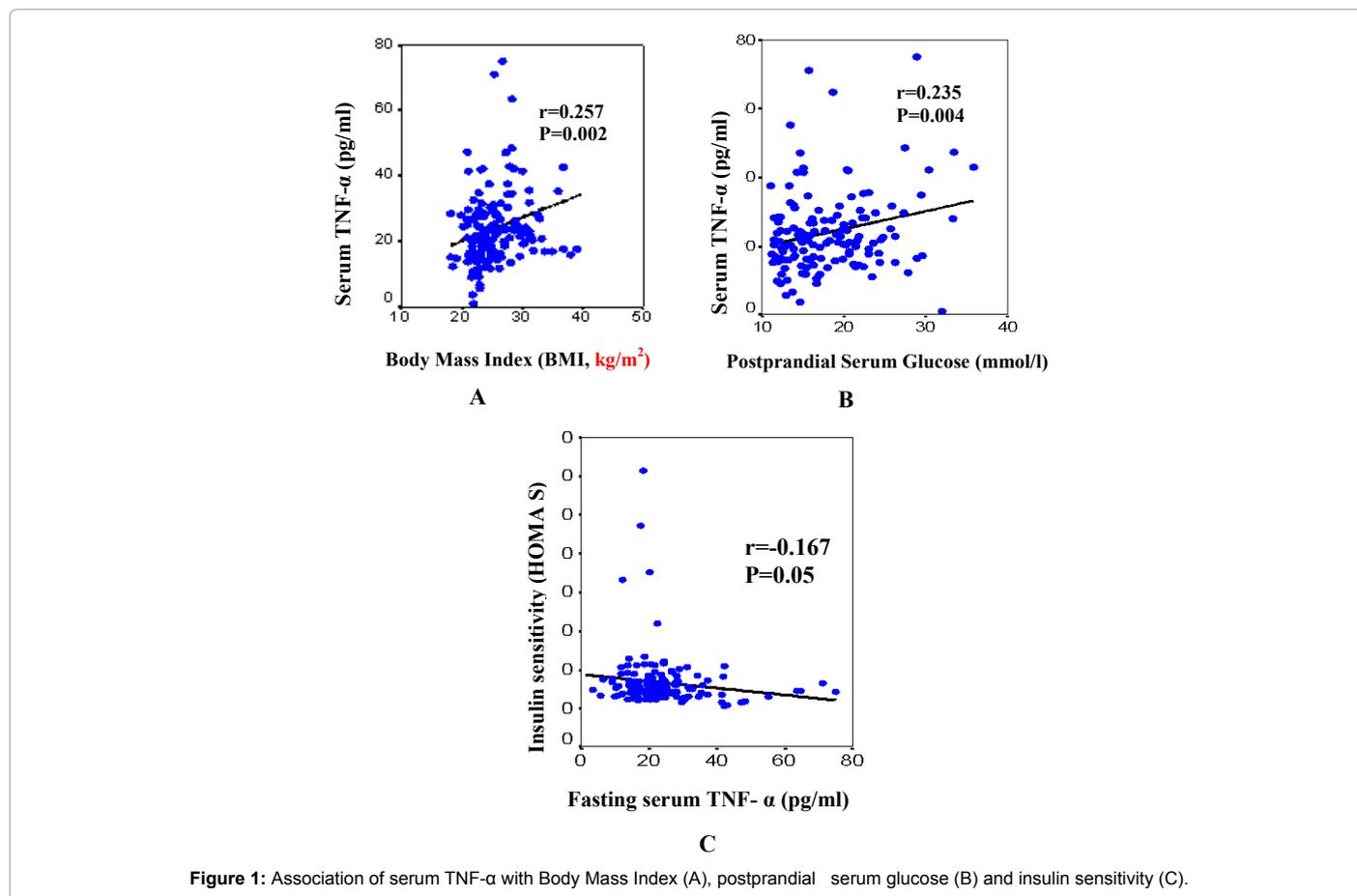


Figure 1: Association of serum TNF- $\alpha$  with Body Mass Index (A), postprandial serum glucose (B) and insulin sensitivity (C).

Model 1			Model 2		
Variables	$\beta$	p	Variables	$\beta$	p
Age	0.116	0.146	Age	0.191	0.023
BMI	0.252	0.003	BMI	0.243	0.006
SBP	0.125	0.377	SBP	0.033	0.823
DBP	0.022	0.872	DBP	0.0001	0.999
Fasting Glucose	-0.338	0.070	HOMA B	-0.112	0.212
PPSG	0.615	0.001	HOMA S	-0.114	0.200
Fasting Insulin	0.116	0.189			

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PPSG: Post-Prandial Serum Glucose

Table 4: Relationship of serum TNF- $\alpha$  with BMI, postprandial glucose and insulin sensitivity (HOMA S) adjusted with other variables using multiple linear regression analysis.

## Discussion

Type 2 Diabetes mellitus has been suggested as a disease of the innate immune system; responsible for an ongoing cytokine mediated acute phase response and low grade chronic inflammation which

may be involved in the atherosclerosis of diabetes mellitus [23]. Insulin resistance is a common feature of type 2 diabetes mellitus, and inflammatory cytokines such as TNF- $\alpha$  and IL-6 have been linked to insulin resistance [24]. The underlying mechanisms of the development of insulin resistance are not clear, but a key mechanism

by which TNF- $\alpha$  was thought to induce insulin resistance involved serine phosphorylation of the Insulin Receptor Substrate-1 (IRS-1) [19]. TNF- $\alpha$  level has been shown to be increased in patients with type 2 diabetes mellitus. However, whether it is involved in the development of type 2 diabetes mellitus or vice versa is not clear. It has been reported that inflammation contributes to insulin resistance in obese and diabetic patients [25]. Inflammatory molecules such as TNF- $\alpha$  and IL-6 may therefore play an important role. It was found that diabetic patients had elevated levels of TNF- $\alpha$ , which reinforces this hypothesis. Epidemiological evidence suggests that inflammatory markers like TNF- $\alpha$  and IL-6 predict the development of diabetes and glucose disorders [26,27]. TNF- $\alpha$  contributes to the pathogenesis of insulin resistance, type 2 diabetes, and abnormal adiposity or lipid disorders [28]. Some authors have found increased serum TNF- $\alpha$  and IL-6 concentration in type 2 diabetic [29,30] and IGT subjects but Choi et al. [31] did not find any association of TNF- $\alpha$  and IL-6 with IGT development. TNF- $\alpha$  have not been extensively studied in diabetic subjects with different BMI group and in different glycemic status levels.

Studied diabetic subjects were categorized according to BMI (Gr1: BMI  $\leq$  23, Gr2: BMI 23.1-27.5, Gr3: BMI >27.5), Gr 3 was found to have significantly ( $p=0.001$ ) higher levels of insulin compared to Gr 1 and Gr 2. When insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were analyzed according to BMI, it has been found that HOMA%B was significantly increased in subjects with BMI >27.5kg/m<sup>2</sup> (Gr3) compared to Gr2, on contrary HOMA%S was significantly decreased in Gr 3 compared to Gr 1 and Gr 2. Therefore BMI 27.5 is a worsening status of overweight where  $\beta$ -cells of the pancreas secrete higher amounts of insulin with less functionality.

In a previous study on Bangladeshi populations the serum TNF- $\alpha$  has been found to be significantly higher in Type 2 DM subjects compared to Control, which supported by another study in India where they found that higher TNF- $\alpha$  level was associated in IGT and Type 2 DM subjects. Studies done in abroad had documented that serum TNF- $\alpha$  concentrations were higher in IGT than in NGT (Normal Glucose Tolerance) while a Korean study found no elevation in serum TNF- $\alpha$  concentrations in prediabetic patients compared to Control. In the present study serum TNF- $\alpha$  was measured in Type 2 DM subjects with different BMI groups and found that serum TNF- $\alpha$  was increased with the increase of BMI. In this study both the Gr2 and Gr3 have shown significantly ( $p<0.05$ ) higher levels of serum TNF- $\alpha$  compared to Gr1. Therefore, BMI might be an important indicator for the increase of serum TNF- $\alpha$  in Bangladeshi type 2 diabetic subjects. When serum TNF- $\alpha$  values were determined according to glycemic status, it was found that TNF- $\alpha$  was increased with increase of both fasting and postprandial serum glucose levels. Serum TNF- $\alpha$  was found to be increased significantly ( $p<0.05$ ) when fasting glucose was more than 16mmol/l and postprandial serum glucose was more than 24mmol/l. Increased serum TNF- $\alpha$  may decrease insulin sensitivity which may play roles in the development of extreme hyperglycemia or vice versa. Therefore both the fasting and postprandial serum glucose at certain levels might have potential association with serum TNF- $\alpha$ .

We have looked the determinants of TNF- $\alpha$  elevation in diabetic subjects using bivariate correlation analysis and it has been found that BMI, waist circumference, hip circumference and postprandial serum glucose is positively ( $r=0.257$ ,  $p=0.002$ ;  $r=0.201$ ,  $p=0.016$  and  $r=0.179$ ,  $p=0.031$  respectively) associated with fasting serum TNF- $\alpha$  in type 2 diabetic subjects. On the other hand serum HDL concentrations and insulin sensitivity showed significantly negative association ( $r=-0.184$ ,  $p=0.027$ ;  $r=-0.167$ ,  $p=0.050$  respectively) with TNF- $\alpha$ . On multiple

linear regression analysis, when other cofactors like age, systolic blood pressure, diastolic blood pressure, fasting glucose and fasting insulin values were adjusted, both BMI ( $p=0.003$ ) and postprandial serum glucose ( $p=0.001$ ) was found to be significantly associated with serum TNF- $\alpha$  and the association of the latter one was found stronger [32-34]. Type 2 diabetes also has become the leading cause of end-stage renal disease in the world, and the number of patients diagnosed each year with end-stage renal disease attributed to type 2 diabetes is rising [35]. There is now evidence that activated innate immunity and inflammation are relevant factors in the pathogenesis of diabetes. Furthermore, different inflammatory molecules, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), play a critical role in the development of diabetic microvascular complications, including nephropathy [36,37]. A previous study showed that development of diabetic nephropathy is commonly thought to result from the cumulative interactions among multiple metabolic and hemodynamic factors which activate common intracellular signaling pathways that in turn trigger the production of cytokines and growth factors, leading to renal disease [38]. Another study showed that the prevalence of nephropathy significantly increased with increased BMI [39]. Therefore the viewpoints of the above discussion could be concluded as: a) increased BMI influences on insulin levels, insulin sensitivity and fasting serum TNF- $\alpha$ . b) after certain levels, both fasting and postprandial serum glucose levels significantly effects on the circulating concentration of TNF- $\alpha$ , c) fasting serum TNF- $\alpha$  shows positive association with BMI and postprandial serum glucose but the later one is more potential.

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