*Article*

# Leptin and Other Factors as Determinants of Insulin Secretion and Sensitivity in Bangladeshi Type 2 Diabetic Subjects

**Roy MN [1], Akter S [2], Jafarullah M [3], Mollah FH [4], Saha AR [5], Ali L[6]**

**Background**: The relative contribution of insulin secretion and sensitivity in the development of Type 2 diabetes mellitus (T2DM) vary from population to population due to the heterogeneous nature of the disease. The study was undertaken to evaluate insulin secretory capacity and sensitivity in a Bangladeshi Type 2 diabetic population and to explore the association of some of the anthropometric and biochemical factors known to modulate B-cell function and insulin action. **Methods**: Ninety one T2DM subjects and 32 age-matched controls were studied for their fasting plasma glucose (FPG), lipids, $HbA_{1c}$ (by HPLC), leptin and C-peptide (ELISA). Insulin secretion (HOMA B) and insulin sensitivity (HOMA S) were calculated by homeostasis model assessment (HOMA). **Results**: Both insulin secretion and sensitivity were significantly reduced in diabetic as compared to control (HOMA B%, geometric mean±SD, 35.65±1.75 vs. 96.29±1.50, $p<0.001$; HOMA S%, 68.66±1.71 vs. 104.951.63, $p<0.001$). However, B-cell dysfunction was predominant than insulin resistance in predicting T2DM as the discriminate function coefficient for HOMA B (1.098) was greater than that for HOMA S (0.821). In T2DM, HOMA B had positive correlation with BMI ($r=0.368$, $p<0.001$) and HOMA S was inversely correlated to BMI ($r=-0.261$, $p<0.01$), WHR ($r=-0.258$, $p<0.01$) and plasma TG ($r=-0.233$, $p<0.001$). On multiple regression analysis HOMA B and HOMA S were found to be inversely associated to FPG ($p<0.001$) and leptin ($p<0.05$) in T2DM.

**Conclusions**: Both insulin secretory dysfunction and insulin resistance are present in Bangladeshi T2DM subjects, but B-cell failure seems to be the predominant abnormality. BMI, plasma glucose, insulin and leptin are the major determinants of insulin secretory capacity and generalized as well as central obesity, plasma glucose, triglycerides, insulin and leptin are among the major determinants of insulin sensitivity in this population.

**Key Words**: Leptin, Insulin, Diabetes

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For author affiliations, see end of text.
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## Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder caused by defects in insulin secretion and action[1]. Both genetic and environmental factors influence B-cell function and tissue insulin sensitivity [2]. Due to heterogeneity known to exist for both of these two factors the relative contribution of insulin secretory dysfunction and insulin resistance in the etiopathogenesis of T2DM are reported to vary substantially from population to population [3]. Bengalis form a major racial group with around 207 million population worldwide and they constitute about 3.4% of the world population [4]. There is no large scale study regarding the prevalence of diabetes in this population, but sporadic works suggest that the

prevalence is almost similar to those reported for South-East Asian population [5].

It seems that a lean phenotype of T2DM in adults found in the Indian subcontinent may be distinct from the more characteristic forms of T2DM found among the Caucasians [1]. In a study among Bangladeshi population, young (mean age 25 years) and nonobese (mean BMI 19.0 kg/m$^2$) T2DM subjects showed substantially reduced insulin secretory capacity with no evidence of insulin resistance in comparison to age- and BMI-matched control subjects [6]. In another study, newly diagnosed obese (age range 33-47 years, mean BMI 30.2 kg/m$^2$) T2DM patients showed both insulin secretory dysfunction and loss of insulin sensitivity with the percentage fall of the former being more than the latter[7]. None of the studies, however, addressed the confounding factors (other than BMI) which may potentially affect B-cell function and insulin sensitivity.

In the above context, the present study was designed to evaluate insulin secretion and sensitivity among T2DM of Bangladeshi population with different ranges of BMI as well as to explore the association of some of the anthropometric and biochemical factors known to modulate B-cell function and insulin sensitivity.

**Methods**

Ninety one (91) newly diagnosed T2DM patients from both sexes, aged between 30-50 years, were selected according to WHO criteria [1]. They were recruited consecutively from those attending the outpatient department of the central hospital (BIRDEM) of the Diabetic Association of Bangladesh (DAB) with a BMI of >18.5 kg/m$^2$. Thirty two (32) age-matched healthy subjects with a BMI of >18.5 kg/m$^2$ were included as control. The study was approved by the Ethical Review Committee of DAB. Subjects were evaluated by clinical and biochemical examination. Anthropometric measurements included height, weight, waist and hip girth. The degree of adiposity was estimated by calculating the BMI and waist hip ratio (WHR). A BMI of 18.5-24.99, 25.0-29.99 and 30.0-39.99 kg/m$^2$ were used to grade the subjects as normal weight, over weight and obese respectively [8].

Laboratory analysis was done with fasting venous blood. $HbA_{1c}$ was measured on the same day by a dedicated HPLC method (BioRad, USA). Plasma was preserved at –70°C for future measurements. The fasting plasma glucose (FPG) and lipids (total cholesterol, HDL-C and TG) were analyzed by enzymatic-colorimetric methods (Randox, UK). Plasma LDL-C level was estimated by the Friedewald's formula. Circulating C-peptide was assayed by chemiluminescence-based ELISA (DPC, USA). Plasma leptin was measured by the enzyme-amplified sensitivity immunoassay (EASIA) method with a commercial EASIA kit (Biosource, Belgium). Intra-assay and inter-assay coefficient of variation for leptin assay were 6.47 % and 3.18 % respectively.

Insulin secretory capacity (HOMA B%) and insulin sensitivity (HOMA S%) were calculated from FPG (mmol/l) and C-peptide (nmol/ml) values by homeostasis model assessment (HOMA) using HOMA-CIGMA software [9].

Statistical analysis was performed with the SPSS software for Windows version 10.0 (SPSS, Inc, Chicago IL, USA). The data were expressed as the mean±SD and/or geometric mean±SD as indicated. In case of data which were non-normally distributed (TG, HOMA B, HOMA S and leptin) log-transformation was done and then used for subsequent statistical analyses; the results were back-transformed to produce geometric means. Differences between group means were compared by unpaired *t* test. Discriminate function analysis was performed to determine the relative contribution of HOMA B and HOMA S in T2DM. Bivariate correlations among parameters were examined using Pearson's correlation coefficients. Multiple regression was performed to determine the association between the dependent and independent variables of interest after adjusting for other potentially confounding independent variables.

**Results**

There was no significant difference in age between control and diabetic groups (37.3±7.4 vs. 40.1±5.8 years). BMI (Kg/m$^2$) differed significantly between the two groups (23.3±2.5 in control vs. 26.5±3.8 in diabetic, p<0.001). The WHR was 0.88±0.06 in control and 0.93±0.07 in diabetic subjects, suggesting significantly higher central body fat distribution in the diabetic (p<0.001). Mean blood pressure (MBP) was significantly higher in diabetic as compared to control (92.3±8.7 vs. 86.7±8.1 mm Hg, p<0.001).

Diabetic subjects had significantly higher plasma total cholesterol and TG levels than control. Plasma HDL-C was significantly lower in diabetic as compared to control (Table I).

**Table – I :** Glycemic and lipidemic status of control and diabetic subjects

| Parameter | Control (n=32) | Diabetic (n=91) |
|---|---|---|
| FPG (mmol/l) | 4.860.57 | 9.60±2.87*** |
| $HbA_{1c}$ (%) | 5.55±0.63 | 9.01±1.92*** |
| T Cholesterol (mg/dl) | 163.8±33.8 | 189.4±35.3** |
| TG (mg/dl)[a] | 114.8±1.5 | 167.4±1.6*** |
| HDL-C (mg/dl) | 39.7±8.8 | 35.3±7.2** |
| LDL-C (mg/dl) | 98.3±28.3 | 116.7±31.2** |

Results are expressed as mean±SD, [a]geometric mean±SD; means compared using unpaired *t* test; *, p<0.05; **, p<0.01; ***, p<0.001. FPG, Fasting plasma glucose; $HbA_{1c,}$ Glycosylated hemoglobin; T Chol, Total cholesterol; TG, Triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol.

HOMA B was significantly reduced in diabetic as compared to control (34.88±1.77 vs. 96.29±1.50%, p<0.001). Diabetic group had significantly lower HOM A S than control (69.49±1.72 vs. 104.95±1.63%, p<0.001). Diabetic subjects had significantly higher plasma leptin levels as compared to control (9.2±2.34 vs. 6.03±2.45 ng/ml, p<0.05) (Table-II).

**Table – II** : Insulinemic and leptinemic status of control and diabetic subjects

| Parameter | Control (n=32) | Diabetic (n=91) |
|---|---|---|
| C-peptide (ng/ml) | 2.32±1.29 | 2.71±1.36* |
| HOMA B (%)[a] | 96.29±1.50 | 34.88±1.77*** |
| HOMA S (%)[a] | 104.95±1.63 | 69.49±1.72*** |
| Leptin (ng/ml) [a] | 6.03±2.45 | 9.20± 2.34* |

Results are expressed as mean±SD, [a] geometric mean±SD; means compared using unpaired *t* test; *, p<0.05; **, p<0.01; ***, p<0.001. HOMA B, Insulin secretory capacity; HOMA S, Insulin sensitivity.

The discriminate function coefficient for HOMA B (1.098) was greater than that for HOMA S (0.821).

HOMA B showed no significant correlation with BMI, WHR, T Cholesterol, HDL-C, LDL-C and $HbA_{1c}$ but was inversely correlated to FPG (r= -0.619, p<0.001) and positively correlated to TG (r=0.389, p<0.001) in control. It had significant positive correlation with BMI (r=0.368, p<0.001) and inverse correlation with both FPG (r= -0.737, p<0.001) and $HbA_{1c}$ (r= -0.602, p<0.001) in T2DM. HOMA S had no significant correlation with BMI, WHR, T Cholesterol, HDL-C, LDL-C, FPG and $HbA_{1c}$ except TG (r= -0.501, p<0.001) in control. In contrast, it was inversely correlated to BMI (r= -0.310, p<0.01), WHR (r= -0.274, p<0.01), FPG (r= -0.276, p<0.01) as well as TG (r= -0.273, p<0.01) in diabetic subjects.

A strong inverse association of glucose (p<0.001) and positive association of C-peptide (p<0.001) with HOMA B were observed in both control and diabetic groups. HOMA B was inversely related to leptin in total diabetic as well as normal weight diabetic (p<0.05) (Table III).

HOMA S was inversely related with glucose (p<0.001) and C-peptide (p<0.001) in both control and diabetic groups. There was no significant association of HOMA S with leptin in control; however, in the obese group they were inversely associated with each other (p<0.05) (Table-IV).

**Table – III :** Multiple regression analysis of the association of HOMA b with variables of interest in control and diabetic subjects

| Variable | Control (n=32) $R^2$=0.989 | | Normal weight Diabetic (n=32) $R^2$=0.993 | | Overweight Diabetic (n=33) $R^2$=0.993 | | Obese Diabetic (n=26) $R^2$=0.991 | | Total Diabetic (n=91) $R^2$=0.990 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Beta | p value | Beta | p value | Beta | p value | Beta | p value | Beta | p value |
| Age | -0.001 | 0.955 | 0.008 | 0.595 | -0.003 | 0.895 | -0.008 | 0.743 | -0.005 | 0.614 |
| Gender | 0.055 | 0.133 | 0.030 | 0.187 | -0.025 | 0.483 | 0.000 | 0.997 | 0.014 | 0.339 |
| MBP | 0.000 | 0.838 | -0.014 | 0.427 | -0.044 | 0.057 | 0.004 | 0.835 | -0.004 | 0.750 |
| BMI | -0.025 | 0.354 | 0.003 | 0.867 | -0.005 | 0.805 | -0.037 | 0.072 | 0.008 | 0.545 |
| WHR | 0.004 | 0.874 | 0.012 | 0.506 | -0.023 | 0.403 | -0.010 | 0.662 | 0.013 | 0.274 |
| FPG | -0.520 | <0.001 | -0.751 | <0.001 | -0.863 | <0.001 | -0.864 | <0.001 | -0.777 | <0.001 |
| $HbA_{1c}$ | 0.026 | 0.222 | 0.004 | 0.868 | -0.058 | 0.136 | -0.028 | 0.351 | -0.014 | 0.401 |
| C-peptide | 0.797 | <0.001 | 0.583 | <0.001 | 0.732 | <0.001 | 0.784 | <0.001 | 0.668 | <0.001 |
| Leptin | -0.016 | 0.681 | -0.058 | <0.05 | -0.043 | 0.233 | 0.037 | 0.109 | -0.032 | <0.05 |

Beta for standardized regression coefficient; $R^2$ for adjusted R Square (Multiple coefficient of determination) HOMA B, Insulin secretory capacity; MBP, Mean blood pressure; BMI, Body mass index; WHR, Waist hip ratio; FPG, Fasting plasma glucose; $HbA_{1c,}$ Glycosylated hemoglobin

**Table – IV** : Multiple regression analysis of the association of HOMA s with variables of interest in control and diabetic subjects

| Variable | Control (n=32) $R^2$=0.989 | | Normal weight Diabetic (n=32) $R^2$=0.933 | | Overweight Diabetic (n=33) $R^2$=0.983 | | Obese Diabetic (n=26) $R^2$=0.985 | | Total Diabetic (n=91) $R^2$=0.957 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Beta | p value | Beta | p value | Beta | p value | Beta | p value | Beta | p value |
| Age | -0.055 | 0.417 | -0.032 | 0.497 | 0.013 | 0.647 | -0.006 | 0.867 | 0.000 | 0.992 |
| Gender | -0.185 | 0.185 | -0.066 | 0.319 | 0.048 | 0.285 | -0.022 | 0.534 | -0.024 | 0.447 |
| MBP | 0.003 | 0.965 | 0.070 | 0.195 | 0.078 | 0.546 | -0.001 | 0.982 | 0.020 | 0.403 |
| BMI | -0.044 | 0.580 | 0.018 | 0.726 | 0.004 | 0.886 | 0.067 | 0.760 | -0.000 | 0.988 |
| WHR | 0.132 | 0.080 | -0.007 | 0.886 | 0.051 | 0.146 | 0.037 | 0.289 | 0.004 | 0.875 |
| FPG | -0.207 | <0.05 | -0.307 | <0.001 | -0.213 | <0.001 | -0.293 | <0.001 | -0.229 | <0.001 |
| $HbA_{1c}$ | -0.00 | 0.277 | 0.025 | 0.736 | 0.065 | 0.181 | 0.018 | 0.684 | 0.033 | 0.377 |
| C-peptide | -1.025 | <0.001 | -0.958 | <0.001 | -0.929 | <0.001 | -0.893 | <0.001 | -0.949 | <0.001 |
| Leptin | 0.122 | 0.308 | 0.118 | 0.054 | 0.050 | 0.269 | -0.091 | <0.05 | 0.053 | 0.074 |

Beta for standardized regression coefficient; $R^2$ for adjusted R Square (Multiple coefficient of determination) HOMA S, Insulin sensitivity; MBP, Mean blood pressure; BMI, Body mass index; WHR, Waist hip ratio; FPG, Fasting plasma glucose; $HbA_{1c,}$ Glycosylated hemoglobin

**Discussion**

It is evident in the present study that both insulin secretion and sensitivity are significantly reduced in Bangladeshi diabetic subjects and the data are in line with the findings of the previous study conducted in the same population [7]. The discriminate function analysis indicates that B-cell dysfunction may contribute more to the development of T2DM in contrast to loss of insulin sensitivity. This observation is not consistent with those of western population where impaired insulin action is thought to be the predominant defect in T2DM [2, 10]. Ethnic variation is the most probable reason for this difference and this further demonstrates the genetic heterogeneity in diabetes.

BMI seems to be a major determinant of insulin secretion in Bangladeshi subjects. In nondiabetic controls (who were selected from a normal BMI range) B-cell function was not affected by BMI as reported in non obese healthy subjects of a Mexican population [11]. In a Bangladeshi population non obese diabetic subjects (BMI of $< 25$ kg/m$^2$) did not show any hypersecretion of insulin [6]; but, Type 2 diabetic subjects with BMI of $> 24.99$ kg/m$^2$ showed hyperinsulinemia in the present study. Hyperinsulinemia has been reported also in obese non diabetic Caucasian [12]. These observations reemphasize the importance of body weight in the regulation of peripheral insulin levels and it becomes more and more important in higher degrees of BMI. Hyperinsulinemia is necessary to compensate tissue resistance to the hormone secondary to obesity [10].

Hyperglycemia (even in a moderate range) appears to be a very sensitive determinant of insulin secretion in T2DM (Table III). In contrast to non diabetic subjects where insulin secretion is linearly related to peripheral glucose, hyperglycemia over a threshold level has a suppressing effect in T2DM (Table III) [13]. The primary metabolic variable glucose, is itself injurious in patients with T2DM. This deleterious effect is often referred to as "glucose toxicity" or "glucose desensitization"[14]. The negative impact of glucose has been clearly shown when plasma glucose concentrations reach the range associated with diabetes [13].. Diabetic patients with poor glycemic control for a long period show suppressed insulin secretion due to glucotoxicity [15].

An inverse association between circulating concentrations of leptin and B-cell function is evident in both male and female T2DM patients. Suppression of insulin secretion by leptin is probably caused by hyper polarization of B-cells resulting from activation of ATP sensitive $K^+$ channels [16] or by reducing the activity of the $Ca^{2+}$-dependent protein kinas C (PKC) signal transduction mechanism [17].

It is interesting to observe that even within a range of normal body weight both BMI and WHR (representing general and central obesity respectively) are important determinants of insulin sensitivity in Bangladeshi diabetic population. Striking association of insulin resistance with central obesity has been demonstrated previously in South Asian men and women [18]. Central obesity is associated with failure of insulin to suppress release of non-esterified fatty acids from intra-abdominal fat cells; this failure would lead to increased hepatic synthesis of VLDL triglycerides [19]. The inverse relationship of fasting plasma TG concentrations with insulin sensitivity evident in this study supports the hypothesis.

In the present study plasma glucose is inversely associated with insulin sensitivity in diabetic subjects, a phenomenon which is probably related to hexosamine accumulation in muscle and fat tissue which, in turn, inhibits glucose transport across the cell membrane [20]. It was stated that as glucose and other substrates increase, they would feed forward in a vicious

cycle that begets more insulin resistance and poorer beta-cell function[13].

The present data demonstrate that insulin resistance is affected by leptin only in obese T2DM subjects, not in the lean ones. This is in contrast to the observation of Segal et al (1996) who found an independent inverse association between them both in lean and obese [21]. It has been demonstrated that leptin decreases insulin sensitivity and reduces insulin-stimulated glucose uptake in rat adipocytes [22]. Leptin antagonizes insulin signaling, by decreasing insulin-induced tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) [23]; increases phosphoenol pyruvate carboxykinase (PEPCK) and decreases glucokinase expression, leading to increased gluconeogenesis [24]. Raised plasma leptin levels in obese subjects and animals implicate an etiological link between leptin expression and insulin resistance, a state that is usually associated with obesity [22].

In conclusion, the present data suggest that both insulin secretory dysfunction and insulin resistance are present in Bangladeshi Type 2 diabetic subjects, but former seems to be more pronounced than the latter. BMI, plasma glucose, insulin and leptin are among the most important determinants of insulin secretory capacity, and generalized as well as central obesity, plasma glucose, triglycerides, insulin and leptin are among the major determinants of insulin sensitivity in Bangladeshi population.

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**Author Affiliations**

*1. Manindra Nath Roy, MBBS, M Phil, MD, Associate Professor of Biochemistry, Begum Khaleda Zia Medical College, Dhaka-1207

2. Salima Akter M Sc, Research Fellow, Department of Biochemistry & Cell Biology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka-1000.

3. Mohammad Jafarullah, MBBS, MD, Associate Professor of Biochemistry, Medical College for Women and Hospital, Uttara, Dhaka-1230.

4. Forhadul Hoque Mollah, MBBS, M Phil, Associate Professor of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka-1000

5. Ajanta Rani Saha, MBBS, DCGH, Medical Officer, Pediatrics OPD, Shaheed Surawardy Hospital, Dhaka-1207.

6. Liaquat Ali, MBBS, Ph D, Professor of Biochemistry and Cell Biology, BIRDEM, Dhaka-1000.

** For correspondence*

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