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# Effect of β-cell secretory status and insulin resistance on the glycemic status of newly diagnosed youth-onset phenotypic type 2 diabetes mellitus

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# Abstract

**Background:** Youth-onset phenotypic type 2 diabetes mellitus (T2DM) often presents with high plasma glucose and hemoglobin A1c (HbA1c).

**Objective:** To assess the relationship of  $\beta$ -cell secretory status and insulin resistance (IR) with plasma glucose and HbA1c at diagnosis in phenotypic T2DM of young.

**Methods:** This cross-sectional study enrolled 72 newly-diagnosed youth-onset phenotypically T2DM patients [age range 19-29, median 27, inter-quartile range (IQR) 24-29 years; 40 (55.6%) female] to see insulin secretory status by fasting C-peptide and insulin resistance by visceral adiposity index (VAI) along with serum triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio. C-peptide was measured by chemiluminescence immunoassay.

**Result:** Median fasting plasma glucose (FPG), 2h plasma glucose (2h-PG) and HbA1c of the participants were 10.8 (IQR 7.1-16.3) mmol/L, 18.0 (IQR 13.1-24.3) mmol/L, and 8.7% (IQR 6.7-11.0) respectively. All glycemic values inversely correlated with fasting C-peptide (FPG:  $\rho$  =-0.48, p<0.001; 2h-PG:  $\rho$ =-0.46, p<0.001; HbA1c:  $\rho$ =-0.44, p<0.001), body mass index (FPG:  $\rho$  =-0.39, p<0.001; 2h-PG:  $\rho$ =-0.35, p<0.001; HbA1c:  $\rho$ =-0.40, p<0.001) and waist circumference (FPG:  $\rho$ =-0.28, p=0.001; 2h-PG:  $\rho$ =-0.25, p=0.002 HbA1c:  $\rho$ =-0.29, p<0.001) whereas neither with VAI (HbA1c:  $\rho$ =-0.04, p=0.757; FPG:  $\rho$ =0.08, p=0.532; 2h-PG:  $\rho$ =0.20, p=0.099) nor with TG/HDL-C ratio (HbA1c:  $\rho$ =0.04, p=0.764; FPG:  $\rho$ =0.14, p=0.228; 2h-PG:  $\rho$ =0.14, p=0.074). In a linear regression model, adjusted for VAI, age and sex, each nmol rise of C-peptide was associated with 3.07 mmol/L fall (95% CI 4.73-1.41) of FPG, 3.22 mmol/L fall (95% CI 5.06-1.37) of 2h-PG and 1.51% fall (95% CI 2.38-0.64) of HbA1c.

**Conclusion:** Plasma glucose and HbA1c of youth-onset phenotypic T2DM at the time of diagnosis is more influenced by  $\beta$ -cell secretory status than insulin resistance. [J Assoc Clin Endocrinol Diabetol Bangladesh, January 2024; 3 (1): 09-15]

Keywords: Type 2 diabetes, youth onset, C-peptide, plasma glucose, insulin resistance

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# Introduction

Type 2 diabetes (T2DM) is the most prevalent form of diabetes and prevalence is increasing alongside cultural and social changes. In addition to adults, its prevalence is also increasing in the youth of Bangladesh.<sup>1</sup> T2DM is a heterogeneous, multifactorial, polygenic disorder. So, defects in insulin secretion, and insulin action/resistance play variable roles in T2DM development. Insulin resistance is a crucial factor in the development of T2DM in adults, but the pathophysiology of diabetes in young people is still not well understood. It is unclear whether insulin resistance or insulin secretion defects are primarily responsible.<sup>2</sup> Accordingly, it is very much difficult to characterize child and adolescent DM due to the variance in mode of presentation.<sup>3</sup>

Youth-onset DM, most of whom are phenotypically T2DM, is a growing public health concern, with significant implications for the affected individuals, their families, and society as youth-onset T2DM is associated with a higher risk of complications than adult-onset T2DM, including cardiovascular disease, neuropathy, retinopathy, and nephropathy related to prolong exposure of hyperglycemia.<sup>4</sup> Prevalence of youth-onset T2DM in United States as observed by the SEARCH for Diabetes in Youth study in 2017 was 0.67 per 1000 in 10-19-year age group.<sup>5</sup> However, in a meta-analysis, the prevalence of all types of diabetes in young age group of Bangladesh was 2.8-6.5%.<sup>1</sup>

Glycemic excursion, defined as the variability of blood glucose levels over time, is a critical determinant of T2DM outcomes, including the risk of complications.<sup>6</sup> The glycemic level at diagnosis is influenced by several factors, including insulin resistance, impaired  $\beta$ -cell function, and glucose toxicity.<sup>7</sup> Insulin resistance refers to a state in which cells fail to respond adequately to insulin, resulting in reduced glucose uptake and increased hepatic glucose production.  $\beta$ -cell dysfunction denotes a state in which  $\beta$ -cells fail to secrete adequate insulin in response to glucose stimulation, leading to impaired glucose tolerance and hyperglycemia.<sup>8</sup>

The relative contributions of insulin resistance and  $\beta$ -cell dysfunction to glycemic excursion in youth-onset T2DM are not well understood. Some studies have suggested that insulin resistance is the primary determinant of glycemic excursion in T2DM while others suggested that  $\beta$ -cell dysfunction significantly contributes to glycemic excursion in these youth-onset T2DM.<sup>9,10</sup>

The purpose of this study was to see the relationship of insulin resistance and  $\beta$ -cell dysfunction to glucose levels in newly diagnosed youth-onset T2DM. Specifically, we examined the relationship of glycemic values [fasting plasma glucose (FPG), 2-hour plasma glucose (2h-PG) and hemoglobin A1c (HbA1c)] to insulin resistance assessed by the surrogate marker of insulin resistance [visceral adiposity index (VAI) and serum triglyceride/high-density lipoprotein (TG/HDL-C) ratio] and  $\beta$ -cell function measured by fasting C-peptide.

# Methods

# Study subjects and design

This cross-sectional study was conducted in the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2022 to December 2022. A total number of 72 young participants with diabetes diagnosed according to the American Diabetes Association (ADA) criteria, 2022 enrolled by non-probability purposive were sampling.<sup>11</sup> As the age range for 'youth-onset' diabetes has not been strictly defined, we used the age range of 19-29 years for the convenience of study. The participants had no ketosis at diagnosis of DM and had most features suggestive of T2DM like overweight/obesity, central obesity, positive family history, features of insulin resistance like acanthosis nigricans, absence of typical symptoms of hyperglycemia at presentation or physical inactivity. Hence, they were termed as 'phenotypical T2DM'. Patients with pregnancy, chronic liver disease, chronic kidney disease, other endocrinopathies, and drugs interfering with endogenous insulin and C-peptide concentration were excluded from this study.

# **Study procedure**

The participants were enrolled from Young Diabetes Clinic, BSMMU on a referral basis within two weeks of diagnosis. Results of the oral glucose tolerance test (OGTT) and fasting lipid profiles including triglycerides (TG) and high-density lipoprotein (HDL) were recorded, and a detailed history and thorough examination were done for each participant. Height was measured by using a stadiometer, standing upright on a flat surface without shoes. Weight was measured by a balance placed on a hard-flat surface. Body mass index (BMI) was calculated in kg/m<sup>2</sup>.<sup>12</sup> Waist circumference (WC) was measured to the nearest centimeter with a flexible tape, while the subjects were in a standing position at the end of gentle expiration. The following anatomical landmarks were used: laterally, midway between the lowest portion of the rib cage and iliac crest, and anteriorly, midway between the xiphoid process of the sternum and the umbilicus.<sup>13</sup> The demographic and clinical features of the patients were recorded in a standard pre-tested structured datasheet. Patients or eligible attendants were questioned about past and family (parents and siblings) history. A fasting blood sample (5 mL) was collected from each

participant for the measurement of C-peptide. During sample collection, participants were either treatment naive or receiving metformin/short acting insulin for <2 weeks. TG/HDL-C ratio was calculated by dividing TG level (in mg/dL) by HDL level (in mg/dL). VAI was calculated using the following formula.<sup>14</sup>

#### For males:

VAI=WC/(39.68+(1.88XBMI))×TG/1.03×1.31/HDL For females:

VAI=WC/(36.58+(1.89XBMI))×TG/0.81×1.52/HDL

(TG and HDL expressed in mmol/L; WC in cm and BMI in  $kg/m^2$ )

#### **Analytic method**

C-peptide was measured by the chemiluminescent immunometric assay by MAGLUMI series chemiluminescence immunometric analyzer, MAGLUMI 2000 plus for the quantitative determination of c-peptide with a measuring range of 0.003-6.600 nmol/L. The intra-assay coefficient of variation was 5%.

#### **Ethical aspects**

Before this study commenced, the Institutional Review Board, BSMMU, Dhaka, Bangladesh approved the protocol. Before enrollment, informed written consent was taken from the individuals or guardians after a full explanation of the purpose of the study.

Table-I:	Characteristics	of the stud	y participants	(n=72)
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#### Statistical analysis

Statistical analyses were performed by using IBM SPSS Statistics for Windows version 25.0. Quantitative data were expressed as mean  $\pm$ SD or median and interquartile range (IQR), whereas qualitative data were expressed as frequency distribution and percentage. Correlation between the variables was done by Spearman's correlation. Multivariate linear regression was done to see the association of FPG and 2h-PG with C-peptide and VAI, in a model adjusted for age. A p-value of less than 0.05 was considered statistically significant.

# Results

A total of 72 newly diagnosed youth-onset phenotypic T2DM patients with a median age of 27 years [inter-quartile range (IQR) 24-29 years] were enrolled. Among them, 55.6% were female, 72.2% had typical symptoms of hyperglycemia, 68.1% had a positive family history while 63.9% had acanthosis nigricans. Median HbA1c, FPG, and 2h-PG of the participants were 8.7% (IQR 6.7-11.0), 10.8 (IQR 7.1-16.3) mmol/L and 18.0 (IQR 13.1-24.3) mmol/L respectively. Median C-peptide level was 1.40 nmol/L (IQR 1.03- 2.10) (Table-I). None had ketosis at diagnosis.

All the values of glycemic status were negatively correlated to fasting C-peptide (FPG:  $\rho$ =-0.48, p<0.001; 2h-PG:  $\rho$ =-0.46, p<0.001; HbA1c:  $\rho$ =-0.44,

Frequency (%) / Median (IQR)										
27 (24-29)										
32 (44.4)										
40 (55.6)										
52 (72.2)										
49 (68.1)										
24.7 (22.9-28.5)										
88.0 (82.0-93.75)										
46 (63.9)										
10.8 (7.1-16.3)										
18.0 (13.1-24.3)										
8.7 (6.7-11.0										
1.40 (1.03-2.10)										

\*Polyuria, polydipsia, weight loss

DM: diabetes mellitus, BMI: body mass index, WC: waist circumference, cm: centimeter, FPG: fasting plasma glucose, 2-h PG: 2-h plasma glucose during oral glucose tolerance test, HbA1c: glycated hemoglobin

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Figure-2: Correlations of plasma glucose values with visceral adiposity index FPG: fasting plasma glucose (red closed circle) 2h-PG: 2h plasma glucose (blue open circle) by Spearman's correlation

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	U	5	1 05		5 0 (	/
Variables	FPG		2h-PG	HbA1c		
	Unstandardized	р	Unstandardized	р	Unstandardized	р
	Beta (95% CI)		Beta (95% CI)		Beta (95% CI)	
Constant	17.99	0.012	14.27	0.002	17.22	< 0.001
C-peptide	-3.07	<0.001	-3.22	0.001	-1.51	0.001
(nmol/L)	(-4.731.41)		(-5.061.37)		(-2.380.64)	
VAI	0.09	0.597	0.24	0.206	0.010	0.910
	(-0.25 - 0.44)		(-0.14 - 0.63)		(-0.17 - 0.19)	
Age	0.03	0.887	0.08	0.747	-0.12	0.297
(years)	(-0.42 - 0.48)		(-0.42-0.58)		(-0.36 - 0.11)	
Sex (male to female)	-1.48	0.272	-2.14	0.154	-1.38	0.053
	(-4.15 - 1.19)		(-5.10 - 0.82)		(-2.78 - 0.01)	

Tabla	<b>TT</b> • 1	Multivariat	linear	regression	anals	reie f	or n	redictors	$\mathbf{of}$	alvernie	values	in	voung	DM	(n-7)	2)
Table-	11.	viuitivailat	mean	regression	anary	515 1	υp	redictors	01	grycenne	values	ш	young .		(11 - 7)	2)

FPG: Fasting plasma glucose, 2h-PG: 2h plasma glucose, VAI: Visceral adiposity index, TG: Triglyceride, HDL: High density lipoprotein.

p<0.001) (Figure-1). In addition, BMI and WC were also negatively correlated with all of them (For BMI: FPG: ρ=-0.39, p<0.001; 2h-PG: ρ=-0.35, p<0.001; HbA1c:  $\rho$ =-0.40, p<0.001; for WC: FPG:  $\rho$ =-0.28, p=0.001; 2h-PG: ρ=-0.25, p=0.002 HbA1c: ρ=-0.29, p<0.001). The values for glycemic state were lower in participants who had acanthosis nigricans in comparison to those who did not had [HbA1c%: 7.6 (6.3-9.6) vs. 11.0 (9.3-13.3), p<0.001; FPG 7.6 (6.4-13.7) vs. 15.5 (10.0-19.8) mmol/L, p<0.001; 2h-PG 15.5 (12.4-21.5 vs. 23.6 (17.7-28.0), p=0.001]. There were no significant correlations of any of these values to VAI (HbA1c: p=-0.04, p=0.757; FPG: p =0.08, p=0.532; 2h-PG: ρ=0.20, p=0.099) (Figure-2) or TG/HDL-C ratio (HbA1c:  $\rho=0.04$ , p=0.764; FPG: ρ=0.14, p=0.228; 2h-PG: ρ=0.14, p=0.074).

The mean C-peptide level of obese/overweight  $(1.85\pm0.73 \text{ nmol/L}, n=53)$  was significantly higher (mean difference 0.90, 95% CI 0.60-1.21; t=-5.94, p<0.001] than that of the normal/underweight (0.94±0.50 nmol/L, n=19). C-peptide was also higher in those with high WHR than those with normal WHR (mean difference 0.75, 95% CI 0.32-1.18, t =3.73, p=0.003).

In multivariate linear regression, a combination of C-peptide, visceral adiposity index (VAI), age and sex accounted for 20.3% of the variability of FPG (R<sup>2</sup>=0.203, adjusted R<sup>2</sup>= 0.155, p=0.004), 21.1% variability of 2h-PG (R<sup>2</sup>=0.211, adjusted R<sup>2</sup>= 0.164, p=0.003) and 21.8% variability of HbA1c (R<sup>2</sup>=0.218, adjusted R<sup>2</sup>= 0.171, p=0.002). Only C-peptide had independent association with FPG ( $\beta$ = -3.07, p <0.001), 2h-PG ( $\beta$ = -3.22, p=0.001) and HbA1c ( $\beta$ = -1.51, p=0.001) (Table-II).

# Discussion

T2DM is heterogenous and multiple risk factor contributes to its development including family history, environmental factors, genetic contribution, and ethnicity.<sup>15</sup> Insulin resistance and  $\beta$ -cell dysfunction are two pathognomic well-known characteristics of T2DM. It is debatable whether insulin resistance,  $\beta$ -cell dysfunction, or both constitute the basic abnormality in T2DM and if one defect predates the other in the disease's natural history.<sup>16</sup> Some studies have observed differences in insulin sensitivity and/or  $\beta$ -cell dysfunction between ethnic groups, while others have found no difference.<sup>17,18</sup> The area is mostly unexplored in youth-onset T2DM.

cross-sectional This study emphasizes the significance of  $\beta$ -cell dysfunction in relation to insulin resistance across the glycemic status in youth-onset T2DM at the time of diagnosis. β-cell secretory capacity was assessed by fasting C-peptide as it is not influenced by exogenous insulin and its long half-life relative to insulin. Insulin resistance was measured by VAI and TG/HDL-C ratios which have good correlation to insulin resistance measured by homeostasis model assessment (HOMA-IR).<sup>18</sup> All the glucose values including FPG, 2hPG and HbA1c was significantly associated with C-peptide level but not VAI or TG/HDL-C. Thus  $\beta$ -cell secretory dysfunction may contribute more to glycemic excursion in this study population.

It is well-accepted that some sort of  $\beta$ -cell dysfunction is present at the time of diagnosis even before overt hyperglycemia. Reduced insulin release in response to glucose and non-glucose

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secretagogues, changes in pulsatile and oscillatory insulin secretion, an abnormality in proinsulin to insulin conversion efficiency, and decreased release of islet amyloid polypeptide (IAPP) may be observed early in the course of T2DM.<sup>8,20,21</sup> Although insulin resistance is present in the vast majority of T2DM patients, it can also occur in the absence of insulin resistance.<sup>22</sup> Furthermore, the majority of insulin-resistant obese people do not develop T2DM. These people stay normoglycemic because they compensate for their decreased insulin sensitivity by increasing insulin secretion. As a result, insulin resistance is not a sufficient cause of T2DM; the development of T2DM must entail a malfunction at the cell level that prevents this compensatory mechanism from functioning.<sup>23</sup> Although there is no doubt that defects in  $\beta$ -cell function exist in all hyperglycemic subjects, when this abnormality begins and what factors may be responsible for this change have been a source of much debate.<sup>24</sup>

There may be an ethnic influence on this variation of glycemic values. Asian Americans with NGT or IFG/IGT are less insulin resistant than all other ethnic groups, while Asian Indians with moderate dysglycemia have significantly lower  $\beta$ -cell function. These discrepancies cannot be explained by variations in age, obesity, insulin sensitivity, or family history.<sup>25</sup> Furthermore, it appears that when glucose intolerance exists, all ethnic groups exhibit evidence of  $\beta$ -cell dysfunction, and this dysfunction is more severe in the presence of diabetes.<sup>26</sup> Current thinking holds that T2DM is caused by a genetic  $\beta$ -cell abnormality that restricts correction for obesity-induced insulin resistance in most cases.<sup>27</sup>

The study examined fasting C-peptide, which is thought to be a good indicator of endogenous insulin secretory status. However, T2DM was diagnosed based on phenotypical/clinical features without assessing the autoimmune markers and monogenic anomalies for insulin secretory capability. A complete review of various kinds of diabetes, assigning a comparison group, measurement of insulin resistance by HOMA-IR, and larger sample size could boost the study's power. Studies that demonstrate the reliability of VAI and TG/HDL-C as surrogate markers of insulin resistance in youth-onset diabetes are lacking. we extrapolated the finding from studies on adult-onset diabetes. Serial follow up of these patients to see the changes over time could be rewarding.

The findings of this study may have important implications for the management and treatment of youth-onset phenotypic T2DM. As  $\beta$ -cell dysfunction is found to be the primary determinant of glycemic excursion in this population, interventions aimed at preserving  $\beta$ -cell function, such as early initiation of insulin therapy, may be more effective than interventions aimed at improving insulin sensitivity in this group of people. Furthermore, a better understanding of the relative contributions of insulin resistance and  $\beta$ -cell dysfunction to glycemic excursion may help identify high-risk individuals who would benefit from more aggressive management of their diabetes.

# Conclusions

Plasma glucose and HbA1c of youth-onset T2DM at the time of diagnosis are more related to  $\beta$ -cell secretory status than insulin resistance. Longitudinal studies are needed to assess the change in insulin-secreting ability of  $\beta$ -cells over time.

## **Conflict of interests**

The authors have no conflicts of interest to disclose.

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## Disclosure

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

## **Financial Disclosure**

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## Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author upon reasonable request.

## Ethical Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of BSMMU, Reg: No. BSMMU/2022/2395, Approved on 08-03-2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRB and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed written consent was taken from the individuals or guardians was obtained from each of the participants included in the study.

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