Glutamic acid decarboxylase positivity in selected group of Bangladeshi type 2 diabetic patients

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Abstract

Background: Many patients with type 2 diabetes mellitus (T2DM) test positive for glutamic acid decarboxylase (GAD). These individuals have been referred to as having latent autoimmune diabetes in adults (LADA) or type 1.5 diabetes. LADA refers to a specific type of diabetes affecting adult patients, characterized by presence of islet auto-antibodies, insulin independence at the time of diagnosis and characterized by slower beta cell destruction. The aim of this study was to identify GAD positivity in a selected group of Bangladeshi T2DM patients and compare the clinical characteristics of GAD positive and negative subjects.

Methods: This cross-sectional study was conducted in 2017 at BIRDEM General Hospital, Dhaka. Recently diagnosed drug-naive patients with T2DM were evaluated. Considering inclusion and exclusion criteria 100 subjects were screened. These patients allowed for the assessment of GAD positivity along with anthropometric and biochemical characteristics.

Results: A total of 100 newly diagnosed (within 6 months) T2DM patients in age group 30-70 years were selected for this study. Of them men and women were 59.6% and 40.4% respectively. The GAD antibody positive was found to be 10%. There was no significant difference in respect of age, body mass index, fasting plasma glucose, HbA1c, total cholesterol, triglycerides, HDL cholesterol, LDL and blood pressure between GAD positive and GAD negative subjects.

Conclusion: The presence of GAD positivity was 10% among adult patients with newly diagnosed T2DM which was very high in Bangladeshi population. Further long term prospective studies need to be essential to identify the actual situation of GAD positive subjects and to determine their clinical course and optimal treatment regimens.

Key words: Type 1 diabetes mellitus, type 2 diabetes mellitus, glutamic acid decarboxylase.

Introduction

The prevalence of diabetes mellitus (DM) is increasing worldwide and it has become a major health problem in the modern world. Type 2 diabetes mellitus (T2DM) is a chronic disorder of carbohydrate, fat and protein metabolism. Approximately 425 million adults have diabetes; by 2045 this will rise to 629 million with 80% of the burden carried by lower middle income group countries including Bangladesh.

T2DM was once considered as disease of older adults but the age of diagnosis is falling and it is now increasingly diagnosed in adolescents and young adults. In the last 25 years, type 1 diabetic patients have significantly increased. From the result of obesity pattern, many young with type 1 diabetics are either overweight or obese at diagnosis. It is difficult for clinicians to distinguish between type 1 and type 2 diabetes based on age at onset and weight.
T2DM with positive auto-antibodies is characterized by insulin independence at the time of diagnosis, a high incidence of relative insulin deficiency and rapid progression to insulin dependence.11-15 This form of diabetes has also been called latent autoimmune diabetes in adults (LADA),14 slowly progressive insulin dependent diabetes mellitus16 or type 1.5 diabetes.17 Researchers hypothesized that glutamic acid decarboxylase (GAD) would be a marker of a subclinical autoimmune process and showed that GAD positivity was associated with a decrease in maximal insulin secretory capacity in non-diabetic subjects.18 GAD positivity may contribute to the heterogeneity in the subset of patients who have this antibody because it is typically associated with type 1 diabetes10, which is largely a disease of reduced beta cell function.19 If that is the case, GAD should also be a predictor of future diabetes in adults.

Epidemiological studies suggest that GAD positivity may account for about 2–12% of all cases of diabetes.12,11 The presence of GAD autoantibody allowed the identification of the group with a more deteriorated beta-cell function and with a more frequent requirement for insulin. Preservation of beta cell function can control glucose excellently and can delay end organ complications for diabetic patients. Early diagnosis and administration of exogenous insulin would preserve the residual pancreatic beta cell function. It is also suggested that active beta cells producing high amounts of insulin are more susceptible to immune destruction and therefore rest for beta cells could preserve them longer.21,22

In this study, we evaluated the prevalence of GAD positivity among recent onset T2DM patients and compared the clinical characteristics of patients with and without GAD.

Methods
This cross-sectional study was conducted at Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, during the period of January to June 2017. One hundred Bangladeshi individuals with newly diagnosed (within 6 months) T2DM and aged between 30 and 70 years were included in this study. Patients with type 1 DM, those who started insulin therapy after diagnosis of diabetes and patients with a history of diabetic ketoacidosis, pregnant patients, taking steroids, taking chemotherapy for malignancy, taking medications for hypertension and dyslipidemia, had chronic liver disease, with acute infection and other disorders that could affect glucose metabolism were excluded from this study. The enzyme linked immune-sorbent assay (ELISA) test for GAD-65 was performed using the reagents from DRG Inc, USA following the manufacturer’s instruction.

Statistical analysis
All quantitative data were expressed as mean ± standard deviation (SD) while categorical variables were expressed as percentages. Continuous variables were compared using independent using chi-square test. All statistical analyses were performed using Statistical Package for Social Science (SPSS) statistical software (version 20.0). A two-tailed p value less than 0.05 was considered statistically significant.

Results
The study population comprised 100 T2DM subjects who attended BIRDEM General Hospital, Dhaka. Of 100 patients, 10 (10%) were positive for GAD. Demographic characteristics of GAD antibody positive group was shown in Table I.

| Table I Demographic characteristics of GAD antibody positive group(N=10) |
|--------------------|-----------|
| Demographic characteristics | 10(10%) |
| Sex | |
| Male | 7(70%) |
| Female | 3(30%) |
| Age at diagnosis (years) | 35.00 ± 4.57 |
| Distribution of patients according to age groups n (%) | |
| 26 – 30 | 2(20%) |
| 31 -35 | 3(30%) |
| 36 – 40 | 5(50%) |
| BMI | |
| Normal weight (< 25) | 6(60%) |
| Over weight (25.1 – 30.0) | 4(40%) |
Among the GAD positive patients, men and women were 70% and 30% respectively. Fifty percent of GAD auto antibody positive patients were between 36-40 years and about 40% patients were overweight.

The two groups, GAD positive and negative had similar demographic characteristics as shown in Table-II. The mean ages of the patients with positive GAD (n=10) and negative GAD (n=90) were 35.0 ± 4.57 and 33.7 ± 4.47 respectively. There was no significant difference in gender distribution between two groups although males were recruited more in both groups (70% vs. 56.7%). In GAD positive and negative subjects, family history of DM was 70.0% and 56.7% respectively. There was no significant difference in component of metabolic syndrome (BMI, waist-to-hip ratio, fasting plasma glucose, HbA1c, systolic blood pressure, diastolic blood pressure, TC, LDL, HDL, triglyceride, creatinine) between GAD positive and negative patients shown in Table III.

### Table II Comparative analysis of demographic characteristics of GAD antibody-positive and negative groups (N=100)

|                          | GAD positive |           | GAD negative |           |       |
|--------------------------|--------------|-----------|--------------|-----------|-------|
|                          | Freq         | Percent   | Freq         | Percent   | P     |
| Sex                      |              |           |              |           |       |
| Male                     | 7            | 70.0      | 53           | 58.9      | 0.496 |
| Female                   | 3            | 30.0      | 37           | 41.1      |       |
| Family history of DM     |              |           |              |           |       |
| Yes                      | 7            | 70.0      | 51           | 56.7      |       |
| No                       | 3            | 30.0      | 39           | 43.3      | 0.384 |
| Physical exercise        |              |           |              |           |       |
| Yes                      | 5            | 50.0      | 60           | 66.7      | 0.295 |
| No                       | 5            | 50.0      | 30           | 33.3      |       |
| Residence                |              |           |              |           |       |
| Rural                    | 0            | 0.0       | 6            | 6.7       | 1.00  |
| Urban                    | 10           | 100.0     | 84           | 93.3      |       |
| Duration of DM (months)  | 2.80 ± 1.39  | 2.77 ± 0.99 | 0.923        |           |       |
| Age (years)              | 35.00 ± 4.57 | 33.72 ± 4.47 | 0.394        |           |       |

### Table III Clinical characteristics of recently diagnosed T2DM patients according to the presence or absence of GAD (N=100)

| Variables                              | GAD positive |                  | GAD negative |                  | p     |
|----------------------------------------|--------------|------------------|--------------|------------------|-------|
| BMI, kg/m²                             | 24.39 ± 1.87 | 25.27 ± 3.63     | 0.479        |                  |       |
| Waist-to-hip ratio (WHR)               | 0.97 ± 0.08  | 0.95 ± 0.07      | 0.447        |                  |       |
| Fasting plasma glucose (mmol/l)        | 7.51 ± 1.37  | 9.01 ± 3.75      | 0.195        |                  |       |
| HbA1c (%)                              | 7.46 ± 1.37  | 8.14 ± 2.15      | 0.333        |                  |       |
| Systolic blood pressure (mmHg)         | 118.00 ± 10.33 | 119.66 ± 11.53 | 0.663        |                  |       |
| Diastolic blood pressure (mmHg)        | 79.0 ± 5.68  | 79.66 ± 7.14     | 0.778        |                  |       |
| Total cholesterol, mg/dl               | 183.40 ± 42.04 | 192.11 ± 42.62  | 0.541        |                  |       |
| LDL cholesterol, mg/dl                | 107.30 ± 28.06 | 112.88 ± 33.69  | 0.616        |                  |       |
| HDL cholesterol, mg/dl                | 35.30 ± 5.94 | 35.32 ± 7.49     | 0.993        |                  |       |
| Triglycerides, mg/dl                  | 206.20 ± 112.19 | 209.57 ± 118.22 | 0.932        |                  |       |
Discussion
In the current study the positivity of GAD antibody was 10% in clinically diagnosed T2DM patients. From the U.K. Prospective Diabetes Study (UKPDS), the overall prevalence of GAD antibodies was 10%\textsuperscript{13} which is similar with our study, where as in the Botnia Study in Western Finland, the prevalence of GAD positivity was 9%.\textsuperscript{12,20} In Ghana GAD positive patients was 13.5% and in China it was 9.2% among T2DM patients.\textsuperscript{21,22} The prevalence of GAD positive antibody was more in males than in females in the present study. There was no significant difference in age between GAD positive and negative groups, which is consistent with other studies.\textsuperscript{22,23} In previous studies of Western countries, LADA patients had a lower BMI, more decreased insulin secretory capacity at diagnosis and more rapid progression to insulin dependence than typical T2DM patients.\textsuperscript{13,15,20} In the current study, the BMI of the patients with positive GAD tended to be lower than that of the patients with negative GAD, which was not a statistically significant difference. Leslie RDet al.\textsuperscript{24} in their study reported that majority of GAD positive patients were usually thin or of normal weight group, while few studies also reported mean BMI of GAD positive patients in the overweight or obese categories.\textsuperscript{20,25}

In the present study, we found out that there was no statistical difference in waist circumference, fasting blood glucose, systolic blood pressure, diastolic blood pressure, TG, HDL, LDL and creatinine levels between GAD-positive and negative groups. These findings are not consistent with Botnia study and ADOPT study.\textsuperscript{18,23} These studies revealed that GAD positive patients had a higher level of serum HDL-C, lower serum TG levels and a lower prevalence of metabolic syndrome than patients with negative anti-GAD. It can be explained that due to small sample size, the study could not differentiate the characteristics of GAD positive and negative subjects in T2DM patients. Therefore, a large-scale, nationwide study is necessary to examine the clinical characteristics related to metabolic syndrome in patients with GAD positive in Bangladesh.

Conclusion
The incidence of anti-GAD in T2DM subjects may be a marker for a group of patients who are at risk of faster metabolic death of beta cells. The presence of studied autoantibodies in patients with T2DM is high (10%). It is emphasized to develop an effective therapy to reduce hyperglycemia and to halt the progressive beta-cell failure in these patients.

Conflict of interest: Nothing to declare.

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