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Role of Glycated Hemoglobin on Islets Cell Autoantibody Mediated Insulin Resistance in Type 2 Diabetic Patients

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Abstract **Original Research Article**

Background: Latent autoimmune diabetes in adults often presents with a clinical phenotype indistinguishable from that of classic Type-2 Diabetes Mellitus (T2DM). Presence of auto antibodies, at diagnosis the secretion function of islets of beta-cell progressively worsens with disease duration which effects on the glycemic control and treatment failure. Among the auto antibodies Islet Cell Autoantibody (ICA) play important role in beta cell destruction leading to diabetes. ***Objective:*** The objective of the study was to find out the relationship between ICA and changes in the Glycosylated Hemoglobin (HbA1c) levels in newly diagnosed T2DM. ***Materials & Methods:*** A total number of 173 T2DM adult subjects of both sexes was selected and tested for presence of ICA autoantibody. ICA was measured by Enzyme Linked Immunosorbent Assay (ELISA) method and HbA1c measured by Immunoassay technique. ***Results:*** The participants divided into two groups according to presence and absence of ICA antibody. Among ICA positive cases, maximum patients were male within 41-50 years. No significant difference between ICA positive and negative patients in respect of age and gender. 12.7% (22 positive cases out of 173) of T2DM patients had been found to be ICA positive which was statistically significant ($p<0.001$). In ICA positive patients mean BMI (kg/m2) was 24.56±3.96 and in among 151 ICA negative cases mean BMI (kg/m2) was 24.90±4.07 which was not statistically significant. Mean of Fasting Blood Sugar(FBS)12.77±3.35 at the time of diagnosis among ICA positive patients is statistically significant ($p<0.001$). At diagnosis, the difference of mean HbA1c is higher in ICA positive patients than in ICA negative patients in newly diagnosed T2DM patient which was statistically significant ($p<0.001$). ***Conclusion:*** HbA1c levels were associated with ICA positive type 2 diabetic patients which indicate HbA1c has a potential diagnostic role to detect beta cell destruction leading to insulin resistance.

Keyword: ICA, T2DM, HbA1c.

INTRODUCTION

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia caused by relative or absolute deficiency of insulin [1]. There are two general types of DM, one is type 1 or insulin dependent diabetes mellitus (IDDM) and other is type 2 or non -insulin dependent diabetes mellitus (NIDDM). Among them, type 2 diabetes is more common and about 90 to 95 % of all cases of DM. According to World Health Organization (WHO) diagnostic criteria of diabetes mellitus are fasting blood glucose ≥7.0 mmol/l, 2 hours after glucose ≥11.1mmol/l and HbA1c ≥6.5% [2]. Chronic complications of DM are microvascular complications and macrovascular complications. The microvascular complications are retinopathy, neuropathy and nephropathy [1]. Within 2019 globally 9.3% (463 million people) people diagnosed as diabetic which rises to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 respectively [3]. The prevalence is higher in urban (10.8%) than rural (7.2%) areas as well as in high-income (10.4%) than low-income countries (4. 0%).Among them 50.1% people living with diabetes do not know that they have diabetes [3]. Prevalence of impaired glucose tolerance (IGT) is estimated to be 7.5% (374 million) in 2019 and projected to reach 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045 globally [3]. The highest regional prevalence of DM was reported for North America (10.2%) and the third highest was South East Asia which is about 7.6% [4]. Bangladesh is situated in the South-East Asian region and here prevalence of DM and IGT was about 8.5% in 2017 and is predicted to rise to 11.1% by 2045 [4]. In Bangladesh, the prevalence of

diabetes among adults (20-79 years) had increased substantially in rural and urban area. A recent scoping review (1994-2013) revealed that the prevalence of type 2 diabetes ranged between4.5% to35% in Bangladesh. Bangladesh was ranked as the eight position diabetic populous country in the time period of 2010-2011 [5-7]. Slowly progressive autoimmune diabetes in adults often presents with a clinical phenotype indistinguishable from that of classic type 2 diabetes. Zimmet introduce the eponym "Latent autoimmune diabetes of adults" (LADA) [8, 9] to describe this subgroup of adult phenotypic T2DM patients positive for autoantibodies. The main pathophysiological defects responsible for Adult-onset autoimmune diabetes include increased insulin resistance and beta cell dysfunction [9]. Islet autoantibody is an antibody that targets autoantigens, which are on the surface of islet cells or within islet cells, or are products of islet cell. The most common are- Islet Cell autoantibodies (ICAs), Glutamic acid Decarboxylase (GAD) autoantibodies, Insulinoma associted Antigen 2(IA-2) autoantibodies, and Insulin Autoantibodies (IAA) [8, 9]. The prevalence of islet autoantibodies in patients with clinically diagnosed type 2 diabetes was investigated in several studies, with reports of ICA had been detected in 10%-23% of adult patients having marker of islet cell-autoimmunity [12]. Patients identified by these autoantibodies show a high risk of progression to insulin-requiring diabetes compared with patients without antibodies. For clinical type 2 diabetic patient ICA to establish the correct type of diabetes at diagnosis are associated with progressive beta cell dysfunction. Islet autoantibodies are associated with beta cell dysfunction rather than key pathogenic factors in islet-cell destruction [12]. Beta cell dysfunction result from inadequate glucose sensing to stimulate insulin secretion therefore glucose concentration increase in the circulation. With systemic insulin resistance, insulin signaling within glucose recipient tissue is defective therefore hyperglycemia developed. Beta cell dysfunction supersedes insulin resistance in inducing diabetes. Both pathological states influence each other and presumably synergistically exacerbate adult type of type 2diabetes [13]. When the body produces insulin under condition of insulin resistance, the cells are unable to absorb or use it as effectively and cause high blood glucose. When glucose levels become higher as the resistance increases and the compensatory insulin secretion fails the liver normally helps regulate glucose level by reducing its secretion of glucose in the presence of insulin. However, in insulin resistance, this normal reduction in the liver's glucose production may not occur, further contributing to elevated blood glucose [14, 15]. Compared to other indices of insulin resistance Glycated hemoglobin (HbA1c) has minimal overlap in values between Normal Glucose Tolerance (NGT) and subjects with type 2 diabetes. HbA1c can be used as a simple and reliable marker of insulin resistance in Normal Glucose Tolerance (NGT) adults with relatively high insulin sensitivity. The HbA1c has been a standard test of long term average blood glucose control for patients with type 2 diabetes and more than 6.5% indicate impaired glycemic control. A repeated HbA1c value of 6.5%or greater is an established diagnostic and therapeutic indicator for patient with diabetes [16, 17]. Others studies showed the relationship among HbA1c, duration of diabetes and also age of the patients. It has been reported that an increase the HbA1c level is usually accompanied by a decline in pancreatic beta cell function [16, 17]. In this study we investigated the relationship between ICA and insulin resistance reflected by serum HbA1C levels of type 2 diabetic patients of Bangladeshi people.

MATERIALS AND METHODS

This study was a cross sectional analytic study conducted in the Department of Immunology and Outpatient Department (OPD) of BIRDEM General Hospital, Dhaka from January, 2015 to June, 2016. A total number of 173 adult diabetic people of both sexes selected on the basis of exclusion and inclusion criteria from OPD. Newly diagnosed type 2 diabetic patients older than 30 years and younger than 55 years with history of diabetes with less than one-year duration were included in this study. Patients diagnosed as type-1diabetics, pregnant women, DM with chronic infection, patient received insulin treatment at diagnosis were excluded. All patients were selected by simple random technique and diagnosed for serum ICA and HbA1c to see correlation between these two markers.5 ml blood sample was collected from each subject and transported to department of immunology, BIRDEM, where serum was prepared and preserved at-80°C for analyses. Islets cell autoantibody (IgG) measured by Enzyme linked immunosorbent assay (ELISA) method using kits globally renowned manufacturer (e.g. DRG Inc., USA; DiaSorin, Italy) and HbA1c measured by immunoassay technique. All test reagents were used within the valid expired date. Quality control of tests was strictly monitored following the instructions from the manufacturers of kits and reagents. Values were expressed as the mean ±SD or as the median and interquartile range in case of a skewed distribution. For comparison between the groups, students "t" testv(unpaired) was done and correlation between variables was measured by correlation tests. Further statistical analysis of the results was done by using software SPSS, version 20.0

RESULTS

Table-1 showed that, out of 173 patients, ICA positive were 22(12.7%) and rest 151(87.3%) patients were ICA negative. Mean score of& range of ICA positive and negative was 1.72±0.64(1.04-3.19) & 0.55±0.16(0.29-0.99) respectively. P value was <0.001, which is statistically significant.

Table-1: ICA status of the study population (N=173)

ICA status	Frequency (n)	Percentage (%)	ICA range Mean ±SD	p-Value
Positive	21	12.6	1.72±0.64(1.04–3.19)	<0.001[s]
Negative	152	87.4	0.55±0.16(0.29–0.99)	
Total	173	100.0		

Unpaired t-test were performed to compare the positive and negative ICA

Regarding respondents sex distribution of ICA positive male was 14(14.6%) and female 8(10.4%). In ICA negative, male was 82(85.4%) and female 69(89.6%). Here patient's gender was not associated with ICA results (Table-2).

Table-2: Distribution of ICA status according to sex (N=173)

Sex	n	ICA Positive	ICA Negative	p-Value
Male	96	14(14.6%)	82(85.4%)	0.411[ns]
Female	77	8(10.4%)	69(89.6%)	
Total	173	22(12.7%)	151(87.3%)	

Data were expressed mean ±SD

Unpaired t-test were performed to compare the positive and negative ICA

ns = Not Significant

Table 3 showed that, among ICA positive patients, maximum 13(14.1%) was in 41-50 years' age group followed by 7(8.9%) 30-40 years. Mean age was 42.91±7 and 40.87±6.75 years in ICA positive cases and ICA negative cases. So age distributions were not associated with ICA results.

Table-3: Age distribution among positive and negative ICA patients

Age in year	n	ICA Positive	ICA Negative	p-Value
30-40	79	7(8.9%)	72(91.1%)	0.190[ns]
41-50	92	13(14.1%)	79(85.9%)	
>50	2	2(100.0%)	0(0.0%)	
Mean ±SD		42.91±7.11	40.87±6.75	

Data were expressed mean ±SD

Chi-square test were performed to compare the positive and negative ICA

ns = Not Significant

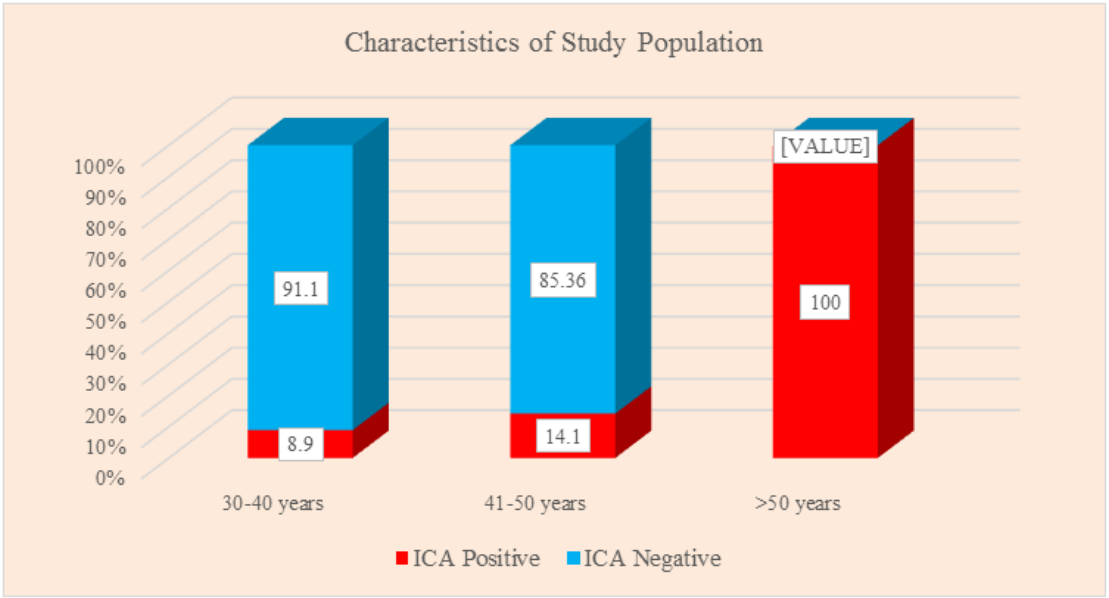

Fig-1: Patients Characteristics

Table-4 showed that, regarding HbA1c, the mean score among 22 ICA positive patientswas 8.10±1.38 and in ICA negative patients, the mean was 6.95±1.57. The changes of mean score of HbA1c between positive and negative was significant (p<0.001).

Table-4: Comparison of HbA1c in T2DM patients (N=173)

Variables	ICA Positive (n=22) Mean ±SD	ICA Negative (n=151) Mean ±SD	p-Value
HbA1c (%) Range	8.10±1.38 (5.53-11.0)	6.95±1.57 (4.17-15.20)	<0.001[s]

Unpaired t-test were performed to compare HbA1c between the positive and negative ICA patients
[s] = Significant

Table-5 showed that. mean FBS of 22 ICA positive patients was 12.77±3.35. On the other hand, ICA negative patients mean was 6.34±2.55. The mean score of FBS is statistically significant between positive and negative ICA patients (p <0.001).

Table-5: Comparison of FBS in ICA positive and negative (N=173)

Variables	ICA Positive (n=22) Mean ±SD	ICA Negative (n=151) Mean ±SD	p-Value
FBS (mmol/L) Range	12.77±3.35 (8.0–18.0)	6.34±2.55 (3.0–18.90)	<0.001[s]

Data were expressed mean ±SD
Unpaired t-test were performed to compare lipid between the positive and negative ICA patients
[s]= Significant

DISCUSSION

Patients with DM and their complication increasing in all over the world especially in our country. The International Diabetes Federation(IDF) estimated 7.1 million people with diabetes in Bangladesh and almost an equal number with undetected diabetes and this number is estimated to double by 2025.According to The International Diabetes Federation, the prevalence will be 13% by 2030 [6]. In developing countries, most of the peoples are suffering diabetes aged between 40 to 60 years and this number is increasing day by day [7]. Chronic hyperglycemia produces macro vascular complications like coronary artery disease, peripheral arterial disease, stroke and microvascular complications like retinopathy, nephropathy, neuropathy [1]. According to IDF (2013), in most countries, diabetes and its complications are the major causes of early death. In the year 2013, diabetes caused about 5.1 million deaths and in every six seconds a person dies from diabetes [3]. Adult onset autoimmune diabetes, the disease is even more heterogeneous than young onset autoimmune diabetes, as the rate of beta cell destruction is highly variable, which is probably due to difference in the penetrance of genetic and immune factors [8, 9]. In this study out of 173 T2DM patients, we found 22(12.7%) were ICA positive) and rest 151(87.3%) were negative. Regarding respondents sex distribution of ICA positive male was 14(14.6%) and female 8(10.4%). In ICA negative, male was 82(85.4%) and female 69(89.6%). In a study of China, positive rate of islet autoantibodies (IAA, ICA, and GADA) was 35.67% with 26.62% for individual IAA, 5.55% for ICA, and 5.91% for GADA, in T2DM patients. None of combinations of such autoantibodies were pragmatic, with the exclusion of AA+ICA (0.74%, *n*=4), IAA+GADA (1.48%, *n*=8),and ICA+GADA(0.18%,*n*=1) [10]. Regarding age of ICA positive patients, we found maximum 13(14.1%) was in 41-50 years' age group followed by 7(8.9%) 30-40 years. Mean age was 42.91±7 and 40.87±6.75 years in ICA positive cases and ICA negative cases. Which were very close. In this study we found that. mean FBS of ICA positive patients was 12.77±3.35. On the other hand, ICA negative patients mean was 6.34±2.55. The mean score of FBS is statistically significant between positive and negative ICA patients (p<0.001). In a Saudi study, the age distribution of the 138 diabetic patients was between 35 and 45 years and only 8.7% were younger than 35. In newly diagnosed Saudi diabetic patients, ICA were found in 13% (18/138) of the patients. Of the 18 ICA-positive patients, 12.8% (6/47) were aged between 35 and 44 years and there was a similar incidence (14.3%; 6/42) of ICA positivity for subjects aged 45 to 54 years. Moreover, in both age groups, ICA-positive female patients constituted 66.7% (8/12) of the patients studied in those two age ranges. Most of these differences were significant (P< 0.001).[11] Regarding HbA1c, in this study we found mean score among 22 ICA positive patients was 8.10±1.38 and ICA negative patients, the mean was 6.95±1.57. The changes of mean score of HbA1c between positive and negative was significant (p<0.001). Most studies suggested that, for clinical T2DM patient ICA are much more common than others [10]. In this study, we screened for ICA antibodies among in newly diagnosed T2DM patients which differ autoimmune diabetes from non-autoimmune diabetes. The main pathophysiological defects responsible for type 2 diabetes mellitus include increased insulin resistance and beta cell dysfunction [9]. In the presence of insulin resistance, progressive loss of beta cell function is a crucial defect. Pancreatic beta cell function plays a major role in determining dysglycemia from the onset of diabetes [14, 15]. Beta cell function starts to decline with higher plasma glucose levels, even within the range of normal plasma glucose levels. According to UK prospective diabetes study (UKPDS) a reduction in Beta cell function of up

to 50% at the time of diagnosis, and this value gradually increases with the progression of diabetes based on their HbA1c levels and compared beta cell function and insulin resistance at different HbA1c level [19]. Insulin resistance may develop in patient with type 2 diabetes at any time but the risk of formation of autoantibodies against Islets beta cell which increased risk of insulin resistance earlier [20, 21]. Due to the clinical interest in insulin resistance, it is of importance to develop a simple test that can be used in routine clinical settings for identifying insulin- resistance individuals in advance. HbA1c has been considering as a potentially good indicator of overall glycemic exposure and likely risk for long term complication. The HbA1c value is an integrated measure of mean glycemia over the preceding 8-12 weeks and is consider the gold standard for monitoring metabolic control in participants with diabetes. It has been reported that increase in the HbA1c level is usually accompanied by a decline in pancreatic beta cell function [16-18]. We analyzed the relation between HbA1c levels and insulin resistance. The ICA positive type 2 diabetic patients with HbA1c value of 8%-9% and >9% had a significantly increased risk of insulin resistance and may contribute to the decreased in beta cell function. The study revealed that high HbA1c level in ICA positive type 2 diabetic patient were associated with decreased beta cell function much earlier than ICA negative patients. Beta cell dysfunction is the critical determinant for type 2 diabetes which is compounded by insulin resistance [17]. The interplay between beta cell dysfunction and insulin resistance trigger hyperglycemia. With beta cell dysfunction, insulin secretion is impaired whereas with insulin resistance, insulin may still be secreted but insulin sensitivity manifest in target tissues. As beta cell dysfunction and insulin resistance exacerbate, hyperglycemia amplifies leading to the progression to type 2 diabetes earlier [13]. The United Kingdom Prospective Diabetes Study (UKPDS) [22] also reported a β cell function decline rate of 5% per year in T2DM. But in a recent study, researchers followed T2DM patients negative for islet autoantibodies for 20 years and found no signs of significant decline in islet β-cell function in these patients [23]. A study conducted among Chinese patients [24] suggested that within one year after diagnosis, the islet function of T2DM patients decreased significantly compared with the control group; but after 10 years, the islet function decreased at a much lower rate, possibly due to repair of islet dedifferentiation after glycemic control [25]. As shown in table 4, the patients with different HbA1c levels in ICA positive type 2 diabetic patients were significantly higher than ICA negative type 2 diabetic patients. Thus, we found that in T2DM patients, the secretion function of islet β-cells decreased with the increase of HbA1c level and the extension of the disease course.

CONCLUSION

As beta cell dysfunction and insulin resistance exacerbate, hyperglycemia amplifies leading to the progression to T2DM. At diagnosis, High HbA1c levels in ICA positive T2DM patients could be used as a simple tool to detect insulin resistance and beta cell dysfunction earlier.

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