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Serum level of Islet cells autoantibodies (anti- ICA and anti-GAD) and HbA1c among Type 2 diabetic patients

Kabir Magaji Hamid [1*], Yazeed Garba Bala [1], Abdullah Sulaiman Mainasara [2], Anas Ahmed Sabir [3], Mohammed Haruna Yeldu [4], Mustapha Umar Kalgo[1], Isah Suleiman Yahaya[5]

[1] Department of Immunology, School of Medical Laboratory Sciences, Usmanu Danfodiyo University, P. M. B. 2346, Sokoto, Nigeria

[2] Department of Chemical Pathology and Immunology, College of Health Sciences, Usmanu Danfodiyo University, P. M. B. 2346, Sokoto, Nigeria

[3] Department of Medicine, College of Health Sciences, Usmanu Danfodiyo University, P. M. B. 2346, Sokoto, Nigeria

[4] Department of Chemical Pathology, School of Medical Laboratory Sciences, Usmanu Danfodiyo University, P. M. B. 2346, Sokoto, Nigeria

[5] Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bayero University. P.M.B. 3011, Kano, Nigeria.

Abstract

Type 2 diabetes is due to the inability of the body to use insulin optimally. Evidences that support pathogenesis of Type 2 diabetes which also encompasses autoimmune aspects is increasing. The study was to determine the serum level of anti-GAD, anti-ICA and HbA1c among Type 2 Diabetic patients in Sokoto, Nigeria. Eighty two fully diagnosed type 2 Diabetic patients were enrolled for the study. Five millilitres of blood sample was withdrawn from each subject and serum was harvested. Anti-GAD and anti-ICA antibodies were analysed using ELISA techniques. Ion-exchange resin method was used for determination of HbA1c. Majority of the diabetic patients 95.1% were positive to anti-GAD while 43.9% were positive for anti-ICA. However, 43.9% have both anti-ICA and anti-GAD, while 4.9% did not have. Of the diabetic patients 51.2% had normal value of HbA1c while 15.9% had poor glycaemic control There was no correlation between anti-ICA and HbA1c ($p = 0.99$). However, there was small, negative correlation between anti-GAD and HbA1c but statistically was not significant ($p = 0.15$). Diabetic patients in this study were likely to progress to insulin resistant condition in future. There were good glycemic control in majority of the diabetic patients.

Keywords: Autoantibodies, Diabetes Mellitus Type 2, Glycated Haemoglobin A, Insulin Resistance, Latent Autoimmune Diabetes in Adults.

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Introduction

Diabetes is a chronic metabolic disease that occurs due to the inability of pancreas to produce enough insulin or inability of the body to utilise the insulin being produced effectively (WHO, 2017) [1]. Type 1 diabetes (T1D) results from the failure of the pancreas to produce insulin, while type 2 diabetes (T2D) results from the inability of the body to use insulin optimally. Gestational diabetes occurs during pregnancy (Fowler, 2008) [2] and there are many other specific types of diabetes due to other causes (ADA, 2015) [3]. Diabetes development based on combined cellular autoimmunity and insulin resistance has been reflected by various terms, such as latent autoimmune diabetes of the adult (LADA) or type 1.5 diabetes (Itariu and Stulnig, 2014) [4].

The assumption that the pathogenesis of T2D also encompasses autoimmune aspects is recognized increasingly based on the presence of circulating autoantibodies against beta cells and self-reactive T cells (Itariu and Stulnig, 2014) [4]. However, controversies still exist on this issue. Initiating events in autoimmunity are mostly unknown (Rosenblum *et al.,* 2015; Jörg *et al.,* 2016) [5, 6]. But islet cell autoimmunity as characteristic of T1D also found in 10-15 % of subjects diagnosed with T2D (Syed *et al.,* 2002) [7].

For autoantibodies to appear, the autoantigen must become available to trigger immune response (Wong and Wen, 2005) [8]. Islet autoantibody comprises a group of autoantibodies directed against islets of Langerhans or insulin secreting β cells (Winter and Schatz, 2011) [9]. The autoantibodies are islet-cell cytoplasmic autoantibodies (ICA), glutamic acid decarboxylase autoantibodies (GADA), insulinoma-associated-2 autoantibodies (IA-2A), insulin autoantibodies (IAA) and zinc transporter 8 autoantibodies (ZnT8A) (Atkinson and Eisenbarth, 2001; Bingley *et al.,* 2003) [10, 11].

Haemoglobin A1c (HbA1c) is formed by non-enzymatic condensation of glucose with the N-terminal valine residue of the β chains of haemoglobin (Unnikrishnan *et al.,* 2012; Lai *et al.,* 2012) [12, 13]. Despite controversies, HbA1c is widely accepted in many countries as a diagnostic test for T2D as well as monitoring (d'Emden *et al.,* 2012; Braatvedt *et al.,* 2012) [14, 15]. It serves as indicator of glycemic control over the last 3 months (Unnikrishnan *et al.,* 2012) [12]. Therefore, it indicates the glucose level that red blood cells have been exposed to during its lifespan, thus important in managing diabetic patients (Shah *et al.,* 2014) [16]. We realise there is paucity of data on prevalence of anti-ICA, anti-GAD and its association with HbA1c in the target community, therefore this study provide an updated information on the said parameters. As such can serve as valuable data for future research.

Materials and Methods

Study area

This is a cross sectional study conducted at the diabetic clinic of Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. The hospital is a tertiary institution located within the Sokoto metropolis. Sokoto is the capital city of Sokoto State, located in the extreme North-west of Nigeria.

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Study Population

Eighty two (82) fully diagnosed diabetic patients attending diabetic clinic of UDUTH, Sokoto were randomly and consecutively selected enrolled into the study. A written informed consent was obtained from all the study participants.

Inclusion and exclusion criteria

Only diabetic patients attending UDUTH and have no history of autoimmunity other than diabetes were enrolled for the research. Diabetic patients attending UDUTH with history of other autoimmune diseases were excluded for the study.

Ethical approval

The ethical approval was obtained from the Ethics and Research Committee of UDUTH (UDUTH/HREC/2017/No. 624). The research was carried out in accordance with the declaration of Helsinki concerning the ethical principles for medical research involving human subjects.

Data collection

A semi structured interviewer questionnaire was administered to all consented diabetic patients and information on their socio-demographic and medical history was obtained.

Sample collection and processing

Five millilitres (5ml) of fresh whole blood was collected from each diabetic patient that meets the inclusion criteria of the study using Monovette vacutainer system and labelled for identification. Two millilitres (2 ml) of the anticoagulated blood was used for HbA1c assay, while three millilitres (3 ml) was centrifuged at 3000 rpm for 20 minutes. The supernatant plasma was used for autoantibodies assay.

Laboratory analysis

Determination of HbA1c

Ion exchange resin method was used for the quantitative determination of HbA1c in the diabetic patients. Kit Cartridges were purchased from Spectrum Biotech Co., Ltd, Egypt. The procedure was performed according to Manufacturer's instruction.

Determination of Autoantibodies

The plasma concentration of anti-ICA and anti-GAD of the diabetic patients were measured using Sandwich ELISA kit (SunLong Biotech Co., Ltd, China). The procedure was performed according to Manufacturer's instructions. The assay range for anti-ICA is 5 IU/L-360 IU/L. Assay sensitivity is 1 IU/L. Assay range for anti-GAD is 36 pg/ml-2000 pg/ml. sensitivity is 6.2 pg/ml.

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Statistical analysis

Statistical Package for Social Science (SPSS) software package version 21 was used for statistical analysis. Continuous variables were expressed as Mean and standard Deviation (SD) whereas categorical variables were expressed as percentages. Test for normality was performed to ascertain normal distribution of the variables. Data was not normally distributed based on tests of normality results: Shapiro-Wilk, supported by Q-Q plot. Spearman's correlation was used to explore the association between the autoantibodies and HbA1c among the diabetic patients. The p value ≤ 0.05 was used to determine the level of statistical significance.

Results

The total number of the diabetic patients that participated in the study was 82. The age range of the patient was 20-80 years with a mean age ± standard deviation (SD) of 54.7±11.6. The mean of HbA1c was 6.03 ± 1.53. The mean of ant-ICA of the diabetic patients was 5.47 ± 2.47, while that of anti-GAD was 804.1 ± 555.5. From table 1, the age group with highest number was 51-60 years with frequency of 30 (36.1%) while the lowest was 20-30 years with frequency of 1 (1.2%). Of the 82 patients, 54 (65.9%) were females while 28 (34.1%) were males. From Table 2, 42 (51.2%) of the diabetic patients had normal value of HbA1c while 13 (15.9%) had poor glycaemic control. As depicted from table 3, 78 (95.1%) had anti- GAD autoantibody while 36 (43.9%) had detectable level of anti-ICA autoantibody in their serum. However, 36 (43.9%) had both anti-ICA and anti-GAD, while 4 (4.9%) did not have. There was no correlation between anti-ICA and HbA1c (r = 0.00, p =0.998). However, there was small, negative correlation between anti-GAD and HbA1c but statistically was not significant (r = –0.157, p =0.158) (Table 4).

Table 1: Frequency distribution of some demographic information of the diabetic patients

Variables	Frequency (N)	Percentage
Age (years)		
20-30	1	1.2
31-40	6	7.3
41-50	24	29.3
51-60	30	36.6
61-70	14	17.1
71-80	7	8.5
Total	82	100
Gender		

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Female	54	65.9
Male	28	34.1
Total	82	100

Table 2: Frequency distribution of HbA1c level among diabetic patients

HbA1c Range (%)	**Frequency (N)**	**Percentage**
Normal (<6)	42	51.2
Good control (6- 6.7)	17	20.7
Fair control (6.8-7.65)	10	12.2
Poor control (> 7.65)	13	15.9
Total	**82**	**100**

Table 3: Frequency distribution of autoantibodies among diabetic patients

Autoantibodies	**Frequency (N)**	**Percentage (%)**
Anti- ICA (IU/L)		
Undetected	46	56.1
Detected	36	43.9
Total	**82**	**100.0**
Anti-GAD (pg/ml)		
Undetected	4	4.9

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Detected	78	95.1
Total	**82**	**100**
Number of autoantibodies		
None	4	4.9
Both (ICA & GAD)	36	43.9
GAD only	42	51.2
Total	**82**	**100**

Table 4: Correlation of autoantibodies with HbA1c

Autoantibodies	**HbA1c (%)**	
	rho	**p-value**
Anti-ICA (IU/L)	0.000	0.998
Anti-GAD (pg/ml)	-0.157	0.158
N	**82**	

Discussion

Type 2 diabetic patients with islet autoantibodies are at risk of progression to insulin treatment compared with those patients not carrying these autoantibodies (Syed *et al.,* 2002) [7]. In this study, anti-ICA was detected in 36 (43.9%) of the diabetic patients. Our study suggests that anti-ICA is not common among the T2D patients and its presence indicated risk of progression to autoimmune diabetes. The presence of one or more islet-specific autoantibodies was a characteristics of autoimmune diabetes (Al-Abady *et al.,* 2016) [17]. The number of positive autoantibodies has been considered a major risk factor for disease progression into LADA (Maioli *et al.,* 2010) [18].

Anti – GAD is the most common anti-islet autoantibodies. According to our finding 78 (95.1%) of the diabetic patients enrolled for the research had detected level of anti-GAD. This findings was higher than the previous study which reported 2.5% in Black South Africans (Panz *et al.,* 2000) [19]. Other studies from different part of the world also reported low prevalence of anti-GAD (Al-

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Abady *et al.,* 2016; Damanhouri *et al.,* 2005; Calsolari *et al.,* 2008; Lee *et al.,* 2009; Khudhair, 2013; Zaharieva *et al.,* 2017) [17, 20, 21, 22, 23, 24]. It has been shown that patients with T2D may produce higher levels of anti-GAD and after a short period of time develop T1D (Al-Abady *et al.,* 2016) [17]. High prevalence of anti-GAD in our study may suggest that most of the patients may progress to insulin dependent in future. The high-titre anti-GAD may serve as predictive of early insulin requirement (Lohmann *et al.,* 2001) [25] and diagnosis of LADA relies primarily on the detection of autoantibodies against GAD 65 in the serum of clinically diagnosed T2D patients (Towns and Pietropaolo, 2011) [26]. Anti-GAD is also detected in adult-onset patients initially diagnosed as having T2D who did not require insulin treatment but may become insulin-dependent within a few years after diagnosis (Yasui *et al.,* 2016) [27].

The presence of both anti-ICA and anti-GAD was observed in 43.9% of diabetic patients in this study. This was higher than previous studies which reported that 11.6% had at least one or more of the autoantibodies (Davis *et al.,* 2005) [28]. A study showed that about 10% of phenotypic T2DM patients were exposed to either one or more of the islet autoantibodies (Naik *et al.,* 2009) [29] Finding in this research may suggest that a reasonable percentage of the study group would likely progress to autoimmune diabetes. Combination of ICA and GAD autoantibodies is a stronger indicator of insulin deficiency than the presence of either autoantibody alone (Lohmann *et al.,* 2001; Davis *et al.,* 2005) [25, 28] especially in patients over the age of 45 years (Turner *et al.,* 1997) [30]. Majority of the participants were more than 40 years (Table 1). Anti-GAD and anti-ICA play a significant role in clinical differentiation T2D from LADA (Huang *et al.,* 2012) [31]. Indeed presence of lower percentage of ICA and/or GAD-Ab among diabetic patients indicate that autoimmune diabetes will progress slowly (Agyei-Frempong *et al.,* 2008) [32].

Glycaemic control is most important attempt in the treatment of diabetes (Damanhouri *et al.,* 2005) [20]. In this study 51.2% have normal glucose level while 20.7% were in good glycemic control. This suggested that most of the participant were not at risk of diabetic complications such as cardiovascular disease. Because individuals with HbA1c of 39–46 mmol/mol (5.7–6.4%) are considered to be at 'increased risk' for diabetes as well as cardiovascular disease (ADA, 2011) [33]. However, HbA1c values depend both on red blood cells lifespan and assay methods (Lai *et al.,* 2012) [13]. Therefore, conditions and medications that affect red blood cell turnover and lifespan lead to false measurements of HbA1c (Radin, 2014) [34]. Our study revealed that there was no significant association between the autoantibodies and HbA1c ($p > 0.05$). Most of our participant were in good glycemic control (Table 2). Autoantibody positivity was associated with relatively poor glycaemic control and rapid progression to insulin therapy [28]. A report showed that 58% of United Kingdom Prospective Diabetes Study Group (UKPDS) patients who were autoantibody-positive were requiring insulin regardless of age (Davis *et al.,* 2005; Turner *et al.,* 1997) [28, 30].

Conclusion

There was high prevalence of anti-GAD (95.1%) among the T2D patients this indicated risk of progressing to LADA. Anti-ICA was not common among the patients. Majority of the T2D patients had normal glucose level or good glycaemic control, thus were not at risk of diabetic complications.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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* Corresponding author: **kabirhamd11@gmail.com**

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