

# The Risk of Islet Cell and Insulin Autoantibodies and Their Predictive Strength as Markers of Type-1 Diabetes in a Cross-Section of Nigerian Population

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## Abstract

**Aim:** We demonstrated the risk of developing islet autoantibodies-Insulin Autoantibodies (IAAs) and Islets cell Autoantibodies (ICAs)-in type-1 diabetic relatives and newly diagnosed type-1 patients compared to non-diabetic controls. We also aimed to determine the predictive strengths of both autoantibodies in the development of type-1 diabetes mellitus, and which of the two autoantibodies is a better predictive marker of type-1 diabetes mellitus among Nigerian adults. **Methodology:** A total number of four hundred and fifty five (455) subjects (211 (46%) males, and 244 (54%) females) aged between 35 - 76 years were recruited for the study. IAA and ICA levels were estimated using ELISA reagents from Biomerica Inc. Other parameters such as fasting blood sugar, urine glucose, and urine protein were assessed using standard biochemical techniques. **Results:** Relatives of type-1 diabetic patients and newly diagnosed type-1 diabetic patients were at greater risk ( $p < 0.05$ ) of testing positive for more than one autoantibody (ICA and IAA) compared to non-diabetic controls. In addition, IAAs appeared to be better predictors or markers of type-1 diabetes mellitus compared to ICAs. **Conclusion:** The present study indicated a greater risk of autoimmune destruction of the insulin producing beta cells of the

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pancrease of the type-1 relatives and newly diagnosed type-1 patients and suggests the need for periodic recruitment of individuals in the general population, siblings and relatives of type-1 diabetic patients for planned intervention trials. In addition, IAAs appeared to be better autoimmune markers of type-1 diabetes compared to ICAs.

## Keywords

Type-1 Diabetes, IAA, ICA, Autoimmune Marker, Edo State

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## 1. Introduction

Type-1 diabetes is an organ-specific autoimmune disease resulting from the failure of the pancreas to produce insulin due to autoimmune destruction of the insulin-producing  $\beta$ -cells in the islets of Langerhans [1]. At the onset of type 1 diabetes, many autoantibodies are detected as autoimmune markers. Historically, the Islet cell (cytoplasmic) autoantibodies (ICAs) and islet cell surface autoantibodies (ICSAs) [2]-[6] were initially described in the 1970s. However, in the 1980s, insulin autoantibodies (IAAs), GAD antibodies (GADAs), islet antigen-2 antibodies (IA-2As), 64-kDa autoantibodies (64KAs), insulin receptor autoantibodies, carboxypeptidase-H autoantibodies, and heat shock protein (HSP) autoantibodies [7]-[11] were recognized.

Amongst these islet autoantibodies, four have emerged as the most useful autoimmune markers of type-1 diabetes: these include ICAs, IAAs, GADAs, and IA-2As [12]. Of these autoantibodies for type-1 diabetes, the IAAs deserve special attention because their legend is unique to the beta cell [1]. They are the first markers to appear during the symptomless period which precedes diabetes and are present in the vast majority of young children destined to develop diabetes [1]. The ICAs are also very important type-1 diabetes biomarkers and have been shown to carry a 74% risk for type-1 diabetes and considered the most sensitive marker for a 5-year prediction of type-1 diabetes in a previous study [13]. They have also been found positive in 70% of Caucasians and 40% of African Americans at the onset of type-1 diabetes [14] [15]. Studies have shown that nondiabetic individuals who express combinations of islet autoantibodies have a much higher risk for type-1 diabetes than individuals who express fewer types of islet autoantibodies [16]-[18].

Islet autoimmunity and type-1 diabetes develop in genetically susceptible individuals, and first-degree type-1 diabetes family history is a major risk factor [19]. Studies [20] [21] have shown that approximately 10% - 13% of children newly diagnosed of islet cell autoantibodies have a first-degree relative affected with type-1 diabetes. An early detection of circulating IAAs and ICAs is therefore important in order to identify individuals in the general population, and relatives of type-1 diabetic patients, who are at greater risk of developing this disease because of their genetic predisposition to diabetes [22].

To the best of our knowledge, there is paucity of studies using IAAs and ICAs as

markers in predicting the development of diabetes mellitus in Nigerian populations. In the present study, we demonstrated the risk of developing islet autoantibodies, IAA and ICA, in type-1 diabetic relatives and newly diagnosed type-1 patients compared to non-diabetic controls. We also aimed to determine the predictive strengths of IAAs and ICAs in the development of diabetes mellitus, and which of the two autoantibodies is a better predictive marker of type-1 diabetes mellitus among Nigerian adults.

## 2. Methodology

### 2.1. Procedure

This study was conducted at Central Hospital, Benin City, Nigeria. A total of 455 persons were initially recruited for this study. Participants included referrals from health care professionals that were based on the individual's perceived risk for development of diabetes, relatives of type I diabetics and volunteered controls. Informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration and the guidelines. A structured health and lifestyle questionnaire was used to collect sociodemographic data such as age at diagnosis, gender, family history of diabetes, drinking, smoking habits and other relevant information related to health and lifestyle of participants. Those included in the study were aged 25 years and above and with body mass index  $\geq 24$  kg/m<sup>2</sup>. Exclusion criteria included long standing illness, endocrine disorders, infectious diseases, recent myocardial infarction (within 6 months), symptoms of chronic heart disease, and use of medications known to impair glucose tolerance. Other exclusion criteria included, diabetes diagnosed by a physician and confirmed by other clinical data, conditions or behaviors likely to affect conduct of the trial, pregnancy and childbearing, major psychiatric disorder and excessive alcohol intake, either acute or chronic.

Participants were asked to fast for 12 - 14 h and to refrain from smoking, exercise, or other unusual activity before the testing of fasting plasma glucose. Those with glucose values in the diabetic range (fasting glucose  $\geq 126$  mg/dl) were asked to return for confirmation at a follow-up visit. The data obtained from the questionnaire and the diabetes prevention screening were used to classify participants as newly diagnosed type-1 diabetics (n = 5), newly diagnosed type-2 diabetics (n = 55), non-diabetic relatives of type-1 patients (n = 150) and non-diabetic controls (n = 250). However, for the sake of this study, we excluded the type-2 diabetics thus reducing the study population to 405 participants. After the initial screening for diabetes, the participants were further screened for islet autoantibody. The newly diagnosed type-1 patients were asked to return for a follow up visit to confirm for type-1 diabetes.

### 2.2. Classification of Type 1 Diabetes

Type-1 diabetes was confirmed during the follow-up visit six months after the initial screening. A classification of type-1 diabetes was defined by the following criteria: onset in patients aged 30 years or less, presentation of acute classical symptoms (polyuria, polydipsia, and polyphagia, fatigue and weakness, weight loss, nausea, and blurred vision),

presence of ketones and requirement of insulin therapy to control hyperglycaemia.

### 2.3. Sample Collection

Blood samples were obtained for plasma glucose measurements in the fasting state. Ten millilitres of blood was collected intravenously, five millilitres was dispensed into a plain container, and the other five millilitres was dispensed into a fluoride oxalate container. The blood samples were spun at 1500 rpm for 10 minutes and the supernatant serum/plasma were separated into separate tubes. The serum/plasma samples were stored at  $-20^{\circ}\text{C}$  for up to 2 weeks prior to the analysis of fasting blood glucose and antibodies. IAAs and ICAs were determined using ELISA reagents from Biomerica Inc, U.S.A. Blood glucose was determined colorimetrically using Randox kits from United Kingdom. Fresh urine samples were voided into clean sterile containers, glucose and protein were immediately detected qualitatively using Combi-9 strip.

### 2.4. Data Analysis

Descriptive data was expressed as mean  $\pm$  Standard error of mean (SEM) for continuous variables and percentages for categorical variables. Logistic regression was used to determine the risk of developing islet autoantibodies and type-1 diabetes. Analysis of variance (ANOVA) was used to compare data. The receiver operating characteristic (ROC) curve was used to compare the predictive strength of ICAs and IAAs. Statistics was done using Statistical Package for Social Sciences program (SPSS) version 20.0. Statistical significance was set at  $p < 0.05$ .

## 3. Results

**Table 1** shows the demographic and clinical characteristics of the study population. Data indicate that type-1 diabetic patients have significantly greater age and fasting blood sugar (FBS) than non-diabetic controls. Type-2 diabetic patients indicated significantly greater age and FBS compared to non-diabetic controls. Type-1 diabetes relatives presented significantly greater FBS, but lower age compared to non-diabetic controls.

The prevalence of single and double autoantibodies during initial screening is shown in **Table 2** for type-1 relatives, newly diagnosed type-1 diabetics, and non-diabetic controls respectively. Data shows that 50 (12.3%) and 49 (12.1%) of the total study

**Table 1.** Demographic and clinical characteristics of the study population.

Variables	Non-Diabetic Controls (n = 250)	Type-1 Diabetic Patients (n = 5)	Type-II Diabetic Patients (n = 50)	Type-1 Diabetic Relatives (n = 150)
Males n (%)	130 (52)	3 (60)	25 (50)	53 (35.3)
Females n (%)	120 (48)	2 (40)	25 (50)	97 (64.7)
Age (years)	32.7 $\pm$ 12.04	49.0 $\pm$ 12.94*	50.8 $\pm$ 14.20*	30.1 $\pm$ 10.73†
FBS (mg/dl)	84.9 $\pm$ 8.0	168.0 $\pm$ 11.66*	114.4 $\pm$ 33.01*	87.3 $\pm$ 11.22*

\*Significantly greater than non-diabetic group; †Significantly lower than non-diabetic group. Abbreviations: FBS- Fasting Blood Sugar.

**Table 2.** The prevalence of single and double autoantibodies according to various groups during initial screening of the entire study population.

Subjects	Number of Subjects	Positivity for Islet Cell Autoantibody alone n (%)	Positivity for Insulin autoantibody alone n (%)	Positivity for both Islet cell and Insulin autoantibodies n (%)
Non-diabetic Type 1 Relatives	150	40 (26.7)	40 (26.7)	40 (26.7)
Type 1 Diabetic patients	5	5 (100)	5 (100)	5 (100)
Non-Diabetic Control	250	5 (2)	4 (1.6)	2 (0.8)
Total	405	50	49	47

population (n = 405) tested positive for ICAs and IAAs respectively. All type-1 relatives that tested positive for ICAs (n = 40) also tested positive for IAAs. Similarly, all newly diagnosed type-1 patients that tested positive for ICAs (n = 5), also were positive for IAAs. The single autoantibodies detected in non-diabetic controls were (n = 5) for ICAs and (n = 4) for IAAs. A total of 47 (11.6%) of the study population tested positive for both ICAs and IAAs. Positivity for >1 autoantibody were 26.7% (n = 40), 100% (n = 5) and 0.8% (n = 2) in relatives of type-1 patients, newly diagnosed type-1 diabetics and nondiabetic controls respectively.

**Table 3** shows the risk of incidence of more than one islet cell autoantibody in type-1 diabetes relatives compared to non-diabetic controls. Data indicate that both ICAs and IAAs were detected in 40 (26.67%) of the 150 type-1 diabetic relatives and in 2 (0.8%) of the non-diabetic control. Logistic regression shows that type-I diabetic relatives were at greater risk (OR, 45.1;  $p < 0.001$ ) of the occurrence of more than one autoantibody compared to the non-diabetic controls. It is noteworthy that none of the 150 non-diabetic relatives of type-1 patients tested positive for type-1 diabetes mellitus at the initial screening.

**Table 4** and **Table 5** show the risk of incidence of more than one islet cell autoantibody in newly diagnosed type-1 diabetic patients compared to non-diabetic controls and type-1 relatives. Data indicate that 5 (100%) of the newly diagnosed type-1 diabetic patients, 2 (1.6%) of the non-diabetic control and 26.7% of the type-1 relatives were positive for both ICAs and IAAs. Logistic regression analysis indicated that the newly diagnosed type-1 diabetics were at greater risk (RR, 125.0;  $p < 0.001$  and RR, 3.75;  $p = 0.002$ ) of more than one autoantibody positivity compared to non-diabetic controls and type-1 relatives respectively.

The association between the prevalence of ICAs/IAAs and development of type-1 diabetes was examined among the study population (**Table 6**). Chi-square test suggests that the presence of more than one autoantibody in undiagnosed cohort may be associated with development of type-1 diabetes. However, because of the lack of cases of type-1 diabetes for those without ICAs/IAAs positivity, the logistic regression analysis was not performed for the odds of developing type-1 diabetes.

The association between the development of type-1 diabetes and titer (log-transformed)

**Table 3.** The risk of more than one islet cell autoantibody incidence in type-1 diabetes relations compared to non-diabetic controls.

	Occurrence of both Islet cell and Insulin autoantibodies	Absence of both Islet cell and Insulin autoantibodies	Total	Odds Ratio (95% CI)	P-Value
Risk Group (Type 1 relatives)	40	110	150	45.09 (11.80 - 171.62)	0.00
Non-Risk Group (Non-diabetic control)	2	248	250		
Total	42	358	400		

**Table 4.** The risk of more than one islet cell autoantibody incidence in newly diagnosed type-1 diabetics compared to non-diabetic controls.

	Occurrence of both Islet cell and Insulin autoantibodies	Absence of both Islet cell and Insulin autoantibodies	Total	Relative Risk (95% CI)	P-Value
Risk Group (Newly Diagnosed Type 1 Diabetics)	5	0	5	125.0 (40.89 - 125.0)	0.00
Non-Risk Group (Non-diabetic control)	2	248	250		
Total	7	248	255		

**Table 5.** The relative risk of more than one islet cell autoantibody incidence in newly diagnosed type-1 diabetics compared to type-1 relatives.

	Occurrence of both Islet cell and Insulin autoantibodies	Absence of both Islet cell and Insulin autoantibodies	Total	Relative Risk (95% CI)	P-Value
Risk Group (Newly Diagnosed Type-1 Diabetics)	5	0	5	3.75 (2.05 - 3.75)	0.002
Non-Risk Group (Non-diabetic control)	40	110	150		
Total	45	110	155		

**Table 6.** Association of prevalence of Islet cell autoantibody/Insulin autoantibody and development of type-1 diabetes.

	Occurrence of Type-1 Diabetes	Absence of Type-1 Diabetes	Total	$\chi^2$	P-Value
Risk group with either Islet cell autoantibody or Insulin autoantibody	5	42	47	38.56	0.00
Non-risk group without autoantibodies	0	358	358		
Total	5	400	405		

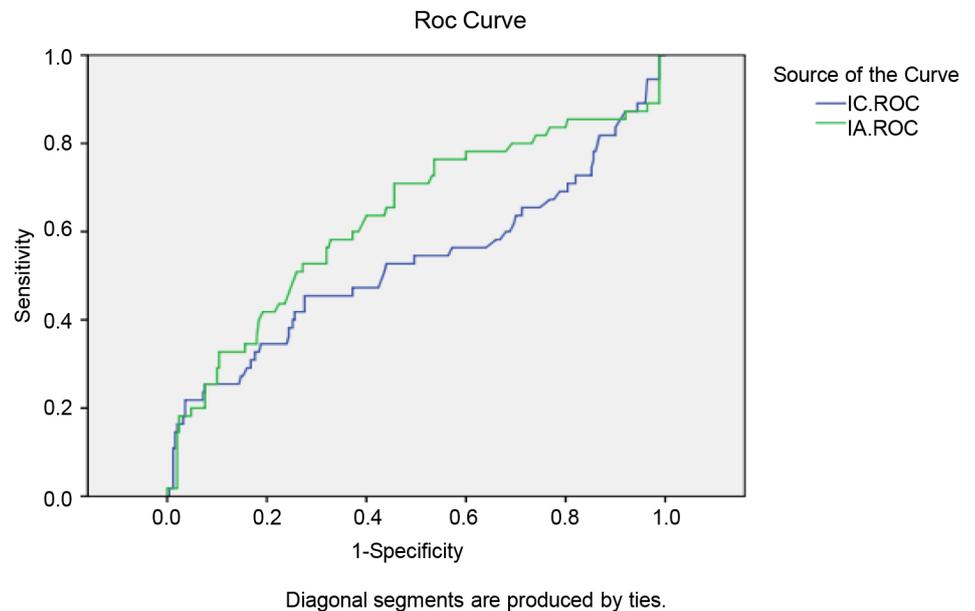
was examined among those who were positive for single autoantibodies in the study population. ICA titer (type-1 diabetes/total = 5 of 50) was not significantly associated with type-1 diabetes ( $p = 0.28$ ). In contrast, IAA titer (5 of 49) was associated with type-1 diabetes ( $p = 0.03$ ). Both ICAs and IAAs exhibited very high sensitivity (100% each).

The area under the receiver operating characteristic (ROC) curve for IAAs (0.633;  $p = 0.002$ ) is greater than that of ICA (0.530;  $p = 0.492$ ; **Figure 1**). This indicates that IAAs are better predictors or markers of type-1 diabetes mellitus than ICAs.

#### 4. Discussion

The principal findings of the present study indicate that non-diabetic relatives of patients with type-1 diabetes and newly diagnosed type-1 diabetic patients were at greater risk of testing positive for more than one autoantibody (ICAs and IAAs) compared to non-diabetic controls. In addition, IAAs appeared to be better predictors or markers of type-1 diabetes mellitus compared to ICAs.

There is a strong evidence to show that the autoimmune nature of type-1 diabetes disease processes is linked to the presence of islet autoantibodies [23]. Similarly, the risk of future type-1 diabetes is directly proportional to the number of autoantibodies positive, in nondiabetic relatives of patients with type-1 diabetes [24]-[26]. The present



Variables	Area	Std. Error	Asymptotic Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
Islet Cell Autoantibody	0.530	0.051	0.492	0.430	0.629
Insulin Autoantibody	0.633	0.046	0.002	0.542	0.724

**Figure 1.** ROC curve showing the predictive strength of both the Islet cell autoantibodies and Insulin autoantibodies as markers of type-1 diabetes mellitus.

study showed evidence of positivity (26.7%) for both ICAs and IAAs and also indicated greater risk for the presence of ICAs and IAAs in non-diabetic type-1 relatives when compared to non-diabetics who are not related to type-1 diabetic patients. The 26.7% positivity for the two autoantibodies, ICAs and IAAs, appears very high compared to a previous study which has shown 2.3% positivity for relatives with more than one antibody [26]. Our findings which indicated greater risk of ICAs/IAAs prevalence in relatives of type-1 patients compared to non-diabetic controls suggests a greater risk of an ongoing autoimmune destruction of the insulin producing beta cell of the pancreas of the type-1 relatives. It also shows that the understanding of the role of islet autoantibodies in prediction of type-1 diabetes comes from carrying out studies in individuals with increased genetic susceptibility, such as first degree relatives. The reason for the very high prevalence rate of islet autoantibodies in this study is not very clear but may be attributed to shared genetic susceptibility and identifies a population within which screening for the type-1 diabetes disease may be justified. The present findings therefore suggest the need for periodic recruitment of non-diabetic relatives of type-1 diabetic patients for planned intervention trials.

Type-1 diabetes is characterized by a lack of insulin production caused by a cellular-mediated autoimmune destruction of pancreatic islet  $\beta$ -cells [27] [28]. In the present study, only two of the autoantibodies, ICAs and IAAs were considered. Our study revealed that 100% of all newly diagnosed type-1 patients had a combination of ICAs and IAAs. In addition, the newly diagnosed type-1 diabetics were at greater risk of autoantibody positivity compared to both the non-diabetic controls and type-1 diabetic relatives. It has been reported that 85% - 90% of the newly diagnosed type-1 diabetic patients are positive for one or more of the islet cell autoantibodies [29]. Thus, it was not surprising that the type-1 diabetics were at greater risk of the presence of  $>1$  islet autoantibodies compared to both the non-diabetic controls and type-1 relatives.

Furthermore, we demonstrated that the prevalence of ICAs/IAAs is significantly associated with the development of type-1 diabetes in the general study population. This was expected since previous studies [30]-[32] have also shown that autoantibodies to islet cell antigens are known predictors of type-1 diabetes. However, due to lack of cases of type-1 diabetes for those without ICAs/IAAs, we couldn't perform logistic regression analysis to determine the level of risk of developing type-1 diabetes.

Previous attempts to identify which of the autoantibodies is the best predictor of type-1 diabetes has failed due lack of clear detection of the order of appearance of the autoantibodies. The present findings indicated that despite equal sensitivity exhibited by both autoantibodies, IAAs appeared to be better predictors of type-1 diabetes compared to ICAs. Logistic regression test indicated significant association between IAAs and type-1 diabetes, while ICAs indicated no association with type-1 diabetes. On the other hand, ROC curve indicated that IAAs are better predictors of type-1 diabetes. A previous study has however shown that IAA screening is less sensitive than screening with ICA [33] [34]. It has also been suggested that ICA positivity appears to confer a higher risk of type-1 diabetes, particularly in individuals with single autoantibody positivity on initial screening [23].

Conclusion: The present findings indicated a greater risk of an ongoing autoimmune destruction of the insulin producing beta cells of the pancreas of relatives of type-1 diabetic patients and newly diagnosed type-1 patients and suggest the need for periodic recruitment of non-diabetic relatives of type-1 diabetic patients for planned intervention trials. In addition IAAs appeared to be better autoimmune markers of type-1 diabetes compared to ICAs.

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