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Original Article

Patterns of Hba1c Levels in Normoglycemic Offspring of T2 Diabetes Mellitus Patients

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Abstract
Background: The risk of developing diabetes mellitus for an individual with a positive family history of the disease is two- to fourfold higher in an offspring of a diabetic compared with offspring of non-diabetic shown by serum glycated hemoglobin (HbA1c) levels. There is paucity of data on pre-diabetes in our environment.
Objectives: This study was designed to determine the baseline HbA1c levels of normoglycemic offspring of type 2 diabetes mellitus (T2DM) patients in Ijebu-ode, Nigeria.
Methods: This is a cross-sectional study of offspring of T2DM patients (ODP) and those of offspring of non-diabetic parents (ONDP). Diabetic offspring were exempted from the study. FBS was determined using enzymatic hexokinase method to determine glucose concentrations and exclude diabetes. Serum HbA1c was measured using standard method. Height and weight were measured using standard methods. Body mass index (BMI) was calculated.
Results: There were 100 ODP and 100 ONDP aged 16 to 40 years. The most populated aged group was 21 to25 years which is 44% (n=88). 6% (n=12) of the study group were obese. 19% were overweight (n=38). The mean weight of ODP was significantly higher than that of ONDP ($P=0.020$). Also, the mean HBA1c of ODP was significantly higher than that of ONDP ($P<0.001$).
Conclusion: The serum HbA1c level was significantly higher among ODP than ONDP. The mean weight was significantly higher in ODP than ONDP.
Keywords: Diabetes Mellitus Type 2, Body Mass Index, Overweight, Pre-diabetic state, Glycated Hemoglobin A

1. Background

The prevalence of type 2 diabetes has increased among youth in the United States; between 2001 and 2009, there was a 30.5% rise in the overall prevalence of diagnosed diabetes.[1,2] Many youth diagnosed with type 2 diabetes have poor glycemic control[2,3] and experience higher rates of cardiovascular disease risk markers, fatty liver disease, and early evidence of microvascular complications.[2,4,5] This highlights the need for early detection of prediabetes to prevent the increase in diabetes and its associated cardiometabolic risk factors. The American Diabetes Association (ADA) recommends glycated hemoglobin (HbA1c) as a diagnostic test for diabetes. This guideline is based on adult epidemiological studies that show an association between increased HbA1c and the risk for microvascular complications.[6-8] Longitudinal studies investigating the relationship between HbA1c in childhood and the risk of developing diabetes are lacking. In the 2016 Standards of Medical Care in Diabetes, the ADA recognized that data supporting HbA1c as a diagnostic measure for diabetes are limited in children and adolescents[9] while noting that past short-term studies did not address the more pertinent relationship between HbA1c and long-term health outcomes. The ADA recommends screening for type 2 diabetes or prediabetes using HbA1c in asymptomatic children and adolescents aged 10 years with a body mass index (BMI) of 85th percentile for age and sex, based on Centers for Disease Control and Prevention growth charts,[10] and at least two additional type 2 diabetes risk factors.[9] Risk factors include type 2 diabetes in a first- or second-degree relative.[9] Measuring HbA1c is convenient in children because it does not require fasting, and a single test can be used to both diagnose and monitor glycemic control, thereby facilitating sample collection and compliance in children. In addition, HbA1c reflects chronic glycemia and has less pre-analytical and analytical variability than fasting plasma glucose (FPG) and 2-h postprandial blood glucose (2hPG).[9,11]

2. Objectives

There is paucity of published work on the level HbA1c in offspring of T2DM patients (ODP) and offspring of non-diabetic parents (ONDP) in our environment. Many previous studies obtained from literature search are from

the Western world and few were from sub-Sahara African. The aim of this study is to determine the pattern of HbA1c in ODP and ONDP. This will serve as a baseline marker of the risk of developing diabetes mellitus.

3. Methods

The present study was designed as a single-center, cross-sectional study and was carried out from March 2019 to December 2019. This study involved selection of 200 subjects: 100 are offspring of diabetic parents whose parents were attending endocrinology clinic and 100 are offspring of non-diabetic parents who were attending general out-patient clinic. The study was conducted at State Hospital, Ijebu-ode, Ogun state a suburban area of South-West, Nigeria. There was gender matching of all participants.

Sample size was performed using formula $(Z_{1-\alpha}/2)^2 \times SD^2/d^2$ where Z = normal variant with α = 0.05, d = 3.5% and SD = 25% of HBA1c from previous study. 5% attrition since human subjects were involved (10). This is equal to $1.96^2(25)^2/3.5^2 + 5\% = 206$ subjects.

Inclusion criteria was all offspring of type 2 diabetes mellitus (T2DM) patients without any history of metabolic problems were randomly selected into the study group. All offspring of non-diabetic parents without any history of metabolic problems were randomly selected into the control group. They were both matched for age and sex. Exclusion criteria was offspring with diabetes mellitus were excluded from the study.

Blood samples were taken from subjects in the morning after fasting for at least 8 to 10 hours. 5 mL of blood was drawn from each subject for glucose estimation (2 mL) and for glycated haemoglobin (3 mL). The enzymatic hexokinase method was used to determine glucose concentrations. The HBA1c were determined by standard laboratory methods as described below.

The weight of subjects were recorded in kilograms (to the nearest 1.0 kg) without them wearing any heavy clothing like a coat, jacket, shoes or agbada, using a calibrated bathroom scale (Soehnle Waagen GmbH and Co. KG,D 71540 Murrhardt/Germany) positioned on a firm horizontal surface.

Height in meters of subjects were measured (to the nearest 0.1 m) using a stadiometer. Subjects stood erect, without shoes and headgears, on a flat surface with the heels and occiput in contact with the stadiometer (Prestige HM0016D) (India).

The BMI was subsequently calculated using the formula: weigh (kg)/height^2 (m^2). The following definitions were utilized: BMI category: Underweight: BMI < 18.5 kg/m^2, Normal weight: BMI 18.5-24.9 kg/m^2, Overweight: BMI 25.0-29.9 kg/m^2 and Obesity: BMI ≥ 30 kg/m.

3.1. Estimation of HbA1c

Plasma was separated from blood cells by centrifugation at 2000 rotation for 10 minutes. Glycosylated HbA1c was detected using fast ion-exchange resin high performance liquid chromatography separation method, (as used by Human-Germany method).

Data was analyzed by student t test was used to compare variability between test and control groups. The data obtained was analyzed using the SPSS version 25.0. P value less than 0.05 was considered statistically significant.

4. Results

There were 100 ODP and 100 ONDP aged 16 to 40 years. The most populated aged group was 21 to 25 years which is 44% (n = 88) (Table 1). 6% (n = 12) of the study group were obese. 19% we overweight (n = 38). Significantly, ODP has a higher weight than ONDP (P = 0.020). Significantly, ODP has a higher HbA1c than ONDP (P < 0.001) (Table 2).

The mean BMI was 25.05 kg/m^2 ± 1.76 in ODP subjects and 23.54 kg/m^2 ± 0.58 in ONDP subjects for age group 26 to 30years. Moreover, aged more than 30 years, the mean BMI for ODP subject was higher than ONDP subjects (26.94 kg/m^2 ± 1.73 versus 24.04 kg/m^2 ± 1.40) (Table 3).

Table 1. Anthropometric Parameters in ODP and ONDP

Variable	Category	Total (N = 200)	ODP (n = 100)	ONDP (n = 100)
Gender, No. (%)	Male	100 (50.0)	50 (50.0)	50 (50.0)
	Female	100 (50.0)	50 (50.0)	50 (50.0)
Age (y), No. (%)	16-20	56 (28.0)	27 (27.0)	29 (29.0)
	21-25	88 (44.0)	48 (48.0)	40 (40.0)
	26-30	40 (20.0)	15 (15.0)	25 (25.0)
	>30	16 (8.0)	10 (10.0)	6 (6.0)
BMI (kg/m^2), No. (%)	Normal weight	150 (75.0)	76 (76.0)	74 (74.0)
	Overweight	38 (19.0)	13 (13.0)	25 (25.0)
	Obese	12 (6.0)	11 (11.0)	1 (1.0)

Table 2. Mean Parameters Measured in ODP and ONDP

Variable	ODP (n = 100) Mean ± SD	ONDP (n = 100) Mean ± SD	T Value	P Value[a]
Age (y)	23.30 ± 0.44	23.44 ± 0.40	0.237	0.813
Height (m)	1.66 ± 0.01	1.64 ± 0.01	1.682	0.094
Weight (kg)	65.61 ± 1.07	62.52 ± 0.77	2.349	0.020
BMI (kg/m^2)	23.83 ± 0.42	23.20 ± 0.29	1.255	0.211
HbA1c (%)	5.13 ± 0.03	4.76 ± 0.05	6.240	<0.001

[a] Independent sample t test.

Table 3. Comparison of Mean BMI and HbA1c in ODP and ONDP at Different Age Groups

Variable	Age Group	ODP (n = 100) Mean ± SD	ONDP (n = 100) Mean ± SD	P Value[a]
BMI (kg/m^2)	16-20 years	23.26 ± 0.46	22.94 ± 0.51	0.645
	21-25 years	23.40 ± 0.52	23.04 ± 0.46	0.612
	26-30 years	25.05 ± 1.76	23.54 ± 0.58	0.335
	>30 years	26.94 ± 1.73	24.04 ± 1.40	0.266
HbA1c (%)	16-20 years	5.03 ± 0.13	4.63 ± 0.07	0.008
	21-25 years	5.09 ± 0.05	4.63 ± 0.13	<0.001
	26-30 years	5.34 ± 0.06	4.75 ± 0.11	<0.001
	>30 years	5.57 ± 0.08	4.88 ± 0.08	<0.001

[a] Independent sample t test.

The mean HbA1c was significantly higher in ODP than ODNP (*P* < 0.001) for age group 26 to 30 years. Also, for subjects aged more than 30 years, the mean HbA1c was significantly higher in ODP than ONDP subjects (*P* < 0.001) (Table 3).

5. Discussion

In the present study, we compared ODP and ONDP aged 16 to 40 years. We found out that the most populated aged group was 21 to 25 years. Only 6% of the study group was obese and 19% were overweight. ODP has a higher weight than ONDP while ODP has a higher HbA1C than ONDP. The mean BMI in ODP subjects was higher than in ONDP subjects in most of the age group. The mean HbA1c in ODP subjects was also higher than HBA1C in ONDP subjects in all age groups. The findings here showed that all the parameters in ODP tend to be on higher side. This cause for a great caution in the risk involved if someone is ODP. This finding supported publication by van der Sande et al[12] which revealed that the risk of developing diabetes mellitus for an individual with a positive family history of the disease is two- to fourfold higher in an offspring of a diabetic compared with offspring of non-diabetic.[12]

Although adults may undergo HbA1c screening regardless of weight, the ADA recommends testing children and adolescents only if their BMI is in the overweight or obese range and if they have two additional risk factors. All children and adolescents in the diabetes care study had at least one risk factor, (obesity). ADA classified the pediatric subjects as having parental diabetes if at least one parent was diagnosed with diabetes before the age of 45 years.[12,13]

Few large longitudinal studies done by National Health and Nutrition Examination Survey (NHANES) have assessed the predictive value of HbA1c measured in childhood and adolescence in predicting incident of diabetes. The prevalence of pre-diabetes defined by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) among 12-19 year old adolescents in the United States based on the 2005-2006 NHANES was 12.7% and 3.4% respectively.[10] In the study done by Lippi and Targhher[11] among subjects aged 10 to 19 years, the IFG prevalence at baseline was 9.2%, and the IGT prevalence, 8.1%, was higher than in NHANES.

Some recent studies have expressed skepticism about using adult HbA1c threshold values for diagnosing pre-diabetes and diabetes in children and adolescents. These studies tend to rely on cross-sectional comparisons of HbA1c with previously established measures of glycemia and showed poor correlation of HbA1c with FPG or 2hPG. Our current study differs, however, because we examined the pattern of HbA1c in offspring, not in associating with IFG or IGT. Clearly, there is little overlap among the categorical definitions of pre-diabetes based on HbA1c, as is well recognized in adults and as it was found by Chan et al[14] in children and adolescents as well as in adult, they suggested the goal of screening is to identify those at high risk of developing diabetes (or who already have it) rather

Research Highlights

What Is Already Known?
- Obesity is a major risk factor for T2DM.

- Clinical evidence indicates a stronger association of diabetes with central obesity than general obesity.

- The risk of becoming a diabetic for an individual with a positive family history of diabetes is two- to fourfold higher in an offspring's of diabetes.

- Individuals with a positive family history of diabetes have higher BMI than controls.

- Obesity and abnormal body fat distribution and IGT, are risk factors to developing type-2 Diabetes Mellitus.

What Does This Study Add?
- The research has proven that pattern of HBA1C of offspring of T2DM may be a pointer to the risk involved if one is an offspring of T2DM patients.
- ODP subjects tend to have higher weight than ONDP.

than detecting those who have pre-diabetes by different criteria. In this respect, the HbA1c performs as well as the other tests.[14,15] Moreover, higher HbA1c at baseline predicted a higher incidence of diabetes in ODP.

5.1. Study Limitations

The limitations of this study were that we did not consider 1° relatives or 2° relatives in particular but only in offspring, however, other family relations were not taken into considerations.

6. Conclusion

In conclusion, the serum HbA1c levels are higher among ODP than ONDP. The mean weight was higher in ODP than ONDP. Based on the outcome of this research, people with family history of T2DM should reduce their tendency to obesity.

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