ISSN: 2476-8642 (Print)
ISSN: 2536-6149 (Online)
www.annalsofhealthresearch.com
African Index Medicus, Crossref, African Journals Online & Google Scholar
C.O.P.E & Directory of Open Access Journals

Annals of Health Research

VOLUME 8
NO. 2
APR. - JUN, 2022

IN THIS ISSUE

PUBLISHED BY THE MEDICAL AND DENTAL CONSULTANTS ASSOCIATION OF NIGERIA, OOUTH, SAGAMU, NIGERIA.
www.mdcan.oouth.org.ng

Annals of Health Research
Volume 8, Issue No 2: 99-108
June 2022
doi:10.30442/ahr.0802-02-161

ORIGINAL RESEARCH

Baseline Plasma Fibrinogen and Glycated Haemoglobin (HbA1c) Levels in Normoglycaemic Offspring of Adults with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 Diabetes mellitus (T2DM) is known to be preceded by a long pre-diabetic stage. Family studies have confirmed that the incidence of T2DM in the first-degree offspring of T2DM patients is higher than in the non-diabetic population. The levels of plasma fibrinogen and HbA1c in offspring of T2DM patients may be markers of the development of T2DM later in life.
Objectives: To determine the plasma fibrinogen and HbA1c levels of normoglycaemic offspring of T2DM patients.
Methods: This study involved randomly selected 100 offspring of T2DM patients (ODP) and 100 offspring of non-diabetic parents (ONDP) aged between 16 and 40 years. Fasting Blood Glucose (FBG), plasma fibrinogen and HbA1c and height and body weight were measured using standard methods.
Results: The mean age of the ODP and ONDP were similar: 23.3±0.44 years and 23.44 ±0.40 years, respectively. The mean BMI was 23.83±0.42kg/m2 for ODP and 23.20±0.29kg/m2 for ONDP. The prevalence of overweight was 13.0% and 25.0% among the ODP and ONDP, respectively. The mean plasma fibrinogen was significantly higher in ODP (322.85 ± 5.15g/l vs 303.11 ±4.92 g/l; p = 0.006). The mean plasma HbA1c was also significantly higher among OND (5.13±0.03% vs 4.76±0.05; p = 0.000).
Conclusions: The plasma fibrinogen and HbA1c levels are higher among ODP than ONDP. This pattern of variations may serve as a reason for instituting precautionary measures since it predates the development of T2DM.

Key words: Body Mass Index, Diabetes mellitus, Fibrinogen, Glycated haemoglobin, Offspring.

Introduction

Diabetes mellitus (DM) is a disorder of intermediary carbohydrate, protein and lipid metabolism. It is characterised by hyperglycaemia, glucosuria, polydipsia, polyuria, polyphagia and weight loss. It is usually associated with secondary alterations in glucose, fat and protein metabolism, leading to many biochemical disorders. It may be characterised by peripheral insulin resistance, impaired regulation of hepatic glucose production with declining β-cell function and eventually, leading to β-cell failure [1].DM has a

wide range of prevalence rates across the country. In the rural parts of Nigeria, it affects 2.2% of the population, whereas, in the urban regions, the prevalence may be as high as 10%. [1 - 3] A study done by Nwafor and Owhoji in 2001 on selected metropolitan cities revealed a prevalence rate of 23.4% among the higher socioeconomic members of a population of the oil industry staff in the urban city of Port Harcourt. [4] This is higher than 16% among the lower socioeconomic group in the same community. [4] The difference in prevalence rates may be attributed to lifestyle westernisation and progressive rural-urban migrations.

The prevalence of DM is increasing worldwide, and it is projected that by the year 2030, over 500 million adults will be affected by the disease. [5] The projected rise could result from urbanisation and the ageing of the population. [6] The projected increase in prevalence is expected to be higher in Africa and Asia, where there is a rapid epidemiological transition. [7] The prevalence rate of DM is still lower in traditional rural than urban communities. [8-10] Previous studies by Bakari *et al.* [4] found the prevalence rate of 1.6% in a suburban Northern Nigerian city, while Erasmus *et al.* reported a prevalence of 1.4% in a rural population of North central Nigeria. [8, 9] Most cases of DM in rural and suburban areas remain undiagnosed, and many patients present for the first time with complications. [11]

The modest improvement in living standards witnessed over the past few years in Nigeria has resulted in the ageing of its populace. Insulin resistance tends to worsen with advancing age. [12-15] This, coupled with decreased physical activity among the aged, increases the risk of Type 2 DM. Of the risk factors for DM reported in many studies, unhealthy dietary habits are the most prevalent; that is not surprising considering the proliferation of fast food outlets in many cities. An unhealthy diet consisting mainly of high-fat, energy-dense foods contributes to the development of obesity and DM. [14, 15]

The American Diabetes Association (ADA) has recently recommended glycated haemoglobin (HbA1c) with a cut-point ≥6.5% for diagnosing DM as an alternative to fasting plasma glucose (FPG ≥7.0 mmol/L)-based criteria. [2] The levels of HbA1c are strongly correlated with FPG. [16] Fasting Blood Glucose (FBG), 2-hour post-glucose load plasma glucose, and oral glucose tolerance tests are recommended for the diagnosis of DM only if HbA1c testing is not possible due to unavailability of the assay or when there are patient factors precluding its interpretations. Glycated Haemoglobin (HbA1c) provides a reliable measure of chronic glycaemia. It correlates well with the risk of long-term DM complications, so it is currently considered the test of choice for monitoring and long-term management of DM. [17] The earliest event associated with atherosclerosis is the accumulation of low-density lipoprotein (LDL) cholesterol and fibrinogen /fibrin in the affected arterial wall. Therefore, it is essential to understand the mechanisms that govern the endothelial changes. [17]

There is a lack of reports on the level of plasma fibrinogen and HbA1c in first degree relatives of DM patients in this environment. Therefore, this study aimed to determine the levels of plasma fibrinogen and HbA1c in the offspring of T2DM patients. This study will serve as a biomarker of the risk of developing DM when compared with the offspring of non-diabetic parents. This, however, may serve as a basis for advice to the general populace about the risk of developing T2DM in the future.

Methods

This study was designed as a cross-sectional, single-centre, cohort study carried out from March to December 2018. This study involved a random selection of 200 subjects: 100 offspring of T2DM patients (ODP) and 100 offspring of non-diabetic parents (ONDP). The study was conducted at the State Hospital, Ijebu-ode, Ogun state, a suburban area of southwest Nigeria. The participants were aged between 16 and 40 years and were matched for sex.

Ethical considerations

Ethical clearance for the study was obtained from the Health Research Ethics Committee (HREC) of Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu (HREC/OOU/014/2018). All the participants in this study gave informed consent for enrolment.

Sample size estimation

This was determined using the formula $(Z_{1-\alpha/2})^2 \times SD^2 / d^2$ where Z= normal variant, d = 3.5%, Type 1 error with SD = 25g/l of fibrinogen from previous study. [18] Additional 5% was added to the calculated sample size for non-response. Therefore, the minimum sample size was equal to $1.96^2(25)^2 / (0.035)^2 = 196+10 = 206$.

Inclusion criteria: Offspring of T2DM patients were randomly selected into the study group, while a similar group of offspring of non-diabetic parents were randomly assigned to the control group.

Exclusion criteria: All the participants with cardiovascular and metabolic disorders, smoking habits and clinical pallor were excluded from both arms of the study.

Clinical procedures

The body weight was recorded in kilograms (to the nearest 1.0 kg) with the subject in light clothing but without shoes, using a calibrated bathroom weighing scale (Soehnle Waagen GmbH and Co. KG, D 71540 Murrhardt/Germany) positioned on a firm horizontal surface. A stadiometer measured the height (to the nearest 0.1m). The subjects stood erect, without shoes, caps or headgears, on a flat surface with the heels and occiput in contact with the stadiometer (Prestige HM0016D, India). The Body Mass Index (BMI) was subsequently calculated using the formula: weight (kg)/ height^2 (metres^2).

Biochemical analyses

Blood samples were drawn from the subjects in the morning after fasting for at least eight hours. The enzymatic hexokinase method was used to determine glucose concentrations. [18] The HBA1c and fibrinogen levels were determined by standard laboratory methods as described below.

Six millilitres of blood samples were drawn from each subject after eight hours of overnight fasting. One millilitre of blood was used to determine the FBG, while three millilitres of blood was centrifuged and the serum analysed for fibrinogen. The remaining two millilitres were transferred into Ethylenediamine tetraacetic acid (EDTA) bottles and analysed immediately for glycated haemoglobin ($HbA1_C$).

Estimation of Plasma fibrinogen

A rapid semi-automated method for determining fibrinogen levels in human plasma was used. This method is referred to as the thrombin time method or fibro-meter method, which is based on the principle that when thrombin is added to suitably diluted plasma, the time of clotting is estimated and determined (as described by Dyr and Vodrážka,1974). [18]

Estimation of HbA1c

Plasma was separated from blood cells by centrifugation at 2000 rotation for 10 minutes. Glycated Haemoglobin (HbA1c) was detected using the Fast Ion-Exchange Resin High-Performance Liquid Chromatography

separation method (as used by the Human-Germany Method). [19]

Statistical analysis

The data obtained were analysed using the Statistical Programme for the Social Sciences (SPSS) version 25.0. The Student's t-test was used to compare variability between the mean values of the test and control groups. A probability value of *P* less than 0.05 was considered statistically significant.

Results

Table I shows that most of the subjects (48.0% of ODP and 40.0% of ONDP) belonged to the 21-25 years age group. The mean age of the ODP and ONDP were similar: 23.3±0.44 years and 23.44 ±0.40 years, respectively. The sex ratio was 1:1 in both arms of the subjects, while the mean BMI was 23.83±0.42 kg/m2 for ODP and 23.20±0.29 kg/m2 for ONDP. The prevalence of overweight was 13.0% and 25.0% among the ODP and ONDP, respectively, whereas 11.0% and 1.0% of ODP and ONDP were obese.

Table I: Distribution of subjects in the ODP and ONDP groups according to age, sex and BMI

Variable	*Category*	*ODP n = 100*	*ONDP n = 100*	*Total n = 100*
Sex	Male	50 (50.0)	50 (50.0)	100 (50.0)
	Female	50 (50.0)	50 (50.0)	100(50.0)
Age Range (Years)	16-20	27 (27.0)	29 (29.0)	56 (28.0)
	21-25	48 (48.0)	40 (40.0)	88 (44.0)
	26-30	15 (15.0)	25 (25.0)	40 (20.0)
	> 30	10 (10.0)	6 (6.0)	16 (8.0)
BMI (kg/m^2)	Normal	76 (76.0)	74 (74.0)	150 (75)
	Overweight	13 (13.0)	25 (25.0)	38 (19.0)
	Obese	11 (11.0)	1 (1.0)	12 (6.0)

Figures in parentheses are percentages of the total in the respective column.

The mean plasma fibrinogen level of the ODP group was significantly higher than the levels for ONDP (322.85 ± 5.15 g/l vs 303.11 ±4.92 g/l; p = 0.006). The mean HbA1c of 5.13±0.03% for ODP subjects was significantly higher than 4.76±0.05% for ONDP (p = 0.000), as shown in Table II.

Table III shows that the mean plasma fibrinogen and mean glycated haemoglobin values were higher among ODP than ONDP across ages. In addition, the mean plasma fibrinogen levels progressively increased with age among ODP with statistical significance (p = 0.01). In contrast, the progressive increase in mean values with age among ONDP lacked statistical significance (p = 0.147). The mean Hb1Ac also progressively with age with statistical significance among ODP (p = 0.025), while a similar progressive increase in mean Hb1Ac with age among ONDP was not significant (p = 0.084).

Discussion

In the present study, no significant difference was observed in the BMI of ODP and ONDP. The levels of HbA1c level conform to what is regarded as the threshold for the onset of DM or prediabetes. Generally, the local pattern (Nigerian) of glycated haemoglobin (HbA1c) level can be distinctly higher for the offspring of diabetic patients. It should be taken as such to prevent DM in this environment. In addition, overweight or obesity predisposes to DM or abnormal glycated haemoglobin levels.

Table II: Comparison of the mean values of age, BMI, plasma fibrinogen and glycated haemoglobin between ODP and ONDP subjects

Variables	*ODP n = 100*	*ONDP n = 100*	*P value*
Mean Age (Years)	23.30±0.44	23.44±0.40	0.813
Mean BMI (kg/m^2)	23.83±0.42	23.20±0.29	0.211
Mean Fibrinogen(g/l)	322.85±5.15	303.11±4.92	0.006
Mean HbA1c (%)	5.13±0.03	4.76±0.05	0.000

Table III: Comparison of mean values of plasma fibrinogen and Hb1Ac among subjects in the ODP and ONDP groups

Age Group (Years)	*Plasma fibrinogen (g/l)*		*Plasma HbA1c (%)*	
	ODP	**ONDP**	**ODP**	**ONDP**
16-20	319.15±6.70	299.90±6.84	5.03±0.13	4.63±0.07
21-25	321.26±10.62	301.89±9.15	5.09±0.05	4.63±0.13
26-30	325.67±16.41	303.26±12.02	5.34±0.06	4.75±0.11
>30	340.70±15.43	319.75±15.54	5.57±0.08	4.88±0.08
F-Test	3.642	1.828	3.157	0.499
P value	0.010	0.147	0.025	0.684

The study found the HbA1c threshold of 5.1% as highly valuable for detecting undiagnosed DM. This agrees with the 6.3% HbA1c threshold for detecting undiagnosed DM among Shanghai adults with sensitivity and specificity of 63% and 96%, respectively. [19] Other studies in East Asian countries showed the optimal HbA1c cut-off for diagnosing DM as 5.6% in Japan [20] and 5.9% in Korea. [21] Researchers found an HbA1c threshold of 6.4% in a Middle Eastern population. [22] Therefore, it is essential to have HbA1c criteria for diagnosing DM in each population. [23-25]

The present study shows that plasma fibrinogen concentration was significantly higher among the offspring of patients with DM. p This finding may explain the theory that suggests that tissue injury, vascular complications and endothelial dysfunctions may long predate the occurrence of T2DM. [26] The raised concentration of pro-inflammatory cytokines and the resultant acute phase response may underlie much of the metabolic clustering, including glucose tolerance. [27] Therefore, an increase in the acute phase proteins explains the elevation of fibrinogen in T2DM hence, the present study shows that the elevated blood levels of fibrinogen and HbA1c could be an early event that precedes the expression of impaired glucose tolerance or any change in asymptomatic offspring of patients with T2DM. [28]

The involvement of elevated plasma fibrinogen as a risk factor for the development of T2DM remains controversial. Biases in these evaluations may exist due to unmeasured confounding factors such as causality between plasma fibrinogen and endothelial events. [29] The elevated fibrinogen levels may result from an inflammatory state caused by the underlying pathology and, therefore, can predispose to the occurrence of T2DM in the future. [29] Nevertheless, further evidence reinforces the hypothesis that the elevated plasma fibrinogen level may directly influence

endothelial events or progression. Intravenous infusion of human fibrinogen into mice, giving a 1.7-fold increase in plasma fibrinogen, has been observed to lead to resistance to thrombolysis, increased thrombus fibrin content, quicker fibrin formation, greater fibrin network density and increased clot strength and stability. [30]

Fibrinogen may favour atherogenesis when converted to fibrin and its atherogenic degradation products or may trigger lipid deposition and local inflammation resulting in the formation, destabilisation, and rupture of atherosclerotic plaques. The promotion of thrombogenesis is another possible mechanism. Fibrinogen acts as a scaffold for blood clots, enhancing platelet aggregation and fibrin formation, thus making thrombi more resistant to lysis. [31] Furthermore, fibrinogen can interact with red blood cells, mediating erythrocyte sedimentation and blood viscosity while permitting red blood cells to attach to thrombi. Besides contributing to thrombus size, structure, and stability, red blood cells can alter fibrin network organisation, suppress plasmin generation and reduce clot permeability, possibly delaying fibrinolysis and prolonging clot resolution, which may contribute to endothelial changes. [31]

The HbA1c is an accurate and easy-to-administer test with on-the-spot results availability. It can be an effective tool in establishing the diagnosis of DM, especially in low- and middle-income countries and hard-to-reach populations. Even though elevated HbA1c has been recommended for the diagnosis of DM, some testing strategies and cut-off ranges are still being debated. However, the combination of Fasting Glucose Tolerance (FGT) and elevated HbA1c significantly enhances the diagnostic accuracy of these individual tests. [29] The prognostic potential of high HbA1c lies in its unique ability to assess retrospective glycaemic control and predict lipid profile in diabetic patients. As the epidemic of DM increases worldwide, the HbA1c test may continue to be implemented as part of the diagnostic and prognostic tools, leading to better patient care and successful clinical outcomes. [29]

The prevalence of T2DM and its cardiovascular complications has increased significantly worldwide. [30] In China, the prevalence rates of DM and prediabetes Mellitus (pre-DM) are also steadily increasing, with a prevalence rate of DM in adults reaching 10.9% and pre-DM reaching 35.7% in 2013. [31] Chronic, low-grade inflammation is a predisposing factor for DM and also contributes to the genesis of diabetes complications. [32] Fibrinogen, one of the subclinical inflammation biomarkers, increases before the onset of DM [33] and elevates from normal glucose regulation (NGR) over pre-DM to DM. [34] It has been demonstrated that plasma fibrinogen level was significantly associated with glucose metabolism [including fasting blood glucose (FBG) and glycated hemoglobinA1c (HbA1c), a measure of long-term glycaemic control] in patients with acute coronary syndromes (ACS). [35] Nevertheless, few reports have explored the relationship between plasma fibrinogen levels and glucose metabolism in patients with new onset stable Coronary Artery Disease (CAD). Moreover, plasma fibrinogen has also been implicated in the development of macrovascular complications and microvascular disorders in DM. [34, 36, 37] In contrast, there has been no study investigating the pattern of plasma fibrinogen levels in individuals with impaired glucose regulation.

Limitations of the study

A prospective study is desired as the inability to measure HbA1c and plasma fibrinogen levels over a long period in relation to other

underlying health challenges in the subjects may be confounding variables in the present study.

Conclusion

This research has demonstrated that plasma fibrinogen and HbA1c levels are elevated in the offspring of T2DM patients, and this may be a pointer to the risk of T2DM in the population studied. Plasma fibrinogen and Hb1Ac may also serve as baseline parameters to further studies in offspring of T2DM patients. Based on the outcome of this study, people with a family history of T2DM need to reduce their tendency to obesity to improve their metabolic health.

Acknowledgements: The authors thank all the study participants and the adjunct staff who assisted with data processing and manuscript drafting.
Authors' Contributions: TEO conceived the study while TLO designed the study. Both TEO and TOP did the literature review. TEO did data analysis and drafted the manuscript, while TLO did data interpretation and revised the draft for sound intellectual contents. All the authors read and approved the final version of the manuscript.
Conflict of interest: None.
Funding: Self-funded.
Publication History: Submitted 21 December 2021; **Accepted** 26 May 2022.

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