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Prevalence of Prediabetes in First Degree Relatives of Patients with Type 2 Diabetes Mellitus in a Tertiary Centre in Southern Nigeria

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Abstract: *Introduction:* Prediabetes confers about a sixfold increased risk of diabetes and a two to threefold increased risk of cardiovascular events. A family history of diabetes is a major risk factor for the development of diabetes. The detection of prediabetes in its early stages in persons at risk could lead to the delay or prevention of the disease and subsequent adverse sequalae. *Methods:* A total of 180 first-degree relatives (FDR) of patients with type 2 diabetes and 90 controls were assessed. A fasting venous blood sample was collected for fasting plasma glucose. Following 75g of anhydrous glucose ingestion, the 2-hour post glucose load and glycated haemoglobin was assessed. Statistical significance was set at a p value <0.05. *Results:* The mean age of the cases who were first degree relatives of type 2 DM was 38.2±12.3 years with a female to male ratio of 1.4:1. The prevalence of prediabetes was 23.9% which was significantly higher than in the controls (10%; χ^2=8.385, p=0.015). Using the various indices of glycaemic control, impaired fasting glucose, impaired glucose tolerance and elevated HbA1c in the FDR's was found in 15.0%, 12.2% and 15.6% respectively. *Conclusion:* Relatives of Type 2 DM patients should be considered as primary target for diabetes preventive programs as this will necessitate institution of effective measures early to delay or prevent the onset of type 2 diabetes mellitus.

Keywords: Pre-Diabetes, First Degree Relatives, Type 2 Diabetes, Nigeria

1. Introduction

Prediabetes, a state that precedes diabetes in most patients who are eventually diagnosed with type 2 diabetes, is said to occur when the blood glucose level is higher than normal but lower than the diabetic range [1] and is a significant risk factor for the development of type 2 diabetes, microvascular and macrovascular disease. [2] There is a sixfold increased risk of diabetes in persons with prediabetes when compared to persons with normal glucose tolerance as well as a two to threefold increased risk of future cardiovascular events. [3] It is estimated that without any lifestyle intervention 15-30% of these people diagnosed with prediabetes will go on to develop diabetes in the next 5 years. [2] According to the to the World Health Organization (WHO), impaired fasting glucose (IFG) is defined as fasting plasma glucose (FPG) of 6.1–6.9 mmol/L (in the absence of impaired glucose tolerance (IGT), while IGT is defined as post load plasma glucose of 7.8–11.0 mmol/L based on a 2-hour 75gram oral glucose tolerance test (OGTT). [4] The former and a haemoglobin A1c levels of 5.7–6.4% are used to make a diagnosis of prediabetes. [5]

It may take many years for the early metabolic abnormalities that precede diabetes, IFG and IGT to progress to diabetes, however, it is currently estimated that up to 70% of

patients with these prediabetic states eventually develop type 2 diabetes. [6] Thus, testing to detect type 2 diabetes and prediabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2) together with the presence of one or more additive risk factors for the development of type 2 diabetes. [7] Family history of type 2 diabetes is a strong risk factor for the disease, however, the factors mediating this excess risk are not fully understood. [8] There is a clear clustering of IGT and type 2 diabetes in families. [9] In offspring and in siblings of patients with type 2 diabetes, the lifetime risk of developing type 2 diabetes has been estimated to be about 40%. [10] If both parents suffer from the disease the risk in insulin resistant children reaches 80%. [11] This actively demonstrates that type 2 diabetes is an inherited disease, although the exact mode of inheritance has not been elucidated. [9]

Eriksson et al in a study to identify the early metabolic defects in persons at increased risk for type 2 diabetes, concluded that abnormalities of glucose metabolism are common in first degree relatives (FDR's) of patients with type 2 diabetes after finding severely impaired first phase insulin secretion in FDR's of patients with type 2 diabetes. [12] A study by Wagner et al reported a 40% increased risk of having prediabetes in FDR's of diabetics. [13] A local study in Ibadan reported that FDR's of Nigerian patients with type 2 diabetes (T2DM) were at a greater risk of future development of the disease compared to those without a family history. [14] Scott et al [15] on investigating the link between family history and risk of type 2 DM, found family history to be associated with a higher incidence of T2DM with the greatest risk observed in those with a biparental family history. Similarly, in a study done to screen for DM in a Nigerian family practice setting, Oyegbade et al [16] demonstrated that a parental history of DM correlated significantly with hyperglycaemia in the offspring.

Nigeria has the highest burden of diabetes in Africa with about 4 million estimated to have diabetes. Equally alarming is that 2 million of these cases are undiagnosed. [17] Unless appropriate action is taken, the increase in diabetic cases is inevitable. Evidence shows that the detection of prediabetes in its early stages could lead to the delay or prevention of the disease and its complications. [1] This would help to reduce costs on our already strained health care in Sub-Saharan Africa and especially here in Nigeria where health care services and accessibility are poor.

The aim of this study was to estimate the frequency of prediabetes in first degree relatives of patients with type 2 diabetes mellitus using fasting plasma glucose, 2hour oral glucose tolerance test (OGTT) and glycated haemoglobin.

2. Methods

2.1. Study Site

This study was carried out at the Medical outpatient clinics and medical wards of the Department of Internal Medicine of the University of Port Harcourt Teaching Hospital (UPTH). This hospital is a tertiary hospital located in Obio-Akpor Local Government Area of Rivers State where it serves Rivers State and neighbouring states of Abia, Bayelsa and Imo.

2.2. Participants

The study population consisted of first-degree relatives of patients with type 2 diabetes mellitus attending the MOPC, on admission in the medical wards or referred from other outpatient clinics of UPTH. A total of a hundred and eighty (180) consecutive first-degree relatives of patients with type 2 diabetes mellitus and ninety (90) controls who were first degree relatives of patients without a history of diabetes mellitus were assessed.

First degree relatives with previously diagnosed diabetes or on glucose lowering medication, glucocorticoids, or hormonal contraceptives, those less than 18 years, pregnant women and lactating mothers as well as those who did not give informed consent were excluded from the study.

2.3. Procedure

The study was a descriptive cross-sectional study. Recruited participants and controls were assessed using a structured questionnaire to obtain demographic data and other disease related variables. Their weight and height were measured to calculate their body mass index which was classified according to the WHO criteria. [18] Waist circumference was measured with a flexible tape and men with a waist circumference greater than or equal to 94.0cm or women with a waist circumference greater than or equal to 80.0 cm were classified as centrally obese. [18]

Two blood samples were collected from the forearm vein of each subject while seated. The first sample was a fasting venous blood sample for fasting plasma glucose and fasting lipid profile [Total Cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglycerides (TG) and low-density lipoproteins cholesterol (LDL-c)]. Patients were then given 75g of anhydrous glucose in 250mls of water to be taken over 5 minutes. Subjects were asked to wait in the clinic for two hours during which they were asked not to take another meal or snack except water. A second sample of blood was taken 2 hours after ingestion of glucose drink for the estimation of 2-hour post glucose load and glycated haemoglobin.

Abnormal lipid profile was defined as hypercholesterolemia with TC > 5.2mmol/l; elevated triglyceride with TG > 1.7mmol/l; and elevated low density lipoprotein cholesterol LDL-c>2.6 mmol/l; and low high density lipoprotein cholesterol with HDL-c < 1.03mmol/l. [19]

Impaired fasting glycaemia (IFG) was defined as blood glucose between 6.1mmol/L- 6.9mmol/L after an overnight fast. Impaired glucose tolerance (IGT) was defined as 2-hour plasma glucose concentration of between 7.8mmol/L – 11.0mmol/L after a 75g oral glucose load (2). IFG, IGT or HbA1c between 5.7% and 6.4% was used to make a diagnosis of prediabetes. The values of HbA1c >6.5%, FBG ≥ 7mmol/L, 2-hour post glucose load ≥ 11mmol/L was used

to make a diagnosis of diabetes. [5]

2.4. Ethical Considerations

Ethical approval was obtained from the ethical board of the hospital and documented informed consent was given by the participants.

2.5. Statistical Analysis

Data was analysed using Statistical Package for Social Sciences (SPSS) version 20.0 Results were presented as mean ± standard deviation for continuous variables and frequencies and percentages for categorical variables. Whereas continuous variables were compared with the student's t-test, categorical variables were compared with the chi-square test or two tailed Fisher's exact test as appropriate. A p value of less than 0.05 was considered statistically significant.

3. Results

A total of 270 subjects were included in this study of which 180 constituted the cases who were first degree relatives of patients with type 2 diabetes and 90 controls who were first degree relatives of patients without type 2 diabetes.

One hundred and four (57.8%) of the cases were females and seventy-six (42.2%) were males, with a female to male ratio of 1.4:1; while fifty-one (56.7%) of the controls were females and thirty-nine (43.3%) were males, with a female to male ratio of 1.3:1. There was no statistically significant difference in sex distribution between the two groups (χ^2 = 0.30, p=0.897). The mean age of the cases who were first degree relatives was 38.2±12.3 years with an age range of 20-75 years while the mean age of the control population was 38.4 ± 11.2 years (p=0.894) with an age range of 22-72 years. The most common age groups were the 20-39 years and 40-59 years respectively among the cases and controls. Table 1 shows the age and sex distribution of the study population.

Table 1. *Age and sex distribution of study population.*

	Cases Frequency (%)	Controls Frequency (%)
Sex		
Female	104 (57.8)	51 (56.7)
Male	76 (42.2)	39 (43.3)
Age category		
20-39 years	114 (63.3)	58 (64.4)
40-59 years	55 (30.6)	26 (28.9)
60-79 years	11 (6.1)	6 (6.9)
Total	180	90

Amongst the cases, 47 (26.1%) had a positive family history of diabetes in only their fathers, 92 (51.1%) had a positive family history of diabetes in only their mothers and 11 (6.1%) had a positive family history of diabetes in only their sisters, while 30 (16.7%) had a positive family history of diabetes in more than one relative. There were no cases with a positive family history of diabetes in their brothers. (See figure 1). Amongst the cases, 127 (70.6%) had a positive family history of hypertension and fifty-three (29.4%) did not have a family history of hypertension. Amongst the controls, 19 (21.1%) had a positive family history of hypertension and 71 (78.9%) did not have a positive family history of hypertension (χ^2 = 59.07, p<0.001).

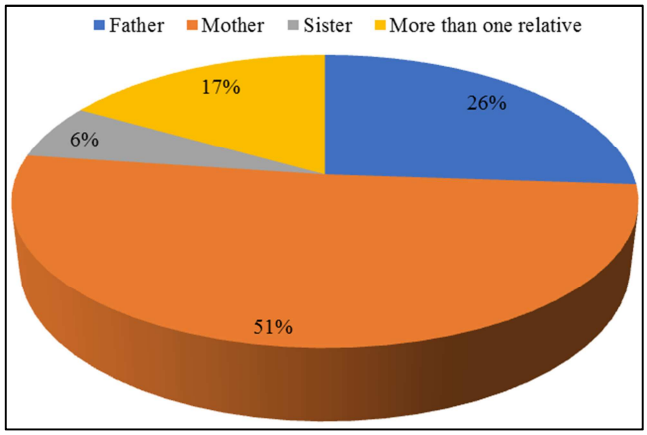
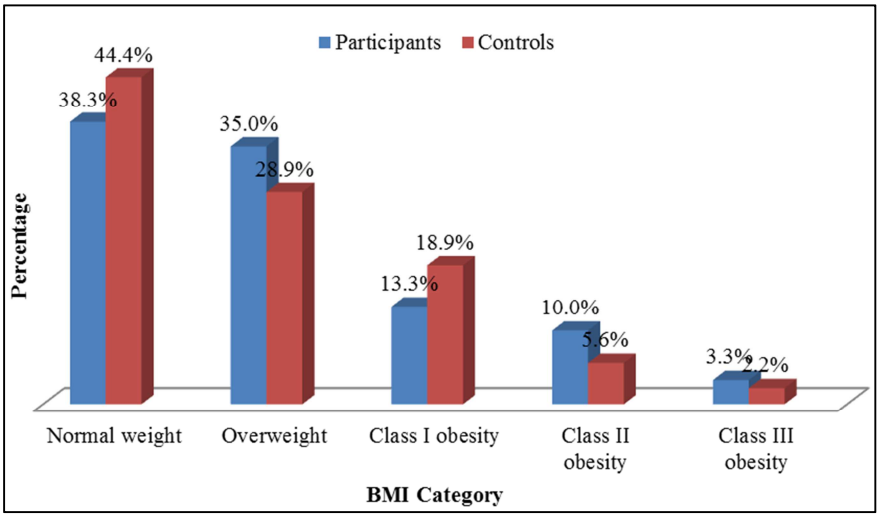


Figure 1. *Family history of diabetes among the cases.*



Key: BMI= body mass index

Figure 2. *BMI categories of study population.*

The mean body mass index (BMI) of the cases was 27.5 ± 5.5 kg/m^2 and ranged from 19.6 kg/m^2 to 48.5kg/m^2; while the mean BMI of the controls was 26.7 ± 5.0 kg/m^2 and ranged from 19.3kg/m^2 to 40.0 kg/m^2. There was no statistically significant difference in mean BMI between cases and controls. (p=0.416).

The BMI among the cases was normal in 69 (38.3%) persons, 63 (35.0%) were overweight, 24 (13.3%) and 18 (10.0%) had class I and class II obesity respectively, while 6 (3.3%) were morbidly obese. This is in comparison to the controls where 40 (44.4%) had a normal BMI, 26 (28.9%) were overweight, 17 (18.9%) had class I obesity, 5 (5.6%) had class 2 obesity and 2 (2.2%) had morbid obesity (χ^2= 4.096, p=0.395) (see figure 2).

The mean waist circumference in the female cases was 89.1±13.5 cm, and the mean in the female controls was 83.8±13.2cm (p=0.023). Central obesity was seen in 75 (72.1%) of the female cases and 27 (52.9%) of the controls (χ^2=4.63; p=0.020). Among the male cases, mean WC was 88.6 ± 13.1 cm versus 81.0 ± 11.6 cm for the controls (p=0.003). Central obesity was seen in 21 (27.6%) of the male cases and 7 (17.9) of the male controls (χ^2=5.18; p=0.359). Ninety-six cases (53.33%) had central obesity compared to 34 controls (48.8%), (χ^2=3.32, p=0.067).

The systolic blood pressure among the cases ranged from 90mmHg to 210mmHg with a mean of 124.7 ± 18.0mmHg, while among the controls, the range was 100 to 140mmHg with a mean of 120.4± 10.3mmHg (p=0.038). The mean diastolic blood pressure among the cases was 79.7 ± 12.5 mmHg with the values ranging from 60mmHg to 130mmHg, while among the controls, the range was 60 to 90mmHg and the mean was 73.5 ± 7.8mmHg (p< 0.001).

The cases compared to the controls, had higher mean triglycerides (TG) only. Higher mean low density lipoproteins cholesterol (LDL-c), total cholesterol (TC) and lower mean high density lipoprotein cholesterol (HDL-c) was seen in the controls (table 2). Twenty-one (23.3%) of the controls had elevated total cholesterol levels while 20 (11.1%) of the cases had elevated total cholesterol levels (χ^2= 6.959, p=0.011); 9 cases (5%) had elevated triglyceride levels and none of the controls had elevated triglyceride levels (χ^2 = 4.655, p=0.031); 144 (80%) of the cases had low HDL-c whereas 82 (91.9%) controls had low HDL-c (χ^2= 5.430, p= 0.020); and finally 91 (50.6%) of the cases had high LDL-c while 76 (84.4%) of the controls had high LDL-c and this was statistically significant (χ^2 = 29.20, p<.001).

Table 2. *Clinical and biochemical characteristics of the study population.*

Variable	Cases Mean (SD)	Controls Mean (SD)	p value
Age (years)	38.2 (12.3)	38.4 (11.2)	0.894
Women (%)	56.7	43.3	0.897
BMI (kg/m^2)	27.5 (5.5)	26.7 (5.0)	0.416
WC (cm) Men	88.6 (13.1)	81.0 (11.6)	0.359
WC (cm) Women	89.1 (13.5)	83.8 (13.2)	0.023
SBP (mmHg)	124.7 (18.0)	120.4 (10.3)	0.038
DBP (mmHg)	79.7 (12.5)	73.6 (7.8)	<0.001
TC (mmol/L)	4.0 (0.1)	4.7 (1.3)	<0.001
TG (mmol/L)	0.8 (0.4)	0.6 (0.3)	<0.001
HDL-c (mmol/L)	0.9 (0.4)	0.8 (0.2)	0.001
LDL-c (mmol/L)	2.7 (0.9)	3.6 (1.3)	<0.001
FBG (mmol/L)	4.9 (0.9)	4.6 (0.9)	0.010
2HPG (mmol/L)	6.3 (1.6)	6.0 (1.7)	0.139
HbA1c	5.1 (0.9)	4.6 (0.8)	<0.001
PD (%)	23.9	10	0.015

Key: BMI=body mass index, WC=waist circumference, SBP = systolic blood pressure, DBP= diastolic blood pressure, TC= total cholesterol, TG= triglyceride, LDL-c=low density lipoprotein cholesterol, HDL-c= high density lipoprotein cholesterol. FBG- fasting blood sugar, 2HPG= 2-hour plasma glucose, HbA1c= glycated haemoglobin, PD (%) = prevalence of prediabetes.

Table 3. *Dysglycaemia in the study population.*

Variable	Cases Frequency (%) N=180	Controls Frequency (%) N=90	χ^2	p value
Prediabetes	43 (23.9)	9 (10.0)	8.385	0.015
IFG (6.1-6.9 mmol/L)	27 (15.0)	4 (4.4)	6.615	0.037
IGT (2HPG 7.8-11.1mmol/L)	22 (12.2)	7 (7.8)	1.348	0.510
Impaired glycated Hb (5.7-6.4%)	28 (15.6)	4 (4.4)	7.097	0.029

Key: IFG= impaired fasting glucose, IGT= impaired glucose tolerance, 2HPG= 2hour plasma glucose, Hb= haemoglobin

Indices of glycaemia

Using the WHO criteria, the frequency of prediabetes, IFG, IGT and impaired HbA1c in the FDR's was found to be 23.9%, 15.0%, 12.2% and 15.6% respectively while the frequency of prediabetes, IFG, IGT and impaired HbA1c in the controls was found to be 10%, 4.4%, 7.8% and 4.4% respectively.

A) Fasting plasma glucose: The mean fasting plasma glucose in the cases was 4.9± 0.9mmol/l and the mean fasting plasma glucose in the controls was 4.6± 0.9mmol/L and this was significantly higher in the cases than controls (p=0.010). Using the W.H.O criteria, impaired fasting glucose (IFG) was seen in 27 (15.0%) of the cases and 4 (4.4%) of the controls (χ^2 = 6.615, p=0.037). Three (1.7%) of the cases and 2 (2.2%) of the controls were found to be elevated FPG of the diabetic range.

B) 2hour plasma glucose after 75gm OGTT: There was no significant difference in the mean 2hour plasma glucose in the cases and controls (6.3±1.6mmol/L and 6.0±1.7mmol/L respectively; p=0.139). Impaired glucose tolerance (IGT) was seen in 22 (12.2%) of cases and 7 (7.8%) of the controls and this was not statistically significant (χ^2= 1.348, p=0.510). Five of the cases (2.8%) and 2 (2.2%) of the controls were found to have elevated 2hour plasma glucose in the

diabetic range.

C) HbA1c: The mean HbA1c in the cases was 5.1±0.9% and the mean HbA1c in the controls was 4.6±0.8% and this was significantly higher in the cases than controls ($p<0.001$). Impaired HbA1c was seen in 28 (15.6%) of the cases and 4 (4.4%) of the controls ($\chi^2=7.097$, $p=.029$). Five (4.4%) cases and 3 (3.3%) of the controls were found to be diabetic.

D) Prediabetes: Presence of prediabetes was significantly higher in the cases than controls. ($\chi^2= 8.385$, $p=0.015$). Forty-three cases (23.9%) were found to be prediabetic compared to nine controls (10%).

4. Discussion

End organ damage to the heart, blood vessels, eyes and kidneys traditionally attributed to be a complications of diabetes have also been described in people with prediabetes. [2] Microvascular and macrovascular damage starts during prediabetes and is associated with an increased risk of cardiovascular disease early in the progression to T2DM. [3]

The present study reported a prevalence of 23.9% of prediabetes in first degree relatives of patients with type 2 diabetes. Out of a total of 180 FDRs, 43 of them were identified as prediabetic based on FBG, HbA1C and 2hour plasma glucose tests. The prevalence of IFG, IGT and impaired HbA1c were 15%, 12.2% and 15.6% respectively. Shrisvastava et al [20] in their study of FDRs recorded a higher prevalence of 29.5% of prediabetes which is higher than the frequency reported in this study. Another study in Turkey recorded a prevalence of 18.4% of IGT in FDRs. [21] Amini et al [22] in Iran recorded a prevalence of IGT and IFG as 19.5% and 17.3% respectively in FDRs. Use of the different diagnostic criteria as well as the geographical and racial populations in these studies may have accounted for the varied prevalence rates. There is a paucity of data on similar studies in FDRs in Nigeria though some studies have been done on IGT in the general population. [23, 24]

Most of the cases had a positive family history of diabetes in their mothers which is similar to a study by Erasmus R et al [25] where family history of diabetes in the cases was more common in the mothers. The authors reported significant maternal aggregation in type 2 diabetics which suggests excess maternal transmission of diabetes amongst offspring. This is in contrast to Nyewe et al [23] who reported a family history more prevalent in the fathers. Majority of the cases also had a family history of hypertension. The prevalence of hypertension in Nigeria in a review article by Ogah et al was 8%-46.4%. [26] This high prevalence may have accounted for the high family history of hypertension. Secondly, the presence of family members with diabetes may account for the high occurrence of family history of hypertension in the cases as the occurrence of hypertension as a co-morbid condition in type 2 diabetes patients has been described. [24] Ogbu et al recorded a prevalence of 25% of prediabetes in hypertensive patients and a prevalence of 14% for unreported diabetes. [24]

This study did not elucidate a significant difference in the mean BMI between the cases and the controls, however, almost two thirds of the study population was overweight/obese. This supports the report by Chukwuonye et al that obesity prevalence in Nigeria is on the rise. [27] The escalating prevalence of obesity has been linked to lifestyle changes such as consumption of high fat western diet common in most Nigerian cities and a reduction in physical activity. Increasing public awareness in this regard may have long term health impacts. Soltanian et al reported a similar finding of a high prevalence of overweight and obesity in first degree relatives. [28]

While the BMI is the most common anthropometric index used to measure total body fat, its use is limited by its inability to assess the presence of central obesity. [29] Therefore, anthropometric indices such as waist circumference which assesses central obesity has been recommended for use and it has been shown to have stronger association with visceral adiposity. [29] Central obesity was common in the female cases (72.1%) and controls (52.9%). The finding in this present study of a higher prevalence of central obesity in first degree relatives when compared to controls was reported by Adeleye et al. [30] The presence of central obesity in the cases significantly increases their cardiovascular risk.

Elevated total cholesterol, elevated LDL-c and a low HDL-c were the most common lipid profile parameters in both the cases and controls. The commonest lipid profile abnormality in the FDR's was low HDL-c which is similar to that reported by Ogedengbe et al [31] where a high prevalence of low HDL-c was reported in FDR's. The high prevalence of dyslipidaemia in the FDR's could be accounted for by the high prevalence of modifiable risk factors like obesity (both overall and central). The presence of hypertension, obesity and dyslipidaemia in the cases demonstrates a high cardiovascular risk in the cases and a holistic approach to their management is necessary to reduce cardiovascular mortality.

5. Conclusion

The global prevalence of prediabetes is on the increase and it has been established that prediabetes is a strong risk factor for diabetes and cardiovascular disease. The findings of this study illustrate the high frequency (23.9%) of prediabetes in first degree relatives of patients with type 2 diabetes compared to the controls (10%) who were FDRs of patients without a family history of diabetes mellitus. There should be emphasis in controlling other risk factors like hypertension, obesity (both central and overall) and dyslipidaemia which were common in first degree relatives with prediabetes in this study. Controlling these risk factors is crucial to minimize cardiovascular morbidity and mortality. Also, the high frequency of prediabetes in this study strongly supports the need for advocacy and education regarding the predisposition to develop type 2 diabetes in FDR's, together with regular screening with a goal to timely intervention to prevent, detect

and treat type 2 DM.

6. Limitations of the Study

1) As the study is cross-sectional, it is limited in its ability to elucidate causal relationships between prediabetes and risk factors.
2) A prospective study would have been useful to elucidate the incidence of incident diabetes in the FDRs.

Disclosure of Conflict of Interest

All the authors do not have any possible conflicts of interest.

Statement of Ethical Approval

Ethical approval was given by the University of Port Harcourt Teaching Hospital Ethical Committee (UPTH/ADM/90/S.II/VOL.X/332).

Statement of Informed Consent

Informed consent was obtained from all individual participants included in the study.

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