

Assessment of some Obesity and Diabetes type 2 markers and their association with fat-mass and obesity-associated gene (FTO) variants in some selected ethnic populations in Niger Delta, Nigeria

ABSTRACT

Aim: To assess the levels of some glycemic parameters and their association with fat-mass and obesity-associated gene (FTO) variants in some selected ethnic populations in Niger Delta, Nigeria

Study design: Case-controlled observational study

Place and Duration of Study: Federal Medical Centre, Asaba, Delta State and Safety Molecular Pathology Laboratory, Enugu, Nigeria, between March 2020 and February 2022.

Methodology: The association between sixteen (16) Single Nucleotide Polymorphisms in the FTO gene and some biomarkers of obesity and type 2 diabetes (fasting blood sugar, HbA1c, adiponectin, insulin, C-peptide, Homeostatic model assessment (HOMA) of β -cell function and insulin resistance (HOMA-IR) and body mass index) was studied in ninety-eight (98) type 2 diabetes (T2D) subjects (78 cases and 20 controls) from four different tribes in the Niger Delta region, Nigeria. Multistage sampling method was employed in the subject selection. The subjects were first separated into two groups – new cases (less than a year of diagnosis as Diabetic) and old cases (one year & above). Equal number of samples was then randomly collected from each of the cluster groups. 10mls of blood was collected into EDTA and plain bottles for the assay of the above-named markers, and were assayed using spectrophotometric and ELISA methods. The data were analyzed using GraphPad Prism, version 8.0.2 and p values less than .05 were considered statistically significant.

Results: Significant association between rs9939609 variant genotype (A) allele of FTO gene with BMI ($p < .01$), HOMA-IR ($p < .01$), and Insulin ($p < .01$) were observed in obese subjects, but only BMI ($p < .01$) with obese and T2D subjects combined. The results also found a moderate to strong correlation between variants rs201041270 (GA/AA) with adiponectin ($p < .05$) and with Insulin ($p < .05$), rs531215275 (CA/AA), mild with C-peptide $p < .05$, rs1410999299 (AG/GG) with C-peptide ($p < .05$), rs145884431 (GA/GG) with HbA1c ($p < .05$), rs146138389 (CT/CC) with insulin ($p < .05$) and rs886052102 (AG/AA) with FBS ($p < .05$) and strongly with HbA1c ($p < .01$).

Conclusion: Knowledge of the dominant SNPs that are consistent with some specific biomarkers in some ethnic groups, may provide platform for prevention of its expression through informed wise choice of lifestyle change and proper dieting.

Keywords: Diabetes type 2, obesity, Fat-mass and obesity-associated gene (FTO), Glycemic markers, FTO gene variants, Niger Delta, Nigeria

1. INTRODUCTION

Obesity and type 2 diabetes (T2D) are complex disorders that present a major public health problem worldwide. Thus, there is an urgent need to identify the risk factors for obesity and T2D, as their prevalence continues to increase in many countries [1]. Studies in Nigeria had reported a higher rate of obesity and cardiovascular risk factors [2]. Thus, Nigeria is not exempted from the scourge. Obesity is defined as a metabolic disorder caused by a hypercaloric diet and/or malnutrition that results in increased accumulation of abnormal body fat and raises the risk of many chronic diseases, including T2D, cardiovascular disease, and cancer [3]. Obesity is a multifactorial condition, determined by environmental and genetic factors, and is a facilitator of several other diseases [4]. Obesity is a complex disorder involving a host of heritable and

behavioral features and it is a major risk factor for type 2 diabetes (T2D). Significant epidemic of obesity and T2D currently represents a major public health problem both in China and worldwide. Approximately 58% of T2D globally can be attributed to overweight and obesity [5]. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes as it accounts for more than 90% of all diabetes cases worldwide [6].

Numerous studies have reported that polymorphisms within the fat-mass and obesity-associated gene (FTO) are strongly associated with obesity [7,8] and obesity is a major risk factor for type 2 diabetes (T2D) [9]. A study by Oyeyemi et al. [10] suggests that environmental/lifestyle factors like physical activity, time spent sitting, and energy intake might be substantial modulator and/or mediator in the association between FTO rs9939609 and BMI in Nigeria. Regarding the FTO variants-T2D association, while several studies have reported that the association between the variants and risk of T2D remained significant after adjustment for BMI, a surrogate measure of obesity, others could not confirm this finding [5]. In many studies examining this issue, the BMI measured at the time of enrolment, i.e., current BMI, which was obtained long time after the diagnosis of T2D, was used for the analyses [9]. Great advances have recently occurred in our understanding of the genetics of T2D, but much remains to be learned about the disease etiology. More than 40 loci associated with T2D or glycemic traits have been reported and reproduced, only a minor part of the genetic component of the disease has been explained, and the causative variants and affected genes are unknown for many of the loci [11]. Several studies have demonstrated that polymorphisms within the fat-mass and obesity associated gene (FTO) are associated with type 2 diabetes (T2D). However, whether the effects of the FTO locus on T2D susceptibility are independent of fat-mass increases remains controversial [12]. Common variants of the FTO (fat mass and obesity associated) gene have been found to be strongly associated with BMI, obesity and type 2 diabetes in white European adults and children [13] the association with type 2 diabetes was entirely explained by the association with BMI. The association of FTO variants with type 2 diabetes and BMI has been independently identified in several white European populations (Dina *et al.* 2007) but the findings are somewhat inconsistent in Asians, which may be the result of varying study designs, inadequate sample sizes or ethnic differences [14].

HbA1c is the most commonly used biomarker to diagnose prediabetes and diabetes. It forms when glucose attaches to the amino-terminal group of the β subunit of haemoglobin. HbA1c reflects chronic glycaemia rather than glucose levels at a single time point. Currently, the ADA criteria for diabetes are HbA1c $\geq 6.5\%$ (48 mmol/mol) and 5.7–6.4% (39–46 mmol/mol) for prediabetes [15]. Increased HbA1c levels are associated with increased morbidity and mortality. In the Norfolk prospective study, higher HbA1c levels were also associated with increased CVD, cancer, and all-cause mortality [16]. Adiponectin, derived from adipose tissue, exhibits insulin sensitizing, anti-inflammatory, and anti-atherogenic properties and is an independent predictor of diabetes [17]. Lower levels of adiponectin are associated with increased IR and obesity, while higher levels have been related to lifestyle intervention groups in diabetes prevention trials [17]. The association of adiponectin with diabetes risk appears to be evident at a much earlier stage in the progression to diabetes; more specifically, lower adiponectin levels were observed a decade before diabetes was diagnosed, particularly in men [17]. The connecting peptide, or C-peptide, is a short 31-amino-acid polypeptide that connects insulin's A-chain to its B-chain in the proinsulin molecule. C-peptide is the part of proinsulin which is cleaved prior to co-secretion with insulin from pancreatic beta cells. C-peptide is a widely used measure of pancreatic beta cell function. It is produced in equimolar amounts to endogenous insulin but is excreted at a more constant rate over a longer time [18]. C-peptide testing is preferable to insulin as a guide to beta cell function. This is because, the degradation rate of c-peptide in the body is slower than that of insulin (half-life of 20–30 min, compared with the half-life of insulin of just 3–5 min), which affords a more stable test window of fluctuating beta cell response.

Homeostatic model assessment (HOMA) of β -cell function and insulin resistance (IR) was first described in 1985 [19]. The technique is a method for assessing β -cell function and IR from basal glucose and insulin or C-peptide concentrations. The HOMA model is used to yield an estimate of insulin sensitivity and β -cell function from fasting plasma insulin and glucose concentrations [19]. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β -cells [20]. The predictions used in the model arise from experimental data in humans and animals. C-peptide, a measure of insulin secretion, can be used in HOMA modeling of both β -cell function and IR. C-peptide is a robust measure of insulin secretion but not of insulin action, and the concept of the model is that insulin sensitivity (%S) is a function of glucose

metabolism driven by the action of insulin [20]. The use of two assays, C-peptide and insulin, to determine β -cell function and insulin sensitivity, respectively, reduces bias. The aim of this study was to assess the levels of some glycemic parameters and their association with fat-mass and obesity-associated gene (FTO) variants in some selected ethnic populations in Niger Delta, Nigeria.

2. MATERIALS AND METHODS

2.1 Study Area

The study was carried out in Niger Delta region of Nigeria, with Federal Medical Centre, Asaba serving as the major point of the sample collection and some analysis. Some samples were also collected at Agbor & Bomadi. The Igbo participants were drawn from the Igbos of Delta State, Rivers State and Imo State; the Ijaw participants were drawn from the Ijaws of Delta State, Bayelsa State and Rivers State.

The Niger Delta was once known as the Oil Rivers, Nigeria's Niger Delta region is a very densely populated region, a major palm oil producer. After its expansion, it became the Niger Coast Protectorate. Stretching directly on the Gulf of Guinea on the Atlantic Ocean in Nigeria, the Niger Delta used to be historically made up of present-day Bayelsa, Rivers, and Delta states are today, made up of nine coastal states. The federal government of Nigeria's current definition states that the delta extends over about seventy thousand km² and makes up almost 7 percent of its landmass. The Niger Delta comprises of level low lying muggy landscape that is befuddled by wandering and anastomosing streams, waterways and brooks [21].

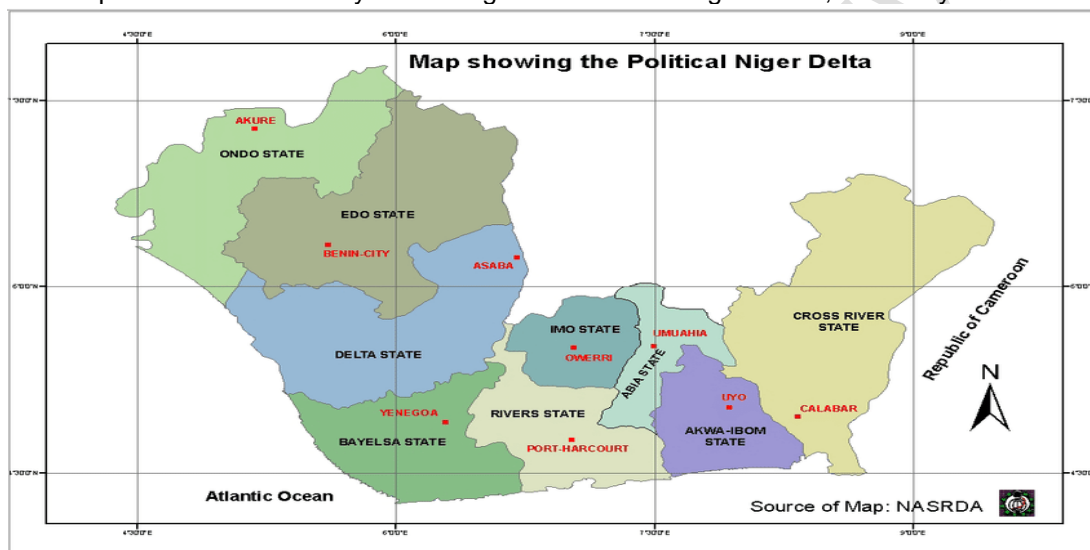


Figure 1: Political Map of the Niger Delta Area.

Asaba, the capital city of Delta State, Nigeria is situated within geographical co-ordinates 6°11'52.23"N 6°43'42.48"E. It is situated on a terrace of the lower Niger River, overlooking the point where the Anambra River flows into it. Beyond the river banks, on the high plains which are far more extensive than the river basins, secondary forest vegetation flourishes.

3.2 Research Design

This is a case-controlled observational study involving the association between FTO gene allele variants and HbA1c, Fasting blood sugar, Insulin, C-Peptides, Adiponectin and HOMA-IR in obese/T2D subjects from selected ethnic groups in Niger Delta, Nigeria. The bio-data and medical history of the subjects was obtained using questionnaire, measuring their weight with a calibrated weighing scale, height and waist circumference.

2.2 Sample Size

A total of 98 subjects enrolled for this study.

98 samples.

$$N = \frac{Z^2 pq}{d^2} \quad (\text{Cochrane, 1977})$$

N = The desired sample size

Z = The Standard Normal deviate usually set at 1.962 corresponding to the 95% Confidence level

p = The SNPs Prevalence rates. (Minor Alleles Frequency of SNPs set at >0.02) [22].

q = 1- p

d = degree of accuracy desired set at 0.05

Minimum Size – 30

By adding 10% of non-respondent = 33

2.3 Sampling Method

Multistage sampling method was employed in the subject selection. The subjects were first separated into two groups – new cases (less than a year of diagnosis as Diabetic) and old cases (one year & above). Equal number of samples was then randomly collected from each of the cluster groups.

2.4 Selection Criteria

2.4.1 Inclusion Criteria

Individuals who are purebred of the selected tribes in Niger Delta, aged at least 21 years diagnosed with T2D for at least one year. Controls: Individuals who are from the selected tribes with no history of diabetes, and a fasting blood glucose of less than 6.5mmol/l. The cluster groups were considered also.

2.4.1 Exclusion Criteria

Individuals not of the selected tribes, those who are not purebred from the selected tribes, those who are critically ill subjects and female participants who are pregnancy.

2.5 Sample Collection and Analysis

2.5.1 Sample Collection

Ten millilitres (10ml) of blood were randomly collected from 19-20 subjects from each of the selected tribes following the sampling methodology described earlier and 20 control made of 5 non-diabetic, non-obese subjects from each of the selected tribes. This was after completing the questionnaire and signing the consent form. Their body weight in kilogram, height in meter and waist circumference in centimeter was also measured and recorded. Order of dispensing and volume of the blood sample: 4.0ml into vacutainer type plain tubes, 4.0ml into vacutainer type EDTA K₃ (1st Tube) & 2.0ml into vacutainer type EDTA K₃ (2nd Tube). All the tubes were appropriately labelled. The sample in the plain tube was allowed to retract, then centrifuged at 3000rpm. The serum was separated into two cryotubes (one for ELISA assays- Adiponectin, Insulin, C-Peptide), labelled and stored at -15^oC to -20^oC. The second EDTA tube for Glycated haemoglobin was stored at 2-8^oC and analysis done within two days of sample collection. The fasting blood sugar was performed immediately.

2.5.2 Sample Analysis

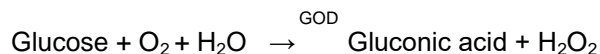
2.5.2.1 Fasting Blood Glucose (FBG)

FBS was performed using glucose oxidase method with kit from Randox Laboratories, UK.

Principle

Glucose is determined after enzymatic oxidation in the presence of glucose oxidase. The hydrogen peroxide formed reacts, under catalysis of peroxidases, with phenol and 4-aminophenazone to form a red-violet quinoneimine dye as indicator.

Reaction Principle



2.5.2.2 Glycosylated Haemoglobin (HbA1c)

Quantitative determination of glycosylated Haemoglobin in blood was done using the modified Ion Exchange Resin method with kit from INTECO Diagnostics, UK

Principle

The percent glycosylated Haemoglobin is determined by measuring the absorbance of the ratio of the glycosylated Haemoglobin and the total Haemoglobin fraction [23].

2.5.2.3 Serum Insulin (Bio-Inteco ELISA Kit)

ELISA method was used to assay for Insulin

Principle

The Insulin quantitative test is based on a solid phase enzyme-linked immunosorbent assay. The system utilizes one insulin antibody for solid phase (microtiter wells) immobilization and another anti-insulin antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution.

2.5.2.3 Serum C-Peptide (Bio-Inteco ELISA Kit)

ELISA method was used to assay for C-peptide

Principle

The C-Peptide quantitative test kit is based on a solid phase enzyme-linked immunosorbent assay

2.5.2.3 Adiponectin (Bioassay ELISA Kit)

ELISA method was used to assay for Adiponectin

Principle

The plate has been pre-coated with human adiponectin antibody. Adiponectin present in the sample is added and binds to antibodies coated on the wells. And then biotinylated human adiponectin antibody is added and binds to adiponectin in the sample. Then Streptavidin-Horseradish Peroxidase is added and binds to the Biotinylated Adiponectin antibody. After incubation unbound Streptavidin-Horseradish Peroxidase is washed away during a wash step. Substrate solution is then added and colour develops in proportion to the amount of human Adiponectin. This reaction is terminated by addition of acidic stop solution and absorbance is measured at 450nm.

2.5.2.4 Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

HOMA-IR index was calculated by using following formula: Fasting Insulin (mU/L) × Fasting Glucose (mmol/L)/22.5 [19].

Healthy Range; 0.5 – 1.4

2.6 Statistical Analysis

The data were analyzed using GraphPad Prism, version 8.0.2, (California, USA). Quantitative variables were expressed as Mean (X) ± standard deviation (SD). One-Way Analysis of Variance (ANOVA) and students' statistical t-test were the inferential statistics used to observe the differences mean values, while Tukey's Post Hoc analysis was also done to observe the differences within different sub-classes. Statistical significance was set at $p < 0.05$.

3. RESULTS AND DISCUSSION

Table 1: One-Way ANOVA Results of Mean±SD of Fasting Blood Sugar, Insulin Resistance and Related Biochemical Parameters of Subjects of Niger Delta Tribes with FTO gene variations

Parameters	Ijaw	Urhobo	Ika	Igbo	Control	Fvalue	pvalue	Remark
FBS (mmol/L)	9.05 ± 3.15 ^a	7.67 ± 3.45 ^a	7.03± 3.20 ^a	9.05 ± 3.04 ^a	4.92 ± 0.66 ^b	7.037	<0.0001	S
HbA1c (%)	9.02 ± 1.44 ^a	8.03 ± 1.75 ^{ac}	8.96± 1.49 ^a	10.08±2.05 ^{ad}	6.57 ± 0.99 ^b	13.77	<0.0001	S
Adiponectin (mg/L)	6.11 ± 2.15	5.43 ± 1.73	5.72 ± 1.32	7.46 ± 1.85	10.30 ± 2.72	0.948	0.4399	NS
Insulin (uIU/ml)	6.19 ± 5.0 ^a	17.66±4.79 ^{bc}	14.92±8.93 ^{bc}	15.60±7.21 ^{bc}	8.96 ± 5.06 ^{ad}	11.46	<0.0001	S
C-Peptide ng/ml	1.06 ± 0.87	0.88 ± 0.74	1.41 ± 1.72	1.08 ± 0.75	0.89 ± 0.56	0.918	0.4564	NS
HOMA-IR	2.56 ± 3.07 ^a	5.96 ± 2.95 ^{bc}	4.66 ± 3.87 ^{ac}	5.17 ± 1.99 ^{bc}	1.97 ± 1.09 ^{ad}	7.719	<0.0001	S
BMI	24.25 ±4.48 ^a	30.25 ± 6.67 ^b	30.28± 5.89 ^b	27.77 ± 5.05 ^a	28.27± 5.31 ^a	3.969	0.0051	S

PostHoc (Tukey's):

Within same row, values with different superscripts (a, b), (c, d) differ significantly when various tribes were compared against each other. S=Significant, NS=Not Significant At p<0.05.

Abbreviations: BMI=Body Mass Index, FBS=Fasting Blood Sugar, HbA1c= Glycated Haemoglobin, HOMA-IR=Insulin Resistance

Table 2: Comparative Results of Mean \pm SD of Fasting Blood Sugar, Insulin Resistance and Related Biochemical Parameters of Subjects of Niger Delta Tribes with FTO gene Variations on Special Diet

Parameters	No special diet	Special diet	T value	P value	Remark
FBS (mmol/L)	8.46 \pm 3.63	7.87 \pm 2.84	0.800	0.426	NS
HbA1c (%)	8.94 \pm 1.79	9.119 \pm 1.891	0.431	0.667	NS
Adiponectin(mg/L)	5.56 \pm 7.06	6.94 \pm 10.78	0.690	0.491	NS
Insulin (uIU/ml)	13.13 \pm 6.979	14.15 \pm 9.02	0.572	0.568	NS
C-Peptide ng/ml	1.05 \pm 0.95	1.19 \pm 1.07	0.558	0.578	NS
HOMA-IR	4.95 \pm 3.95	4.14 \pm 2.04	1.120	0.266	NS
BMI	28.46 \pm 6.67	27.73 \pm 5.17	0.539	0.590	NS

S=Significant, NS=Not Significant At $p < 0.05$.

Abbreviations: BMI=Body Mass Index, FBS=Fasting Blood Sugar, HbA1c= Glycated Haemoglobin, HOMA-IR=Insulin Resistance

Table 3: Association of FTO rs73609956 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameters	TT	TA/AA	GLR, P value	PC, p value	T-test, p value
FBS (mmol/L)	8.16 \pm 3.34	8.93 \pm 1.69	0.6877	0.6877	0.6957
HbA1c (%)	9.03 \pm 1.85	8.73 \pm 1.33	0.3831	0.3831	0.7833
Adiponectin(mg/L)	6.32 \pm 9.04	2.77 \pm 0.45	0.6154	0.6154	0.5013
Insulin (uIU/ml)	13.72 \pm 7.93	10.37 \pm 8.72	0.3353	0.3353	0.4762
C-Peptide ng/ml	1.09 \pm 1.10	1.53 \pm 1.00	0.2601	0.2601	0.4973
HOMA-IR	4.59 \pm 3.24	4.33 \pm 4.15	0.4044	0.4044	0.8911
BMI	28.18 \pm 6.00	27.00 \pm 7.65	0.2073	0.2073	0.7416

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, $p @ < 0.05$. T= Wild (Dominant), A=Polymorphic.

Table 4: Association of FTO rs116753298 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	CC	CT/TT	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.24 \pm 3.34	6.56 \pm 1.54	0.6416	0.6416	0.2683
HbA1c (%)	9.06 \pm 1.83	8.82 \pm 1.99	0.7034	0.7034	0.7792
Adiponectin(mg/L)	6.40 \pm 9.22	3.46 \pm 0.537	0.9084	0.9084	0.4802
Insulin (uIU/ml)	13.69 \pm 7.90	11.72 \pm 9.76	0.7036	0.7036	0.5969
C-Peptide ng/ml	1.13 \pm 1.11	1.01 \pm 1.00	0.5305	0.5305	0.8043
HOMA-IR	4.63 \pm 3.27	3.08 \pm 2.41	0.7816	0.7816	0.3017
BMI	28.46 \pm 5.96	25.06 \pm 5.70	0.4830	0.4830	0.2195

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, $p @ < 0.05$. C= Wild (Dominant), T=Polymorphic.

Table 5: Association of FTO rs201041270 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	GG	GA/AA	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.16 \pm 3.32	8.57 \pm 3.16	0.9356	0.9356	0.7768
HbA1c (%)	8.98 \pm 1.85	9.43 \pm 1.45	0.5156	0.5156	0.5699
Adiponectin(mg/L)	6.31 \pm 4.12	4.55 \pm 2.67	0.0198	0.0198	0.6432
Insulin (uIU/ml)	13.58 \pm 8.01	13.72 \pm 7.32	0.0464	0.0464	0.9678
C-Peptide ng/ml	1.12 \pm 1.11	0.95 \pm 0.90	0.0034	0.0034	0.7146
HOMA-IR	4.57 \pm 3.29	4.80 \pm 2.91	0.2005	0.2005	0.8688
BMI	28.28 \pm 6.12	26.35 \pm 4.44	0.0943	0.0943	0.4536

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, $p @ < 0.05$. G= Wild (Dominant), A=Polymorphic.

Table 6: Association of FTO rs531215275 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	CC	CA/AA	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.29 ± 3.36	7.21 ± 2.52	0.9747	0.9747	0.4129
HbA1c (%)	8.99 ± 1.83	9.27 ± 1.91	0.8983	0.8983	0.7237
Adiponectin(mg/L)	6.30 ± 5.20	4.88 ± 3.90	0.2171	0.2171	0.6891
Insulin (uIU/ml)	13.58 ± 7.97	13.64 ± 7.98	0.2718	0.2718	0.9854
C-Peptide ng/ml	1.03 ± 1.01	1.93 ± 1.62	0.6985	0.6985	0.0374
HOMA-IR	4.64 ± 3.34	3.97 ± 1.92	0.0502	0.0502	0.6023
BMI	27.98 ± 6.12	29.71 ± 4.87	0.4372	0.4372	0.4703

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. C= Wild (Dominant), A=Polymorphic.

Table 7: Association of FTO rs146056278 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	TT	TC/CC	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.17 ± 3.32	8.95 ± 2.61	TFP	TFP	0.7456
HbA1c (%)	9.01 ± 1.82	9.60 ± 2.82	TFP	TFP	0.6537
Adiponectin(mg/L)	6.27 ± 8.99	2.75 ± 0.63	TFP	TFP	0.5838
Insulin (uIU/ml)	13.45 ± 7.97	18.90 ± 1.41	TFP	TFP	0.3404
C-Peptide ng/ml	1.09 ± 1.09	1.50 ± 1.56	TFP	TFP	0.6121
HOMA-IR	4.51 ± 3.25	7.45 ± 1.63	TFP	TFP	0.2087
BMI	28.17 ± 6.09	26.75 ± 0.78	TFP	TFP	0.7441

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. C= Wild (Dominant), A=Polymorphic. TFP=Too few pairs available for analysis

Table 8: Association of FTO rs1410999299 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameters	AA	AG/GG	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.21 ± 3.35	7.92 ± 2.59	0.5280	0.5280	0.8480
HbA1c (%)	9.09 ± 1.83	8.02 ± 1.70	0.7144	0.7144	0.2088
Adiponectin(mg/L)	6.37 ± 5.15	3.38 ± 1.28	0.7367	0.7367	0.4704
Insulin (uIU/ml)	13.63 ± 7.9	12.96 ± 8.33	0.1962	0.1962	0.8557
C-Peptide ng/ml	1.12 ± 1.10	0.92 ± 1.02	0.0360	0.0360	0.6934
HOMA-IR	4.60 ± 3.28	4.36 ± 3.03	0.2214	0.2214	0.8726
BMI	28.33 ± 6.08	25.16 ± 4.35	0.2256	0.2256	0.2562

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. A= Wild (Dominant), G=Polymorphic.

Table 9: Association of FTO rs79206939 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameters	GG	AG/AA	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.17 ± 3.32	8.62 ± 2.99	0.9794	0.9794	0.7915
HbA1c (%)	9.01 ± 1.86	9.22 ± 1.25	0.5349	0.5349	0.8211
Adiponectin(mg/L)	6.37 ± 9.09	2.67 ± 0.49	0.1119	0.1119	0.4220
Insulin (uIU/ml)	13.64 ± 7.95	12.68 ± 8.50	0.2789	0.2789	0.8144
C-Peptide (ng/ml)	1.10 ± 1.10	1.27 ± 1.04	0.9197	0.9197	0.7577
HOMA-IR	4.60 ± 3.27	4.35 ± 2.95	0.4687	0.4687	0.8818

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. G= Wild (Dominant), A=Polymorphic.

Table 10: Association of FTO rs145884431 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	AA	GA/GG	GLR, P value	PC, p value	t-test, p value
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FBS (mmol/L)	8.12 ± 3.17	8.92 ± 4.66	0.8147	0.8147	0.5418
HbA1c (%)	8.989 ± 1.859	9.35 ± 1.59	0.0117	0.0117	0.6146
Adiponectin(mg/L)	6.48 ± 4.26	3.05 ± 0.72	0.5419	0.5419	0.3337
Insulin (uIU/ml)	13.47 ± 7.93	14.80 ± 8.27	0.4525	0.4525	0.6751
C-Peptide ng/ml	1.12 ± 1.12	1.01 ± 0.82	0.8606	0.8606	0.8130
HOMA-IR	4.64 ± 3.37	4.01 ± 1.40	0.3465	0.3465	0.6278
BMI	28.35 ± 6.10	25.90 ± 4.83	0.9480	0.9480	0.3067

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. A= Wild (Dominant), G=Polymorphic.

Table 11a: Association of FTO rs61743972 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameters	AA	GA/GG	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.27 ± 3.32	6.98 ± 2.77	0.1159	0.1159	0.3977
HbA1c (%)	9.01 ± 1.86	9.08 ± 1.26	0.8689	0.8689	0.9415
Adiponectin (mg/L)	6.39 ± 4.15	2.94 ± 0.26	0.4790	0.4790	0.4034
Insulin (uIU/ml)	13.29 ± 7.47	18.08 ± 13.44	0.3931	0.3931	0.1925
C-Peptide ng/ml	1.14 ± 1.11	0.58 ± 0.44	0.6987	0.6987	0.2677
HOMA-IR	4.58 ± 3.31	4.580 ± 2.183	0.3139	0.3139	0.9958
BMI	28.07 ± 6.11	29.12 ± 4.75	0.5710	0.5710	0.7075

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. A= Wild (Dominant), G=Polymorphic.

Table 11b: Association of FTO rs2014496428 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	TT	CT/CC	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.27 ± 3.23	7.23 ± 4.21	0.5465	0.5465	0.4605
HbA1c (%)	9.08 ± 1.84	8.21 ± 1.58	0.7557	0.7557	0.2658
Adiponectin(mg/L)	6.26 ± 4.14	5.11 ± 3.34	0.9163	0.9163	0.7624
Insulin (uIU/ml)	12.97 ± 7.37	21.25 ± 11.0	0.1275	0.1275	0.0129
C-Peptide ng/ml	1.13 ± 1.11	0.83 ± 0.92	0.5643	0.5643	0.5254
HOMA-IR	4.45 ± 3.14	6.21 ± 4.32	0.9375	0.9375	0.2032
BMI	28.22 ± 6.18	27.03 ± 3.43	0.7618	0.7618	0.6442

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. T= Wild (Dominant), C=Polymorphic.

Table 11c: Association of FTO rs146138389 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameters	TT	CT/CC	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.22 ± 3.28	7.62 ± 4.11	0.6989	0.6989	0.7246
HbA1c (%)	9.09 ± 1.81	7.62 ± 1.74	0.8315	0.8315	0.1183
Adiponectin(mg/L)	6.35 ± 4.09	2.97 ± 0.55	0.0665	0.0665	0.4629
Insulin (uIU/ml)	13.16 ± 7.43	21.78 ± 13.3	0.8933	0.8933	0.0332
C-Peptide ng/ml	1.13 ± 1.10	1.23 ± 1.09	0.7707	0.7707	0.8292
HOMA-IR	4.51 ± 3.27	6.05 ± 2.46	0.5672	0.5672	0.3586
BMI	28.18 ± 6.05	27.18 ± 5.98	0.2558	0.2558	0.7459

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. T= Wild (Dominant), C=Polymorphic.

Table 12: Association of FTO rs886052102 variant glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameters	GG	AG/AA	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.19 ± 3.33	12.88 ± 9.36	0.4705	0.4705	0.0171

HbA1c (%)	9.00 ± 1.86	9.53 ± 0.66	0.0054	0.0054	0.6246
Adiponectin(mg/L)	6.31 ± 5.20	4.88 ± 4.09	0.3144	0.3144	0.8210
Insulin (uIU/ml)	13.48 ± 8.07	13.83 ± 7.64	0.3656	0.3656	0.9411
C-Peptide ng/ml	1.13 ± 1.10	0.50 ± 0.43	0.5935	0.5935	0.3298
HOMA-IR	4.58 ± 3.29	4.67 ± 2.08	0.1779	0.1779	0.9660
BMI	28.14 ± 6.10	28.03 ± 3.53	0.4078	0.4078	0.9767

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. G= Wild (Dominant), A=Polymorphic.

Table 13: Association of FTO rs14474317 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	AA	GA/GG	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.12 ± 3.17	9.57 ± 5.63	0.8129	0.8129	0.3943
HbA1c (%)	8.97 ± 1.82	10.05 ± 1.89	0.3839	0.3839	0.2516
Adiponectin(mg/L)	6.13 ± 5.04	7.15 ± 5.98	0.3144	0.3144	0.8250
Insulin (uIU/ml)	13.56 ± 7.93	14.08 ± 8.92	0.4732	0.4732	0.9010
C-Peptide ng/ml	1.14 ± 1.11	1.00 ± 0.87	0.3148	0.3148	0.8401
HOMA-IR	4.47 ± 2.91	6.87 ± 7.61	0.8315	0.8315	0.1494
BMI	28.38 ± 6.04	23.38 ± 2.78	0.1357	0.1357	0.1049

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. G= Wild (Dominant), A=Polymorphic.

Table 14: Association of FTO rs886052103 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	TT	CT/CC	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.16 ± 3.34	8.93 ± 1.69	0.6877	0.6877	0.6957
HbA1c (%)	9.03 ± 1.85	8.73 ± 1.33	0.3831	0.3831	0.7833
Adiponectin(mg/L)	6.33 ± 4.043	2.77 ± 0.45	0.6154	0.6154	0.5013
Insulin (uIU/ml)	13.72 ± 7.92	10.37 ± 8.72	0.3353	0.3353	0.4762
C-Peptide ng/ml	1.09 ± 1.01	1.53 ± 1.00	0.2601	0.2601	0.4973
HOMA-IR	4.597 ± 3.24	4.33 ± 4.15	0.4044	0.4044	0.8911
BMI	28.18 ± 6.00	27.00 ± 7.65	0.2073	0.2073	0.7416

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. T= Wild (Dominant), C=Polymorphic.

Table 15: Association of FTO rs8050136 variant with glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	CC	AC/AA	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.05 ± 3.22	8.84 ± 3.66	0.8330	0.8330	0.4227
HbA1c (%)	8.92 ± 1.89	9.47 ± 1.45	0.5257	0.5257	0.3143
Adiponectin(mg/L)	6.79 ± 4.67	3.27 ± 1.36	0.4334	0.4334	0.1803
Insulin (uIU/ml)	13.63 ± 7.97	13.39 ± 7.98	0.7729	0.7729	0.9162
C-Peptide (ng/ml)	1.09 ± 1.12	1.18 ± 0.98	0.3132	0.3132	0.7743
HOMA-IR	4.43 ± 2.78	5.32 ± 4.95	0.9604	0.9604	0.3550
BMI	27.60 ± 5.81	30.65 ± 6.53	0.1581	0.1581	0.0849

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. C= Wild (Dominant), A=Polymorphic.

Table 16: Association of FTO rs9939609 variant glycemic parameters of Obese|T2D in Niger Delta tribes using Dominant Model

Parameter	TT	AT/AA	GLR, P value	PC, p value	t-test, p value
FBS (mmol/L)	8.42 ± 3.20	7.353 ± 3.595	0.4002	0.4002	0.2371
HbA1c (%)	9.11 ± 1.94	8.68 ± 1.33	0.4110	0.4110	0.4016
Adiponectin(mg/L)	5.79 ± 7.74	7.60 ± 12.48	0.9864	0.9864	0.4607

Insulin (uIU/ml)	13.34 ± 8.12	14.50 ± 7.30	0.9125	0.9125	0.5968
C-Peptide ng/ml	1.07 ± 1.01	1.24 ± 1.09	0.4138	0.4138	0.5777
HOMA-IR	4.54 ± 3.13	4.74 ± 3.74	0.8588	0.8588	0.8275
BMI	26.62 ± 5.03	33.74 ± 6.16	0.0010	0.0010	<0.0001

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. T= Wild (Dominant), A=Polymorphic.

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Table 17: Association of FTO rs9939609 variant with glycemic parameters of Obese in Niger Delta tribes using Dominant Model

Parameters	TT (Obese)	TA/AA (Obese)	GLR, P value	PC, p value	T-test, p value
FBS (mmol/L)	8.17 ± 2.93	6.98 ± 3.42	0.0695	0.0695	0.2740
HbA1c (%)	8.83 ± 1.81	8.88 ± 1.38	0.4010	0.4010	0.9355
Adiponectin(mg/L)	6.05 ± 4.64	8.78 ± 4.15	0.4851	0.4851	0.4272
Insulin (uIU/ml)	12.22 ± 6.30	16.42 ± 5.73	0.0031	0.0031	0.0541
C-Peptide (ng/ml)	1.36 ± 1.47	1.27 ± 1.05	0.5141	0.5141	0.8483
HOMA-IR	4.28 ± 2.92	4.93 ± 2.59	0.0199	0.0199	0.5084
BMI	30.30 ± 5.50	36.22 ± 4.67	0.3666	0.3666	0.0023

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. T= Wild (Dominant), A=Polymorphic.

Table 18: Association of FTO rs531215275 variant with glycemic parameters of Obese in Niger Delta tribes using Dominant Model

Parameters	CC (Obese)	CA/AA (Obese)	GLR, P value	PC, p value	T-test, p value
FBS (mmol/L)	7.49 ± 2.88	6.63 ± 2.01	0.4903	0.4903	0.6265
HbA1c (%)	8.68 ± 1.55	9.07 ± 0.66	0.1836	0.1836	0.7061
Adiponectin(mg/L)	7.872 ± 13.96	3.13 ± 0.25	0.2682	0.2682	0.4664
Insulin (uIU/ml)	14.99 ± 5.480	16.23 ± 7.75	0.1846	0.1846	0.7196
C-Peptide (ng/ml)	1.23 ± 1.31	2.80 ± 1.80	0.4423	0.4423	0.0673
HOMA-IR	5.02 ± 2.89	4.50 ± 1.71	0.9354	0.9354	0.7625
BMI	33.71 ± 4.95	34.53 ± 1.43	0.3480	0.3480	0.7795

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. C= Wild (Dominant), A=Polymorphic.

Table 19: Association of FTO rs8050136 variant with glycemic parameters of Obese in Niger Delta tribes using Dominant Model

Parameters	CC (Obese)	CA/AA (Obese)	GLR, p value	PC, p value	T-test, p value
FBS (mmol/L)	7.388 ± 3.01	7.17 ± 2.01	0.6345	0.6345	0.8597
HbA1c (%)	8.48 ± 1.73	9.13 ± 1.53	0.3552	0.3552	0.3787
Adiponectin(mg/L)	8.54 ± 11.41	3.03 ± 0.80	0.4967	0.4967	0.2160
Insulin (uIU/ml)	14.93 ± 4.96	14.53 ± 7.9	0.5807	0.5807	0.8673
C-Peptide ng/ml	1.34 ± 1.45	1.500 ± 1.22	0.5770	0.5770	0.7849
HOMA-IR	5.01 ± 3.06	4.08 ± 1.33	0.6076	0.6076	0.4448
BMI	33.11 ± 4.44	35.57 ± 5.74	0.3784	0.3784	0.2299

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. C= Wild (Dominant), A=Polymorphic.

This study (Table 1) observed a significant difference in the values obtained between the control and case in all the tribes in the FBS ($p < .01$), HbA1c ($p < .01$), Insulin ($p < .01$), HOMA-IR ($p < .01$) and BMI ($p < .01$), but none in Adiponectin ($p > .05$) and C-Peptide ($p > .05$). There were no differences between the FBS of the cases in the different tribes, but there was a difference in the HbA1c between the Urhobor/Isoko group and those of the Igbo group. This difference may not be unconnected to issue of management, as HbA1c measures blood glucose over a period of three months and is a better marker for monitoring treatment.

HbA1c reflects chronic exposure to glucose, it is particularly useful for lifestyle modification counselling [24]. Also, there were differences between the Ijaw tribe (lower values) and the others in terms of HOMA-IR (Table 1). This suggests there could be a lower risk of insulin resistance with the Ijaw diabetics than the other tribes. The Urhobo/Isoko showed higher levels of insulin resistance. HOMA-IR analysis allowed assessment of inherent B-cell function and insulin sensitivity and could characterize the pathophysiology in those with abnormal glucose tolerance [20]. A higher BMI values was observed among the Urhobo/Isoko and Ika group suggesting a higher prevalence of obesity (Table 1). Energy balance due to type of food consumption and physical activity may play a role here. Obesity is the result of a positive energy balance, whereby energy intake exceeds expenditure, resulting in the storage of energy, primarily as lipids in white adipocytes. Energy balance is modulated by food consumption and physical activity [25]. The World Health Organization (WHO) defines overweight as a body mass index of $>25\text{kg/m}^2$ and obesity as BMI of $>30\text{kg/m}^2$ the WHO has reported that, globally, overweight and obesity represent the fifth leading risk for death; furthermore, 44% of the Diabetes burden 23% of the ischemic heart disease burden, and 7-41% of certain cancer burdens are related to overweight and obesity [26]. Obesity is a major risk factor for type 2 diabetes [5] and an independent risk factor for diabetes and either BMI or waist-to-hip has been commonly used as a surrogate measures of adiposity [12,27]. The pattern seen with C-Peptide is not unexpected as C-Peptide is a useful tool in the classification and differentiation of diabetes into type 1, type 2 and MODY. It is also associated with duration of disease as well as age of diagnosis [28].

This work found a significant correlation between rs9939609 variant genotype of FTO gene with metabolic traits indices in obese against non-obese (Tables 16 and 17) by the attendant increases in BMI ($p<.01$), HOMA-IR ($p<.05$), and Insulin ($p<.01$) values with the carriers of the risk allele (A) in the obese subjects, but more strongly and only with BMI ($p<.01$) for with obese and T2D subjects combined (Table 16). This may be suggesting that the effect of rs9939609 with T2D in Niger Delta population could be obesity mediated and not independently. This is in line with the findings among African-American in the ARIC Study conducted by Chauhan et al. [29] in north Indian population and by Yang et al. [30] in a multiple population involving East Asia, South Asia, North America and North African, but concurrent and independent association with both obesity and T2D was observed by Yajnik et al. 2008 in South Asian Indians, Li et al. [14] in South Asia and Sabarneh et al. [6] in Palestine. However, Hennig et al. [31] and Apal Sammy et al. [26] found no association among Malaysian Malays and the mostly lean homogenous Mandinka Gambians. A genome-wide associated study confirmed that rs9939609 variant located within the first intron of the FTO gene predisposes European population to diabetes through an effect on body mass index (BMI) [32]. Variants in the fat mass and obesity-associated gene FTO have been identified as the strongest common genetic risk factors for obesity and T2D. The first reported association of an FTO variant with obesity and T2D was for variant rs9939609 in a European population [32]. Since then, the genetic association of rs9939609 with obesity and T2D has been demonstrated in a Korean population [33]. Indians [29]. African ancestry & African - American [34], Palestine [6] and some other studies have also shown that the association of FTO variants with obesity or T2D is not ethnic dependent [5]. In a pilot study conducted in Nigeria in 2017, Oyeyemi et al. [10] analyzed SNP rs9939609 of the FTO gene in a group of people with obesity and control. Individual with the FTO risk allele (A) had significantly high obesity risk factors (BMI, WC etc.) and this was also in tandem with some earlier studies [35]. This study is in agreement with their findings, thus suggesting an association between FTO rs9939609 and obesity. However, a 2009 study did not find any influence by FTO gene variation on measures of body mass in Gambians living a traditional lifestyle. They were described as lean population. Henning et al. 2009 infer that it is possible that any effect of FTO genotype on body mass is of limited relevance in a lean population

where little excess food is available, compared to similar ethnic populations where food supply is enormous.

The study (Table 3, 4, 5, 6, 7, 8, 9 & 10) found correlation between variants rs201041270 (GA/AA) with adiponectin ($p<.05$) and with Insulin ($p<.05$), rs531215275 (CA/AA), mild with C-peptide ($p<.05$), rs146056272 (TC/CC) with creatinine ($p<.01$), rs1410999299 (AG/GG) with C-peptide ($p<.05$), rs145884431 (GA/GG) with HbA1c ($p<.05$) & MDRD ($p<.05$), rs146138389 (CT/CC) with insulin ($p<.05$) and rs886052102 (AG/AA) with FBS ($p<.05$) & strongly with HbA1c ($p<.01$). Adiponectin, exhibits insulin sensitizing, anti-inflammatory, and anti-atherogenic properties and is an independent predictor of diabetes. HbA1c is the most commonly used biomarker to diagnose prediabetes and diabetes. HbA1c reflects chronic glycaemia rather than glucose levels at a single time point. C-peptide is a widely used measure of pancreatic beta cell function. It is produced in equimolar amounts to endogenous insulin but is excreted at a more constant rate over a longer time [18].

With the significant association shown by these other variants discussed above with T2D markers such as adiponectin, C-peptide, HbA1c and fasting insulin without corresponding effect on BMI, we can infer that these variants genotype (rs201041270, rs531215275, rs1410999299, rs145884431, rs146138389 & rs886052102) (Tables 11, 12,13,14,15,16, 17, 18 and 19) exercises their effect on T2D independent of BMI in the Niger Delta population, with rs 886052102 having the strongest association. This finding is somewhat new and may be supporting the school of thought about ethnic/population context of the various FTO gene variants. This is consistent with results from other studies that suggest different FTO gene variants associated with T2D, obesity or T2D/obesity either together or differently in different ethnic or geographical populations [22]. Evidence of statistical interaction between race and the FTO polymorphism shown after combining African-American and white participants further suggests that the influence of the FTO gene on diabetes susceptibility may be context dependent (Bressler *et al.* 2010). There is also the speculation of genetic architecture of diabetes differing in different ethnic group and variation in other genetic or environmental factors that contribute to the development of T2D may underlie in the apparent disparate effects of the FTO gene in different populations [27].

4. CONCLUSION

The study found a strong association between the variant genotype rs9939609 with obesity in Niger Delta tribes, but no significant independent association with T2D. The type 2 diabetes risk resulting from rs9939609 variant of the FTO gene in this region may be obesity mediated as evidenced by the increases observed in the BMI of the carriers of the risk allele (A). However, findings showed a significant association between some other variants with type 2 diabetes independent of body mass index, especially the rs886052102 and rs201041270 genotype variants.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

Ethical approval and permission were sought and obtained from the ethical committee of Federal Medical Centre, Asaba (Appendix I). Informed consent of the participants involved

was also obtained using the consent form (Appendix II) and anthropometric data was obtained via a questionnaire.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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