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Lipid Modulation in Subjects with Type 2 Diabetes Expressing the TCF/L2 Gene in Some Tribes in Nigeria

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Abstract

The transcription factor 7-like 2 (TCF7L2) gene plays a vital role in glucose and lipid metabolism, with several variants, including rs1790314 and rs12255372, linked to type 2 diabetes mellitus (T2DM). This study aims to evaluate lipid modulation among individuals with T2DM who express the TCF7L2 gene in specific tribes in Nigeria. A descriptive, cross-sectional design was used. Fasting blood samples were collected from 160 T2DM patients attending two tertiary hospitals in the state for routine diabetic check-ups. Standard questionnaires collected data on lifestyle, duration of diabetes, sex, and medication used. Biochemical parameters—fasting blood glucose (FBG), HbA1c, and lipids—were analysed using standard methods. The TCF7L2 variants were genotyped through BigDye Terminator sequencing, with results processed via Bioinformatics Algorithm Trace Edit and aligned with MAFFT. Gene variants and genotype frequencies were estimated by direct gene counting. Biochemical data and TCF7L2 variant results were analysed with GraphPad Prism and Microsoft Excel. The distribution of variants showed a CC genotype for rs1790314 at 32.5%, and a CT/TT mutant at 11.25%. For rs12255372, the GG genotype was observed at 41.25%, with a GT/TT variant at 3.75%. Notably, the use of standard anti-diabetic medications such as biguanides (metformin and Glucophage) and sulfonylureas (Amaryl) was associated with dyslipidemia. Males with T2DM exhibited significant dyslipidemia, characterised by reduced HDL-C and elevated triglycerides (TG), along with increased atherogenic markers like the TC/TG ratio. Additionally, the CT/TT polymorphism of rs1790314 correlated with higher TG, TC/TG ratio, and TC/HDL ratio, as well as decreased HDL-C in T2DM individuals. In summary, subjects expressing TCF7L2 gene variants show associations with dyslipidemia, and T2DM patients with mutant T alleles in both variants had significantly higher levels of HbA1c, lipid parameters, and atherogenic markers among the tribes studied.

Introduction

Recent findings suggest that variations in the transcription factor 7-like 2 (TCF7L2) gene significantly impact the development and progression of type 2 diabetes (Zhang et al., 2006; Del Bosque-Plata et al., 2021) [1,2]. Type 2 diabetes is a complex metabolic disorder with major genetic influences (WHO, 2024) [3]. Currently, strong associations exist between genetic markers and the disease's progression and underlying mechanisms (Grant et al., 2006; Zhang et al., 2025) [4,5]. Most recently, Del-Bosque-Plata et al. (2021) [2] identified several single-nucleotide polymorphisms (SNPs) and a microsatellite marker within a specific linkage disequilibrium (LD) block on chromosome 10q linked to type 2 diabetes risk. Although the exact functional causal variant remains unknown, the association is of interest as new data emerge, suggesting that the TCF7L2 gene might be involved in the development of type 2 diabetes through its functions in the Wingless-type (Wnt) signalling pathway (Del Bosque-Plata *et al.*, 2021; Zhang *et al.,* 2006) [1,2].

Type 2 Diabetes mellitus is an adverse and chronic metabolic condition characterised by sustained hyperglycemia resulting from an abnormal increased resistance to the action of insulin or the inability of the body to produce enough insulin to overcome the resistance (WHO, 2024; Zhang *et al.*, 2025*)* [3,5]. T2DM is characterised by insulin resistance and hyperglycemia (WHO, 2024; Zhang *et al.*, 2025*)* [3,5]. Insulin is crucial in the regulation of the body's metabolism and activation of Phosphoinositide-3-Kinase (PI3K)/Protein Kinase B (Akt) signalling pathway. This pathway is responsible for the actions of insulin on glucose and lipid metabolism once insulin binds to glucose molecules. (Apostolopoulou *et al.*, 2025; Zhang *et al.*, 2025) [6,5]. Derangements in the insulin signalling pathway usually result in decreased insulin levels and sensitivity, leading to T2DM and complications when unattended (Zhang *et al.*, 2025) [5]. Diabetes-associated dyslipidaemia received much attention in recent years and became the subject of numerous review papers (Hirano,2018; Taskinen and Boren, 2015) [7,8]. Alteration of the blood lipid profile in diabetes is linked to elevated hepatic production of triglyceride-rich lipoproteins, leading to the increased formation of atherogenic very low-density lipoprotein.

The growing burden of type 2 DM and its complications in Nigeria creates substantial costs for the government, society, and particularly for those affected. Until recently, the rise in type 2 DM was attributed to a combination of environmental influences and significant polygenic hereditary factors (Pappachan *et al.,* 2024) [9], with heritability estimates ranging from 20% to 80%. Thus, this study aims to explore the influence of TCF7L2 gene variants on the pathogenesis and progression of type 2 DM, using lipid profile and lipid indices markers in Rivers State, Nigeria.

Materials and Methods

Study Design

A descriptive cross-sectional study design was adopted involving 160 diabetic subjects recruited from two tertiary hospitals in Rivers State. Random blood samples and other information were collected using a standardised questionnaire from 160 subjects within the age range of 30-60 years, following ethical approval and informed consent in four major tribes (Ijaw, Ikwerre, Igbo and Ogoni), who are up to the fourth generation.

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Selection Criteria

Subjects included in the study were patients between 30 and 60 years old attending the endocrinology or internal medicine clinic of RSUTH and UPTH, Port Harcourt, diagnosed with T2DM at least 2 years ago. Those with complications or co-morbidities such as hypertension, obesity, and overweight were considered. Also, healthy individuals with no history of cancer, metabolic diseases, or nuclear and mitochondrial DNA-related diseases that may affect the DNA were recruited as control cases. Those that did not conform to the criteria were not included in the study.

Ethical Approval and Consideration

Ethical clearance was obtained from three Ethics Committees before conducting the study, with reference letters of MH/PRS/391/VOL.2/779, RS/REC/2021113, and UPTH/ADM/90/S. II/VOL. XI/1255, respectively. In addition, written informed consent was obtained from each participant before data and sample collection were carried out.

Clinical Data and Questionnaire

Clinical data were collected from patients' files to help guide the selection and subgrouping criteria under the supervision of the attending medical officer, and Nurses at the nurses' stations were sampling. In addition, other relevant information was collected using a standardised questionnaire. Biophysical and anthropometric data were also taken during this time using the appropriate recommended equipment.

Specimen Collection and Preparation

Samples measuring 7ml of whole blood were collected using the venipuncture technique and dispensed into EDTA containers, and Lithium heparin vacutainer tubes in the proportion of 3ml and 4ml, respectively, for the investigation of glycated haemoglobin, molecular investigations and other lipid parameters. The glycated haemoglobin was done immediately. Samples for other lipid parameters were stored at -4 °c after separation.

Estimation of Glycated Haemoglobin (HbA1c) using turbidimetric inhibition Immunoassay

Principle: Photometric measurement of turbidity by the end-point method at 600nm to directly determine HbA1c in whole blood. Total haemoglobin and HbA1c have the same unspecific adsorption rate to latex particles when mouse anti-human HbA1c monoclonal antibody is added. Latex HbA1c- mouse anti-human HbA1c antibody complex is formed. Agglutination is formed when the goat anti-mouse IgG polyclonal antibody interacts with the monoclonal antibody.

Estimation of Total cholesterol (TC) as described by Stavropoulous et al. 1975

Principle: Cholesterol in the presence of cholesterol esterase and oxidase is oxidised to cholestanone and hydrogen peroxide. In the presence of the peroxidase enzyme, hydrogen peroxide is oxidised in chromogen to give a pink colouration. The intensity of the colour generated is directly proportional to the concentration of glucose in the specimen.

Determination of Triglycerides (TG) as Described by Flegg et al. 1973

Principle: Triglyceride is hydrolysed to free glycerol and fatty acids by the enzyme lipase. The liberated free glycerol content in the presence of ATP leads to the production of glycerol-1-phosphate. In the presence of ADP kinase, phosphoenolpyruvate is produced. In the presence of pyruvate kinase, pyruvate is produced and then oxidised by NADH to oxygen molecules that react with chromogen to make a pink colour.

Estimation of high-density lipoprotein cholesterol (HDL-C) Described by Stavropoulous et al., 1975

Principle: HDL cholesterol in the protein-free filtrate, in the presence of cholesterol esterase and cholesterol oxidase, is oxidised to choleone and hydrogen peroxide. In the presence of the peroxidase enzyme, hydrogen peroxide is oxidised in chromogen to yield a pink colouration. The intensity of the generated colour is directly proportional to the concentration of glucose in the specimen.

Estimation of Low-Density Lipoprotein (LDL-C) as Described by Friedwald et al. 1972

Low-density lipoprotein (LDL-C) was calculated as described by Friedwald and colleagues using the Friedwald equation: LDL-C (mmol/L) = TC-(TG/2.2 + HDL-C).

Estimation of Castelli Risk Indices I & II as Described by Koleva *et al*. 2015.

Castelli Risk Indices I and II were calculated as TC/HDL-C and LDL-C/HDL-C, respectively, as documented by Koleva *et al*. 2015.

Typing of TCF7L2 Variants

The TCF7L2 gene variants were typed using the BigDye Terminator sequencing technique.

DNA Extraction: The DNA from the various samples was extracted using the Quick-DNA Miniprep kit supplied by Inqaba West Africa, following the Zymo Research instructions. The tubes containing the buffer in which the vaginal swabs were immersed were vortexed, 400ul of the buffer was transferred to a 1.5ml tube, 20ul of proteinase K and 400ul of Biofluid(red) were added, mixed and incubated at 55 °C for 20 minutes. Four hundred and twenty microliters of Genomic Binding Buffer were added and mixed thoroughly by vortexing. The mixture was transferred to a Zymo spin IIC-XLR column in a collection tube and centrifuged at 12000xg for 1 min. The collection tube was discarded with the flow through, and a new collection tube was added, containing 400 µl of DNA pre-wash buffer to the spin column. After centrifuging at 12000xg, 500ul of DNA wash buffer was added and spun at 12000xg. The spin column was then transferred to a collection tube, and 200 µl of DNA wash buffer was added and spun at 12000 × g for 1 min. The spin column was finally transferred to a new 1.5 ml tube, and 50 µl of DNA elution buffer was added directly to the matrix and spun at top speed for 1 min. The harvested product was stored at -20 °c for quantification and amplification.

DNA Quantification: The extracted genomic DNA was quantified

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using the Nanodrop 1000 spectrophotometer. The equipment software was launched by double-clicking on the Nanodrop icon. The equipment was initialised with 2 µl of sterile distilled water and blanked using normal saline. Two microlitres of the extracted DNA were loaded onto the lower pedestal, and the upper pedestal was brought down to contact the extracted DNA on the lower pedestal. The DNA concentration was measured by clicking on the "measure" button.

Amplification of TCF7 Gene: The TCF7 gene of the isolates was amplified using the TCF7F: 5'- CAGTCTAGGCTTGAACTC-3' and TCF7R: 5'- TAACCTCTCCACACTGCT-3, primers on an ABI 9700 Applied Biosystems thermal cycler at a final volume of 30 microlitres for 35 cycles. The PCR mix included: the X2 Dream Taq Master mix supplied by Inqaba, South Africa (Taq polymerase, DNTPS, MgCl), the primers at a concentration of 0.4M and the extracted DNA as template. The PCR conditions were as follows: Initial denaturation, 95°C for 5 minutes; denaturation, 95°C for 30 seconds; annealing, 53°C for 30 seconds; extension, 72°C for 30 seconds for 35 cycles and final extension, 72°C for 5 minutes. The product was resolved on a 1% agarose gel at 120v for 15 minutes and visualised on a blue light transilluminator.

Restriction Fragment Length Polymorphism: The salt was used to digest the PCR amplicons by incubating the enzyme-amplicon mix to a final volume of 20 µl at 50°C for 1 hour. The mix was resolved on 1% agarose in an electric field and visualised on a blue light transilluminator.

Statistical Analysis

Statistical analyses of the data obtained were performed using GraphPad Prism version 9.02. Descriptive and inferential statistics were employed in the analysis of the data. Descriptive statistics involve mean and standard deviation, while inferential statistics involve students' statistical t-test, Pearson's correlation, general linear regression, and One-Way ANOVA. Statistical significance was set at $p<0.05$. Gene counting was adopted to quantify the alleles of the gene variants and genotype frequencies in patients and controls.

Results

The results of lipid parameters of those with better glycemic control (HbA1c of ≤ 6.5) compared to subjects with poor glycemic control (HbA1c≥6.5). The comparative result indicated no significant differences in the lipid parameters considered at $p<0.05$. Furthermore, atherogenic indices considered also did not indicate significant differences between those with better glycemic control (HbA1c of ≤ 6.5) and subjects with poor glycemic control (HbA1c≥6.5).

The lipid parameter results for individuals who exercise regularly as a means of glycemic control (HbA1c of ≤ 6.5) compared to those who do not are shown in (Tables 2) and (Table 3). The comparison found no significant differences in lipid parameters at $p<0.05$. Additionally, atherogenic indices also showed no significant differences between those who exercise regularly and those who do not, when controlling for glycemic levels (HbA1c≤6.5).

The lipid parameters of diabetic subjects on different medications expressing the TCF7L2 Gene are shown in Table 4. The ANOVA result indicated that Amarl had a significantly lower value ($F=11.72$, $p<0.0001$) of total Cholesterol (TC) compared to other diabetic medications considered at $p<0.05$. In addition, users of Glucophage indicated significantly higher values of HDL-C ($F=47.1$, $p<0.001$) compared to other groups using Metformin, Amarl, and Galvusmet medication. However, other lipid parameters and atherogenic indices did not indicate significant differences at $p<0.05$.

The results of lipid parameters in diabetic subjects of different sexes expressing the TCF7L2 gene are shown in Table 5. The comparative results indicated that females had significantly lower values ($F=11.72$, $p=<0.0001$) for TG ($F=2.648$, $p=0.0100$) and HDL-C ($F=2.209$, $p=0.0306$) compared to male subjects, with a significance level set at $p<0.05$. Additionally, the TC/TG ratio showed significantly lower values ($F=3.619$, $p=0.0006$) in females compared to male subjects. However, other lipid parameters and atherogenic indices did not show significant differences at $p<0.05$.

The Association of the rs1790314 Variant of the TCF7L2 Gene on lipid indices in T2D subjects using the Dominant Model are depicted in Table 6. The results showed no association between the dominant and polymorphic variants. However, comparative analysis revealed that subjects with the dominant allele (CC) had significantly higher triglyceride (TG) levels ($p=0.0040$) than those with the polymorphic allele (CT or TT), at $p < 0.05$. In addition, the total cholesterol/triglyceride (TC/TG) ratio was significantly greater ($p < 0.001$) in subjects with the polymorphic allele (CT or TT) compared to those with the dominant allele (CC) at $p<0.05$. Furthermore, the TC/HDL ratio was also significantly elevated ($p=0.0089$) in subjects with the polymorphic allele (CT or TT) in comparison to those with the dominant allele (Cc) at $p < 0.05$. Lastly, the TG/HDL ratio was significantly higher ($p=0.0023$) in dominant (Cc) subjects compared to those with the polymorphic allele (CT or TT) at $p<0.05$.

Association of the rs12255372 Variant of the TCF7L2 Gene on lipid indices of T2D Subjects using the Dominant Model are Table 7. The result obtained indicated no association between the dominant and polymorphic variants at $p<0.05$.

Table 1: Diabetic Subjects on Lipid of T2D Subjects with Good and Poor Glycaemic Control Expressing TCF7L2 gene variants

Parameters	GGC (HbA1c<, =6.5) (n=10)	PGC (HbA1c>6.5) (n=62)	T value	P value	Remark
TC (mmol/L)	4.244±1.118	4.494±1.109	0.6291	0.5313	NS
TG (mmol/L)	0.9222±0.3114	1.082±0.4565	1.015	0.3137	NS
HDL (mmol/L)	0.9111±0.2619	0.9226±0.2563	0.1251	0.9008	NS
LDL (mmol/L)	3.052±1.103	3.138±1.045	0.2292	0.8194	NS
TC/HDL Ratio	5.033±1.897	5.151±1.608	0.2003	0.8418	NS
TC/TG Ratio	4.970±1.596	4.692±1.858	0.4254	0.6719	NS
TG/HDL Ratio	1.070±0.4380	1.192±0.3666	0.9078	0.3672	NS

Keys: GGC= Good Glycaemic control, PGC=Poor Glycaemic control, TC= Total Cholesterol, TG=Triglyceride, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, NS=Not Significant at $p<0.05$

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Table 2: Diabetic Subjects on Lipid and Atherogenic Indices of T2D Subjects Based on Exercise Expressing the TCF7L2 Gene

Parameters	Exercise (n=38)	No Exercise (n=34)	T value	P value	Remark
TC (mmol/L)	4.63 ±1.164	4.224±1.015	1.570	0.1209	NS
TG (mmol/L)	1.12 ±0.5139	1.00±0.339	1.102	0.2742	NS
HDL (mmol/L)	0.90 ±0.2589	0.927 ±0.26	0.4398	0.6614	NS
LDL (mmol/L)	3.33 ±1.100	2.86 ±0.9335	1.899	0.0617	NS
TC/HDL Ratio	5.44 ±1.735	4.86 ±1.510	1.481	0.1432	NS
TC/TG Ratio	4.85 ±2.095	4.53 ±1.430	0.7167	0.4760	NS
TG/HDL Ratio	1.25 ±0.3949	1.119±0.342	1.466	0.1472	NS

Keys: TC= Total Cholesterol, TG=Triglyceride, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, S=Significant, NS=Not Significant at p<0.05

Table 3: Diabetic Subjects on Lipid and Atherogenic Indices of T2D Subjects Based on Tribe Expressing the TCF7L2 Gene

Parameters	Ogoni (n=26)	Ikwerre (n=18)	Ijaw (n=16)	Igbos (n=9)	F value	P value	Remark
TC (mmol/L)	4.50 ±1.12	4.61 ±1.38	4.23±0.73	4.36 ±1.20	0.3690	0.7756	NS
TG (mmol/L)	1.10 ±0.55	1.02 ±0.41	1.02 ±0.29	1.06 ± 0.36	0.1553	0.9259	NS
HDL (mmol/L)	0.89 ±0.29	1.01 ±0.23	0.87 ±0.26	0.87±0.16	1.061	0.3717	NS
LDL (mmol/L)	3.16 ±0.97	3.21 ±1.29	3.02 ±0.64	3.02 ± 1.47	0.1207	0.9476	NS
TC/HDL Ratio	5.37 ±1.62	4.75 ±1.43	5.12 ±1.23	5.43 ± 2.67	0.5858	0.6265	NS
TC/TG Ratio	4.76 ±1.95	5.03 ±1.92	4.45 ±1.41	4.60 ± 2.11	0.2898	0.8326	NS
TG/HDL Ratio	1.24 ±0.37	1.02 ±0.33	1.23 ± 0.39	1.24 ± 0.40	1.477	0.2289	NS

Keys: TC= Total Cholesterol, TG=Triglyceride, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, S=Significant, NS=Not Significant at p<0.05

Table 4: Diabetic Subjects on Lipid and Atherogenic Indices of T2D Subjects Based on Type of Diabetic Medication

Parameters	Metformin (n=)	Amarl (n=)	Galvusmet (n=)	Glucophage (n=)	F value	P value	Remark
TC (mmol/L)	4.481±0.99^{a}	2.5±0.40^{b}	4.700±0.10^{a}	4.311±1.09^{a}	11.72	<0.0001	S
TG (mmol/L)	1.114±0.4912	1.000±0.40	1.13 ±0.5508	0.93±0.31	0.7267	0.5399	NS
HDL (mmol/L)	0.95±0.27^{a}	1.07±0.23^{a}	0.93±0.25^{a}	1.08±1.15^{b}	47.72	<0.0001	S
LDL (mmol/L)	3.120±0.9267	3.540±2.797	3.350±0.5567	3.088±1.150	0.1891	0.9034	NS
TC/HDL Ratio	5.045±1.677	4.737±2.355	5.263±1.286	4.526±1.735	0.4017	0.7522	NS
TC/TG Ratio	4.593±1.865	4.96 ±1.367	4.920±2.489	5.083±1.895	0.3057	0.8212	NS
TG/HDL Ratio	1.190±0.3775	0.97 ±0.4119	1.167±0.2838	1.184±0.4198	0.2945	0.8292	NS

Keys: TC= Total Cholesterol, TG=Triglyceride, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, S=Significant, NS=Not Significant at p<0.05. PostHoc: Values in the same row with different superscripts differ significantly at p<0.05.

Table 5: Diabetic Males Against Female Subjects on Lipid and Atherogenic Indices

Parameters	Male (n=38)	Female (n=34)	T value	P value	Remark
TC (mmol/L)	4.36 ±1.018	4.53±1.19	0.6409	0.5238	NS
TG (mmol/L)	0.91±0.48	1.19±0.37	2.648	0.0100	S
HDL (mmol/L)	0.84±0.25	0.98±0.24	2.209	0.0306	S
LDL (mmol/L)	3.19 ±1.034	3.06 ±1.07	0.549	0.5845	NS
TC/HDL Ratio	5.52 ±1.88	4.83±1.35	1.755	0.0837	NS
TC/TG Ratio	5.50±2.13	4.04±1.17	3.619	0.0006	S
TG/HDL Ratio	1.09 ±0.39	1.25 ±0.35	1.746	0.0852	NS

Keys: TC= Total Cholesterol, TG=Triglyceride, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, S=Significant, NS=Not Significant at p<0.05

Table 6: Association of the rs1790314 Variant of the TCF7L2 gene on Lipid and Atherogenic Indices of T2D Subjects using the Dominant Model

Parameters	CC (n=52)	CT/TT (n=18)	GLR, P value	PC, p-value	T-test, p-value
TC (mmol/L)	4.46±1.19	4.46±0.84	0.7221	0.7221	0.9994
TG (mmol/L)	1.15±0.45	0.81±0.32	0.5521	0.5521	**0.0040**
HDL (mmol/L)	0.94±0.27	0.86±0.19	0.3097	0.3097	0.2725
LDL (mmol/L)	3.03±1.09	3.39±0.88	0.2017	0.2017	0.2000
TC/HDL Ratio	3.11±1.67	5.15±1.64	0.2016	0.2016	**0.00896**
TC/TG Ratio	4.21±1.43	6.14±2.11	0.3999	0.3999	**<0.0001**
TG/HDL Ratio	1.261±0.3595	0.9561±0.3265	0.6536	0.6536	**0.0023**

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. C= Wild (Dominant), T=Polymorphic. *Significant Association, R^2 =Coefficient of Determination, r= Pearson's coefficient, n= number of subjects with Dominant or Polymorphic Alleles

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Table 7: Association of the rs12255372 Variant of the TCF7L2 gene on Lipid and Atherogenic Indices of T2D Subjects using Dominant Model

Parameters	GG (n=66)	GT/TT (n=6)	GLR, P value	PC, p value	T-test, p value
TC (mmol/L)	4.488±1.142	4.456±1.112	0.0685	0.0685	0.8706
TG (mmol/L)	1.045±0.4415	1.066±0.4443	0.3205	0.3205	0.7904
HDL (mmol/L)	0.9313±0.2557	0.9186±0.2561	0.0656	0.0656	0.7750
LDL (mmol/L)	3.157±1.083	3.122±1.051	0.3373	0.3373	0.8479
TC/HDL Ratio	5.108±1.672	5.146±1.642	0.2016	0.2016	0.8963
TC/TG Ratio	4.823±1.845	4.708±1.824	0.1672	0.1672	0.7162
TG/HDL Ratio	1.141±0.3600	1.183±0.3739	0.1178	0.1178	0.5102

GLR=General Linear Regression, PC=Pearson's Correlation, t-test=students' statistical test, p @ <0.05. G= Wild (Dominant), T=Polymorphic. *Significant Association, R^2 =Coefficient of Determination, r= Pearson's coefficient, n= number of subjects with Dominant or Polymorphic Alleles

Results of Sequence Alignment and Frequency Distribution of the Genotypes and Alleles of the Gene Variants in T2DM Subjects

The results of the sequence alignment of rs7903146 and rs12255372 are shown in (Figure 1) and (Figure 2), respectively. The nucleotide sequence alignment for the selected subjects revealed a nucleotide substitution of T in place of C (C/T) representing the known SNP rs7930416, while in the alignment of rs12255372, the substitution occurred in a manner that T replaced G (G/T), constituting the known SNP rs12255372 of the TCF7L2 Gene.

Furthermore, the genotypic and allelic frequency distributions of the gene variants were also investigated as shown in Table 8a, 8b, 8c and 8d, respectively. The results indicated that the Ikwerre had the highest dominant homologous genotype (CC) of 33.3% for the polymorphic variant rs7903146 of the TCF7L2 gene, while the Ijaws had the highest heterozygote genotype (CT) of 46.15% for the gene variant rs7903146. Also, the result shows that the Ogoni tribe harboured the

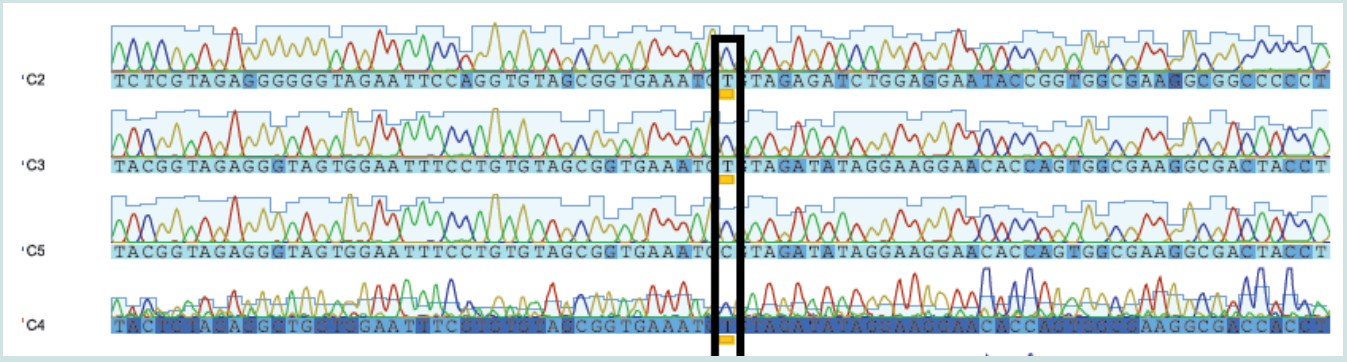

Figure 1: Sequence alignment of the TCF7 gene showing the nucleotide substitution C/T (rs7903146).

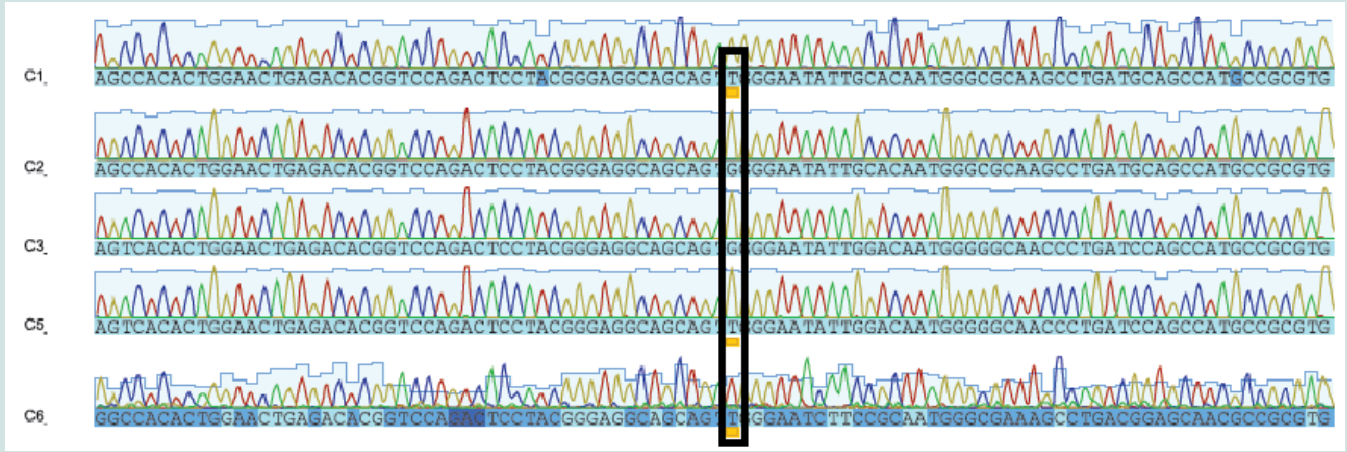

Figure 2: Sequence alignment of the TCF7 gene showing the nucleotide substitution G/T (rs12255372)

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Table 8a: Genotype Frequencies Distribution of rs7903146 by Tribes

rs7903146	Ikwerre		Ijaw		Ogoni		Igbo		Total	
Genotypes	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
CC	36(33.3%)	8(28.017%)	26(24.07%)	8(28.57%)	30(21.43%)	4(14.29%)	16(14.81%)	8(28.57%)	108	28
CT	4(15.38%)	2(25.0%)	12(46.15%)	2(25%)	6(23.08%)	4(50%)	4(15.38%)	0(0%)	26	8
TT	0(0%)	0(0%)	2(33.33%)	0(0%)	4(66.67%)	2(50%)	0(0%)	2(50%)	6	4
Total	**40(28.57%)**	**10(25%)**	**40(28.57%)**	**10(25%)**	**40(28.57%)**	**10(25%)**	**20(14.29)**	**10(25%)**	**140**	**40**

Table 8b: Allelic Frequency Distribution of rs7903146 in the Various Tribes

rs7903146	Ikwerre		Ijaw		Ogoni		Igbo		Total	
Allele	Test	Control	Test	Control	Test	Control	Test	Control	T	C
C	76(31.57%)	18(28.13%)	64(26.67%)	18(26.67%)	64(26.67%)	12(18.75%)	36(15%)	16(25%)	240	64
T	4(10%)	2(12.5%)	16(40%)	2(12.5%)	16(40%)	8(50%)	4(10%)	4(25%)	40	16

Table 8c: Genotype Frequencies Distribution of rs12255372 by Tribes

rs12255372	Ikwerre		Ijaw		Ogoni		Igbo		Total	
Genotypes	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
GG	36(30%)	8(22.22%)	36(30%)	10(27.78%)	36(30%)	10(27.78%)	12(10%)	8(22.22%)	120	36
GT	4(25%)	(0%)	4(25%)	(0%)	2(12.5%)	(0%)	6(37.5%)	(0%)	16	(0%)
TT	(0%)	2(50%)	(0%)	(0%)	2(100%)	(0%)	(0%)	2(50%)	2	4
Total	**40(28.57%)**	**10(25%)**	**40(28.57%)**	**10(25%)**	**40(28.57%)**	**10(25%)**	**18(13.04%)**	**10(25%)**	**138**	**40**

Table 8d: Allelic Distribution of rs12255372 in the Various Tribes

rs12255372	Ikwerre		Ijaw		Ogoni		Igbo		Total	
Allele	Test	Control	Test	Control	Test	Control	Test	Control	Test	Con
G	72(28.57%)	16(22.22%)	76(30.16%)	20(27.78%)	74(29.37%)	20(27.78%)	30(11.99%)	16(22.22%)	252	72
T	8(33.33%)	4(50%)	4(16.67%)	(0%)	6(25%)	(0%)	5(25%)	4(50%)	24	8

Igbo respectively. There is no significant difference in the frequency distribution of alleles by tribe.

homozygote genotype (TT) at 66.67% in the test subjects and 50% also in the control subjects, along with some of the Igbo control subjects at 50%. Similarly, (Table 8c) revealed a unified homozygote dominant genotype (GG) of 36% of the rs12244372 polymorphic variant amongst the tribes included in the study, with the exception of the Igbo tribe having the homozygote genotypic frequency of 10%. Also, the GT/TT genotype was predominantly high in the Ogoni tribe. In like manner, the allelic frequency distribution for the mutant allele (T) was seen to be notably higher among the Ogonis and Ijaws for the rs7903146 gene variant (40%) and predominantly high for the rs12255372 polymorphic variant amongst the Ikwerres (33.33%). The mutant alleles were also seen amongst the control subjects for both rs7903146 and rs12255372 variants of the TCF7L2 gene in the study population (Tables 8b and 8d).

The frequency distribution of rs7903146 genotypes by tribe revealed that of the 140 subjects, 36(33.3%), 26(24.07%), 30(21.43%) and 16(14.81) CC dominant genotype were seen in the Ikwere, Ijaw, Ogoni and Igbo tribes respectively, 4(15.38%), 12(46.15%), 6(23.08%) and 4(15.38%) heterozygote CT genotype were also seen in the Ikwere, Ijaw, Ogoni and Igbo tribes respectively. The frequency distribution of the genotypes by tribe varied from one tribe to the other, but these differences were not statistically significant. However, the results further showed that the TT genotype was found in 2(33.33%) and 4(66.67%) subjects of the Ijaw and Ogoni tribes, while 2(50%) controls from the Ogoni and Igbo extractions harboured the (TT) homozygote mutant genotype.

The allelic distribution of **rs7903146,** showed that of the 140 subjects who enrolled into this study, 76(31.57%), 64(26.67%), 64(26.67%) and 36(15%) dominant C alleles were harbored by the Ikwere, Ijaw, Ogoni and Igbo respectively while 4(10%) and 16(40%) mutant T allele were haboured by the Ikwerre, Igbo, Ijaw and Ogoni respectively. There is no significant difference in the frequency distribution of alleles by tribe.

The frequency distribution of rs12255372 genotypes by tribe revealed that of the 140 subjects, 36(30%), 36(30%), 36(30%) and 12(10%) dominant homozygote (GG) genotype were seen in the Ikwerre, Ijaw, Ogoni and Igbo tribes respectively, 4(25%), 4(25%),4(25%) and 6(37.5%) GT genotype was also observed in the Ikwere, Ijaw, Ogoni and Igbo tribes respectively. The frequency distributions of the dominant genotypes by tribe were observed to be the same for all tribes except for the Igbo; however, they were not statistically significant. The results further showed that the mutant homozygote (TT) genotype was found in 2(100%) test subjects of the Ogoni tribe, while the control subjects from the Ikwerre and Igbo extraction also harboured the homozygote mutant (TT) genotype (50% respectively).

The allelic distribution of **rs12255372** showed that of the 140 subjects who enrolled into this study, 72(28.57%), 76(22.22%), 74(29.37), 30(11.99%) dominant G alleles were harbored by the Ikwerre, Ijaw, Ogoni and Igbo respectively while 8(33.33%) 4(16.67%) 6(25%) and 5(25%) mutant T alleles were haboured by Ikwerre, Ijaw, Ogoni.

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Discussion

The use of diabetes medications for treating T2DM has been recognised as a contributor to lipid dyslipidaemia (Piccirillo *et al.,* 2023) [10]. T2DM significantly increases the risk of cardiovascular diseases due to episodes of hyperglycemia and variations in blood sugar levels. Dyslipidemia, identified by elevated triglycerides, increased LDL levels, and decreased HDL in diabetes, is known as diabetic dyslipidemia, which in turn accelerates atherosclerosis and contributes to cardiovascular morbidity and mortality.

In this study, it was observed that significantly lower total cholesterol (TC) levels in T2DM patients taking Amarl were found, while those using Glucophage showed significantly higher HDL cholesterol (HDL-C) levels. This contradicts the findings of Buse *et al.* (2004) [11], who indicated that biguanides (including metformin and Glucophage) at higher doses lower TC without directly impacting HDL-C. Buse *et al.* also noted unclear effects of anti-diabetic medications like sulphonylureas (e.g., Amarl) on serum lipids; however, this study showed Amarl resulted in a notable reduction in TC among T2DM patients. According to Piccirillo et al. (2023) [10], traditional anti-diabetic drugs, including sulphonylureas (Amarl), repaglinide, voglibose, Rosiglitazone, Pioglitazone, Acarbose, Nateglinide, and Miglitol, as well as Biguanides (Metformin and Glucophage), can reduce plasma glucose levels but often lack sufficient cardioprotective effects, leading to dyslipidaemia. They further reported that newer anti-diabetic medications such as sodium glucose transporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP4i), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) significantly enhance lipid profiles and outcomes, thus preventing or mitigating diabetes-induced cardiovascular diseases.

The differences in sex regarding the impact and severity of T2DM indicated significantly higher values among females compared to males. Our findings were contrary to the reports of Martey *et al.,* (2015) [12], who observed no significant differences in the BMI of male and female T2DM subjects. Elekima & Ugwu, (2018) [13], reported that higher values of WHR are associated with cardiovascular diseases as well as metabolic syndromes such as T2DM, which were positively correlated with increased levels of some lipid particles like vLDL, LDL-C, and TG.

In this study, we found that female subjects with T2DM had significantly higher levels of TG and HDL compared to their male counterparts. This aligns with Ozder's (2014) [14] findings, which also reported elevated TG levels in females; however, it contradicts our observation that there were no significant differences in HDL-C levels between the sexes. Our results regarding elevated TG levels are consistent with Antwi-Baffour *et al.* (2018) [15], who found significantly higher TG values in female T2DM subjects. Furthermore, the higher TC/TG ratio (the atherogenic index) in male T2DM subjects compared to females also aligns with findings from Antwi-Baffour *et al.* (2018) and Liqun *et al.* (2022) [15,16], who reported increased lipid ratios in male T2DM subjects. Notably, our study did not find significant differences in the TC/HDL and TG/HDL-C ratios, which contradicts Antwi-Baffour *et al.* (2018) [15] and Liqun *et al.* (2022) [16], who documented higher TC/HDL and TG/HDL ratios in male T2DM subjects compared to females. Lastly, Athyros *et al.* (2018) [17], Wang & Ahmadizar (2021) [18], and John *et al.* (2021) [19] noted that complex dyslipidaemia can occur in both the development and progression of T2DM, suggesting that effective lipid management may mitigate cardiovascular complications in diabetic patients.

The significantly lower HDL values and higher TC/TG ratio in T2DM subjects indicate a higher level of harmful lipids (TG, LDL, TG/HDL-C, LDL-C/HDL-C) in males compared to females, which could increase the risk for T2DM complications. Furthermore, our results suggest that T2DM-associated coronary risks are higher in males than in females.

The observed non-significant differences in the values of renal, metabolic, and inflammatory markers challenge the findings of Martey *et al.* (2015) [12], who reported significant differences in the mean values of metabolic markers between female and male T2DM subjects. Furthermore, females exhibited a notably longer mean disease duration than their male counterparts.

When examining the duration of the disease, the observed non-significant differences in renal, metabolic, and inflammatory marker values contradict findings by Martey *et al.* (2015) [12] and Bartimaeus & Ken-Ezihuo (2016). Martey *et al.* (2015) [12] found significant differences in the average values of metabolic markers in T2DM patients, whereas Bartimaeus & Ken-Ezihuo (2016) noted that a diabetes duration of 8 years or more is linked to impaired creatinine levels in T2DM subjects. Furthermore, Kumsa *et al.* (2021) [20] indicated that a study in Brazil found serum creatinine impairment correlated with prolonged T2DM duration and reduced GFR in diabetic individuals.

In their study, John *et al.* (2021) [19] reported much higher levels of HbA1c, FBG, and inflammatory markers, including cytokines, alongside significant dyslipidemias characterised by elevated triglycerides, increased LDL-C levels, and decreased HDL-C levels in individuals with T2DM, depending on the disease duration. This contrasts with our findings.

The differences between their findings and ours may stem from the fact that the majority of our participants were hospital-based and received comprehensive monitoring, which accounted for various diabetic complications. This crucial distinction could clarify the disparities observed between our research and that of John *et al.* (2021) [19].

González-Sánchez *et al.* (2008) [21] reported that Type 2 Diabetes Mellitus (T2DM) is a chronic systemic metabolic disorder influenced by multiple genetic and environmental factors, which leads to hyperglycaemia. The transcription factor 7-like 2 (TCF7L2) gene is part of the Wnt signalling pathway and is crucial for glucose and lipid metabolism. Various TCF7L2 variants, such as the rs7903146 and rs12255372 polymorphisms, are associated with the pathophysiology of T2DM.

In our study, the non-significant relationship between BMI, WHR, and the CT/TT polymorphisms of TCF7L2 rs7903146 variants (Table 8a) parallels the findings of Nguimmo-Metsadjio e*t al.* (2017) [22], who reported no link between BMI, obesity, and CT /TT polymorphisms among T2DM subjects in the Cameroonian population. Additionally, our results showed no association between BMI, HbA1c, and the SNPs rs7903146 and rs12255372 aligned with

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the observations of Faranak *et al.* (2012) [23], who also found no relationship between these variants and age, BMI, or HbA1c in T2DM patients within the Iranian population. Notably, they mentioned a significant association between anthropometric indices, such as WHR and BMI, particularly among individuals of African descent, including African-Americans. Table 8a of our results indicates that BMI and WHR were significantly higher in T2DM subjects expressing the TCF7L2 gene linked to obesity.

The notably elevated levels of TG in CT/TT polymorphism observed in our study (Table 8b) align with findings by Ngwa *et al.* (2015) [24], Perez-Martinez *et al.* (2012) [25], and Gunavathy *et al.* (2023) [26], who noted significant associations between the TCF7L2 rs7903146 CT/TT and rs12255372 GT/TT genotypes and the risk of hypertriglyceridaemia in individuals with T2DM. Conversely, our findings contradict those of Nguimmo-Metsadjio *et al.* (2017), who found no link between lipid particles and C/T and T/T polymorphisms in T2DM subjects from the Cameroonian population. Additionally, the significantly higher TC/TG ratio, TC/HDL ratio, and marked decrease in TG/HDL in the CC/TT polymorphism (Table 8b27) reflect similar results reported by Perez-Martinez *et al.* (2012) [25] and Engwa *et al.* (2021) [27], which investigated the impact of Single Nucleotide Polymorphisms (SNPs) of rs7903146 and rs12255373 of TCF7L2 C/T and G/T polymorphisms, respectively, on lipids in the Nigerian population. Perez-Martinez *et al.* (2012) [25] documented significantly elevated levels of triglycerides (TG), total cholesterol, LDL-cholesterol, and Apo B in both fasting and postprandial states among subjects carrying the T allele of SNPs of 7903146 of TCF7L2 C/T. Engwa *et al.* (2021) [27] indicated that the TT genotype was more prevalent in T2DM patients (25.7%) compared to non-diabetic controls (11.5%). Consequently, the TCF7L2 G/T polymorphism of rs12255373 was associated ($P < 0.05$) with T2DM.

The reason for elevated levels of TG and lipid ratios (atherogenic indices) among subjects with genetic variants of the TCF7L2 gene, featuring the T and G polymorphic alleles, remains unclear. However, it might relate to the inhibition or alteration of the transcription factor that affects adipogenesis or adipokine regulation via the Wnt signalling pathways. Poor regulation of these pathways in lipid metabolism could predispose these individuals to hypertriglyceridemia and higher atherogenic indices, particularly in those with T2DM. Increased adiposity correlates with obesity, both of which are significant risk factors for metabolic conditions like T2DM and cardiovascular disease (CVD).

Conclusion

The distribution of TCF7L2 gene variants in 1790314 subjects with the CT/TT polymorphism revealed a CC genotype at 32.5%, whereas the CT/TT mutant variant was present at 11.25% among individuals with T2DM. Likewise, the TCF7L2 gene variants in 12255372 subjects with GT/TT polymorphism displayed a GG genotype at 41.25%, while the GT/TT mutant variant had a prevalence of 3.75% among T2DM subjects in the study population.

Furthermore, T2DM patients of Ijaw ethnicity faced a heightened risk of developing complications associated with T2DM and cardiovascular disease (CVD), attributed to their greater waist-to-hip ratio (WHR) compared to other ethnic groups in the study. However, anti-diabetic medications such as biguanides (Metformin and Glucophage) and sulphonylureas (Amarl) not only reduce plasma glucose levels in T2DM subjects but are also linked to lipid dyslipidaemia, leading to hypocholesterolaemia and increased levels of HDL-C among users. Males face a heightened risk of developing complications related to T2DM and CVD, stemming from pronounced dyslipidaemia. The dyslipidaemia observed in males is characterised by reduced HDL-C and TG levels and increased markers indicating atherogenic risk, such as the TC/TG ratio.

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