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Association of PPARG genotypes with biochemical markers in type 2 diabetes mellitus among a Nigerian population

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Abstract

Background: This study investigated the role of PPARG genetic variants in type 2 diabetes mellitus complications among individuals in Ekiti State, Nigeria. The focus was on understanding how these genetic variants may influence biochemical markers and, consequently, the risk of complications.

Methods: We recruited 74 diabetic patients and 20 controls from a university teaching hospital. Ten milliliters of whole blood samples were collected by venipuncture and divided into two 5-milliliter aliquots. One aliquot was placed in an EDTA bottle, and the other in a fluoride oxalate bottle, before centrifugation to obtain plasma. PPARG genotyping and biochemical marker analyses, including Cystatin C, ALT, CK-MB, and IL-10, were performed.

Results: Significant differences in PPARG genotype distribution were observed, with the GG genotype being more common in diabetic individuals. Diabetic subjects showed elevated Cystatin C, ALT, and CK-MB levels, along with reduced IL-10, particularly among females. PPARG genotypes were associated with several biochemical markers, notably Cystatin C ($p = 0.002$), ALT ($p = 0.030$), and FBS ($p = 0.017$).

Conclusion: These findings highlight a complex relationship between PPARG genotypes and the pathophysiology of diabetes in the Nigerian population, emphasizing the potential for personalized medicine approaches in type 2 diabetes mellitus management.

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Highlights

What is current knowledge?

The PPARG gene plays a crucial role in regulating glucose and lipid metabolism, and its genetic variants are associated with T2DM susceptibility and progression. There are limited data on PPARG gene and a critical knowledge gap in African populations.

What is new here?

The GG genotype of PPARG is significantly more prevalent among diabetic individuals and is linked to elevated levels of Cystatin C and ALT, suggesting early renal and hepatic dysfunction. Reduced IL-10 levels in female diabetic subjects indicate a potential influence of PPARG variants on chronic inflammation, a hallmark of T2DM pathophysiology.

Introduction

Diabetes mellitus is a chronic condition that is increasingly prevalent worldwide, particularly in developing countries like Nigeria (1,2). Currently, the estimated prevalence of diabetes in Nigeria stands at 5.7%, posing significant health challenges for the population. This is particularly concerning given the high rates of complications associated with diabetes, including nephropathy, neuropathy, and cardiovascular disease, which can severely impact the quality of life and increase healthcare costs (3-7).

Type 2 diabetes mellitus (T2DM) arises from a complex interplay of genetic and environmental factors. Among the genetic influences, the peroxisome proliferator-activated receptor gamma (PPARG) gene plays a crucial role in regulating glucose and lipid metabolism (8,9). Specific variants of this gene have been linked to increased susceptibility to T2DM and its complications. However, research focusing on the PPARG gene within African populations remains limited, highlighting a gap in understanding its significance in the context of T2DM in Nigeria (10).

In Ekiti State, the burden of diabetes presents a notable public health challenge, yet data regarding genetic predispositions, particularly concerning PPARG variants, are scarce. Identifying these genetic factors is essential for developing personalized strategies for diabetes prevention and treatment (10). This study aimed to investigate the role of PPARG variants in Nigerian T2DM patients and their possible associations with diabetes-related complications. By enhancing our understanding of these genetic influences, we hope to contribute valuable insights that could lead to improved and personalized diabetes care tailored to the unique genetic landscape of the Nigerian population.

Methods

Study area and population

This study was a cross-sectional study with a control arm that examined the relationship between PPARG genotypes and biochemical markers among diabetic and non-diabetic individuals in a Nigerian population. The study was conducted in Ado-Ekiti, the capital city of Ekiti State, Nigeria (7°40'N, 5°16'E). Ado-Ekiti, with a population of 308,321 (2006 census), is characterized by undulating terrain and prominent inselbergs. The study population comprised patients attending the endocrinology clinic of a hospital.

Sample size calculation

The sample size was determined based on the prevalence rate of the study and calculated using the formula recommended by Uzoagulu (1998). The sample size was calculated based on the expected effect size, a power level of 80%, and a significance level of 0.05.

$$N = \frac{Z^2 \alpha P(1-P)}{d^2}$$

where N = the number of patients to be sampled
$Z\alpha$ = the standard normal deviation corresponding to a 95% confidence level = 1.96
P = prevalence (5.6% from Elegbede *et al.*, 2022)
d = the degree of accuracy desired (2% = 0.02).

$$N = \frac{(1.96)^2 \times 0.56(1-0.56)}{(0.02)^2} = 82$$

The calculated sample size was 82. With a 15% attrition rate (12.3), the total minimum sample size was approximately 94 subjects.

Sample size justification and sampling

The study included 74 diabetic patients and 20 non-diabetic controls, a sample size chosen to provide preliminary insights into genetic and biochemical associations in this population. Age and gender matching were performed to minimize confounding. While relatively modest, this sample size allows for identifying significant trends that could inform larger future studies.

Inclusion and exclusion criteria

The inclusion criteria encompassed male and female diabetic patients aged 18-65 years. Subjects who tested positive for malaria and chronic diseases such as

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HIV, tuberculosis, and hepatitis B virus were excluded to minimize confounding factors.

Data collection

We collected demographic and socioeconomic data using a self-administered questionnaire and whole blood samples from all consenting subjects via venipuncture.

Biochemical analysis

We assayed the subjects' FBS, AST, ALT, CK-MB, total protein, Cystatin C, urea, creatinine, and IL-10 levels, and then analyzed the subjects' samples molecularly. FBS, AST, ALT, CK-MB, total protein, urea, creatinine, and Cystatin C levels were measured using the colorimetric-spectrophotometric method, while the IL-10 level was assessed using the ELISA method.

Cystatin C, ALT, CK-MB, and IL-10 were selected based on their relevance to diabetes complications. Cystatin C is a sensitive marker of renal function, often elevated in early diabetic nephropathy. ALT serves as an indicator of liver health, pertinent given the association of diabetes with non-alcoholic fatty liver disease. CK-MB is a cardiac marker, relevant due to the increased cardiovascular risk in diabetics, and IL-10 is an anti-inflammatory cytokine, representing the role of chronic inflammation in T2DM.

Molecular analysis

Genotyping of the CAPN10 (rs384257) polymorphism was performed using PCR amplification. The reaction mixture (25 µL) contained 10 µL genomic DNA, 21 µL S4 fidelity PCR (Dye) Master Mix, and 1 µL each of forward and reverse primers (10 mmol). PCR conditions were as follows: initial denaturation at 98°C for 2 min, followed by 35 cycles of 98°C for 10 s, 59°C for 15 s, and 72°C for 30 s, with a final extension at 72°C for 5 min. PCR products were visualized on a 3% agarose gel stained with SYBR Safe under UV illumination.

Statistical analysis

Data were analyzed using SPSS Version 23.0 (Chicago, USA). Chi-square tests were used for categorical variables, while t-tests or ANOVA were used for continuous variables, with statistical significance set at $p < 0.05$.

Results

Table 1 indicates that approximately 70% of participants in both the case and control groups were over 50 years old, with average ages of 52 and 50, respectively. The gender distribution was similar, with women comprising 70-75% of each group, and there were no significant differences in age or sex. Figure 1 shows the distribution of three PPARG genotypes (GG, GS, and SS), with the case group exhibiting higher frequencies for the GG (44 vs. 11), GS (18 vs. 5), and SS (12 vs. 4) genotypes compared to the control group, suggesting an association with diabetes risk.

Table 2 compares hepatic, renal, and cardiac markers between the diabetic subjects and the healthy controls, while Tables 3 and 4 disaggregate results by gender. Among the diabetic patients, the prevalence of the GG genotype was higher (59.5%) compared to the controls (55%). The diabetic subjects showed elevated levels of Cystatin C (1.46±0.48 mg/L vs. 0.98±0.33 mg/L, p=0.001), ALT (71.85±4.07 U/L vs. 27.51±3.28 U/L, p=0.001), and CK-MB (11.84±2.79 ng/mL vs. 9.73±2.44 ng/mL, p=0.003). The female diabetic subjects had significantly lower IL-10 levels compared to their male counterparts (88.08±46.99 pg/mL vs. 176.14±28.05 pg/mL, p=0.001).

As shown in Table 5, significant variations were observed in the biochemical markers across different PPARG genotypes. For example, the GG genotype was associated with higher Cystatin C levels (1.36±0.26 ng/mL, p=0.002) and ALT (29.23±4.36 U/L, p=0.030), suggesting potential organ-specific impacts of this genotype on renal and hepatic functions.

Table 1. Sociodemographic data of subjects

Variables	DM Subjects (%)	Controls (%)	Df	X^2 value	p-value
Age group (n=94)					
21-30 yrs	4 (5.4)	0	-	-	-
31-40 yrs	10 (13.5)	3 (15.0)	3	1.566	0.667
41-50 yrs	7 (9.5)	3 (15.0)	-	-	-
Above 50 yrs	**53 (71.6)**	**14 (70.0)**	-	-	-
Mean ±SD	51.64±9.95	50.30±9.02	-	0.543	0.589
Sex (n=94)					
Male	22 (29.7)	5 (25.0)	1	0.172	0.678
Female	**52 (70.3)**	**15 (75.0)**			

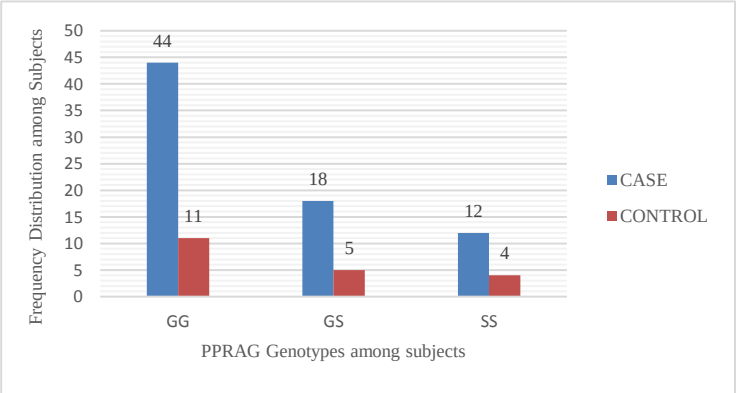

Figure 1. Distribution of PPARG genotypes among diabetic and non-diabetic participants

Table 2. Comparison of biochemical markers between diabetic and non-diabetic participants

Parameter	Subject	Control	T-value	P-value
	Mean±SD	Mean±SD		
Cystatin C (ng/ml)	1.46±0.48	0.98±0.33	4.235	0.001*
CK-MB (U/L)	11.84±2.79	9.73±2.44	3.074	0.003*
ALT (U/L)	71.85±4.07	27.51±3.28	6.989	0.001*
AST (U/L)	15.38±6.45	11.30±2.66	2.756	0.007*
TP (g/dl)	5.63±2.47	2.02±0.34	6.487	0.001*
IL- 10 (IU/L)	95.67±48.59	160.85±22.29	4.129	0.001*
FBS (mmol/L)	6.57±1.95	6.43±2.48	0.273	0.785
Creatinine (mmol/L)	118.17±47.41	100.64±10.41	1.040	0.303
Urea (mmol/L)	5.99±1.56	5.72±0.86	0.754	0.453

* Statistically significant

NB: CK-MB: Creatine Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TP: Total Protein, IL-10: Interleukin-10, FBS: Fasting Blood Sugar

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Table 3. Comparison of biochemical markers between diabetic and non-diabetic male participants

Parameter	Subject (n=22)	Control (n=5)	T-value	P-value
	Mean± SD	Mean± SD		
Cystatin C (ng/ml)	1.28±0.18	1.00±0.38	2.498	0.019*
CK-MB (U/L)	11.17±2.18	9.06±2.26	1.945	0.063
ALT (U/L)	71.80±2.59	35.91±6.52	2.582	0.016*
AST (U/L)	14.55±5.63	13.60±2.07	0.365	0.718
TP (g/dl)	4.77±2.59	2.20±0.37	2.188	0.038*
IL- 10 (IU/L)	113.61±48.61	115.00±48.79	0.058	0.955
FBS (mmol/L)	6.82±2.29	5.34±0.97	1.393	0.176
Creatinine (mmol/L)	107.10±19.84	106.20±10.96	0.098	0.932S
Urea (mmol/L)	6.15±1.55	5.12±0.30	1.456	0.158

* Statistical significance
NB: CK-MB: Creatine Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TP: Total Protein, IL-10: Interleukin-10, FBS: Fasting Blood Sugar

Table 4. Comparison of biochemical markers between diabetic and non-diabetic female participants

Parameter	Subject (n=52)	Control (n=15)	T-value	P-value
	Mean± SD	Mean± SD		
Cystatin C (ng/ml)	1.53±0.54	0.97±0.34	3.830	0.001*
CK-MB (U/L)	12.12±2.98	9.95±2.53	2.554	0.013*
ALT (U/L)	71.87±4.53	23.96±3.69	6.907	0.001*
AST (U/L)	15.73±6.79	10.53±2.42	2.899	0.005*
TP (g/dl)	5.99±2.36	1.95±0.32	6.574	0.001*
IL-10 (IU/L)	88.08±46.99	176.14±28.05	4.595	0.001*
FBS (mmol/L)	6.79±2.75	6.46±1.79	0.544	0.588
Creatinine (mmol/L)	123.23±54.49	98.48±9.64	1.742	0.086
Urea (mmol/L)	5.92±1.58	5.91±0.89	0.023	0.982

* Statistical significance
NB: CK-MB: Creatine Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TP: Total Protein, IL-10: Interleukin-10, FBS: Fasting Blood Sugar

Table 5. Comparative analysis of average variables across genotype categories among diabetic subjects in Ekiti state

Variables	PPARG Genotype			F-value	p-value
	GG	GS	SS		
Cystatin C (ng/ml)	1.36±0.26	1.79±0.78	1.32±0.22	6.722	0.002*
CK-MB (U/L)	11.62±2.68	12.09±3.22	12.23±2.66	0.319	0.728
ALT (U/L)	29.23±4.36	14.33±4.11	41.00±9.32	3.675	0.030*
AST (U/L)	16.14±7.21	13.67±5.11	15.17±5.06	0.934	0.394
TP (g/dl)	5.43±2.50	6.78±1.70	4.62±2.87	3.277	0.044*
IL- 10 (IU/L)	107.70±51.42	80.74±42.76	73.97±32.34	3.642	0.031*
FBS (mmol/L)	6.36±1.77	6.12±1.59	8.00±2.51	4.324	0.017*
Urea (mmol/L)	5.80±1.62	6.14±1.85	6.54±0.93	1.290	0.282
Creatinine (mmol/L)	113.52±43.68	109.52±23.13	140.93±66.03	2.080	0.133

* Statistical significance
NB: CK-MB: Creatine Kinase, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TP: Total Protein, IL-10: Interleukin-10, FBS: Fasting Blood Sugar

Discussion

The study highlights the role of the PPARG gene in metabolic regulation, suggesting that tailoring diabetes management based on genotype could help mitigate specific risks, such as renal or hepatic complications, thereby enhancing treatment efficacy for Nigerian diabetics. The demographic characteristics of the study population reveal a significant prevalence of individuals over 50 years old, consistent with the typical age of onset for T2DM, which increases significantly after age 45 (11). The higher percentage of the female participants (70-75%) may reflect gender-specific health-seeking behaviors or a higher prevalence of T2DM among women in this population, despite global trends showing a slightly higher prevalence in men (12).

Findings from this study on PPARG genotypes in the Nigerian diabetic population provide significant insights into the relationship between genetic factors and organ health markers, particularly Cystatin C and ALT. Elevated levels of Cystatin C indicate early renal dysfunction, a common complication associated with diabetes, while increased ALT levels suggest potential liver involvement. The association of the GG genotype with poorer biochemical outcomes emphasizes the importance of considering genetic factors in assessing the risk of T2DM and in treatment planning (13-18).

The study found that the diabetic subjects exhibited elevated levels of Cystatin C (1.46 mg/L vs. 0.98 mg/L in controls, p=0.001) and ALT (71.85 U/L vs. 27.51 U/L, p=0.001), indicating potential organ dysfunction. The presence of the GG genotype was more frequent in the diabetic group, aligning with previous research linking PPARG polymorphisms to T2DM risk. Lower levels of IL-10 in the diabetic females suggest chronic low-grade inflammation, which is often associated with diabetes. The elevated CK-MB levels in the diabetic females indicate potential subclinical cardiac damage, supporting findings that diabetes increases the risk of cardiovascular complications (19).

The observed reduction in IL-10 levels and elevation in other inflammatory markers among the diabetic participants may indicate a hyperglycemia-induced inflammatory response, consistent with prior studies demonstrating that acute hyperglycemia can increase inflammatory cytokines due to oxidative stress mechanisms (20).

The study's modest sample size and ethnic specificity may limit the generalizability of the results. Additionally, the cross-sectional design restricts the ability to establish causality in the observed associations. The associations between PPARG genotypes and various biochemical markers provide new insights into the mechanisms by which PPARG might influence diabetes pathophysiology. For instance, higher levels of Cystatin C in the GS genotype may indicate a link between PPARG and renal function, consistent with studies showing that PPARG agonists can improve renal outcomes in diabetic patients (21). Elevated ALT levels in the SS genotype could suggest a relationship between PPARG and hepatic function, aligning with research on PPARG's role in hepatic lipid metabolism and insulin sensitivity (22).

Moreover, higher levels of IL-10 in the GG genotype suggest a potential anti-inflammatory effect, supported by evidence that PPARG activation can modulate inflammatory responses (23). Finally, higher fasting blood sugar levels in the SS genotype indicate a potential association with poorer glycemic control, consistent with studies linking specific PPARG polymorphisms to increased diabetes risk and altered insulin sensitivity (24). These findings underscore the complex interplay between PPARG genotypes, diabetes, and various organ systems, suggesting that PPARG may influence diabetes pathophysiology through multiple mechanisms. However, further research, including functional studies and larger cohorts, is necessary to fully understand these relationships and their clinical implications. The study's modest sample size and ethnic specificity may limit the generalizability of the results. Additionally, the cross-sectional design restricts the ability to establish causality in the observed associations.

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Conclusion

This study underscores the complexity of T2DM pathophysiology and the importance of considering genetic and biochemical factors in diabetes research and clinical practice. These findings may pave the way for more targeted interventions and personalized medicine approaches in managing T2DM.

This study provides a detailed analysis of the relationship between PPARG genotypes and T2DM in a Nigerian population, highlighting critical demographic and biochemical characteristics (11-14). Key findings include the higher prevalence of the GG genotype among diabetic individuals and significant associations between PPARG genotypes and markers of organ function, such as elevated Cystatin C and ALT, which suggest early renal and hepatic involvement. Furthermore, lower IL-10 levels among diabetic patients may indicate a genetic influence on inflammatory processes in T2DM (17-24).

These insights enhance our understanding of how PPARG genotypes contribute to T2DM susceptibility and complications in this population, underscoring the potential for incorporating genetic markers into personalized diabetes management (15). Further research with larger and more diverse cohorts, as well as functional analyses, is needed to validate these findings and explore the mechanisms by which PPARG genotypes affect diabetes pathophysiology (16). Such studies could ultimately support targeted prevention strategies and tailored treatment approaches for T2DM patients based on genetic profiles.

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Ethical statement

We obtained ethical clearance for this study from the Ethics and Research Committee of the University Teaching Hospital (Protocol Number: EKSUTH/A67/2022/12/022). Additionally, the research adhered to ethical principles, including:

i. Informed Consent: Each participant received a written informed consent form along with the questionnaire, ensuring their consent to participate.

ii. Data Confidentiality: Findings from the study were kept confidential and shared only among co-investigators.

iii. Beneficence: The findings were provided to the managing clinical team at no charge.

iv. Voluntariness: All subjects had the option to decline participation in the study when approached.

Conflicts of interest

The authors declare that there are no conflicts of interest to disclose.

Author contributions

DOA participated in research design, sample collection/analysis, and manuscript writing. MFO participated in research design and overall research supervision. GOD participated in data collation and manuscript writing. COU participated in sample collection and sample analysis. OBO participated in research design, data analysis, and manuscript writing.

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