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Relationship between the rs2241766 ADIPOQ Polymorphism in a Black African Population and the Occurrence of Type 2 Diabetes

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disease, characterized by chronic hyperglycemia. This pathology is linked to various genes whose interaction with the environment promotes its development. The aim of this work was to determine the relationship between the rs2241766 (T/G) polymorphism of the ADIPOQ gene with type 2 diabetes in the black population. **Material and Methods:** This work was a case-control study, involving type 2 diabetics subjects (n = 94) and controls (n = 82). The study took place from September 2022 to September 2023. Patients were recruited in the Endocrinology Department of the Libreville University Hospital Center. Analysis was performed in the Biochemistry laboratory of the University of Health Sciences in Libreville and at the Research Institute of Health Sciences of Bobodioulasso. Genomic DNA was extracted using the protocol Qiagen kit and the PCR-RFLP method was used to determine the rs2241766 (T/G) polymorphism of the ADIPOQ gene. **Results:** Only 2 genotypes were found in this population, the TT genotype and the GT genotype. The proportions were not different between the two groups (p = 0.1095) neither the distribution of G and T alleles (p = 0.1095). On the other hand, the HDL hypocholesterolemia was frequent in subjects with the GT genotype compared to TT heterozygous (51.1% *vs* 48.9%, p = 0.0280; OR = 0.55 [0.30 - 1.01]). **Conclusion:** There was no association between the rs2241766 (T/G) variant of the ADIPOQ gene and the occurrence of type 2 diabetes in this population. On the other hand, a relationship between HDL hypocholesterolemia and the GT genotype has been established.

Keywords

Type 2 Diabetes Mellitus, Polymorphism, rs2241766, ADIPOQ, PCR-RFLP

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by chronic hyperglycemia. It is caused by the combination of defective insulin secretion by the β cells of the pancreas and/or inability to respond appropriately or more simply a resistance of the target tissues to the action of insulin [1]. People living with diabetes are predisposed to the risk of developing a number of serious and fatal complications [2]. In Africa, the number of diabetics was 24 million in 2021 [3]. This number is expected to increase by 129% to 55 million by 2045. [3]

The pathology is multifactorial involving genetic factors. Indeed, the identification of gene architecture has been of great interest for risk prediction and preventive interventions for type 2 diabetes, for better management, or to eliminate the occurrence of the disease [4]. Among the genes regularly studied is the ADIPOQ gene coding for adiponectin. Indeed, the encoded protein is involved in the regulation of glucose homeostasis. To carry out its biological functions, adiponectin binds to two ubiquitous membrane receptors, ADIPO R1 and ADIPO R2, but the first is abundant in muscle [5] [6]. This binding induces the adapter protein APPL1 which will bind to the IRS-1 and IRS-2 proteins and form an APPL1/IRS/IR complex. The IRS proteins thus activated induce the PI3K pathway [5] [6]. Several studies have shown that single nucleotide polymorphisms of adiponectin are associated with diabetes [7]. However, due to the existence of genetic and environmental variations between populations, we therefore proposed to search for a relationship between the rs2241766 (T/G) polymorphism and the occurrence of type 2 diabetes in a black African population. It is located on chromosome 3q27 and is composed of 3 exons and 2 introns. Among the single-nucleotide polymorphisms of the ADIPOQ gene, the variant rs2241766 (T/G) carrying a mutation in exon 2 was detected. This mutation is a replacement of thymine by guanine. The amino acid glycine is preserved despite the mutation. However, biochemical studies have demonstrated a probable instability of the mRNA obtained, confirmed by a reduction of the mRNA to 80% following the presence of the G allele. Thus the G allele would be responsible for the drop in the level of adiponectin and associated with obesity and insulin resistance in type 2 diabetes [8] [9] [10] [11].

2. Methodology

This case-control study, was validated by the National Ethics Committee of Gabon under the reference PROT N˚015/2018/PR/CNE, followed by informed consent from each participant according to the Helsinki recommendations. [12]. The study took place from September 2022 to September 2023 in the endocri-

nology department of the Libreville University Hospital Center, in the Biochemistry laboratory of the University of Health Sciences of Libreville (USS) and at the Research Institute of Health Sciences (IRSS) of Bobodioulasso. The diagnosis of type 2 diabetes mellitus was based of the American Diabetes Association criteria [13].

2.1. Patients

The panel is composed of subjects aged to 20 years or more. The cases were diabetics' subjects followed and treated at the Endocrinology Department of the Libreville University Hospital Center (CHUL), while the controls were patients who came to the Biochemistry laboratory of the USS for a check-up, with normal fasting blood sugar and not have had any Family history of diabetes during the study period. Other types of diabetes and pregnant women and those who refused to participate were excluded from this study.

2.2. Methods

After recruitment, the study population received a questionnaire providing information on sociodemographic parameters, followed by taking anthropometric parameters and taking a blood sample. The anthropometric parameters concerned weight, height, abdominal circumference and blood pressure. The weight was obtained using a personal scale (TEFAL) and the height in meters (m) using a measuring rod. Abdominal circumference was measured using a tape measure, and body mass index in Kg/m^2 (BMI) was calculated by dividing weight (kg) by height (m) squared ($BMI = P/T^2$ (kg/m^2). The measurement of blood pressure (BP) was made with a blood pressure monitor (BEURER), after 5 minutes of rest. Blood samples were taken fasting, in a tube containing EDTA (genetic analysis), a fluoride-oxalate tube (glycemia), and a dry tube (lipids dosage). The biochemical dosages (triglycerides, blood glucose, total cholesterol, HDL cholesterol) were carried out according to the BIOLABO kit protocols using the Mindray BS200® spectrophotometer. LDL cholesterol was obtained by the Friedewald equation, after verifying that the concentration of triglycerides was less than 4 mmol/L [14]. For molecular analyses, genomic DNA was extracted by the Qiagen kit, using the "DNeasy Blood and tissue" protocol, on a sample of 250 µL of whole blood. Then, the PCR-RFLP method was used to determine the rs2241766 polymorphism of the ADIPOQ gene. Gene amplification was carried out with a reaction mixture obtained from 5 µl of FIREPol ®master mix (1X) (Solis BioDyne, Estonia), 1.5 µl of each primer (10 pmol/µl) and 11 µl of sterile water. Thus 19 µl of the reaction mixture and 6 µl of the DNA sample for a total volume of 25 µl were distributed into the sterile wells of a microtiter plate for gene amplification using a thermal cycler (Eppendorf®). The primer sequences were as follows: Forward: 5'GCA GCT CCT AGA AGTAGA CTC TGC TG3'; Reverse: 5'GCA GGT CTG TGATGAAAGAGGCC3' [9]. The PCR steps were composed of an initial denaturation at 95˚C for 4 minutes, followed by a cycle

composed of a denaturation step at 94˚C for 35 s, an annealing at 55˚C for 40 s and extension at 72˚C for 30 s. This cycle was repeated 35 times and ended with a final elongation at 72˚C for 5 min and a refrigeration phase at 4˚C for 10 minutes. At the end, the amplicons were analyzed on 2% agarose gel electrophoresis with ethidium bromide to allow observation of the fragments obtained under ultraviolet light by a Fisher® Bioblock Scientific transluminator. Then, the PCR products were digested with the restriction enzyme SmaI from Biolabs New England. According to their modified protocol, 10 µl of PCR products were digested with 10 units of the enzyme at 25˚C and analyzed on a 2% agarose gel.

2.3. Statistical Methods

The data was collected from a standardized information sheet. This sheet contained sociodemographic and anthropometric data. Excel and SPSS software were used respectively for data entry and analysis. Comparison of quantitative variables between groups was carried out by the ANOVA test. The Chi-square test was used to compare the distribution of qualitative variables between groups, accompanied by the Odds Ratio (OR) and the 95% confidence interval (CI). Verification of compliance with Hardy Weinberg equilibrium in the distribution of different polymorphisms within the population was carried out using the χ^2 conformity test. And the differences were considered significant when the p-value was equal to or less than 0.05 ($p \leq 0.05$).

3. Results

The study population consisted of 183 subjects including 95 diabetics and 88 controls. Table 1 summarizes the sociodemographic and biological parameters of the panel. The mean age was 48.9 ± 13.5 years and the body mass index (BMI) was on average 27.4 ± 5.6 kg/m^2. It was 28.0 ± 5.8 kg/m^2 for the cases compared to 26.3 ± 5.1 kg/m^2 for the controls ($p = 0.0053$). Concerning the biological data, HDL cholesterol was on average 1.2 ± 0.4 mmol/L, with 1.3 ± 0.4 *vs* 1.1 ± 0.4 mmol/L respectively in diabetics and controls ($p = 0.0175$).

Concerning the rs2241766 (T/G) polymorphism of the ADIPOQ gene, the genetic profile presented a band of 390 bp for PCR products (Figure 1). Gene digestion by enzyme restriction SmaI showed that one band of 390 bp (uncut fragment) represented the TT homozygote and three bands (digested fragments) of 390 bp, 217bp, 173 bp for the GT heterozygote (Figure 2). So, the electrophoretic profile obtained showed the presence of only two genotypes, the homozygous TT genotype and the heterozygous GT. Among the two groups of individuals, the proportions of the different genotypes found were similar, i.e. 57.9% *vs* 47.7% and 42.1% *vs* 52.3% for the respective proportions of the GT and TT genotypes in diabetics versus controls ($p = 0.1095$). At the same time, the same observation was made on the distribution of the G and T alleles in the two groups (0.1095) (Table 2). In addition to the distribution of genotypes between controls and cases, a comparison between other variables studied according to

the genotypes obtained was made and was summarized in Table 3. The analysis of these data showed that HDL hypocholesterolemia was frequent in subjects with the GT genotype *versus* TT heterozygous individuals (51.1% *vs* 48.9%, p = 0.0280; OR = 0.55 [0.30 - 1.01]). However, there were no significant differences between the other parameters studied according to genotype.

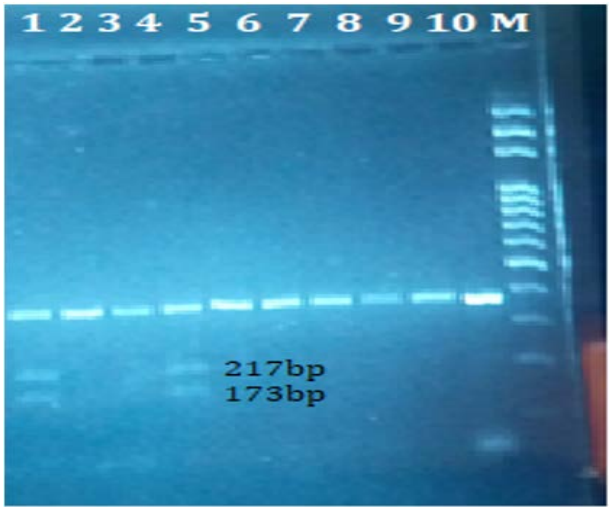
Table 1. Sociobiological parameters of the study population.

Variables	Total	Diabetics	Controls	*P*-Value
n (%)	176	94 (54.4)	82 (46.6)	
Age (years) m ± SD	48.9 ± 13.5	54.4 ± 10.9	39.5 ± 12.4	0.0000
Weight (kg) m ± SD	74.9 ± 15.3	76.3 ± 16.0	72.5 ± 13.7	0.0239
Height (cm) m ± SD	1.66 ± 0.08	1.65 ± 0.06	1.66 ± 0.08	0.1292
Waist circumference (cm) m ± SD	95.0 ± 14.8	98.3 ± 14.8	89.3 ± 12.9	0.0000
BMI (kg/m^2) m ± SD	27.4 ± 5.6	28.0 ± 5.8	26.3 ± 5.1	0.0053
Systolic blood pressure (mm Hg) m ± SD	136.1 ± 24.3	142.3 ± 24.8	125.1 ± 18.9	0.0000
Diastolic blood pressure (mm Hg) m ± SD	85.2 ± 18.5	88.7 ± 19.1	79.1 ± 15.6	0.0010
Glycemia (mmol/L)	6.9 ± 3.5	8.2 ± 3.8	4.8 ± 1.2	0.0000
Total cholesterol (mmol/L)	4.5 ± 1,1	4.6 ± 1.1	4.5 ± 1.1	0.3237
Triglycerides (mmol/L)	0.8 ± 0.4	0.9 ± 0.5	0.6 ± 0.3	0.0000
HDL-C (mmol/L)	1.2 ± 0.4	1.3 ± 0.4	1.1 ± 0.4	0.0175
LDL-L (mmol/L)	3.0 ± 1.1	2.9 ± 1.1	3.2 ± 1.1	0.0149

Data were means ± SD (Standard Deviation); Body mass index (BMI); High-density lipoprotein cholesterol (HDL-C); and Low-density lipoprotein cholesterol (LDL-C).

Lanes (1-7): PCR amplicons, lane 8: Negative control, lane 9: positive control, M: 100 bp DNA ladder.

Figure 1. Gel picture showing PCR results.



Lanes (1, 4): heterozygote GT, lanes (2, 3, 5 - 9): homozygote TT, lane 10 (positive control), M: 100 bp DNA ladder,

Figure 2. Gel picture showing ADIPOQ exon 2 gene Digestion by SmaI on agarose 2%.

Table 2. Comparison of the distribution of genotypes and gene alleles in diabetics and controls

Genes	Total	Diabetics	Controls	Odds ratio	*P*-Value
Genotypes					
GG	0 (0.0)	0 (0.0)	0 (0.0)		0.1095
GT	94 (53.4)	53 (57.6)	41 (48.8)		
TT	82 (46.6)	39 (42.4)	43 (51.2)		
Alleles					
G	94(26.7)	53 (28.8)	41 (24.4)	1.50 [0.80 - 2.70]	0.1095
T	258(73.3)	131 (71.2)	127(75.6)		

Table 3. Comparison of variables according to the rs2241766 (T/G) genotypes of the ADIPOQ gene.

Variables m ± SD n (%)	GT	TT	OR 95% CI	*P*-Value
Age (years) m ± SD	48.8 ± 13.1	47.9 ± 15.0		0.6814
BMI (kg/m^2)	27.2 ± 5.9	27.5 ± 5.6		0.6853
Systolic blood pressure (mm Hg)	134.6 ± 25.0	133.8 ± 24.5		0.8452
Diastolic blood pressure (mm Hg)	84.5 ± 18.5	84.2 ± 19.4		0.9236
Waist circumference (cm)	92.4 ± 13.6	95.1 ± 13.6		0.1935
Glycemia (mmol/L)	6.5 ± 3.2	6.6 ± 4.0		0.8238
HDL-C (mmol/L)	1.2 ± 0.5	1.2 ± 0.4		0.7564
Central obesity				
Yes	24 (25.5)	21 (25.6)	1.0 [0.50 - 1.90]	0.4946
No	70 (74.5)	61 (74.4)		

Continued

Hyperglycemia				
Yes	32 (34.0)	22 (26.8)	0.71 [0.37 - 1.36]	0.3036
No	62 (66.0)	60 (73.2)		
Hypertriglyceridemia				
Yes	4 (4.3)	5 (6.1)	1.46 [0.37- 5.60]	0.5799
No	90 (95.7)	77 (93.9)		
Hypocholesterolemia HDL				
Yes	48 (51.1)	30 (36.6)	0.55 [0.30 - 1.01]	0.0280
No	46 (48.9)	52 (63.4)		
Metabolic syndrome				
Yes	45 (47.9)	40 (48.8)	1.03 [0.57 - 1.87]	0.9042
No	49 (52.1)	42 (51.2)		

4. Discussion

The aim of the work was to investigate the relationship between the rs2241766 (T/G) polymorphism of the ADIPOQ gene and type 2 diabetes. The average body mass index of the study population was 27.4 ± 5.6 kg/m^2 which demonstrates general overweight but is more accentuated at the abdominal level, demonstrated by an average abdominal perimeter which was 95.1 ± 14.8 cm. Furthermore, excess weight was significantly more marked in diabetics than in controls (p = 0.0118). The authors Ovono *et al.*, 2018, then Agyemang *et al.*, 2019 found similar results, respectively in the Gabonese and Ghanaian populations [15] [16]. The single-nucleotide polymorphism rs2241766 (T/G) of the ADIPOQ gene was determined during this study. Thus, observation of the genetic profiles obtained showed the presence of two genotypes, namely the homozygous TT genotype and the heterozygous GT. The proportions between the two groups of individuals were comparable. At the same time, the same observation was made on the distribution of the G and T alleles in the two groups. This result is consistent with that of Tsai *et al.*, in 2014 in taiwan area and that of Farooq *et al.*, in 2018 [17] [18]. Indeed, these authors showed that there was no association between the rs2241766 (T/G) polymorphism of the ADIPOQ gene and type 2 diabetes. Concerning this study, the lack of association between the mutation and type 2 diabetes could be explained by the fact that the adiponectinemia of the subjects is preserved following the conservation of the amino acid despite the mutation. On the other hand, other authors have found an association between this polymorphism and the occurrence of type 2 diabetes. These were the works of Gao *et al.*, in 2013, Hussain *et al.*, in 2018 and those of Hamidi *et al.*, in 2022 [19] [9] [20]. Concerning the absence of the GG genotype in this study, this could be justified by its low sampling compared to those of other studies. Indeed, some authors were able to find this genotype but in very low proportions despite the fact that their sampling was higher than that of this work. [21] [18]. Furthermore, the mutation could be responsible for the elimination of the restriction site of the same enzyme.

Furthermore, a comparison between the genotypes obtained and the other parameters studied was carried out. Data analysis showed that there was no association between insulin resistance, body mass index, obesity and GT genotype. The observation on obesity, a study by Jiefu *et al.* in 2016 found the same result [22]. On the other hand, the results provided by Wu in 2014 through a meta-analysis were discordant [23]. Regarding the lipid profile, the study showed an association between HDL hypocholesterolemia and the G allele of the rs2241766 (T/G) ADIPOQ polymorphism in the GT heterozygote. This observation could be explained by the fact that HDL hypocholesterolemia is a component of the metabolic syndrome, the prevalence of which is high in this population [24]. Indeed, several studies have shown a significantly positive correlation between plasma adiponectin and HDL cholesterol levels in diabetics or not. The protein would be responsible for an increase in HDL levels via an increase in the production of apo-AI. While other authors have shown a negative correlation between adiponectinemia and serum triglycerides. [25] Thus hypoadiponectinemia induced by the mutation present in the GT genotype would induce not only HDL hypocholesterolemia but also hypertrilyceridemia which are two components of the metabolic syndrome.

In addition, other authors have demonstrated that the G allele increases the risk of metabolic syndrome, which supports this observation [26] [27]. Finally, the limitation of this work was based on the lack of adiponectinemia in the study population. This result would have allowed us to investigate the association between this polymorphism and hypoadiponectinemia.

5. Conclusion

The study aimed to investigate the relationship between the rs2241766 (T/G) polymorphism of the ADIPOQ gene and type 2 diabetes mellitus within the Gabonese population. There was no association between this variant and the occurrence of type 2 diabetes in this population. On the other hand, a relationship between HDL hypocholesterolemia and the presence of the GT genotype has been established. This suggests checking the relationship between this variant and lipid profile disturbance in type 2 diabetics.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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