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G894T Polymorphism (rs1799983) of the Endothelial Nitric Oxide Synthase (eNOS) Gene and Coronary Artery Disease in Cotonou (Benin)

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Abstract

Coronary artery diseases comprise a spectrum of disorders affecting the heart and blood vessels, characterized by reduced blood supply to the heart, often resulting from narrowing or obstruction of the coronary arteries. These conditions arise from an interaction between environmental and genetic factors, including the endothelial nitric oxide synthase (eNOS) gene. This study aimed to investigate the involvement of eNOS gene polymorphism in the occurrence of coronary artery disease in the Beninese population of Cotonou. An unmatched case-control observational analytical study was conducted from June to December 2019. The G894T polymorphism (rs1799983) of the eNOS gene was analyzed using the restriction fragment length polymorphism (RFLP) technique, following DNA extraction from whole blood samples. Fasting hyperglycemia was observed in 28.9% of cases compared to 2.6% of controls, and Asp298/Asp298 homozygosity was found in 7.89% of cases versus 2.63% of controls. Although the difference was not statistically significant, a trend toward an association with cardiovascular pathology was observed. This study revealed a high frequency of metabolic abnormalities in cases compared to controls and suggests a potential association between Asp298 allele homozygosity of the eNOS gene and the occurrence of cardiovascular diseases. The G894T polymorphism (rs1799983) of the eNOS gene may play a role in reducing nitric oxide bioavailability and endothelial dysfunction.

Keywords

Coronary Artery Disease, eNOS, Metabolic Abnormalities, Polymorphism

1. Introduction

Cardiovascular diseases, particularly coronary artery diseases, represent a major cause of mortality worldwide, with an increasing burden in low- and middle-income countries such as Benin [1] [2]. Coronary artery diseases result from a complex atherosclerotic process influenced by both environmental and genetic factors [3]. Among the molecular factors involved in the pathophysiology, nitric oxide (NO) plays a crucial role as a vasodilator, anti-inflammatory, and antithrombotic mediator [4]. The synthesis of nitric oxide in the endothelium is catalyzed by the enzyme endothelial nitric oxide synthase (eNOS), encoded by the NOS3 gene [5]. The eNOS gene, located on chromosome 7 (7q35-36), spans 21 kb and comprises 26 exons and 25 introns [6]. Approximately 10 polymorphic loci are distributed throughout the promoter, exonic, and intronic regions of the eNOS gene [7]. A common mutation resulting in amino acid substitutions in mature proteins is the G894T or Glu298Asp (rs1799983) variant, where a guanine-to-thymine substitution leads to the replacement of glutamic acid (Glu) with aspartic acid (Asp) at position 298 in exon 7 [7]. This genetic variant has been associated with impaired NO production and endothelial dysfunction, potentially contributing to the development of atherosclerosis and coronary artery diseases [7] [8]. Studies conducted across diverse populations have demonstrated significant associations between the G894T polymorphism and coronary artery disease risk, although findings sometimes vary across ethnic and geographic contexts [9] [10]. In sub-Saharan Africa, data regarding this association remain scarce, particularly in Benin, where cardiovascular diseases are increasingly prevalent yet remain understudied from a molecular perspective. This study aims to investigate the contribution of the eNOS G894T polymorphism to coronary artery disease in the Beninese population of Cotonou, with the objective of enhancing understanding of underlying genetic factors.

2. Methods

2.1. Study Setting

The Cardiology Department of the Hubert Koutoukou Maga National Hospital and University Center (CNHU-HKM) in Cotonou served as the recruitment site for study participants. All laboratory procedures were conducted at the Histology, Reproductive Biology, Cytogenetics, and Medical Genetics Laboratory (LHBRCGM) of the Institute of Applied Biomedical Sciences (ISBA) in Cotonou.

2.2. Study Design and Period

An observational analytical case-control study was conducted from June to December 2019. Case identification required retrospective review of patient medical records.

2.3. Study Population

The study population consisted of patients undergoing treatment for coronary ar-

tery disease at the CNHU-HKM Cardiology Department and healthy control subjects without coronary artery disease recruited from the general population.

2.4. Inclusion Criteria

Cases were defined as patients receiving monitoring or hospitalization for coronary artery disease at the CNHU-HKM Cardiology Department who provided informed consent. Controls were individuals without coronary artery disease who similarly provided informed consent.

2.5. Exclusion Criteria

All subjects (both patients and controls) who declined participation or failed to provide complete necessary information were excluded from the study.

2.6. Sampling

Our study is an unmatched case-control study. Cases included all patients diagnosed with coronary artery disease and admitted to the cardiology department of CNHU-HKM during the study period who met the inclusion criteria. Controls were selected independently from the general population and were matched to cases based on age group and sex to minimize confounding factors related to these variables. This means that controls were not matched individually to cases, but rather selected to reflect the overall distribution of cases in terms of age and sex.

2.7. DNA Extraction and G894T (rs1799983) eNOS Gene Genotyping

Following medical record review using a standardized data collection form, supplemented by phone calls and patient interviews, 5 mL of peripheral blood was collected from each participant into EDTA-containing tubes. DNA extraction was performed using the organic phenol-chloroform method [11] [12]. DNA quantification was determined using a UV-visible spectrophotometer (Thermo Scientific Evolution 60S). The G894T polymorphism (rs1799983) of the eNOS gene was analyzed by conventional PCR in a 25 µL reaction mixture containing 1 × PCR buffer, 0.2 µM dNTPs, 1.5 mM $MgCl_2$, 0.2 µM of each primer (forward and reverse) (Table 1), and 0.08 U of Taq polymerase. Amplification was followed by digestion with MboI restriction endonuclease at 37˚C for 16 hours and resolution by electrophoresis on a 2.5% agarose gel [7]. The 206 bp PCR product was digested into 119 bp and 87 bp fragments when the T nucleotide was present at position 894 (corresponding to Asp298) [7]. The reaction mixtures were subjected to the amplification programs detailed in Table 2.

Table 1. Primer sequence for eNOS.

Primers	Meaning	Sequences	Height (pb)
eNOS	Fw	5’ CATGAGGCTCAGCCCCAGAAC 3’	206
	Rv	5’ AGTCAATCCCTTTGGTGCTCAC 3’	

Table 2. Amplification program for the G894T (rs1799983) polymorphism in eNOS genes

	Amplification program				
Gene eNOS	**Denaturation**	**Denaturation**	**Hybridation**	**Elongation**	**Elongation**
	95˚C (5 min)	95˚C (1 min)	60˚C (1 min)	70˚C (5 min)	72˚C (10 min)
	30X				

2.8. Study Population

Informed consent was obtained from all participants prior to their inclusion in the study. All collected data were treated with strict confidentiality. Patient anonymity was maintained throughout the research process, and specific approval was obtained before blood sample collection.

2.9. Ethical Consideration

Informed consent was obtained from patients before their inclusion in the study. The information collected during this survey was strictly confidential. Patient anonymity was maintained, and their consent was obtained before blood samples were taken.

3. Results

3.1. Socio-Epidemiological Characteristics

The study enrolled 76 participants, comprising 38 cases and 38 matched controls. The mean age of the study population was 53.09 ± 11.03 years (range: 35 - 78 years). The 35 - 45 age group was most represented, constituting 34.2% of participants. Cases demonstrated a significantly higher mean age (58.52 ± 9.73 years) compared to controls (47.65 ± 9.56 years). Male participants predominated (84.2%), with an overall sex ratio of 5.33 (4.33 among cases and 6.6 among controls). Hypertension and diabetes were the most prevalent cardiovascular risk factors (CVRFs) among patients, with 18 cases (47.4%) presenting more than two concurrent CVRFs.

3.2. Clinical Presentations of Coronary Artery Disease

Among the 38 cases, 30 patients (78.9%) presented with ST-segment elevation myocardial infarction (STEMI), while the remaining 8 patients (21.1%) exhibited non-ST-segment elevation acute coronary syndrome (NSTEMI) with elevated troponin Ic levels.

3.3. Biochemical Parameters

Significant differences in metabolic parameters were observed between groups. Fasting hyperglycemia was present in 11 cases (28.9%) compared to 1 control (2.6%). Total hypercholesterolemia was identified in 1 case versus 2 controls, while LDL hypercholesterolemia was documented in 6 cases and 8 controls. A substantial proportion of cases (18/38, 47.4%) demonstrated HDL hypocholester-

olemia compared to controls (8/38, 21.1%). Hypertriglyceridemia was observed in 4 cases and 1 control. Abnormal serum creatinine levels were noted in 34.2% of cases compared to 2.6% of controls. Assessment of renal function using the simplified MDRD formula revealed reduced glomerular filtration rate in 20 cases (52.6%) versus 1 control (2.6%).

3.4. G8947 Polymorphism (rs 1799983) of the eNOS Gene

Search for the eNOS gene in subjects

Genotyping analysis

Figure 1 shows the profiles of the subjects after agarose gel electrophoresis of the PCR products following enzymatic digestion with MboI.

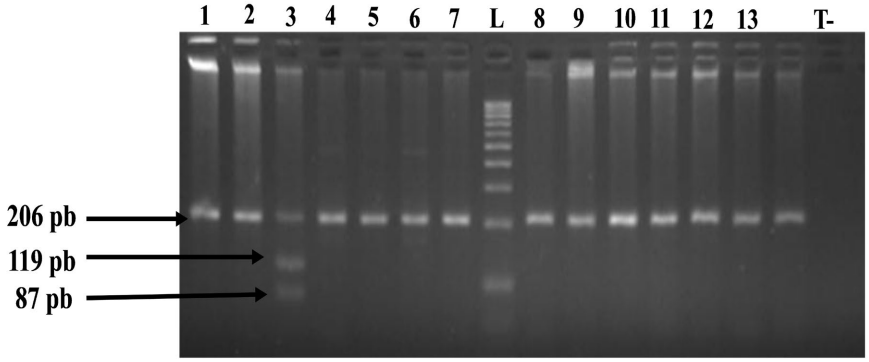

Figure 1. Electrophoretic profile of subjects after enzymatic digestion.

Biallelic polymorphism in exon 7 of the NOS 3 gene detected by enzymatic digestion with MboI restriction of the 206 bp PCR product. Migration wells 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 showed restriction patterns corresponding to homozygosity for Glu298; migration well 3 showed a restriction pattern corresponding to homozygosity for Asp298. Homozygosity for Asp298 was found in 03 (7.89%) cases and 01 (2.63%) controls.

No formal a priori sample size calculation could be performed because the study included all eligible cases of coronary artery disease available during the study period. However, a post hoc power analysis was performed to assess the study's ability to detect the observed effect size. With a total sample of 76 participants (38 cases and 38 controls) and an allele frequency of Asp298 ranging from 2.6% in controls to 7.9% in cases, the study had an estimated statistical power of approximately 60% - 70% to detect an odds ratio of 3.0 or greater at a significance level of 5%. Although modest, this level of power is acceptable for exploratory genetic association studies conducted in low-resource settings and confirms the relevance of the observed trend toward an association between Asp298 homozygosity and coronary artery disease. Larger studies will nevertheless be necessary to confirm these results with higher statistical power. Table 3 shows us the genotype and allele frequencies, Hardy-Weinberg equilibrium, an association test, and a χ^2 test.

Table 3. Genotypic and allelic frequencies, Hardy-Weinberg equilibrium, and an association test and a χ^2 test.

Group	Genotypes (n)	Genotypes frequencies (%)	Alleles (n)	Alleles frequencies (%)	HWE χ^2 (p)
Subjects (n = 38)	Glu/Glu = 35	92.1%	Glu = 70	92.11%	38.00 ($p \approx 7.07 \times 10^{-10}$)
	Glu/Asp = 0	0.0%	Asp = 6	7.89%	
	Asp/Asp = 3	7.9%			
Control subjects (n = 38)	Glu/Glu = 37	97.4%	Glu = 74	97.37%	38.00 ($p \approx 7.07 \times 10^{-10}$)
	Glu/Asp = 0	0.0%	*Asp = 2*	2.63%	
	Asp/Asp = 1	2.6%			

3.5. Interaction between the G894T (rs1799983) Polymorphism of the eNOS Gene and Predisposition to Coronary Artery Disease

The impact of the G894T (rs1799983) polymorphism of the eNOS gene on susceptibility to coronary artery disease and their reciprocal interaction were assessed using the logistic regression model summarized in Table 4.

Table 4. Impact of the G894T eNOS polymorphism on susceptibility to coronary artery disease.

	Control subjects	Subjects	OR**	IC	RPr***
Negative	37 (51.39%)	35 (48.61%)	1	-	1
Positive	01 (25%)	03 (75%)	3.17	1.34 - 29.09	1.54

*reference modality; **: odds ratio, also known as relative risk ratio, is a statistical measure expressing the degree of dependence between qualitative random variables; ***: prevalence ratio.

With an odds ratio of 3.17, we can say that subjects carrying the G894T allele of the eNOS gene are 3.17 times more likely to develop coronary artery disease than controls.

4. Discussion

This study investigated cases with coronary artery disease and control subjects with a mean age of 53.09 ± 11.03 years. Our findings are consistent with research by Arafa *et al.* [13] in 2018, who reported a mean age of 55 ± 9.9 years in an Egyptian case-control population, though their study examined both eNOS and Apo E genes as potential risk factors for coronary artery disease. Similarly, work by Younan *et al.* in 2014 identified a mean age of 51.71 ± 8.97 years in an Egyptian population with coronary and carotid atherosclerotic disease [14].

The results of our study revealed a high frequency of metabolic disorders among patients compared to controls, particularly regarding glycemic parameters, lipid profile, and renal function. Fasting hyperglycemia was observed in 28.9% of cases versus 2.6% of controls, suggesting a higher prevalence of glucose

regulation disorders among cases. Hyperglycemia is a well-established risk factor for renal and cardiovascular complications and is frequently associated with lipid abnormalities such as hypertriglyceridemia and reduced HDL cholesterol [15]. Regarding lipid profile, one case exhibited total hypercholesterolemia compared to two controls. HDL-C hypocholesterolemia was significantly more prevalent in cases (47.4%) than controls (21.1%), consistent with the typical dyslipidemic phenotype observed in patients with chronic kidney disease (CKD) [15] [16]. This observation aligns with work by Shiqi *et al.* in 2021, which demonstrated that an elevated TG/HDL-C ratio serves as an independent predictor of declining glomerular filtration rate (GFR), particularly in elderly subjects [17]. Abnormal serum creatinine levels were present in 34.2% of cases compared to only 2.6% of controls, indicating moderate to severe renal impairment. This trend was confirmed by GFR assessment using the MDRD formula, which revealed reduced GFR in 52.6% of cases versus a single control (2.6%). These findings are consistent with existing literature. In a retrospective cohort study, Nagayama *et al.* observed that lipid disorders, particularly elevated triglycerides and reduced HDL-C, are significantly associated with progressive GFR decline [18]. Furthermore, work by James demonstrated that the TG/HDL-C ratio is a robust predictive marker for chronic kidney disease risk, independent of other metabolic factors [19]. This association may be explained by mechanisms of lipotoxicity, endothelial dysfunction, and chronic inflammation observed in contexts of lipid abnormalities and metabolic stress [20].

The human endothelial nitric oxide synthase (eNOS) gene is considered one of the genes associated with cardiovascular conditions. In the present study, homozygosity for the Asp298 allele of the eNOS gene was identified in 7.89% of cases versus 2.63% of controls. Although this difference was not statistically significant due to the relatively small sample size, it suggests a potential association between the Asp/Asp genotype and coronary artery disease occurrence. This finding aligns with several previous studies indicating that the Asp298 variant of the eNOS gene may impair endothelial nitric oxide synthase activity, thereby reducing nitric oxide (NO) production—a crucial vasodilator regulating vascular tone and endothelial function [7] [8] [21]. NO plays an important protective role in cardiovascular function by inhibiting platelet aggregation, vascular smooth muscle cell proliferation, and leukocyte adhesion to the vascular wall [22]. Decreased NO production may promote prothrombotic phenomena, vascular inflammation, or endothelial dysfunction, all of which are implicated in the pathophysiology of cardiovascular diseases [4] [23].

Recent and classic studies show that the Glu298Asp (rs1799983) polymorphism of the eNOS (NOS3) gene plays an important role in the pathophysiology of coronary artery disease. In a study conducted in 2024 by Vecoli1 *et al.* involving 506 patients suspected of having stable coronary artery disease, the Asp298 allele was independently associated with induced myocardial ischemia, even after adjusting for obstructive coronary lesions and other traditional risk factors [24]. This is consistent with the results found in our study, except that the sample size in our study

is not significant. In terms of coronary heart disease (CHD), a meta-analysis of 39 case-control studies (7489 cases, 7051 controls) showed that the Asp genotype (vs. Glu) is significantly associated with increased susceptibility to CHD [25]. Earlier, another meta-analysis of 26 studies (23,028 subjects) had already shown that Asp/Asp homozygosity moderately increases the risk of ischemic heart disease (OR ≈ 1.31) [26].

A major meta-analysis combining 39 studies involving over 10,000 coronary artery disease cases revealed a significant association between Asp/Asp homozygosity and increased coronary artery disease risk (OR = 1.31; 95% CI: 1.13 - 1.51) [24] [25]. Similarly, a study conducted in Greece demonstrated that individuals carrying the Asp298 allele had an almost twofold increased risk of myocardial infarction [26] [27]. However, the low frequency of this homozygosity in both groups, along with the modest difference between cases and controls, requires cautious interpretation. Moreover, studies conducted in different populations have reported variable frequencies of this mutation, suggesting potential influences of ethnic or environmental factors on the distribution of eNOS gene polymorphisms [28] [29]. However, the low frequency of this homozygosity in both groups, as well as the modest difference between cases and controls, must be interpreted with caution.

It is important to note that multifactorial diseases such as coronary artery diseases sometimes exhibit variable phenotypes across populations [30]. It should be noted that Fathelbab's 2025 study of 100 patients with acute coronary syndrome who underwent coronary angiography showed that the c.894G>T polymorphism of eNOS is associated with an increased risk of coronary artery dilation but does not appear to contribute significantly to atherosclerotic coronary artery disease [31]. Although several studies have reported an association between eNOS gene polymorphism and coronary artery diseases, other investigations, particularly those by Hibi *et al.* and Yoon *et al.*, found no relationship between this polymorphism and coronary artery disease risk [32] [33].

It is important to note that multifactorial diseases such as coronary artery disease sometimes present a variable phenotype from one population to another [30]. Although several studies have reported a link between eNOS gene polymorphism and coronary artery disease, other studies, notably those conducted by Hibi *et al.* and Yoon *et al.*, have reported that there is no link between this polymorphism and the risk of developing coronary artery disease [28] [34]. This perfectly illustrates the multifactorial nature of coronary artery disease, with interaction between genetic susceptibility factors and environmental factors.

Our study warrants further investigation on a larger sample size in order to analyze the combined effect of this mutation with other cardiovascular risk factors (hypertension, smoking, diabetes, dyslipidemia, etc.). In addition, a functional analysis could be considered in order to better understand the pathophysiological impact of the Asp/Asp genotype in the Beninese population.

5. Limits

This study has several limitations. The relatively small sample size limits statistical power and may restrict the detection of modest associations. Selection bias cannot be ruled out due to the participant recruitment methods. Finally, despite adjusting for relevant variables, residual confounding factors remain possible, particularly those that were not measured.

6. Conclusion

This study demonstrated a high prevalence of metabolic abnormalities among cases, including fasting hyperglycemia, low HDL cholesterol, moderate hypertriglyceridemia, and impaired renal function. The findings suggest a potential association between Asp298 allele homozygosity of the eNOS gene and cardiovascular disease development. Although the frequencies observed in our sample do not establish statistical significance, they align with existing literature that attributes a potential role to this polymorphism in reducing nitric oxide bioavailability and promoting endothelial dysfunction. However, ethnic variability and genotype-environment interactions may influence both the distribution and clinical expression of this variant. Future large-scale studies incorporating combined genetic approaches and precise clinical data are necessary to confirm these observations and further elucidate the contribution of the Asp298 polymorphism to cardiovascular risk in the Beninese population.

Conflicts of Interest

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

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