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XbaI and EcoRI polymorphism of apolipoprotein B 100 gene and lipids abnormalities in HIV infected patients

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Abstract: Human Immuno-deficiency Virus (HIV) infection is associated with lipoprotein abnormalities leading to cardiovascular diseases. Few reports are available about plasma apoproteins concentration abnormalities and apolipoproteins genes mutations in infected persons. This study aimed to investigate the association between lipoprotein abnormalities and the Apolipoprotein B100 gene Xba1 and EcoR1 polymorphisms in HIV infected patients. A total of 87 controls and 70 HIV-infected antiretroviral-naive patients were included. Their serum lipids and apolipoproteins profiles were determined. In subjects with dyslipidemia, the molecular characterization of the apolipoprotein B100 gene was carried out using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Total cholesterolemia (1.82±0.46 g/L *vs* 1.97±0.44 g/L) and apolipoproteinemia A1 (1.20±0.25 g/L *vs* 1.43±0, 24g/L) were lower in HIV-positive (*p=0.038* and *0.0001* respectively) but the atherogenic index ApoB100/ApoA1 (0.79±0.32 *vs* 0.69±0.22) was higher in HIV-positive (*p=0.041*). Apo B100 gene mutations related to both polymorphisms studied were found in the 2 groups.Hyperapolipoproteinemia B100 and normal LDL Cholesterolemia were predominant regardless of the polymorphism (Xba1 or Eco R1) and allele statut (mutant or wild). HIV-positive patients were more at risk of cardiovascular diseases. The mutations of the ApoB100 gene have been found but their established relationship with dyslipoproteinemias is to be confirmed.

Keywords: lipoproteins, Apoproteins mutations, PCR-RFLP, HIV-ART-naive positive.
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INTRODUCTION

In West African countries, Côte d'Ivoire has the highest rate of HIV infection with a prevalence rate of 3.2% in the adult population **[1, 2**]. The natural evolution of this infection is accompanied by disorders of the serum lipid levels. However, oil profiles described are sparse, especially for total cholesterol (CT) **[3, 4, 5]**. Essentially they consisted of high density cholesterol (HDL-C) and low density cholesterol (LDL-C) and an increase in triglycerides (TG) **[4, 6]**. During antiretroviral therapy (ART), these disorders consisted of decreased HDL-C **[3]** and increased LDL-C which together constitute a highly atherogenic lipid profile **[7, 8, 9]**. Often increased plasma LDL-C is associated with increased apolipoproteinemia B (ApoB) **[7**]. Therefore, HIV positive patients receiving ART or not, have lipid metabolism abnormalities or dyslipidemia that exposes them to cardiovascular disease, such as atherosclerosis **[10]**.

In the literature, several data describing the lipid metabolic disorders in HIV-positive patients have been reported, but those concerning apoprotein abnormalities are rare. However, apolipoproteins are the major proteins transporting and guiding metabolism of blood lipids in high density lipoprotein (HDL) and low density lipoproteins (LDL). To our knowledge, very few reports and data concerning the molecular abnormalities affecting the genes of these apolipoproteins in HIV-positive patients are available. Knowing that all proteins are encoded by a specific gene, we put forward a hypothesis that there are abnormalities in the gene of apoproteins which transport plasma lipids or their genetic expressions.

The aim of this study was to investigate the relationship between lipoprotein abnormalities and the polymorphism of the ApoB100 gene during HIV infection.

MATERIAL AND METHODS

Period of study and study population

From February 2013 to march 2015, in Abidjan (Côte d'Ivoire), the study enrolled 87 healthy voluntary blood donors from the National Blood Transfusion Center (CNTS) and 70 HIV-infected antiretroviral-naive patients from the Blood donors monitoring center (CMSDS).The study population consisted of a group of assumed healthy subjects apt to donate blood according to the CNTS criteria on blood donation [**11**]. The second group consisted of HIV-positive ART-naive patients. Each group had a properly filled medical card. However, only subjects with a disturbed lipid balance were retained for molecular biology analyzes.

Concerning ethical considerations, the study protocol were validated by the CNTS ethics committee and the participants gave their informed consent to participate in the study. The identification of each subject was done under anonymity by assigning them a code.

Primers and endonucleases used

The primers were synthesized by SIGMA-ALDRICH. Their sequences were as follows: Bc1 (forward): batch HA06611949 (5'-GGAGACTATTCAGAAGCTAA-3') / Bc1R (reverse): batch HA06611950 (5'-CTGAGAGAAGTGTCTTCGAAG-3') for the study of Xba1 polymorphism andBc2 (forward): batch HA06611951 (5'-GAAGAG CCTGAAGACTGACT-3') / Bc2R (reverse): batch HA06611952 (5'-CTCGAAAGGAAGTGTAATCAC-3') for the study of EcoR1 polymorphism. Enzymatic digestion was performed using the 2 restrictive enzymes: Xba1 (recognized sequence: 5'T / CTAGA3') and EcoR1 (recognized sequence : 5'G / AATTC3') [**12**].

Type of study

A cross-sectional study was carried out, involving first the measurement of substrates in serum (TG, total cholesterol and its fractions, Apolipoprotein A1 and Apolipoprotein B100). Then the concordance between the disorders in the lipid balance (TG, TC and its fractions) and those of the apoproteins (A1 and B100) were analyzed in order to highlight the one that would allow a better detection of cardiovascular risk. In the second step, we carried out the molecular characterization of the apolipoprotein B100 gene. This second step was performed only in subjects with a lipoprotein abnormalities in order to enhance the possibilities to observe molecular abnormalities.

Sample collection and storage

Blood samples were collected through venipuncture at the elbow after fasting for at least 12 hours. The blood were collected in 2 tubes: one tube without anticoagulant for the determination of lipids and apolipoproteins and another tube containing Ethylene Diamine Tetra Acetic Acid (EDTA) for molecular biology analyzes. After centrifugation, serum, plasma and cells were aliquoted and frozen at -80°C when the analysis were to be done later.

Methods of biological analysis

Determination of lipoprotein contents

Lipid parameters in serum, particularly TG, TC, HDL-C and LDL-C were determined, using the COBAS INTEGRAS 400 PLUS (Roche, France) by enzymatic colorimetric test according to Trinder. ApoA1 and ApoB100 were mesured by immune turbidimetry.

Determination of the ApoB100 Xba1 and EcoR1 gene polymorphism

Total genomic DNA was isolated from peripheral blood leukocytes using ion exchange resin column through the Qiagen® kit method **[13]**. A final volume of 100 µl pure DNA was obtained. Concentration (µg / mL) and purity of DNA extracted was checked using ultra-violet visible spectrophotometry at absorbance 260 nm and 280 nm. Each extract was then divided into 2 aliquots in cryotubes; one of them was stored at 4 ° C until amplification and the second at -80°C for further analyzes.

PCR of each sample was carried out in a total volume of 50 Ml comprised 1.5 Ml of each primer (10 Mm), 5Ml of a mixed solution of the 4 dNTP (2 Mm), 1.5 Ml of $MgCl_2$ (50 Mm), 5 Ml of 10X buffer solution, 0.5 Ml Taq polymerase (5 U / Ml), 5 Ml genomic DNA and 30 Ml waters. The PCR program was performed on an ABI 2720 Thermal Cycler (Life Technology). The PCR programs consisted of initial denaturation for 5 min at 95°C,

followed by 33 cycles of denaturation at 95°C for 45 sec., hybridization at 58°C. for 45 sec and elongation at 72°C. for 45 sec and then a final elongation at 72°C for 10 min and finally 4°C continusly [**14, 15**]. The final amplification products were submitted to digestion with respective restriction enzymes: Xba1 (T / CTAGA) and EcoR1 (G / AATTC) **[12, 15, 16]** after mix and incubation at 37 °C over night.

After the digestion step, the DNA fragments were separated by electrophoresis on 2% agarose gel with ethidium bromide (ETB). The revelation of the migrated fragments was done under ultraviolet light (UV) and the gel images were stored as photographic and electronic file (**Figure 1**).

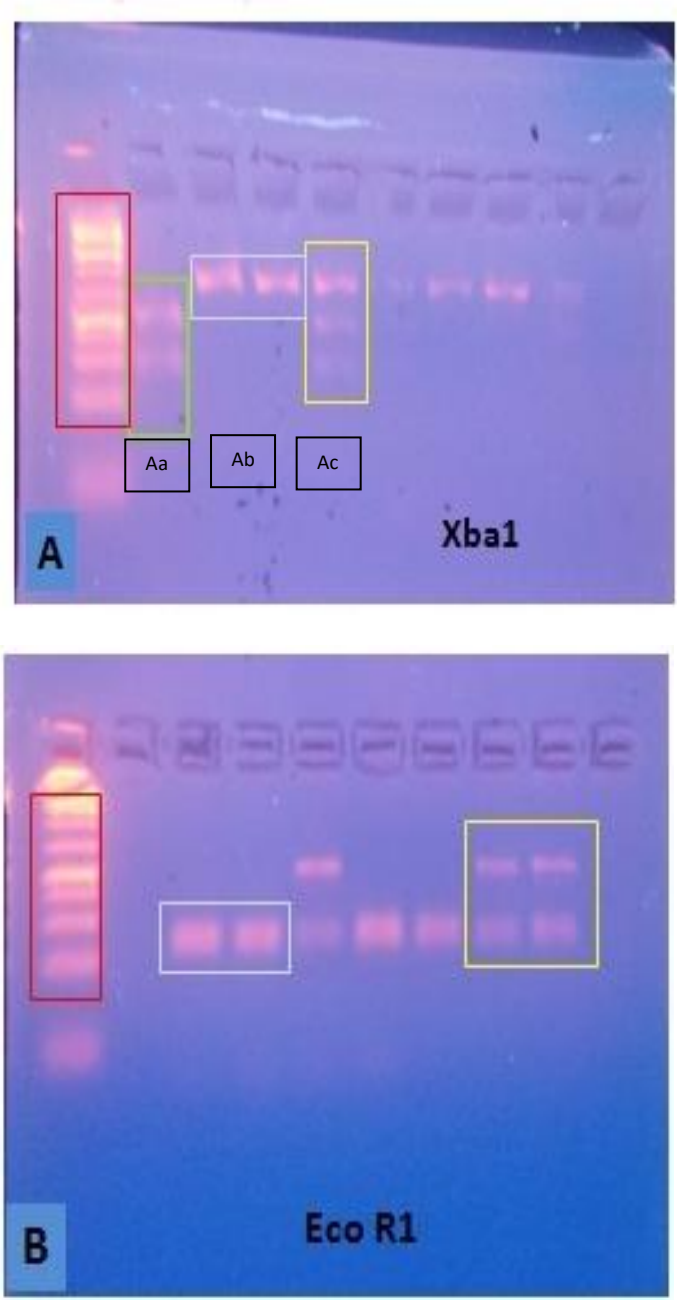

Figure 1: Electrophoretic profiles of ApoB100 gene amplicons. **A:** Genotypes of Xba1 Polymorphism; Profile (Aa): Homogeneous population of digested DNA fragments (mutant DNA= X+/+), Profile (Ab): homogeneous population of undigested DNA fragments (wild DNA= X-/-), Profile (Ac): heterogeneous population of Undigested DNA fragments and digested DNA fragments (mixture of wild and mutant type DNA= X+/-).
B: genotypes of Eco R1 polymorphism, Profile (Ba): homogeneous population of digested DNA fragments (wild DNA= E+/+), Profile (Bb): heterogeneous population of digested and undigested DNA fragments (mixture of wild and mutant DNA= X+/-)

STATISTICAL ANALYSIS

The data collected was analyzed using the SPSS 16.0 software. The presence of DNA digestion was noted (+) and its absence (-). Quantitative variables were expressed as mean ± SD, minimum and maximum. The qualitative ones were expressed as percentages (%) and numbers (n).The comparisons were made using statistical tests: Student t test for the quantitative values of normal distribution and Chi 2 for the qualitative values. The tests were considered significant at risk $\alpha < 0.05$.

RESULTS

Sociodemographic characteristics

In this study, we recruited 157 subjects, of whom 55.4% (n = 87) were presumed to be healthy and 44.6% (n = 70) were HIV-positive. The average age of the study population was 37.62 ± 9.73 years and there was a male predominance (sex ratio: 2.27). The mean BMI of HIV-positive was higher than that of the presumed healthy subjects (25.03 ± 4.81Kg / m2 vs 23.49 ± 3.53 Kg / m^2; p = *0.025*).

Biochemical characteristics

The prevalence of apoprotein abnormalities and that of classic lipid abnormalities was respectively 77,07% and 49,68%. The HIV-positive group had lower mean of total cholesterol and apoproteinemia A1 than the healthy group (*p = 0.038* and *p <0.0001* respectively) but they had higher mean value of atherogenic index ApoB100 / ApoA1 (p = 0.041) (Table I). The analysis of the concordance between lipid parameters measurement and apolipoproteins one showed that apoprotein abnormalities were more sensitive in the search for atherogenic risk than those of classic lipids abnormalities (X^2 : *p = 0.013;* Kappa: k = 0,17).

Table I: Comparison of Mean Concentrations of Biochemical Parameters

Parameter	Healthy subject (n=87)	HIV-positive (n=70)	P-value
	mean±SD (g/L)	mean±SD (g/L)	
TG	1,06±0,04	1,19±0,64	0,138
T C	1,97±0,44	1,82±0,46	0,038
HDL-C	0,55±0,16	0,50±0,23	0,083
LDL-C	1,08±0,37	1,17±0,43	0,14
APO A1	1,43±0,24	1,20±0, 25	0,000
APO B	0,97±0,30	0,90±0,27	0,121
TC/HDL-C	3,88±1,50	4,55±4,43	0,134
APO B /APO A1	0,69±0,22	0,79±,32	0,041

Table 2: Frequency of genotypes and alleles

Genotypes and alleles	Global Frequency N=16	Healthy subjects N=5	HIV-positive N=11
Xba 1 Polymorphism			
Wild genotype (X-/-)	10 (62,50%)	3 (30,00%)	7 (70,00%)
Mutant / wild genotype (X-/+)	5 (31,20%)	2 (40,00%)	3 (60,00%)
Mutant genotype (X+ /+)	1 (6,20%)	0 (0,00%)	1 (100,00%)
Wild Allele (X-)	25 (78, 13%)	8 (80,00%)	17 (77,27%)
Mutant Allele (X+)	7 (21,87%)	2 (20,00%)	5 (22,73%)
EcoR 1 Polymorphism			
Wild genotype (E+/+)	12 (75,0%)	3 (25,00%)	9 (75,00%)
Mutant /wild genotype(E+/-)	4 (25,0%)	2 (50,00%)	2 (50,00%)
Mutant genotype (E-/-)	0 (0,00%)	0 (0,00%)	0 (0,00%)
Wild allele E+	28 (87,50%)	8 (80%)	20 (90,90%)
Mutant allele E-	4 (12,50%)	2 (20%)	2 (9,09%)

Table 3: Analysis of the presence of alleles and variations of B100 apolipoproteinemia and LDL cholesterol

Alleles	Apoproteinemia B100		
	Low < 0,50 g/L	Normal 0,50 à 0,82 g/L	High > 0,82 g/L
Xba 1 Polymorphism			
Allele (X-)	1 (10,00%)	2 (20,00%)	7 (70,00%)
Allele (X+)	0 (0,00%)	1 (16,70%)	5 (83,30%)
EcoR 1 Polymorphism			
Allele E+	0 (0,00%)	3 (25,00%)	9 (75,00%)
Allele E-	1 (25,00%)	0 (0,00%)	3 (75,00%)
	LDL-C		
	Normal < 1,60 g/L		High ≥ 1,60 g/L
Xba 1 Polymorphism			
Allele X-	9 (90,00%)		1 (10,00%)
Allele X+	4 (66,70%)		2 (33,33%)
EcoR 1 Polymorphism			
Allele E+	9 (75,00%)		3 (25,00%)
Allele E-	4 (100%)		0 (0,00%)

Molecular characterization

The two polymorphisms of the apoB100 gene studied were found in the 2 groups of the study population. Of the 3 possible expected genotypes in each case, we found three genotypes of Xba1 polymorphisms: X -/-, X-/+ and X +/+ and two of Eco R1 polymorphism: E +/+ and E +/- (Figure 1 and Table II) were found. Mutant alleles were more frequent in HIV-positive (Table II). The link between the Apo B100 genotypes and the levels of serum lipids showed that normal LDL cholesterolaemia and hyper-apoproteinemia B100 were predominant (Table III).

DISCUSSION

The study population was predominantly male and young. This double characteristic is one of CNTS voluntary blood donors. Indeed, it has already been demonstrated that most of the voluntary donors in the CNTS were young and male gender [**11**].

HIV-positive had higher BMI than the controls. This weight gain in HIV-positive was due to a healthy lifestyle. This could be explained by the quality of the medical care given to the patients of this center thanks to its multidisciplinary medical team. Similar results were reported in previous studies **[8, 17]**.

The prevalence of apoprotein abnormalities was higher than that of classic lipid abnormalities. Comparing the two groups, we observed statistically significant a lower apoproteinemia and increased APO B 100/APO A1 ratio in HIV-positive population which are cardiovascular risk factors. In fact, a study carried out in ART-naive patients reported a high incidence of dyslipidemia with lower HDL and hypertriglyceridemia [**18**]. Other studies reported high prevalence of dyslipidemia in HIV-positive **[8, 9, 17, 19].** The concordance between lipid parameters measurement and apolipoproteins one showed that apoprotein abnormalities were more sensitive in the search for atherogenic risk than those of classic lipids abnormalities. This result suggested that in lipoprotein abnormalities, apolipoproteins are the first components to be disrupted during HIV infection. In fact, apolipoproteins A1 and B100 are the major proteins transporting blood lipids in high density lipoprotein (HDL) and low density lipoproteins (LDL, V-LDL). So normally, lipids abnormalities should appear after apoproteins ones.

The mutations related to the 2 polymorphisms (Xba1 and Eco R1) were found in both the healthy

group and the HIV-positive group. In our study, there was also a mutant for the 2 alleles of the Xba1 (X +/+) polymorphism. The study of Jaime SC and al. [20] in Mexico and that of Kodogo in Zimabwé et al. (2016) reported the presence of the 3 possible genotypes (wild : X-/-, wild / mutant : X-/+ and mutant : X+/+). However, a study carried out in China with a large population, found no mutants for these two alleles (X+/+) [**15**]. This difference could be explained by the genetic variability between their study populations and ours. The differences can also be explained by the study population's size. The study done by Scartezini M and al. [21] which investigated the Xba1 and Eco R1 polymorphisms found all possible genotypes (wild, mutant / wild, mutant) while we did not find the mutant genotype for the E alleles (E -/-). This could be explained due to the fact that our population was small, but also due to genetic variability.

Hyperapoproteinemia B was predominant regardless of the polymorphism (Xba1 or Eco R1) and the allele (mutant or wild), but LDL cholesterolemia was normal in most cases. Concerning the Xba1 polymorphism, the study of Liu and al. **[15]** reported results which were different from ours. In their study, Apoproteinemia B was normal in all cases while LDL cholesterol was significantly higher in mutants / wild (X -/+). It has also been shown that there is a relationship between increased total cholesterolemia, LDL cholesterolemia, serum ApoB100 and portability of the mutant allele (X+) of the Xba1 polymorphism **[15, 14]**. Kallel and al. **[22]** reported that the mutant allele of Xba1 increases serum lipid concentrations.

CONCLUSION

This cross-sectional study comparing the two groups of subjects was undertaken to investigate the relationship between the occurrence of dyslipidemia and the polymorphism of the ApoB100 gene during HIV infection. We found that atherogenic risk was more common among HIV-positive. In addition, protein disorders were included more frequent than lipid disorders in the search for dyslipidemias. The polymorphism of the ApoB100 gene (Xba1 and Eco R1) was present in both healthy and HIV-positive subjects. However, their link with dyslipidemia in Côte d'Ivoire is to be confirmed.

DECLARATIONS

Ethics approval and consent to participate :
All participants were informed about the risks and benefits associated with their participation in the present study. All of them gave their consent to participate. Data collected during this study were done according to study protocol approved by the National Ethics Committee of Côte d'Ivoire. The committee's reference number is : N° 3766/MSHP/30/Juillet 2009.
Availability of data and material : The data used and/or analysed during the current study can be obtained from the corresponding authors on reasonable request.

Competing interests : The authors declare that they have no competing interests.

Authors' contributions

This work was carried out in collaboration between all authors. Author KF was responsible for the literature searches, wrote the first manuscrit of the protocol, performed the datas collection, perormed the molecular biolgie analysis, the data analysis and their interpretation, and wrote the first manuscrit of the article. Author EAA take care of the literature searches, gave the final approval of the study design the protocole on the biochemistry side. Author TT provided technical supervision of molecular biology analyzes : PCR, electrophoresis and RFLP experiments. Authors ABC performed the RFLP reactions. Authors HAML and AHFT proof read the article. Author DAJ gave the final approval of the study design and protocole on the molecular biologie side. He gave the final approval of the article version to be published in collaboration with author MD. Author MD coordinated data collection, biochemical and molecular biological sides of the study. All authors have read and approved the final manuscript.

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