Association of Biomarkers with Atherosclerosis and Risk for Coronary Artery Disease in Patients with HIV

Maria da Conceição Brandão de Arruda Falcão[1], Josefina Cláudia Zírpoli[1], Valéria Maria de Albuquerque[2], Brivaldo Markman Filho[1], Nelson Antônio Moura de Araújo[1,2], Creso Abreu Falcão[2], Demócrito de Barros Miranda-Filho[2], Ricardo Alencar de Arraes Ximenes[1,2], Maria de Fátima Militão de Albuquerque[3], Heloísa Ramos Lacerda[1,2]

Universidade Federal de Pernambuco[1]; Universidade de Pernambuco[2]; Instituto Aggeu Magalhães, Fundação Oswaldo Cruz[3], Recife, PE - Brazil

Abstract

Background: The massive use of Highly-Active Antiretroviral Therapy (HAART) in individuals with human immunodeficiency virus (HIV) coincided with an increase in cardiovascular disease, a major cause of morbidity and mortality in this group.

Objective: To determine the frequency of carotid atherosclerosis and the association between biomarker levels and carotid intimal-medial thickening in HIV-positive individuals treated for HIV at referral centers in Pernambuco.

Methods: This was a cross-sectional study of 122 HIV-positive patients. Subclinical carotid atherosclerosis was considered with the presence of increased intimal-medial thickness of the common carotid artery > 0.8 mm or plaques in the carotid ultrasound. The following inflammatory biomarkers were analyzed: IL6, IL1-β, TNF-α, high-sensitivity CRP, sVCAM-1 and sICAM-1.

Results: Of the 122 patients analyzed, most were men (60.7%) aged > 40 years (57.4%) receiving HAART (81.1%). The prevalence of atherosclerosis was 42.6% (52 cases). Patients older than 40 years and intermediate or high Framingham score were more likely to develop atherosclerosis at the univariate analysis. Age older than 40 years (OR = 6.57, 95%CI: 2.66 to 16.2, p = 0.000), male gender (OR = 2.76, 95%CI: 1.12 to 6.79, p = 0.027) and presence of syndrome metabolic (OR = 2.27, 95%CI: 0.94 to 5.50, p = 0.070) were associated with atherosclerosis at the multivariate analysis. Elevated levels of inflammatory cytokines and adhesion molecules were not associated with the presence of atherosclerosis.

Conclusion: There was no association between inflammatory biomarkers, adhesion molecules and presence of carotid atherosclerosis. However, a higher chance of subclinical atherosclerosis was observed in men, those older than 40 years, with intermediate / high Framingham score or metabolic syndrome. (Arq Bras Cardiol 2012;99(5):971-978)

Keywords: Atherosclerosis; risk factors; coronary disease; HIV.

Introduction

In spite of the intensive worldwide effort to contain the spread of the Human Immunodeficiency Virus (HIV) epidemics, epidemiological data are still alarming. The latest estimate from the World Health Organization (WHO) reported that in 2009 there were approximately 33.4 million people living with HIV worldwide[1]. In Brazil, the number of cases diagnosed and reported from 1980 until June 2010 was 592,914[2].

The introduction of Highly-Active Antiretroviral Therapy (HAART) resulted in changes in the course of the natural history of HIV infection[3-4]. While treated patients experienced improvement in survival with viremia control, HAART coincided with changes in the spectrum of diseases found in these patients and the therapy adverse effects assumed an increasingly important role. In this context, an increased rate of cardiovascular disease of atherosclerotic origin was observed in these patients[5-7].

Considering that atherosclerotic Coronary Artery Disease (CAD) is an important cause of morbidity and mortality in the population of HIV-positive patients, its onset seems to be due to chronic viral infection and side effects of antiretroviral drugs, which together result in metabolic disturbances (glucose intolerance, diabetes mellitus, dyslipidemia, lipodystrophy) and endothelial damage[5-10].

The HIV-related endothelial dysfunction mechanism could include, in addition to the influence of viral proteins, the vascular inflammatory effects[7]. The process is mediated by cytokines (IL-1β, IL-6), the tumor necrosis factor alpha (TNF-α) and the endothelial intercellular cell adhesion molecule - ICAM 1 and vascular - VCAM-1[11]. Cytokine dysregulation, activation of macrophages and smooth muscle cells promote increased atheroma formation[12-14], an aggravating factor for cardiovascular disease progression. Thus, identifying which molecules are biomarkers to predict the risk of Cardiovascular Disease (CVD) in patients with HIV appears to be of great

Mailind Address: Heloisa Ramos Lacerda •
Depto de Medicina Clínica, Bloco A do Hospital das Clínicas da UFPE
Av. Moraes Rego,1235. Postal Code 50670-901, Recife, PE - Brazil
E-mail: helramos@terra.com.br, heloisa.ramos@pq.cnpq.br
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importance.

The present study aims to determine the association between levels of inflammatory biomarkers, risk factors for CAD and the presence of carotid atherosclerosis in HIV-positive patients, with and without use of HAART.

Material and Methods

This is a cross-sectional observational study, aligned to a cohort of patients for the study of cardiovascular disease and metabolic disorders in HIV-positive individuals aged 18 and older. The study was carried out from 2008 to 2010 and included the basal analysis of 122 patients included in the cohort. Subjects were selected consecutively and treated at Hospital Universitário Oswaldo Cruz (HUOC) of Universidade de Pernambuco and Hospital Estadual Correia Picanço (HCP) of the Department of Health of the State of Pernambuco.

All HIV-positive patients treated in the outpatient clinics of HUOC and HCP who agreed to participate in study signed a free and informed consent form and were subsequently submitted to: interview with standardized questionnaire; anthropometric (weight, height, waist circumference) and blood pressure measurements, blood sampling for measurements of total cholesterol and fractions, triglycerides, fasting glucose, high-sensitivity C-reactive protein (HS-CRP), inflammatory cytokines (IL-1β, IL-6, TNF-α), adhesion molecules (ICAM -I and VCAM-I) and carotid Doppler ultrasonography. Information on use of HAART, as well as TCD4 count and viral load were obtained from medical records.

We used frozen plasma samples in blood collection tubes with EDTA from the Cardiovascular Disease cohort study carried out in HIV-positive patients from the city of Recife, state of Pernambuco, Brazil. The frozen samples were sent to be submitted to multiplex bead-array assay (MBAA). The tests were performed at Instituto Genesis, São Paulo, strictly according to the manufacturer's protocol for plasma samples.

Before adding the samples to a sample plate to be assayed, aliquots were gently agitated and then centrifuged at 13,200 rpm for 10 min at 48°C. Dilutions of plasma samples and standards were prepared according to the manufacturer's instructions. We used two different sets of multiplex tests: a) the Panel for Human Cardiovascular Disease 3Kit Immunoassay LINCOplex - 3-plex, Linco / Millipore, Billerica, Massachusetts, USA - (HCVD3-67CK), to measure IL-1ß, IL-6, TNF-α, and b) the Panel for Human Cardiovascular Disease LINCOplex 1 Kit - 2-plex, Linco / Millipore - (HCVD1-67AK), to measure sVCAM-1 and sICAM-1. We used an instrument based on fluorescent beads (Luminex-100, Luminex Corporation, Austin, Texas, USA) to read each multiplex plate. The data of Luminex plates were analyzed using the Milliplex Analyst software, v3.4 (Millipore; VigeneTech Inc., Boston, Massachusetts, USA) and five parameters of logistic curve fitting. The use of MBAA is justified by the fact that the measurement of multiple cytokines could be analyzed in a single serum sample.

The HS-CRP was measured by nephelometry, using kits from Beckman Coulter Immage Immunochemistry Systems. Cutoffs for the markers were adopted according to the literature: concentrations of IL-6 ≥ 0.11 pg / mL[15]; IL-1 β ≥ 0.08 pg/mL[15]; TNF-α ≥ 1.2 pg/mL[16]; ICAM-I ≥ 502 pg/mL[17]; VCAM-I ≥ 710 pg/mL[17]; CRP ≥ 3.0 mg/L[18].

The B-mode carotid artery ultrasonography was performed using a high-resolution 12 MHz transducer (GE Vivid 7 2007; General Electric).

Each subject was examined in the supine position, in a semi-darkened room, with the neck positioned at 45º for left carotid assessment and counter rotation for the evaluation of the right carotid artery. Images of the posterior wall of the distal part of the right and left common carotid arteries (1 to 2 cm proximal to the bulb) were evaluated by the same echocardiographist, who was blinded to patients' clinical and laboratory data. Subclinical atherosclerosis was defined as the mean of three measurements of the posterior wall of the right and left carotid arteries > 0.8 mm and/or presence of plaque.

The statistical analysis was performed using the STATA 9.1 software. The chi-square test or Fisher exact test was used for the analysis of qualitative variables was applied, as necessary. The nonparametric Mann-Whitney test was used to compare the quantitative variables. The variables with p values < 0.25 were included in the multivariate logistic regression analysis. The significance level was set at 0.05.

This study was approved by the Research Ethics Committee of Complexo Hospitalar HUOC, Procape and UFPE, Protocol #16.2009.

Results

Risk factors and characteristics related to treatment, biomarkers and adhesion molecules, as well as biological characteristics of the 122 patients included in the study are shown in Table 1.

The patients were in stable condition, without concomitant opportunistic infections. Ninety-nine patients (81.1%) used HAART; of these, only 35 (35.3%) were treated with Protease Inhibitors (PI). The most often used PI was lopinavir/ ritonavir in 19 (53.6%) cases. Of the 122 patients included in the study, 57.4% belonged to the age range > 40 years and 60.7% were males. Eighty-seven subjects (71.3%) had dyslipidemia and 99 individuals (81.1%) were on HAART, with a median of 3.3 years of therapy. The study population showed a prevalence of 18.8% of hypertension, 5.7% of diabetes and 40.2% of overweight/obesity; 27.9% were smokers and 19.3% had a family history of CAD (Table 1).

The prevalence of atherosclerosis using the evaluation criteria of intimal-medial thickness of the carotid artery and/or the presence of atheromatous plaque was 52 cases, accounting for 42.6% (95%CI: 33.7% - 51.9%) of individuals; among those who used antiretroviral therapy the prevalence was 42 cases of the total 99 patients undergoing treatment, totaling 42.4% (95% CI: 32.7% - 52%) (Table 2).

At the univariate analysis, subclinical atherosclerosis was associated with age, as patients older than 40 years were 6.3 times more likely to develop atherosclerosis. Regarding gender, although the association is not significant, but borderline (p = 0.096), men had a 1.89-fold higher chance of having atherosclerosis. The use of antiretroviral therapy was not associated with atherosclerosis, as well as the treatment time. Regarding the Framingham score, patients classified as

Table 1 – Association between carotid atherosclerosis and biological characteristics related to biomarkers and HIV, in HIV-positive patients treated in HUOC and HCP

Characteristics	All patients	Atherosclerosis		OR (95%CI)	p-value
		Yes	No		
Biological					
Sex					
Female	48 (39.3%)	16 (33.3%)	32 (66.7%)	1.0	-
Male	74(60.7%)	36 (48.6%)	38 (51.4%)	1.89 (0.89 – 4.02)	0.096
Age range					
≤ 40 years	52 (42.6%)	10 (40.0%)	42 (60.0%)	1.0	-
> 40 years	70(57.4%)	42 (60.0%)	28 (40.0%)	6.30 (2.72 – 14.6)	0.000
Biomarkers					
sVCAM-1					
< 710 pg/mL	53 (43.4%)	20 (37.7%)	33 (62.3%)	1.0	-
≥ 710 pg/mL	69 (56.6%)	32 (46.4%)	37 (53.6%)	1.43 (0.68 – 2.96)	0.339
sICAM-1					
< 502 pg/mL	118 (96.7%)	50 (42.4%)	68 (57.6%)	1.0	-
≥ 502 pg/mL	04 (3.3%)	02 (50.0%)	02 (50.0%)	1.36 (0.18 – 9.98)	0.762
TNF-alpha					
< 1.2 mg/mL	38 (31.2%)	19 (50.0%)	19 (50.0%)	1.0	-
≥ 1.2 mg/mL	84 (68.8%)	33 (39.3%)	51 (60.7%)	0.65 (0.30 – 1.40)	0.269
IL 6					
< 0.11 pg/mL	32 (26.2%)	15 (46.9%)	17 (53.1%)	1.0	-
≥ 0.11 pg/mL	90 (73.8%)	37 (41.1%)	53 (58.9%)	0.79 (0.35 – 1.78)	0.572
IL1-Beta					
< 0.08 pg/mL	109 (89.3%)	46 (42.2%)	63 (57.8%)	1.0	-
≥ 0.08 pg/mL	13 (10.7%)	06 (46.1%)	07 (53.9%)	1.17 (0.37 – 3.72)	0.786
US CRP					
< 3.0 mg/L	75 (61.5%)	32 (42.7%)	43 (57.3%)	1.0	-
≥ 3.0 mg/L	47 (38.5%)	20 (42.5%)	27 (57.5%)	0.99 (0.48 – 2.08)	0.990
HIV-related					
HAART use					
No	23 (18.9%)	10 (43.5%)	13 (56.5%)	1.0	-
Yes	99 (81.1%)	42 (42.4%)	57 (57.6%)	0.96 (0.38 – 2.39)	0.927
Time of HAART					
Does not use	23 (18.9%)	10 (43.5%)	13 (56.5%)	1.0	-
< 5 years	69 (56.6%)	27 (39.4%)	42 (60.9%)	0.83 (0.32 – 2.17)	0.713
5 years and more	30 (24.5%)	15 (50.0%)	15 (50.0%)	1.30 (0.43 – 3.87)	0.638
Level of CD4 nadir					
≥ 200 cells/mm^3	45 (37.2%)	23 (51.1%)	22 (48.9%)	1.0	-
< 200 cells/mm^3	76 (62.8%)	29 (38.2%)	47 (61.8%)	0.59 (0.28 – 1.24)	0.166
Current CD4 level					
≥ 200 cells/mm^3	104 (86.0%)	47 (54.8%)	57 (45.2%)	1.0	-
< 200 cells/mm^3	17 (14.0%)	05 (29.4%)	12 (70.6%)	0.50 (0.16 – 1.54)	0.229
Maximum viral load					
< 100.000 cp/mm^3	53 (49.5%)	21 (39.6%)	32 (60.4%)	1.0	-
≥ 100.000 cp/mm^3	54 (50.5%)	24 (44.4%)	30 (55.6%)	1.22 (0.56 – 2.63)	0.614
Current viral load					
Undetectable	47 (40.5%)	17 (36.2%)	30 (63.8%)	1.0	-
Detectable	69 (59.5%)	33 (47.8%)	36 (52.2%)	1.62 (0.76 – 3.46)	0.215

OR: odds ratio / CI: confidence interval.

Table 2 – Association between carotid atherosclerosis and factors related to risk of CAD and laboratory tests in HIV-positive patients treated in HUOC and HCP

Characteristics	All patients	Atherosclerosis		OR (95%CI)	p-value
		Yes	No		
Risk factors for CAD					
Hypertension					
No	99 (81.1%)	40 (40.4%)	59 (59.6%)	1.0	-
Yes	23 (28.9%)	12 (52.2%)	11 (47.8%)	1.61 (0.65 – 4.00)	0.306
Family history of CAD					
No	92 (80.7%)	40 (43.5%)	52 (56.5%)	1.0	-
Yes	22 (19.3%)	08 (36.4%)	14 (63.6%)	0.74 (0.28 – 1.94)	0.545
Diabetes					
No	115 (94.3%)	49 (42.6%)	66 (57.4%)	1.0	-
Yes	07 (5.7%)	03 (57.4%)	04 (42.6%)	1.01 (0.21 – 4.72)	0.990
Smoking					
No	88 (72.1%)	40 (45.5%)	48 (54.5%)	1.0	-
Yes	34 (27.9%)	12 (35.3%)	22 (64.7%)	0.65 (0.29 – 1.48)	0.310
Abdominal circumference					
Unaltered	87 (74.4%)	36 (41.4%)	51 (58.6%)	1.0	-
Altered	30 (25.6%)	15 (50.0%)	15 (50.0%)	1.42 (0.61 – 3.26)	0.413
BMI					
< 25 kg/m^2	70 (59.8%)	28 (40.0%)	42 (60.0%)	1.0	-
≥ 25 kg/m^2	47 (40.2%)	23 (48.9%)	24 (51.1%)	1.43 (0.68 – 3.02)	0.340
Metabolic Syndrome					
No	74 (64.4%)	28 (37.8%)	46 (62.2%)	1.0	-
Yes	41 (35.6%)	22 (53.7%)	19 (46.3%)	1.90 (0.87 – 4.12)	0.103
Framingham score					
No	93 (80.2%)	35 (37.6%)	58 (62.4%)	1.0	-
Yes	23 (19.8%)	15 (65.2%)	08 (34.8%)	3.10 (1.19 – 8.07)	0.020
Laboratory assessment					
HDL					
Unaltered	48 (41.7%)	18 (37.5%)	30 (62.5%)	1.0	-
Altered	67 (58.3%)	31 (46.3%)	36 (53.7%)	1.43 (0.67 – 3.06)	0.349
LDL					
$<$ 130 mg/dL	91 (79.8%)	38 (41.8%)	53 (58.2%)	1.0	-
$\geq$ 130 mg/dL	23 (20.2%)	11 (47.8%)	12 (52.2%)	1.28 (0.51 – 3.20)	0.600
Total cholesterol					
$<$ 200 mg/dL	81 (69.2%)	34 (42.0%)	47 (58.0%)	1.0	-
$\geq$ 200 mg/dL	36 (30.8%)	16 (44.6%)	20 (55.4%)	1.10 (0.50 – 2.44)	0.803
Level of triglycerides					
$<$ 150 mg/dL	62 (53.0%)	23 (37.1%)	39 (62.9%)	1.0	-
$\geq$ 150 mg/dL	55 (47.0%)	28 (50.9%)	27 (49.1%)	1.76 (0.84 – 3.67)	0.134

OR: odds ratio; CI: confidence interval; CAD: coronary artery disease.

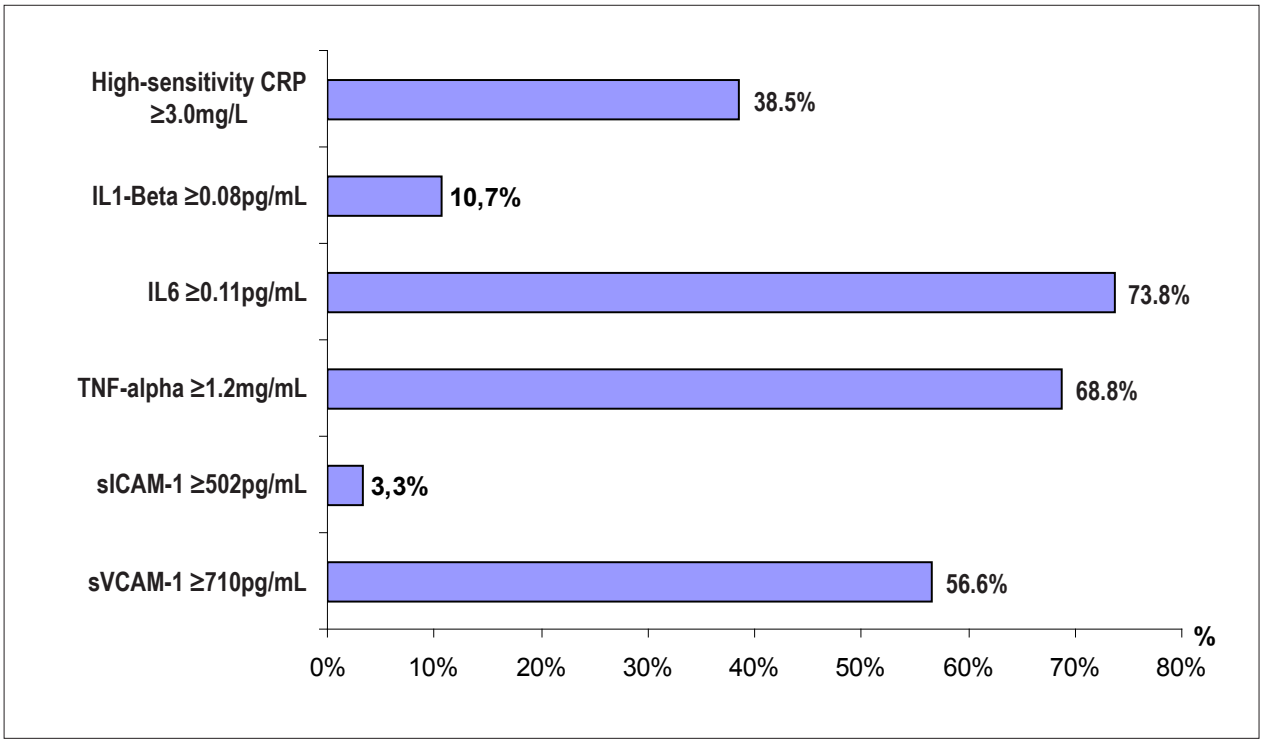

Figure 1 – *Frequency distribution of inflammatory biomarker levels in the HIV-positive patients treated in HUOC and HCP.*

Table 3 – Association between biomarkers (median) and carotid atherosclerosis in HIV-positive patients treated in HUOC and HCP

Biomarkers	Atherosclerosis		p-value*
	Yes	No	
	median (P_{25}; P_{75})	median (P_{25}; P_{75})	
sVCAM-1	877.4 (541.3; 1.076.6)	730.8 (525.5; 964.3)	0.251
sICAM-1	154.8 (117.9; 197.4)	146.7 (118; 197.4)	0.772
TNF-alpha	1.72 (0.87; 4.1)	3.0 (1.05; 4.91)	0.287
IL6	0.58 (0.11; 3.51)	1.38 (0.13; 3.34)	0.530
High-sensitivity CRP	2.45 (1.07; 4.28)	1.68 (0.88 – 5.03)	0.576

P_{25}: 25th Percentile / P_{75}: 75th Percentile
** Mann-Whitney non-parametric test*
*** Statistically significant difference (p < 0.05)*
**** IL1-Beta has undetectable values by the laboratory method*

having medium or high cardiovascular risk were 3.1 times more likely to have atherosclerosis (p = 0.02). The association with metabolic syndrome had a significance tendency (p = 0.103), with a 1.9-fold higher risk of having atherosclerosis. There was no significant association between atherosclerosis and cholesterol, triglycerides levels and BMI or waist circumference measurements (Table 2).

The increase in biomarkers was observed in 69 patients (56.6%) for VCAM-1, in 4 patients for ICAM-1 (3.3%), in 84 (68.8%) for TNF-α, in 90 patients (73.8%) for IL-6 and 13 patients (10.7%) for IL-1β (Figure 1).

The analysis of the association between biomarker levels and the presence of atherosclerosis showed no statistically significant association (Tables 1 and 3).

At the multivariate analysis, only age > 40 years (OR = 6.57; 95%CI: 2.66 - 16.2, p = 0.000), male gender (OR = 2.76; 95%CI: 1.12 - 6.79, p = 0.027) and the presence of metabolic syndrome (OR = 2.27; 95%CI: 0.94 - 5.50, p = 0.070) were associated with atherosclerosis (Table 4).

Table 4 – Multivariate model of association between carotid atherosclerosis and the factors studied in HIV-positive patients treated in HUOC and HCP

Related Factors	OR ((95%CI))	p-value
Age range		
≤ 40 years	1.0	-
> 40 years	6.57 (2.66 – 16.2)	0.000
Sex		
Female	1.0	-
Male	2.76 (1.12 – 6.79)	0.027
Metabolic Syndrome		
No	1.0	-
Yes	2.27 (0.94 – 5.50)	0.070

Discussion

The present study is one of the first to join up the main biomarkers such as interleukins, adhesion molecules, HS-CRP and subclinical atherosclerosis assessed by carotid ultrasonography in HIV-positive patients. A total of 122 HIV-infected patients, most of them with prior use of HAART for a period exceeding one year were evaluated. The prevalence of atherosclerosis was 42.6% (52 individuals). In accordance with the literature, we observed that in the population studied, male patients aged ≥ 40 years with metabolic syndrome and medium/high Framingham score showed increased chance of developing subclinical atherosclerosis.

Risk factors for CAD, use of HAART and HAART time and measurement of biomarkers were the parameters used to verify the prediction of atherosclerotic event. Although several studies have suggested that biomarkers such as cytokines (IL-1β, IL-6 and TNF-α) and HS-CRP as risk factors associated with the chronic progression of atherosclerotic plaque[14], the present study found no statistically significant association between them. These findings disagree with the ones by Ross et al.[19], who found a positive correlation between levels of sVCAM and TNF-alpha and carotid thickening in HIV-positive patients[19], and Ford et al., who also determined an association between high levels of sVCAM and D-dimer and the risk of myocardial infarction[20].

However, after the compilation of results from several studies on the capacity of biomarkers to predict CVD risk in the presence of HIV infection, Worm and Hsue concluded that elevated levels of CRP and IL-6 predicted higher mortality in HIV-positive individuals. However, the same authors believe that the usefulness of biomarkers in predicting CVD in this population is not so clear, as the studies assessed small samples and other chronic infections such as that caused by hepatitis C virus and other risk factors such as smoking and metabolic disorders (also capable of inducing chronic inflammation) are present in that population, introducing important confounding factors in this evaluation[21].

As for HS-CRP, the literature data are conflicting. Pearson et al.[22] showed that HS-CRP has not been a good marker to predict the extent of atherosclerotic disease, demonstrating a poor correlation between the levels of this marker and the extent of atherosclerosis, measured by both Doppler ultrasonography of the carotid arteries and computed tomography[22] for coronary calcium. Some studies, in contrast, suggest a positive correlation between this marker and imaging tests that measure the extent of atherosclerosis[23], even though research is still needed to better define the association between inflammatory markers and atherosclerotic mass. As for HIV-infected individuals, Triant VA et al.[24] found that increased levels of HS-CRP were associated with increased risk of myocardial infarction in HIV-infected patients[24].

Inflammatory markers can measure other characteristics rather than atherosclerotic mass. These characteristics may include the activity of the lymphocyte and macrophage population or the degree of plaque destabilization leading to ulceration and thrombosis[25], as well as mortality in HIV-infected patients[26]. All these factors (lymphocyte and macrophage activation) are modified by chronic HIV infection[27], a fact that may account for the high percentage of cytokine levels demonstrated here and the lack of association of biomarkers and carotid atherosclerosis in this population.

It is likely that the combined use of current biomarkers as markers of atherosclerotic disease can result in better risk stratification for CAD, as they measured different moments of the atherosclerotic process.

Or, on the other hand, the advanced knowledge of molecules and cells in the physiopathology of atherosclerotic lesions will allow the development of new molecular markers that can be measured in plasma and used to determine CAD risk.

Conclusion

The analysis of the study population of HIV-positive patients with and without HAART use showed that 42.6% of patients had carotid atherosclerosis (thickening and/or plaque), being more prevalent in male patients 40 years and older, with Framingham score classified as medium / high cardiovascular risk and metabolic syndrome.

The inflammatory biomarkers sVCAM-1, TNF-alpha and IL-6 were the ones with higher frequency of alterations in their normal

levels. In this population there was no association between biomarker levels and the presence of carotid atherosclerosis.

The prevention of CVD in HIV-positive patients should start by raising awareness of this population and the physicians, with sporadic control of hypertension, smoking, diabetes, dyslipidemia, excess weight and eating habits, as alterations in the aforementioned factors can result in changes in Framingham scores and metabolic syndrome, which are associated with atherosclerosis.

The use of carotid Doppler ultrasonography is useful in patients older than 40 years, metabolic syndrome and Framingham score indicating intermediate/high cardiovascular risk, as it can demonstrate the presence of subclinical atherosclerosis in this group at highest risk for the disease and guide CAD prevention therapy.

Prospective cohort studies are needed to evaluate the predictive value of biomarkers, individually or in combination, to predict cardiovascular events and death from cardiovascular disease in the HIV-infected group.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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