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Calcium Score in the Evaluation of Atherosclerosis in Patients with HIV/Aids

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Abstract

Background: Antiretroviral therapy has dramatically increased life expectancy in patients with HIV/AIDS although atherosclerosis has been associated with long-standing therapy.

Objective: To investigate the prevalence of atherosclerosis in patients with AIDS undergoing antiretroviral therapy and the influence of different schemes and duration of treatment.

Methods: HIV/AIDS patients were approached during routine consultations. Those who had been on antiretroviral therapy for at least two years had their blood collected for analysis of lipid profile and fasting glycemia and underwent cardiac CT for quantification of calcium score within six days at the most. Atherosclerosis was defined as calcium score greater than zero (CAC>0). Traditional risk factors, metabolic syndrome and Framingham score were analyzed.

Results: Fifty-three patients performed cardiac CT. Twenty-seven (50.94%) were male, mean age 43.4 years; 20.00% had hypertension, 3.77% diabetes, 67.92% hypercholesterolemia, 37.74% hypertriglyceridemia and 47.17% low HDL. Thirteen (24.53%) met criteria for metabolic syndrome and 96.23% were classified in Framingham score as "low risk." Ten patients (18.87%) were smokers. Mean duration of antiretroviral treatment was 58.98 months. Coronary atherosclerosis occurred in 11 (20.75%) patients. Duration of antiretroviral therapy was not related to atherosclerosis (p = 0.41) and there were no significant differences between different antiretroviral regimens (p = 0.71). Among traditional risk factors, smoking (OR = 27.20; p = 0.023) and age (OR = 20.59; p = 0.033) were significant in the presence of atherosclerosis. There was a trend towards a positive association of atherosclerosis with hypercholesterolemia (OR = 8.30; p = 0.0668).

Conclusion: Factors associated with atherosclerosis were age, smoking and hypercholesterolemia. Duration and type of antiretroviral therapy had no influence on the prevalence of atherosclerosis. (Arq Bras Cardiol 2011;97(5):427-433)

Keywords: Calcium/blood; atherosclerosis/blood; HIV; acquired Immunodeficiency syndrome; antiretroviral therapy, higly active/adverse effects.

Introduction

Aggressive antiretroviral therapy has dramatically increased life expectancy in patients with HIV/AIDS and, as result of this greater longevity[1], the side effects of this therapy have been increasingly evidenced.

Early atherosclerosis has been associated with long-standing and aggressive antiretroviral therapy. Likewise, cardiovascular disease, which is directly linked to atherosclerosis, is more prevalent in HIV-infected individuals when compared with the general population[2]. Several complementary methods have been employed for the detection of atherosclerosis, one of which – multi-slice computed tomography – measures the calcium score. The amount of calcium detected by cardiac CT directly correlates with the presence and severity of coronary stenosis[3]. This method can be employed even in asymptomatic patients with a high negative predictive value, i.e. a calcium score of 0 is associated with a 96-100% likelihood of no coronary disease[4].

The literature on the prevalence of atherosclerosis detected by coronary calcium score in HIV-positive patients is scanty. In view of this, we decided to undertake a study aimed at depicting the prevalence, the risk profile and the influence of the type of antiretroviral schema in the development of atherosclerotic disease, at an early stage, in a group of patients using their first antiretroviral schema.

Methods

The study was approved by the Ethics Committee of Hospital Universitário Oswaldo Cruz (HUOC) and all the volunteers taking part in this study gave their written informed consent. A convenience sample was obtained from patients attending

the Infectious Diseases Clinic of HUOC and the HIV Clinic of Hospital Correia Picanço (HCP). Patients were approached by interviewers during routine consultations and those who agreed to participate in the study answered the questionnaire and had their anthropometric measurements taken.

The individuals selected for the study were HIV/AIDS patients older than 18 years of age on antiretroviral therapy for at least two years with no change in their antiretroviral schema during this period. Patients known to have coronary artery disease (CAD) were excluded, as well as those with clinical signs of active infections, those hospitalized in the previous three months and pregnant patients.

After answering the questionnaire, the volunteers had their blood collected for hematological and biochemical tests and were referred to a cardiologist. After physical examination and screening for exclusion criteria, the patients underwent a cardiac CT for determination of calcium score. The tomograph used was the Philips 10-channel "Brilliance" and the images were analyzed by a single examiner.

The presence of atherosclerosis was defined as a calcium score greater than zero (CAC > 0)[5].

The cardiovascular risk was classified as low, intermediate or high according to the calcium score: low – a calcium score of less than 100Au, intermediate – between 101 and 400Au, and high – greater than 400Au.

The criteria for the diagnosis of the metabolic syndrome (MS) were those of the National Cholesterol Education Program (NCEP)[6], i.e. the presence of three or more of the following: waist circumference > 102 cm in men and >88 cm in women; serum triglycerides > 150 mg/dl, HDL-cholesterol < 40 in men or < 50 in women; blood pressure > 130 x 85 mmHg; and fasting plasma glucose > 110 mg/dl. The Framingham score was calculated according to pre-determined criteria and the patients were classified as low, intermediate or high risk[7].

Risk factors such as dyslipidemia, smoking, diabetes mellitus, overweight, hypertension and sedentary lifestyle were analyzed, in addition to gender and age. Despite the fact that most of these risk factors are considered for the purposes of classifying the Framingham score, each of them was analyzed separately based on their importance. HDL-cholesterol < 40 in men and HDL < 50 in women were classified as low HDL[8]. The patients had their blood pressure measured on at least two separate occasions and those who had systolic pressure > 140 or diastolic pressure > 90 mmHg, according to the VII Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[9], were classified as having hypertension.

The presence of diabetes mellitus was considered in patients with a reported history of diabetes and the use of oral hypoglycemic agents or insulin, as well as the finding of fasting plasma glicemia > 126mg/dL.

The information on antiretroviral schema was obtained from hospital medical records. The patients were classified as "using" or "not using" schemas containing protease inhibitors. Patients who changed their antiretroviral therapy, but remained in the same drug class were not excluded.

A descriptive analysis was carried out to detail the results. Data were expressed in relative (percentages) and absolute (N) frequencies for the qualitative variables and by mean, median, standard deviation, minimum and maximum for the quantitative variables. To test the assumption of normality of the variables involved in the study, Shapiro-Wilk test was applied. For a comparative analysis of the quantitative variables, Student's t-test was used and, for the qualitative variables, the chi-square test and, when necessary, Fisher's test. Variables with statistical significance (p > 0.20) in the univariate analysis were confirmed by the multivariate analysis. The results with p values < 0.05 were considered statistically significant. The software used was the Excel 2000 and R v2.8.0.

Results

Sixty-three patients underwent the cardiac CT, but ten patients were excluded after retrospective analysis of their medical records. The sample consisted of 53 patients.

Twenty-seven of the patients were male (50.94%), with ages ranging from 22 to 69 years and a mean age of 43.4 years. Hypertension was present in 12 (22.64%) patients and diabetes in only two (3.77%). Thirty-six patients (67.92%) had total cholesterol ≥ 200mg/dl. Nineteen patients (37.74%) had serum triglycerides > 150mg/dl. Low HDL-C was detected in 25 patients (47.17%). Thirteen patients (24.53%) met the criteria for MS. Fifty-one patients (96.23%) were classified on the basis of their Framingham score as "low risk," two patients (3.77%) as "intermediate risk," and no patient as "high risk." Only 10 patients were smokers (18.87%).

With respect to the antiretroviral schema, 16 patients (30.19%) were using a protease inhibitor, while 37 (69.81%) were not. The mean duration of therapy was 58.98 months (range, 24-166 months) (Table 1).

Coronary atherosclerosis detected by the calcium score, the primary objective of the study, was found in 11 patients (20.75%).

When the continuous variables were analyzed (Table 2), it was found that hypercholesterolemia (high total cholesterol or LDL-cholesterol), low HDL-cholesterol, hypertriglyceridemia, overweight, or diabetes did not influence the presence of atherosclerosis.

In the analysis of the categorical variables, gender, hypertension and the presence of MS did not influence the development of atherosclerosis, while LDL-cholesterol ≥ 130mg/dL and total cholesterol > 200 mg/dL showed a tendency to be associated with atherosclerosis (Table 3).

The duration of antiretroviral therapy was not related to the development of atherosclerosis (p = 0.41) (Table 2), and there were also no significant differences between groups of patients using different antiretroviral schemas (p = 0.71) (Table 3).

The presence of atherosclerosis detected by calcium score was significantly higher in smokers (OR = 27.20; p = 0.023) (Table 3). We also detected the direct influence of patients' age on the development of atherosclerosis (OR = 20.59; p = 0.033) (Table 2). These data were confirmed when multivariate analysis was performed (Table 4). This analysis also showed a trend towards a positive association of atherosclerosis with hypercholesterolemia (OR = 8.30; p = 0.0668).

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Discussion

Coronary atherosclerosis detected by CT cardiac calcium score was evidenced in 11 patients (20.75%). This finding is in agreement with the literature, where similar numbers were found when adjusted for the age of the patients studied (mean, 43.4 years)[10]. Talwani et al[11] had previously reported that the calcium score in the HIV-positive population on antiretroviral therapy for at least 6 months was not significantly different from that of persons not carrying the virus. Kingsley et al[10] found a positive calcium score in 12% of patients under 45 years of age and HIV positive and in 23% of patients aged 40-45 years. However, that study has shown a higher percentage of coronary atherosclerosis in HIV patients using antiretroviral therapy than in healthy controls when all age groups were included (40 *vs.* 20%).

Age had a direct influence on the development of atherosclerosis. Therefore, it may be hypothesized that the absence of any significant difference in the prevalence of atherosclerosis in relation to the healthy population is due to the fact that the population studied was quite a young one. Age, therefore, is one of the major risk factors for the development of atherosclerosis in people with AIDS[12] similar to the general population[13].

The mean duration of use of antiretroviral therapy in this population was 58.98 months, probably not long enough for the development of atherosclerosis. Kingsley's study also showed that atherosclerosis detected by the calcium score was significantly higher only in patients who had been on antiretroviral therapy for at least eight years[10], which is the period of time probably necessary for developing the disease. Atherosclerotic disease in a HIV-patient is a result of many different factors. One of the most important of such factors is the lipid metabolism[2]. There is a primary reduction of HDL-cholesterol resulting from immune activation by HIV and from the hypercatabolic state of the disease and by the decreased activity of the LCAT protein in the liver, thereby reducing the release of plasmatic cholesterol[14]. Hypertriglyceridemia is another major modification in the metabolism of patients with AIDS. This is due to the rise in interferon-α, which leads to a reduced clearance of triglycerides, thus increasing the serum concentration[14]. In addition, the inhibition of the low density lipoprotein receptor-related protein (LRP)[15] results in a lower uptake of triglycerides by the liver and less cleavage of these fatty acids and glycerol. Antiretroviral therapy has an even greater effect on the lipid metabolism. Aggressive antiretroviral regimens increase the production of VLDL, potentiate the breaking of lipoproteins rich in triglycerides, leading to a higher serum concentration[16]. There is also the accumulation of intramyocellular fat and mitochondrial dysfunction[14]. In addition to the effect of antiretroviral therapy on the lipid metabolism, its effect on insulin resistance and the metabolic syndrome is also important[2]. The high prevalence of smoking in the HIV-infected population is another frequently reported risk[1]. All these factors lead to a greater prevalence and intensity of atherosclerosis in patients with AIDS.

The negative data regarding the prevalence of atherosclerosis in individuals with HIV on antiretroviral therapy for at least two years are important in daily clinical practice. Although our study had a rather small sample, the data suggest that a longer period of antiretroviral therapy is required for the detection of atherosclerosis, even when a method such as cardiac CT is employed. These data have also been confirmed by the study of Kingsley et al[10].

It is known that protease inhibitors are more related to lipid changes, glucose intolerance and MS. Johnsen

Table 1 - Characteristics of the study population

Variables	Total population	Without atherosclerosis	With atherosclerosis
n	53	42 (79.25%)	11 (20.75%)
Age (mean years)	43.40	41.78	49.74
Male sex (%)	50.94	47.62	63.64
Hypertension (%)	22.64	23.81	18.18
Smoking (%)	18.86	11.9	45.45
Metabolic syndrome (%)	24.53	21.43	36.36
Total cholesterol (mean in mg/dl)	184	178.00	211.27
HDL-cholesterol (mean in mg/dl)	46.40	46.52	44.18
Triglycerides (mean in mg/dl)	154	140.50	199.5
Blood glucose (mean in mg/dl)	95.80	93.79	99.73
LDL-cholesterol (mean in mg/dl)	129.02	115.67	180.94
BMI	23.98	24.44	22.14
Positive family history for CAD	48	35 (73.00%)	13 (27.00%)
Duration of antiretroviral treatment (in months)	58.98	56.29	69.27

BMI - Body mass index; CAD - Coronary artery disease.

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et al[17] demonstrated increased carotid thickening in patients using protease inhibitors, which is suggestive of its atherosclerotic potential and subsequent induction of cardiovascular disease. The relationship of the prevalence of atherosclerosis with the type of antiretroviral therapy (with or without protease inhibitors) was the purpose of this study. There was no significant difference in the prevalence of atherosclerosis between the two classes of drugs concerned. It is worth emphasizing that in most studies which found a greater degree of atherosclerosis and cardiovascular events such as myocardial ischemia in patients using protease inhibitors, ritonavir and indinavir were the drugs mostly associated with atherosclerosis[10,18]. Only 30% of the population of this study were using protease inhibitors, and out of these, only two were using indinavir and not a single one was on ritonavir in high doses. New antiretroviral drugs, even in the protease inhibitors class of drugs such as atazanavir, which have a safer lipid profile than their counterparts in the past[19], have been used in recent years. All these factors may account for the fact that there was no difference in the prevalence of atherosclerosis among users of protease

Table 2 - **Distribution of continuous variables associated with atherosclerosis**

	n	Least	High	Mean	Deviation	p-value
Age (Years)						
Atherosclerosis						
No	42	22	58	41.79	8.31	0.0333
Yes	11	31	69	49.45	9.89	
Duration of antiretroviral treatment (months)						
Atherosclerosis						
No	42	24	126	56.29	28.27	0.4105
Yes	11	34	166	69.27	43.26	
Glycemia (mg/dL)						
Atherosclerosis						
No	42	64	285	93.79	32.23	0.3338
Yes	11	63	197	99.73	34.46	
Triglycerides (mg/dL)						
Atherosclerosis						
No	42	37	366	140.50	78.09	0.2033
Yes	11	63	521	199.55	140.76	
Total cholesterol (mg/dL)						
Atherosclerosis	42					
No		84	252	178.00	37.89	0.1090
Yes	11	121	311	211.27	60.76	
HDL-cholesterol (mg/dL)						
Atherosclerosis						
No	42	3	82	46.52	13.70	0.4646
Yes	11	35	52	44.18	5.98	
LDL-cholesterol (mg/dL)						
Atherosclerosis						
No	35	53.2	231	115.67	40.48	0.1230
Yes	9	60.0	400	180.94	128.23	
BMI (kg/m²)						
Atherosclerosis						
No	40	17.20	34.80	24.44	4.02	0.0864
Yes	10	16.40	27.80	22.14	3.43	

BMI - Body mass index.

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inhibitors. A recent meta-analysis reviewed data from six cross-sectional, seven case-control and 13 cohort studies reporting carotid ultrasound intima-media thickness (CIMT), focal plaque incidence or coronary artery calcium (CAC) involving 5456 HIV positive patients. Weighted mean difference for CIMT by protease inhibitors exposure and the odds ratio for a focal carotid plaque or CAC were evaluated. The authors concluded that protease inhibitors exposure did not significantly affect CIMT, carotid plaque, or CAC and that there was evidence of publication bias in those studies. Stratified analysis and meta-regression using the same data showed that outcomes were influenced by study design, age, gender and smoking[12].

This study revealed no significant differences regarding the development of atherosclerosis in relation to gender or the presence of the majority of risk factors - low HDL-cholesterol,

Table 3 - Distribution of categorical variables associated with atherosclerosis

	Atherosclerosis				OR	95% CI		p-value
	Yes		No			Lower	Higher	
	n	%	n	%				
Gender								
Women	4	36.36	22	52.38	1.00			
Men	7	63.64	20	47.62	1.88	0.48	8.42	0.3442
Smoking								
No	6	54.55	37	88.1	1.00			
Yes	5	45.45	5	11.9	5.85	1.24	29.00	0.0230
Metabolic Syndrome								
No	7	63.64	33	78.57	1.00			
Yes	4	36.36	9	21.43	2.08	0.44	8.90	0.3054
Hypertension								
No	9	81.82	32	76.19	1.00			
Yes	2	18.18	10	23.81	0.75	0.09	3.66	0.6914
Positive family history for CAD								
No	7	70.00	28	73.68	1.00			
Yes	3	30.00	10	26.2	1.22	0.21	5.57	0.8156
Triglycerides								
< 150	5	45.45	28	66.67	1.00			
≥150	6	54.55	14	33.33	2.34	0.59	9.80	0.963
Total cholesterol								
≤ 200	5	45.45	31	75.61	1.00			
> 200	6	54.55	11	24.39	3.28	0.81	14.04	0.0728
HDL-cholesterol								
Normal	6	54.55	22	52.38	1.00			
Low	6	45.45	20	47.62	0.92	0.22	3.62	0.8981
Normal - HDL> 40 men /> 50 women								
LDL-cholesterol								
< 130	3	33.33	25	71.43	1.00			
≥130	6	66.67	10	28.57	5.00	1.10	27.60	0.0442
Type of Antiretroviral Schema								
2NRTI** + NNRTI*	7	63.64	30	71.43	1.00			
2NRTI + PI***	4	36.36	12	28.57	1.43	0.31	5.87	0.7164

*NRTIs - reverse transcriptase inhibitors of nucleoside analogues; ** NNRTI - non-reverse transcriptase inhibitors of nucleoside analogues; *** PI - protease inhibitor. CAD - Coronary artery disease.*

Table 4 - Multivariate analysis of factors related to atherosclerosis

Multivariate Model	Odds	CI 95%		p value
		Lower	Higher	
Age > 53 years	20.59	1.37	699.04	0.0435
Smoking - Yes	27.20	3.17	633.35	0.0083
Cholesterol > 200 ml/dL	8.30	1.4	170.2	0.0668
Triglycerides > 150 + ml/dl	2.95	0.9	24.40	0.2569

hypertriglyceridemia, diabetes and, in particular, MS. It is known that these risk factors, particularly low HDL-cholesterol, hypertriglyceridemia and MS, are significantly more prevalent in the HIV/AIDS population[2,16,20,21], especially those with established cardiovascular disease. The increased risk of systemic arterial hypertension in patients with AIDS who develop hypertriglyceridemia[22], an additional cardiovascular risk factor for this group of patients, is also described. Thus, this study set out to show the direct influence of these factors in atherosclerosis detected on the basis of the calcium score. There was no association of atherosclerosis with these traditional risk factors. The risk factor involved in the development of atherosclerosis was smoking, age and hypercholesterolemia. Despite the lack of significant values, most of our results showed a trend towards a higher prevalence of traditional risk factors in the population with atherosclerosis with the exception of body mass index, which showed a tendency towards a negative association. These data may have been influenced by the small size of the sample.

The Framingham score was determined for this population in order to estimate cardiovascular risk at 10 years. Ninety-six percent of patients had a low Framingham score. This is mainly due to the lower age of patients in the study. There was no significant association between a higher Framingham score and a positive calcium score. On this basis, it may be hypothesized that the Framingham score is not the best tool for determining cardiovascular risk in this particular population, as suggested before[23]. However, as this study did not include a follow-up to confirm the occurrence of subsequent cardiovascular events, such a hypothesis may not be valid.

The results of this study should be interpreted with a number of reservations. The small number of patients included may have influenced the results; several issues could certainly be clarified with a larger sample size. Although the sample calculation in a prevalence study is of fundamental importance, this study, which is of a purely descriptive nature, did not set out to determine the prevalence of atherosclerosis in this population, but merely to describe it and report associated risk factors. The low age of patients may also account for a lower incidence of atherosclerosis than that found in other studies. Researchers should be encouraged to carry out larger studies in order to test the hypotheses raised here.

Conclusion

this study showed a low prevalence of atherosclerosis in patients with HIV/AIDS using antiretroviral therapy for at least two years (similar to that of the general population). Among the risk factors evaluated, only age, smoking and hypercholesterolemia were associated with the development of atherosclerosis. The short duration of use of the therapy and the young age of the study population may have influenced the results. Thus, despite the proven scientific evidence of the relationship of antiretroviral therapy to atherosclerosis in the patient with AIDS, the study revealed that a prolonged time of exposure to this treatment is required for atherosclerosis to be detected by means of cardiac CT. This is of extreme clinical importance, since knowing the best time to make the diagnosis avoids unnecessary expenses for the health syst

Potential Conflict of Interest

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

Study Association

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