ABSTRACT

Current treatment for human immunodeficiency virus (HIV) infection has improved survival and allowed infected patients to develop atherosclerotic coronary artery disease (CAD). Specific strategies to reduce cardiovascular risk in the infected population have not been developed. It is necessary to know the magnitude of cardiovascular risk in this population. Objectives: This study aimed to assess cardiovascular risk using a well-known clinical score and to investigate coronary artery calcium scoring (CACS) in this population. Methods: This was a cross-sectional study. Adults with HIV infection were studied. Demographic, clinical and anthropometric data, serum glucose and lipids were obtained. Cardiovascular risk was calculated through Framingham risk score (FRS) and CACS. Categorical variables were compared by Chi-square or Fisher's exact test, and continuous variables were analyzed by Student t test or Mann-Whitney test. An analysis of concordance between FRS and CACS was performed using kappa statistic. Results: Forty patients, aged 45.9 ± 8.1 years, were studied. Age of risk for CAD were found in 30.0%, hypertension in 55.0%, diabetes in 10.0%, smoking in 35.0%, dyslipidemia in 67.5% and family history of CAD in 57.5%. Altered levels of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were found in 30.0%, 25.0% and 82.5%, respectively. HDL-cholesterol and triglycerides were altered more frequently among protease inhibitors users. The FRS classified the risk as low for 72.5%, moderate for 25.0%, and high for 2.5%. CACS > 0 was found in 32.5% of the patients, in 67.5% the score was low, in 17.5% moderate, and in 15.0% high. Concordance between FRS and CACS showed a kappa = 0.435. Conclusions: There is a high prevalence of risk factors for CAD in the studied population, with dyslipidemia being the most frequent. HDL-cholesterol and triglycerides were the most frequently altered factors and were associated with the use of protease inhibitors. Risk assessed by the FRS was low in most cases. CACS > 0 was found in 32.5%, demonstrating the need to re-evaluate the strategies for assessing cardiovascular risk in the HIV-infected population.

Keywords: coronary artery disease; HIV; cardiovascular diseases; HIV protease inhibitors.

INTRODUCTION

Infection with human immunodeficiency virus (HIV) is a public health problem worldwide. In 2009, the United Nations estimated that worldwide 33.3 million people were infected with HIV, being 1.4 million in South and Central Americas.¹ In Brazil, updated data up to June 2010 accounted for 592,914 cases of acquired immunodeficiency syndrome (AIDS) reported since 1980, with 38,538 new cases reported in 2009.^{2,3} Public expenditures with hospitalizations and complications due to AIDS in Brazil amounted to about 8.2 million dollars in 2008 only, confirming the magnitude of the problem.³⁻⁵

Since 1996, with the advent of new antiretroviral therapies (ART), there have been significant gains in the fight against HIV infection, with increased life expectancy of these patients.4-6 This allowed, on the other hand, individuals with HIV infection to develop chronic diseases common to the general population, among which atherosclerotic cardiovascular disease (ACVD), more specifically represented by atherosclerotic coronary artery disease (CAD), started to be highlighted. In the mid-90s, there was emphasis on reports of myocardial infarction (MI) in young patients infected with HIV and the possible association between HIV infection and increased risk of CAD.5-7 Subsequent studies confirmed an

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We declare no conflict of interest.

©2011 Elsevier Editora Ltda. Este é um artigo Open Access sob a licença de CC BY-NC-ND increased incidence of CAD in these individuals and over time, CAD has become a major cause of morbidity and mortality in this population.⁶⁻⁹

In the general population, the "IV Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention" of the Brazilian Society of Cardiology recommends the use of stratification of cardiovascular risk and sets lipid targets for prevention and treatment of atherosclerosis.⁸ For that purpose, the use of the Framingham Risk Score (FRS) is indicated. The coronary artery calcium scoring (CACS), obtained through computed tomography, is considered an aggravating risk factor for CAD when the individual's percentile adjusted for age and sex is > 75%.^{8,9}

In these guidelines some recommendations are proposed for special groups, such as individuals with HIV infection, for whom the risk assessment for CAD through the FRS and lipid profile is suggested.⁸ The "Recommendations for Antiretroviral Therapy in Adults Infected with HIV: 2008" also recommend that patients with HIV infection should be evaluated in order to identify the degree of cardiovascular risk. The approach is again based on the FRS, respecting some specific characteristics of this group, such as the use of protease inhibitors (PI).¹⁰ In this population, the use of complementary examinations is suggested, including imaging assessment such as CACS as an attempt to achieve better cardiovascular risk stratification.¹⁰

MATERIAL AND METHODS

We studied HIV positive individuals over 18 years of age receiving care at specialized centers for treating HIV-infected patients, who presented no cardiovascular symptoms or history of CAD. By that it is understood: (I) myocardial infarction documented in hospital records or by clinical history associated with diagnostic methods; (II) stable or unstable angina, documented in hospital records, medical report or classical clinical history; (III) asymptomatic ischemic heart disease, but with coronary angiography showing a lesion > 50% in one or more coronary arteries or cardiac imaging assessment documenting ischemic alterations; (IV) previous CABG surgery; (V) prior coronary angioplasty; (VI) documented cerebrovascular accident; (VII) aortic aneurysmal disease or aortic stenosis; (VIII) peripheral artery disease documented by imaging method.

All patients who agreed to participate were seen by a multidisciplinary team consisting of cardiologists, social worker and nutritionist. Demographic, clinical, and anthropometric data were obtained, including traditional risk factors for cardiovascular disease¹¹⁻¹³ [age (\geq 45 years for men and \geq 55 years for women), smoking (current smoking or stopped within the past 30 days), family history of early CAD (myocardial infarction or death from CAD of first-degree relatives, if male aged < 55 years and females aged < 65 years), systemic arterial hypertension (SAH with previous diagnosis and/or use of antihypertensive medication), dys-

lipidemia (previous diagnosis and/or medication to reduce lipid levels) and diabetes mellitus (DM, with prior diagnosis and/or medication to reduce blood glucose)], current ART and PI use, body mass index (BMI, calculated as the ratio between the weight in kilograms and squared height in meters and considered normal from 18.5 to 24.9 kg/m², overweight 25.0 to 29.9 kg/m² and obesity \geq 30.0 kg/m²);^{14,15} abdominal circumference (AC, measured in cm, at the umbilicus and considered abnormal when $> 10^2$ cm in men and > 88 cm in women¹⁵⁻¹⁷), systemic blood pressure measurements at rest, with blood pressure (SBP) levels were \geq 140 mmHg or if diastolic blood pressure (DBP) levels were \geq 90 mmHg.¹⁸

All patients underwent glucose, triglycerides, HDLcholesterol, LDL-cholesterol and total cholesterol (TC) measurements after a 12-hour fasting period. For female patients of childbearing age, a qualitative beta-human chorionic gonadotropin (beta-HCG) was also performed, due to the subsequent performance of the CT scan, which involves radiation emission.

Serum glucose, TC, LDL-cholesterol and triglycerides were considered abnormal if, respectively, greater than 100 mg/dL,¹⁹ 200 mg/dL, 100 mg/dL and 150 mg/dL¹¹; HDL-cholesterol was considered low when less than 40 mg/dL and altered, according to sex, when < 45 mg/dL in men and < 55 mg/dL in women.²⁰

The CT scan was performed in a 64-detector CT scanner (Somatom Sensation 64, Siemens) within one week after the collection of laboratory tests. The Agatston score^{21,22} was used in order to measure CACS,²³⁻²⁵ and percentiles were generated according to age and sex.^{24,26} The risk was categorized as "low" when there was no calcium in the coronary arteries (CACS = 0),²⁷ "moderate" when the CACS was less than or equal to the third quartile (75th percentile)²⁸ for age and sex, and "high" when CACS was greater than the third quartile for age and sex.^{8,27,28}

The FRS was classified as "low" risk when the rate obtained was < 10%, "moderate" when the percentage was \geq 10% and \leq 20%, and "high" when > 20%.^{8,29,30} Variables with normal distribution were expressed as mean \pm standard deviation, and the variables with other distributions were described as median and interquartile range. Categorical variables were compared by Chi-square or Fisher's exact test, and continuous variables by Student t test or Mann-Whitney test. An analysis of agreement between the CACS and the FRS risk assessments was performed using kappa statistic. The reclassification of risk by CACS and based on the FRS was calculated as the percentage of individuals who changed the classification by the CACS stratification. In all analyses, a p value < 0.05 was considered significant. The statistical program used was R, version 2.12.1.31

RESULTS

We studied 40 patients, aged 45.9 ± 8.1 years, ranging from 31 to 64 years. Only two (5%) were older than 60 years. Males accounted for 52.5% of the sample. The demographic and clinical characteristics of studied subjects are shown in Table 1. Two or more risk factors were found in 82.5% of patients and 5.0% had five risk factors. The age of risk for CAD was observed in 30.0% of individuals. A total of 27.5% individuals had altered blood pressure, and among individuals known to be hypertensive, 50% showed altered blood pressure. BMI was $25.3 \pm 3.4 \text{ kg/m}^2$, being classified as normal in 50.0% of subjects, 42.5% as overweight and obesity in 7.5%. The AC was 89.6 ± 9.7 cm in men, and in females, 88.3 ± 9.7 cm. There were significantly more women than men with altered AC (52.6% and 4.8% respectively, p = 0.001).

Table 1. Population characteristics

Variable	
Age (years)	45.9 ± 8.1
Men	21 (52.5%)
SAH	22 (55.0%)
Type II diabetes	4 (10.0%)
Dyslipidemia	27 (67.5%)
Family history of early CAD	23 (57.5%)
Smoking	14 (35.0%)
Smoking load (pack/years)*	8.7*
AC- men (cm)	89.6 ± 9.7
AC- women (cm)	88.3 ± 9.7
BMI (kg/m ²)	25.3 ± 3.4
SBP (mmHg)	124.2 ± 21.9
DBP (mmHg)	80.0 ± 10.9
Glucose (mg/dL)	100.4 ± 13.8
TC (mg/dL)	188.7 ± 33.7
LDL-cholesterol (mg/dL)	112.5 ± 28.8
HDL-cholesterol -men (mg/dL)	37.0 ± 11.0
HDL-cholesterol- women (mg/dl)	42.6 ± 11.9
Triglycerides (mg/dL)	158.5*
FRS (%)	4.0*
CACS	0.0*
Protease inhibitor use	21 (52.5%)

*median; SAH, systemic arterial hypertension; CAD, coronary artery disease; AC, abdominal circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FRS, Framingham Risk Score. Fasting blood glucose was $100.4 \pm 13.8 \text{ mg/dL}$, and 42.5% of patients had altered glucose levels ($\geq 100 \text{ mg/dL}$). Regarding the lipid profile, TC was $188.7 \pm 33.7 \text{ mg/dL}$ (127-268 mg/dL), and 30.0% of patients had altered TC levels ($\geq 200 \text{ mg/dL}$). LDL-cholesterol was $112.5 \pm 28.8 \text{ mg/dL}$ (59-184 mg/dL) and was $\geq 130 \text{ mg/dL}$ in 25.0% of the individuals. HDL-cholesterol was $39.7 \pm 11.6 \text{ mg/dL}$ (20-71 mg/dL), being $37.0 \pm 11.0 \text{ mg/dL}$ in men and $42.6 \pm 11.9 \text{ mg/dL}$ in women. HDL cholesterol was considered abnormal for age and sex of individuals in 82.5% and < 40 mg/dL in 57.5%. Median triglyceride was 158.5 mg/dL (43-412 mg/dL, being the first quartile equal to 104.0 mg/dL and the third quartile, 274.5 mg/dL). Triglycerides were altered ($\geq 150 \text{ mg/dL}$) in 52.5% of the sample.

All patients were on ART, and 52.5% on PI. Table 2 shows comparisons between patients who were on PI or not. No significant differences were detected, except for altered HDL-cholesterol adjusted for sex, which was more frequent in the group on PI (p = 0.040), and for altered triglycerides, which were more common in individuals who were on PI.

Assessment of cardiovascular risk through the FRS showed that the 10-year risk of MI or death due to CAD had a median of 4.0%, 2.0% in the first quartile and 10.0% in the third quartile. In this sample, 72.5% of patients were classified as low risk, 25.0% as moderate risk and 2.5% (only one individual) as high risk.

The CACS had a median equal to zero, its value ranging from zero to 632 points. Coronary calcification was found (CACS > 0) in 32.5% of individuals. Patient characteristics according to the presence of coronary calcification are shown in Table 3. Subjects with coronary calcification were significantly older than patients without coronary calcification (p = 0.015). However, other significantly different variables were not found between subjects with and without coronary calcification.

According to the percentiles of CACS, 67.5% of patients had low risk, 17.5% had moderate risk, and 15.0% had high risk. The assessment of agreement between the FRS and CACS showed that 22 subjects (75.8%) with low FRS were also considered low risk by CACS, 4 (40.0%) of those with moderate risk by the FRS, had moderate risk by CACS and 100% of those with high risk by the FRS had high risk by CACS, with a kappa value of 0.435 (Table 4).

DISCUSSION

Antiretroviral therapy has made HIV infection a chronic condition, and although it is not curable, it is treatable. This fact has allowed the infected population to age and be subject to chronic diseases such as cardiovascular disease, especially CAD. Thus, it is extremely important to know the cardiovascular risk of these patients in order to plan possible interventions that might reduce this risk. The present study assessed patients with HIV infection in order to

	With use n = 21 (52.5%)	Without use n = 19 (47.5%)	p-value
AC (cm)	90.4 ± 11.2	87.4 ± 7.5	0.336
BMI (kg/m ²)	25.9 ± 3.9	24.6 ± 2.8	0.248
Glucose (mg/dL)	102.2 ± 12.7	98.5 ± 14.9	0.404
TC (mg/dL)	192.2 ± 27.9	184.7 ± 39.5	0.493
Altered TC	38.1%	21.1%	0.240
LDL-cholesterol (mg/dL)	112.1 ± 26.5	112.8 ± 31.8	0.936
LDL-cholesterol < 100 mg/dL	33.3%	26.3%	0.629
HDL-cholesterol (mg/dL)	38.7 ± 8.8	40.7 ± 14.3	0.581
HDL-cholesterol < 40 mg/dL	57.1%	57.9%	0.962
Altered HDL-cholesterol	95.2%	68.4%	0.040
Triglycerides (mg/dL)	219.0*	130.0*	0.040
Triglycerides $\geq 150 \text{ mg/dL}$	71.4%	31.6%	0.012
FRS (%)	4.0%*	3.0%*	0.375
CACS	0.0*	0.0*	0.782
Coronary calcification	33.3%	31.6%	0.906

Table 2. Comparisons according to the use of protease inhibitors

Value expressed as percentages or mean ± standard deviation; *median; AC, abdominal circumference; IMC, body mass index; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FRS, Framingham Risk Score; CACS, coronary artery calcium score.

Table 3. Comparison between patients with or without coronary calcification

	With calcification Without calcification		p-value	
	n = 13 (32.5%)	n = 27 (67.5%)	P	
Age (years)	50.3 ± 7.3	43.8 ± 7.7	0.015	
Men	9 (42.8%)	12 (57.1%)	0.141	
SAH	8 (36.3%)	14 (63.6%)	0.564	
Type II diabetes	2 (50.0%)	2 (50.0%)	0.392	
Dyslipidemia	9 (33.3%)	18 (66.6%)	0.584	
Family history of early CAD	8 (34.7%)	15 (65.2%)	0.720	
Smoking	4 (28.5%)	10 (71.4%)	1.000	
Smoking load (pack/years)	5.0*	15.7*	0.229	
AC (cm)	90.5 ± 10.3	88.3 ± 9.3	0.506	
BMI (kg/m ²)	24.9 ± 3.1	25.5 ± 3.6	0.627	
SBP (mmHg)	117.6 ± 17.3	127.4 ± 23.5	0.194	
DBP (mmHg)	78.4 ± 8.7	80.7 ± 11.9	0.543	
Glucose (mg/dL)	100.1 ± 14.0	100.1 ± 13.9	0.833	
TC (mg/dL)	196.6 ± 32.2	184.8 ± 34.3	0.309	
LDL-cholesterol (mg/dL)	108.4 ± 29.5	114.4 ± 28.8	0.546	
HDL-cholesterol (mg/dL)	39.6 ± 12.1	39.7 ± 11.7	0.975	
Triglycerides (mg/dL)	193.0*	140.0*	0.525	
FRS (% in 10 years)	8.0%*	3.0%*	0.142	
Protease inhibitor use	33.3%	66.6%	0.906	

*median; SAH, systemic arterial hypertension; CAD, coronary artery disease; AC, abdominal circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein, FRS, Framingham Risk Score.

	CACS		Total	
	Low	Moderate	High	
FRS				
Low	22	3	4	29
Moderate	5	4	1	10
High	0	0	1	1
Total	27	7	6	40

Table 4. Agreement between risks assessed by FRSand CACS

FRS, Framingham Risk Score; CACS, coronary artery calcium scoring.

determine the prevalence of traditional cardiovascular risk factors, assessing the risk of CAD through previously validated clinical scores and investigate the use of CACS for the diagnosis of subclinical coronary atherosclerosis and as an additional method for risk stratification in this population.

In this sample, the mean age was 45.9 ± 8.1 years and only 30% were at the risk age. Therefore, it can be considered a young population for the development of CAD, but comparable to other studies of populations with HIV.^{6,30-33} However, a high proportion of patients (82.5%) had two or more traditional risk factors, highlighting the importance of proper stratification of cardiovascular risk in this group. SAH was present in 55% of patients, being more frequent than in other studies, which showed prevalence rates of 35% to $41\%^{34,35}$ and 27.5% of the patients had altered blood pressure levels. These findings are similar to those found in the general Brazilian population, in which the levels of hypertension control are still suboptimal,^{18,36} indicating the need for greater attention to blood pressure control in the HIV-infected population.¹⁸

Prevalence of smoking among HIV-infected patients of 47% to 71% has been reported, much more elevated than in the general population.^{34,37} The prevalence observed in our sample was 35% lower than the rates cited above, but still twice the 17.5% prevalence of the Brazilian population in 2008.³⁸ Dyslipidemia was the most frequent risk factor found in 67.5% of individuals. In the study by Cahn et al.,³⁹ the prevalence of dyslipidemia in the Brazilian population with HIV infection was 57.3%.

The levels of TC and LDL-cholesterol were slightly higher than the percentage described in the study by Kingsley et al.⁴⁰ HDL-cholesterol levels were altered in the majority of the studied population (82.5%). The study by Kingsley et al.⁴⁰ identified only 40% of individuals with low HDL-cholesterol, whereas in our population, 57.5% were identified at this level. However, it is noteworthy that these authors did not take into account the adjustment of HDL-cholesterol according to sex. As for triglycerides, our results are also similar to those previously described (38%).⁴⁰

In this population, 52.5% of patients were using PI, which is similar to another Brazilian study.³⁹ No significant differences in levels of TC and LDL-cholesterol were found in our sample among individuals using PI or not, similarly to other studies, i.e., minor alterations in these lipid fractions.⁴¹⁻⁴³ However, HDL-cholesterol, corrected for age and sex, was significantly more frequent among patients using PI. This difference has been reported in the literature, associated with risk of MI.⁴⁴ It was also possible to demonstrate the association between the use of PI and increased levels of triglycerides, and the median in the group that used PI was 219 mg/dL, compared to 130 mg/dL in the group that did not use PI. This association has also been previously described.⁴⁵

Risk assessment through the FRS showed that the population of this sample had low risk (FRS median of 4.0% and the third quartile of 10.0%), which can be explained by their age, predominantly young. Notably, one fourth of individuals were classified according to the FRS as having moderate risk, and 2.5% as having high risk. A significant proportion of individuals with moderate risk underscores the importance of a refinement of risk stratification of this population in order to establish the best treatment and reduce the incidence of adverse cardiovascular events.

Screening for subclinical atherosclerosis through CACS showed that about one third of patients had coronary calcifications, an indicator of the presence of atherosclerosis. Studies carried out in the general population have shown that at the age range of 40-45 years, there is a prevalence of coronary calcification of 13.3% to 21%.46,47 The frequency of calcification found in this sample was similar to the study by Crum-Cianflone et al.⁴⁸ among individuals with HIV infection, in which 34% of patients showed calcification in the coronary arteries. Patients with calcification in the coronary arteries were significantly older than those without calcification, which has been shown in other studies of patients with and without HIV infection.^{32,40,47,49} Although other studies have already reported an association between coronary calcification in individuals with HIV and other variables (SBP, triglycerides, TC, smoking, FH of CAD, dyslipidemia)^{30,40} these associations were not found in our population, possibly due to the small sample size.

The agreement between the risk stratification by FRS and the CACS showed a kappa of 0.435. In this study, we did not have access to the clinical follow-up of patients, and therefore could not make any inference regarding the accuracy of these two forms of risk stratification to predict the occurrence of events. Although it was not possible to establish the best score for risk prediction in this population, it was possible to verify the frequency of modifications in risk classes defined by the FRS provided by CACS. The reclassification of risk occurred in 32.5% of individuals, and from the category of low risk by FRS, 24% had their risk increased (10.3% to moderate risk and 13.7% to high risk). From the category of moderate risk (the most widely described as the main indication for refinement of risk assessment), 10% had their risk increased and 50% had the risk decreased.

The effect of CACS on moderate-risk individuals by the FRS was consistent with published data, which showed a higher frequency of reclassifications exactly in this category.⁵⁰⁻⁵² This capacity of CACS makes it attractive to refine risk stratification in the HIV-infected population. For individuals considered high risk by CACS, the therapeutic approach would possibly be changed.^{8,11}

CONCLUSIONS

One of the limitations of the study was the unavailability of data like the time of HAART, use of PI and HIV infection, which may be correlated with the occurrence of CAD. Larger studies with long-term clinical followup are necessary to confirm the findings and allow obtaining a precise risk score, specific for the needs of this population.

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