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Marina Fayos[1]
Francisco Arnaiz de las Revillas[2]
Vicente González Quintanilla[3]
Claudia González-Rico[4]
Concepción Fariñas-Álvarez[5]
José Antonio Parra[6]
María Carmen Fariñas[7]

Progression of subclinical cardiovascular disease in patients with HIV

[1] Infectious Diseases Service. Hospital Universitario Marqués de Valdecilla-IDIVAL Current address: Department of Infectious Diseases. Hospital Universitario 12 de Octubre. Madrid. Spain.
[2]Infectious Diseases Service. Hospital Universitario Marqués de Valdecilla-IDIVAL. CIBERINFEC, Santander. Spain.
[3]Neurology Service. Hospital Universitario Marqués de Valdecilla-IDIVAL. Santander. Spain.
[4]Infectious Diseases Service. Hospital Universitario Marqués de Valdecilla-IDIVAL. CIBERINFEC. Santander, Spain.
[5]Quality Unit. Hospital Universitario Marqués de Valdecilla-IDIVAL. CIBERINFEC. Santander, Spain.
[6]Radiology Department. Hospital Universitario Marqués de Valdecilla-IDIVAL. University of Cantabria. Santander. Spain.
[7]Infectious Diseases Service. Hospital Universitario Marqués de Valdecilla-IDIVAL. University of Cantabria. Santander. CIBERINFEC. Spain.

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ABSTRACT

Introduction. Human immunodeficiency virus (HIV) infected patients are at increased risk of cardiovascular disease (CVD). Multidetector computed tomography (MDCT) stratifies cardiovascular risk in asymptomatic patients with subclinical atherosclerosis. The aim of this study was to determine the ability of MCTD and clinical and laboratory parameters to assess subclinical CVD progression in HIV patients.

Material and methods. Prospective longitudinal cohort study of patients with at least 10 years of HIV infection and 5 years of antiretroviral therapy history, low cardiovascular risk and monitored for 6 years (2015–2021). All patients underwent clinical assessment, blood analysis, carotid ultrasound, and gated MDCT in 2015 and 2021.

Results. Sixty-three patients (63.5% male) with a mean age of 49.9 years (standard deviation [SD], 10.5) were included in 2015; 63 of them were followed until 2021. Comparing the results from 2015 with those from 2021, Systematic Coronary Risk Estimation-2 (SCORE2) was 2.9% (SD, 2.1) vs. 4.4% (SD, 3.1); Multi-Ethnic Study of Atherosclerosis score (MESA risk) was 3.4 (SD 5.8) vs. 6.0 (SD 8.6); coronary artery calcification CAC) score >100 was 11.1% vs. 25.4% (P < 0.05); and 11% vs. 27% had carotid plaques (P = 0.03).

Conclusions. After six years of follow-up, an increase in SCORE2, carotid plaques, CAC scoring and MESA risk was observed. MDCT findings, along with other clinical and laboratory parameters, could play an important role as a marker of CVD progression in the evaluation of patients with HIV and low cardiovascular risk.

Keywords: HIV; subclinical cardiovascular disease; multidetector computed tomography; coronary calcium score; intima media thickness.

Correspondence:
María Carmen Fariñas.
Infectious Diseases Service. Hospital Universitario Marqués de Valdecilla-IDIVAL. University of Cantabria. Santander. CIBERINFEC.
Av. de Valdecilla s/n, 39008. Santander, Cantabria. Spain.
E-mail: mcarmen.farinas@scsalud.es

Progresión de la enfermedad cardiovascular subclínica en pacientes con VIH

RESUMEN

Introducción. Los pacientes infectados por el virus de la inmunodeficiencia humana (VIH) tienen mayor riesgo de enfermedades cardiovasculares (ECV). La tomografía computarizada multidetector (TCMD) estratifica el riesgo cardiovascular en pacientes asintomáticos con aterosclerosis subclínica. El objetivo del estudio fue determinar la capacidad de la MCTD y los parámetros clínicos y de laboratorio para evaluar la progresión subclínica de la ECV en pacientes con VIH.

Material y métodos. Estudio de cohorte longitudinal prospectivo de pacientes con al menos 10 años de infección por VIH, 5 años de tratamiento, bajo riesgo cardiovascular y seguimiento durante 6 años (2015-2021). Se realizó evaluación clínica, análisis de sangre, ecografía carotídea y TCMD en 2015 y 2021.

Resultados. En 2015 se incluyeron 63 pacientes (63,5% varones) con una edad media de 49,9 años (desviación estándar [DE], 10,5); y fueron seguidos hasta 2021. Comparando los resultados de 2015 y 2021, la Estimación Sistemática de Riesgo Coronario-2 (SCORE2) fue del 2,9% (DE, 2,1) vs. 4,4% (DE, 3,1); La puntuación del Estudio Multiétnico de Aterosclerosis (riesgo MESA) fue de 3,4 (DE 5,8) vs. 6,0 (DE 8,6); el score de calcificación de la arteria coronaria (CAC) >100 fue del 11,1% vs. 25,4% (P < 0,05); y el 11% vs. 27% tenían placas carotídeas (P = 0,03).

Conclusiones. Después de seis años de seguimiento, se ha observado un aumento en SCORE2, placas carotídeas, CAC y MESA. El TCMD, junto con otros parámetros clínicos y de laboratorio, podría desempeñar un papel importante como marcador de progresión de ECV en la evaluación de pacientes con VIH y bajo riesgo cardiovascular.

Palabras clave: VIH; enfermedad cardiovascular subclínica; tomografía computarizada multidetector; puntuación de calcio coronario; grosor íntima media.

INTRODUCTION

Patients infected with human immunodeficiency virus (HIV) are at a higher risk than the general population for developing cardiovascular disease (CVD) [1]. This may be related to various factors, such as genetics, traditional cardiovascular risk factors, antiretroviral treatment (ART), and inflammatory and immunological changes related to HIV itself, regardless of immunovirological control [1]. Therefore, the estimation of an individual's risk of CVD with the greatest possible accuracy is essential for ensuring preventive measures are taken when necessary and should be part of the clinical management of all patients with HIV [1]. In developed countries, the most common cardiovascular manifestation in patients with HIV is ischemic heart disease; therefore, the early diagnosis of CVD is critical to the prevention of acute events, such as acute myocardial infarction or stroke [2].

Cardiovascular manifestations of HIV have changed over the last few decades, following the advent of ART [3]. The overall morbidity and mortality associated with HIV have decreased, although the incidence of coronary heart disease, peripheral artery disease, and heart failure has increased [3]. HIV-related CVD occurs after years of infection, and its prevalence is increasing, due to improved life expectancy in HIV-positive patients treated with ARTs.

A global approach is necessary to prevent atherosclerosis and evaluate risk factors associated with CVD [4]. Cardiovascular risk can be estimated using conventional equations, such as the Framingham score [5] and Systemic Coronary Risk Estimation (SCORE) [6]. In the 2021 European Society of Cardiology preventive guidelines [7], the Systemic Coronary Risk Estimation-2 (SCORE2) algorithm was updated to estimate the 10-year risk of CVD-related death, considering age, sex, lipid levels, smoking status, and blood pressure [8]. In 2022, the National AIDS Plan consensus document on the use of ART in patients with HIV recommended careful cardiovascular risk monitoring in patients who receive integrase inhibitors.

Multidetector computed tomography (MDCT) is useful in the assessment of the extent and severity of atherosclerosis in the vasculature, and in determining coronary artery calcification (CAC) scoring [9]. This score can then be used to classify cardiovascular risk, in addition to conventional risk factors, and may therefore be utilized to make decisions in patients with calculated risks [10]. The Multi-Ethnic Study of Atherosclerosis score (MESA risk) [11] can estimate 10-year CVD risk using traditional risk factors (age, gender, ethnicity, diabetes, smoking status, lipid profile and systolic blood pressure) and CAC. The presence of carotid plaques, measured via ultrasound and CAC, has been found to be a good indicator for further clinical, prognostic, and mechanistic studies of HIV-associated atherosclerosis [12].

The aim of the present study was to determine in patients with at least a 10-year history of HIV and low cardiovascular risk, estimated by classical cardiovascular risk factors, the progression of subclinical coronary atherosclerosis over 6 years, using clinical, blood and imaging tests.

METHODS

Design and inclusion. Prospective longitudinal cohort study of patients with at least 10 years of HIV and 5 years of ART history, monitored by the Infectious Diseases Service of the University Hospital of Santander, Spain, between 2015 and 2021. The inclusion criteria in 2015 were as follows: > 18 years old with HIV; > 10 years since diagnosis; > 5 years of ART; low cardiovascular risk based on the SCORE index; and no previous cardiovascular events. The exclusion criteria were as follows: patients who were not virally suppressed; active or former smokers in the 15 years prior to inclusion; patients who had received < 5 years of ART; the presence of known CVD; patients with systemic inflammatory diseases; and patients who did not sign the informed consent form. Screening was performed on 1,332 patients, with a total of 77 patients being eligible in 2015. During the 6-year follow-up, 14 patients were lost, as follows: 6 did not want to continue the study; 4 were unavailable for testing; and 4 died due to non-cardiovascular causes (Figure 1). During the follow-up period, three patients presented with cardiovascular events (two ischemic strokes and one acute coronary syndrome), and nine developed solid organ tumors.

Data collection assay. Anthropometric and blood analysis data were collected through direct interviews with the patients in 2015 and 2021. In addition to SCORE, SCORE2 was also calculated in both 2015 and 2021, following the last European Society of Cardiology preventive guidelines [7]. Carotid intima-media thickness test (CIMT) was determined via carotid ultrasound, and coronary calcium quantification was determined via gated MDCT, based on the Agatston score, which is the sum of the calcium scores (measured as the Agatston scores of all plaques) in the left main coronary, left anterior descending, left circumflex coronary, right coronary, and posterior descending arteries. Scoring was performed using the current guidelines on CAC screening for cardiac risk assessment [13]. All clinical and analytical data were collected first in 2015 and again in 2021. MDCT was performed in 63 patients in 2015 and in 57 patients in 2021, while carotid ultrasound was performed in 63 patients in 2015 and in 52 patients in 2021. All results were analyzed and compared, and clinical data were collected and reviewed from medical records in the 63 patients included in this study. The following HIV-related parameters were measured: CD4 cell concentration, nadir CD4 cells, and zenith viral load. In addition, erythrocyte sedimentation rate (ESR), ultra-sensitive C-reactive protein (US-CRP), complete blood counts and a lipid profile including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides were recorded.

All 63 patients underwent MDCT on a 64-slice CT scanner to determine CAC in both 2015 and 2021 (Optima; GE Healthcare, USA). Coronary visualization was achieved without contrast using the high-resolution volume mode, and a prospective acquisition technique with heart rate monitoring was used. The amount of calcium in the coronary arteries was

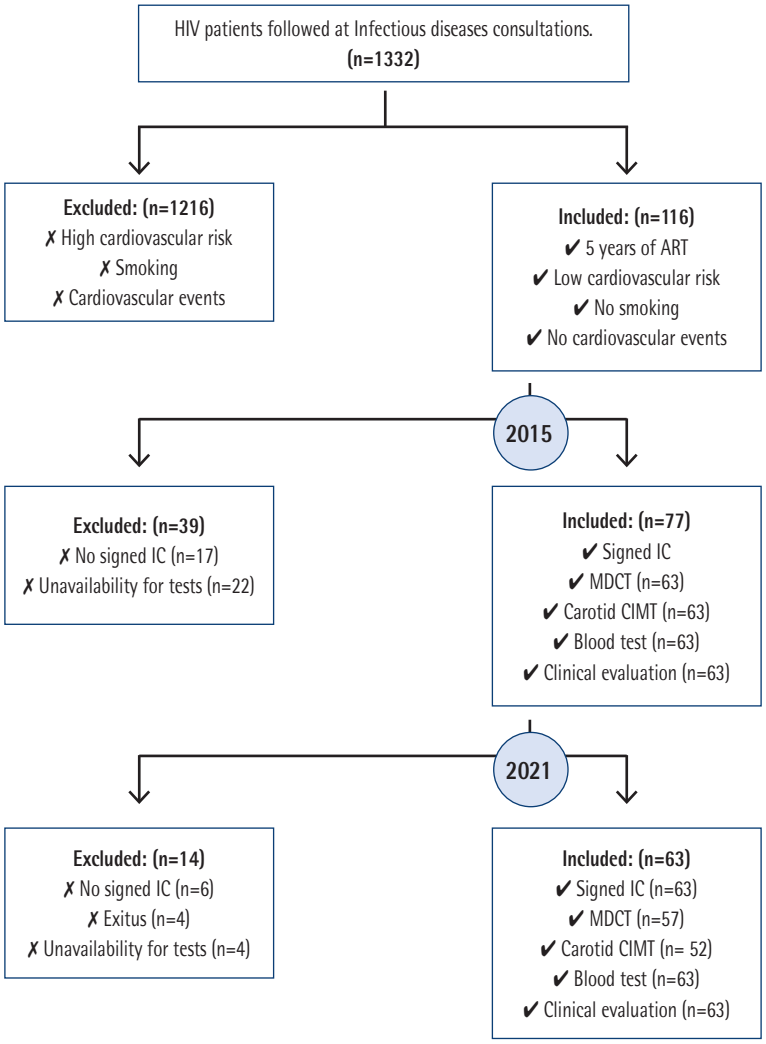

Figure 1 | **Inclusion criteria algorithm.**

Legends: HIV: human immunodeficiency virus. ART: antiretroviral therapy. IC: informed consent. MDCT: multidetector computed tomography. CIMT: carotid intima-media thickness test.

measured using SmartScore® software, and the amount of calcium was expressed using the Agatston score. Patients were categorized into 4 groups, based on their CAC score: 0 (normal); 1–100 (low-to-moderate cardiovascular risk); 101–400 (moderate-to-high cardiovascular risk); and > 400 (high cardiovascular risk) [7]. A CAC score > 100 indicates a high probability of coronary artery disease. According to CAC results, MESA risk [11] was calculated in 2015 and 2021.

CMIT measurements were performed by the same accredited neurologist in 2015 and 2021 using a high-frequency linear transducer (Siemens Acuson X300). All measurements were made using longitudinal and transverse images of the common carotid artery with an 8 MHz probe. For each participant, three measurements were taken on each side, and the result was expressed as the mean CIMT value. Pathological CIMT was defined as ≥ 0.9 mm thickening of the intima-media layer of the arterial wall, and carotid atherosclerosis plaque was defined as a protrusion in the arterial lumen > 1.5 mm, > 50% thickening of the surrounding CIMT, or as the demonstration of a focal protrusion > 0.5 mm in the arterial lumen.

Ethical considerations. The study was performed according to Helsinki Declaration. The protocol was reviewed and approved by the Clinical Research Ethics Committee of Cantabria (Ref: 2015.09, 2021.308) according to local standards. Informed consent was obtained from each patient in 2015 and in 2021.

Table 1 Clinical and analytical characteristics of the study population.

Parameter	Patients 2015 (n = 63) n (%)	Patients 2021 (n = 63) n (%)	P-value*
Age, yr. (mean ± SD)	49.9 ± 10.5	54.4 ± 11.2	-
Sex, male (%)	40 (63.5)	40 (63.5)	-
10-year SCORE	0 (0-1.5)	1 (0-2)	.000
Mean BMI (kg/m2)	26.3 ± 4.2	27.4 ± 4.3	.02
Smoker			.000
Active	3 (4.8)	5 (7.9)	-
Former smoker	24 (38.1)	26 (41.3)	-
Never	36 (57.1)	32 (50.8)	-
Median pack-years	12 (7-22)	12 (7-21)	.09
DM	1 (1.6)	7 (11.1)	.01
HBP	11 (17.5)	27 (42.9)	.001
Statin treatment	8 (12.7)	20 (31.7)	.000
Lipid profile			
HDL cholesterol	51.6 ± 18.8	55.0 ± 25.4	.27
LDL cholesterol	109.1 ± 34.5	120.3 ± 42.8	.033
Total cholesterol	183.4 ± 50.5	190.6 ± 48.8	.36
Triglycerides	152.8 ± 125.0	143.8 ± 109.4	.50
Kidney function			
Creatinine (mg/dL)	0.88 ± 0.2	0.92 ± 0.25	.02
CKD-EPI (ml/min/1.73 m2)	87 ± 8.4	81 ± 12.9	.000
HIV			
Zenith VL	245,135 ± 758,358	245,135 ± 758,358	-
TCD4 (cells/uL) lymphocytes	693.6 ± 373.6	609.5 ± 286.1	.011
TCD4/TCD8	0.9 ± 0.4	1.0 ± 0.5	.017
Months since HIV diagnosis	207.9 ± 81.8	267.9 ± 81.8	.24
ART (months)	167.2 ± 75.3	227.6 ± 75.3	-
Inflammation markers			
ESR	12.8± 10.9	17.5 ± 19	.03
US-CRP	0.13 ± 0.13	1.7 ± 1.6	.000

BMI, body mass index; SD, standard deviation; VL, viral load; HIV, human immunodeficiency virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DM: diabetes mellitus; HBP, high blood pressure; ESR, erythrocyte sedimentation rate; US-CRP, ultra-sensitive C-reactive protein; SCORE, Systemic Coronary Risk Estimation. *Two-tailed chi-square test for qualitative variables and Student's t test for paired two-tailed data for quantitative variables.

Table 2 SCORE (Systemic Coronary Risk Estimation), SCORE2 (Systemic Coronary Risk Estimation-2), MESA risk (Multi-Ethnic Study of Atherosclerosis score), Coronary artery calcium (CAC), and carotid intima-media thickness test (CIMT) results.

Parameter	Patients 2015 (n = 63)	Patients 2021 (n = 63)	P-value*
SCORE mean ± SD	0.9 ± 1.2	1.4 ± 1.7	.000
SCORE2 mean ± SD	2.9 ± 2.1	4.4 ± 3.1	.000
MESA risk mean ± SD	3.4 ± 5.8	6.0 ± 8.6	.000
Agatston mean ± SD	85.4 ± 415	242.5 ± 10,169.5	.04
0 (normal)	45/63 (71.4)	28/57 (49.1)	.000
1-100 (low-to-moderate CVR)	11/63 (17.5)	13/57 (22.8)	.23
> 100	7/63 (11.1)	16/57 (28.1)	.000
101-400 (moderate-to-high CVR)	4/63 (6.3)	12/57 (21.1)	.006
> 400 (high CVR)	3/63 (4.8)	4/57 (7)	.000
CIMT			
CIMT (mm), mean ± SD	0.74 ± 0.15	0.82 ± 0.14	.000
CIMT (mm) > 0.9, n (%)	10/63 (15.8)	14/52 (26.9)	.01
Carotid plaques, n (%)	7/63 (11.1)	15/52 (28.8)	.03

SCORE, Systemic Coronary Risk Estimation; SCORE2, Systemic Coronary Risk Estimation-2. MESA risk: Multi-Ethnic Study of Atherosclerosis score; CAC, coronary artery calcium; CVR, cardiovascular risk; CIMT, carotida intima-media thickness; SD, standard deviation. *Two-tailed chi-square test for qualitative variables and Student's t test for paired two-tailed data for quantitative variables.

Statistical analysis. Quantitative data were presented as mean and standard deviation (SD), or as median with absolute ranges or interquartile ranges (Q1-Q3). Qualitative variables were summarized using absolute and relative frequencies, along with 95% confidence intervals (CI). Each variable was assessed for its parametric or non-parametric distribution using the Kolmogorov-Smirnov test. To detect differences between two quantitative variables, paired Student's t-test was used, while the chi-square test was employed for comparisons between two qualitative variables. Pearson's correlation coefficient (R) with a linear regression model was utilized for correlation analysis between two parametric quantitative variables. Multiple linear regression analysis was performed for certain quantitative variables, both unadjusted and adjusted for age, sex, and cardiovascular risk factors. A two-tailed P value of < 0.05 was considered statistically significant. Statistical analyses were conducted using STATA/IC 16.1.

RESULTS

Demographics and comorbidities. The study population included in 2015 was 77 patients, but only 63 patients were compared between 2015 and 2021 and were included in the analysis as mentioned above (Figure 1).

Table 3 **Correlation between coronary artery calcium (CAC), carotid intima-media thickness test (CIMT), coronary artery calcium score (SCORE), classic cardiovascular risk factors and HIV-related analytical parameters.**

Parameter	CAC correlation in 2021		CIMT correlation in 2021	
	R	P-value	R	P-value
SCORE in 2021	0,13	0,34	0,53	0,0001
SCORE2 in 2021	0.3	0.03	0.55	0.000
MESA risk 2021	0.79	0,000	0.54	0.000
CIMT in 2021	0.26	0,07	-	-
Classical CVR factors in 2021				
HBP	-0,19	0,16	-0,24	0,09
DM	-0,45	0,001	-0,49	0,001
Sex	-0,17	0,21	-0,3	0,03
Age	0,19	0,15	0,45	0,001
Tobacco	0,11	0,43	0,03	0,85
BMI	-0,08	0,6	0,16	0,27
Lipid profile				
LDL cholesterol	-0,21	0,13	0,03	0,85
HDL cholesterol	-0,14	0,31	-0,13	0,37
Total cholesterol	-0,2	0,15	0,01	0,96
Triglycerides	0,04	0,8	0,22	0,12
HIV factors				
CD4 2021	-0,06	0.66	-0,16	0,25
Nadir CD4 at diagnosis < 200	0,15	0,28	0,29	0,04
Zenith VL > 200,000	0,03	0,84	0,17	0,23
Months on ART	0,04	0,76	0,04	0,79
ART (months)				
PIs	-0,05	0,74	0,12	0,42
NRTIs	0,02	0.9	0,06	0,69
NNRTIs	-	0,71	0,3	0,03
INIs	0,05	0,27	0,18	0,21
Inflammation markers				
ESR	0,42	0,002	0,3	0,03
US-CRP	0,29	0,04	0,06	0,68

R, Pearson correlation coefficient; CAC, coronary artery calcium score; SCORE, Systemic Coronary Risk Estimation; CIMT, carotid intima-media thickness; CVR, cardiovascular risk; HBP, high blood pressure; DM, Diabetes mellitus; LDL, low-density lipoprotein; HIV, human immunodeficiency virus; VL, viral load; ART, antiretroviral therapy; PIs, Protease inhibitors; NRTIs, Nucleoside reverse transcriptase inhibitors; NNRTIs, Non-Nucleoside transcriptase inhibitors; INIs, integrase inhibitors; ESR, erythrocyte sedimentation rate; US-CRP, ultra-sensitive C-reactive protein.

The clinical and analytical characteristics are listed in Table 1. The mean ± SD age in 2015 was 49.9 ± 10.5 years, and most patients were men (63.5%). In 2015, 17.5% (n = 11) of the patients had high blood pressure and 12.7% (n = 8) were receiving statin treatments. In 2021, 42.9% (n = 27) had high blood pressure, while 31.7% (n = 20) were receiving statins. LDL went from a mean of 109.1 ± 34.5 mg/dL to 120.3 ± 42.8 mg/dL, and total cholesterol went from 183.4 ± 50.5 mg/dL to 190.6 ± 48.8 mg/dL. The value of ESR increased from 4.7 mm/h (P = 0.03), and US-CRP 1.6 mg/mL (P < 0.01). A decrease in renal function was observed, evidenced by an increase in creatinine of 0.04 mg/dL (P < 0.05).

Table 4 **Correlation between coronary artery calcium (CAC) score and the presence of carotid plaques in 52 patients in 2021.**

CAC in 2021	Carotid plaque in 2021 (n = 52)		
	No, n/N (%)	Yes, n/N (%)	P-value*
0 (normal)	23/24 (95.8)	1/24 (4.2)	.000
1–100 (low-to-moderate CVR)	8/10 (80)	2/10 (20)	.12
101–400 (moderate-to-high CVR)	2/11 (18.2)	9/11 (81.8)	.000
> 400 (high CVR)	1/4 (25)	3/4 (75)	.023

CAC, coronary artery calcium; CVR, cardiovascular risk; CIMT, intima-media thickness. *Two-tailed chi-square test for qualitative variables.

SCORE2 risk, CAC score and MESA risk results. In cardiovascular risk assessment, the mean SCORE in 2015 was 0.9 ± 1.2, compared to 1.4 ± 1.7 ($p < 0.05$) in 2021. Likewise, the SCORE2 in 2015 was 2.9 ± 2.1 compared to 4.4 ± 3.1 ($p < 0.05$) in 2021.

MDCT findings are presented in Table 2. In 2015, 22 patients (34.9%) exhibited coronary plaques, compared to 29 (46%) in 2021 ($P < 0.05$). In 2015, 7 patients (11.1%) had a CAC score > 100, compared to 16 (25.4%) in 2021 ($P < 0.05$). In the group at low cardiovascular risk (SCORE < 1), most patients (14/19; 73.7%) had a normal CAC score (CAC = 0). However, the remaining 5 (26.3%) low-risk patients had findings of low-to-moderate CAC (CAC 1–100) ($P = 0.007$). In the group at high cardiovascular risk (SCORE > 5), all patients (3/3) had a CAC score > 100 ($P = 0.036$). MESA risk in 2015 (including cardiovascular risk factors and CAC) was 3.4 ± 5.8 compared to 6.0 ± 8.6 ($p < 0.05$) in 2021.

The correlation between CAC, SCORE, SCORE2, MESA risk, classic cardiovascular risk factors (high blood pressure, diabetes mellitus, sex, tobacco use), HIV-related factors, and carotid plaques is shown in Table 3. A strong positive correlation of CAC in 2021 with MESA risk was found ($R = 0.79$, $P = 0.000$). Also, a significant moderate positive correlation of CAC in 2021 was found with SCORE2 ($R = 0.3$, $P = 0.03$), and the inflammation markers ESR ($R = 0.42$, $P = 0.002$) and uCRP ($R = 0.29$, $P = 0.04$). A multivariate analysis of CAC, adjusted for parameters of cardiovascular risk (age, sex, high blood pressure, diabetes mellitus, cholesterol, triglycerides, and body mass index) was performed, with an R of the CAC score of 0.19 ($P = 0.04$).

After 6 years of follow-up, 2 episodes of cerebral stroke and 1 episode of acute myocardial infarction occurred. One of the patients had a cerebral stroke in 2015 and died before 2021 due to advanced prostate cancer. This patient, therefore, was excluded from the 2021 study. Another patient suffered a stroke in 2017, with a high SCORE2 of 6 in 2015 and 12 in 2021, a low-to-moderate CAC score of 12 in 2015 with a moderate-to-high CAC score of 245 in 2021; and a high MESA risk in 2015 (4) and 2021 (6). The patient who suffered acute myocardial infarction in 2012, had a high SCORE2 in 2015 and 2021 (9), and a very high CAC (3,212 in 2015 and 7,900 in 2021) and MESA risk (33 in 2015 and 47 in 2021). MDCT was useful in detecting a pulmonary nodule in 4 patients and a renal nodule in 1 patient.

Carotid plaques and Intima-media thickness results. The mean CIMT was 0.74 mm ± 0.15 in 2015, compared to 0.82 mm ± 0.14 in 2021 ($P < 0.05$). There was a significant difference between the presence of CIMT > 0.9 mm and carotid plaques in 2015 and 2021, as shown in Table 2. There were no cases of carotid stenosis greater than 50%.

Table 3 shows the correlation between CIMT, SCORE, SCORE2, MESA risk, classical cardiovascular risk factors (high blood pressure, diabetes mellitus, sex, tobacco use), HIV-related factors, and carotid plaques. A moderate positive correlation of CIMT in 2021 was found with SCORE2 ($R = 0.55$, $P = 0.000$), MESA risk ($R = 0.54$, $P = 0.000$), SCORE ($R = 0.53$, $P = 0.000$), age ($R = 0.45$, $P = 0.001$) and ESR ($R = 0.3$, $P = 0.03$). When categorized by CAC there was a significant increase in carotid plaques in patients with a CAC score > 100 ($P < 0.05$). (Table 4).

DISCUSSION

A higher incidence of atherosclerosis among HIV-infected patients has been demonstrated in previous studies [14-16], and subclinical atherosclerosis can be assessed using the CAC score [17-19]. In the present study, we evaluated the usefulness of MDCT in quantifying the progression of coronary calcium levels and assessing the evolution of cardiovascular risk in a cohort of patients with long-term HIV. The detection of subclinical coronary atherosclerosis through CAC and CIMT metrics allowed us to identify patients with HIV with an underestimated cardiovascular risk based on classic cardiovascular risk factors but a high risk of experiencing fatal cardiovascular events, who will benefit from primary preventive treatment. Each diagnostic test and its relationship with the HIV-related parameters are discussed below.

During the 6 years of follow-up in patients with at least 10 years living with HIV, we observed a significantly increased incidence of classic cardiovascular "classical" factors, such as Diabetes Mellitus and high blood pressure. As well as signif-

icant increase in creatinine, ESR, US-CRP, and a decrease in CD4 T cell levels.

Searching for subclinical atherosclerosis we observed a significantly accelerated progression of subclinical CAC after six years of follow-up, like other studies. Soares et al. [19] observed in their meta-analysis that HIV patients have higher prevalence of noncalcified coronary plaques measured by coronary CT angiography and similar prevalence of CAC measured by MDCT, compared with HIV- negative individuals. The aim of our study was instead to detect the progression of CAC rather than studying its prevalence. Also, we didn't perform coronary CT angiography, so noncalcified plaques were not analyzed. Volpe et al. [20] found comparable findings after a 6-year follow-up of 211 HIV-positive participants, and Guaraldi et al. [21] also found similar findings after 11 months of follow-up in 132 HIV-positive men on ART. In the present study, MESA risk and SCORE2 were also significantly increased in HIV patients, with a strong correlation between MESA risk and CAC, and a moderate correlation between SCORE2 and CAC. Based on these results, it could be suggested that a low SCORE or SCORE2 may underestimate the presence of subclinical cardiovascular disease. These findings are similar to those of Rueda-Gotor et al. [22], who also concluded that SCORE underestimates the cardiovascular risk in rheumatologic patients. Thus, MDCT and MESA risk may be useful for evaluating HIV patients with a low to moderate cardiovascular risk and SCORE2. These patients may benefit from intensity primary preventive treatment of cardiovascular risk factors, such as Diabetes Mellitus and high blood pressure, since a detected higher-than-expected CAC and MESA risk, increase their calculated cardiovascular risk [7, 11]. In addition, it has been suggested that patients who may benefit from the preventive management of cardiovascular risk factors, to repeat CAC scoring at an interval of 5 years for patients with a CAC score of 0, and a 3–5-year interval for patients with a CAC score > 0 [23].

The only patient who experienced a stroke during the follow-up period in the present study had a high SCORE2 (6,12), a moderate-high MESA risk (4, 12) in 2015 and 2021, and low-to-moderate CAC score in 2015, and moderate-to-high CAC score in 2021. In this case, MDCT had a good ability to predict an ischemic episode in an HIV patient with subclinical cardiovascular disease and a moderate risk of cardiovascular events in 2015. This could suggest that both SCORE2, MESA risk and MDCT could detect the evolution of cardiovascular disease, during the 6 years of follow-up.

Regarding the relationship between CD4 cell count and viral load at HIV diagnosis, analyzed in 2015 and 2021, we observed in 2015 that low CD4 cell count, and high zenith viral load were associated with a higher CAC score, despite a low SCORE2 index [24]; however, after 6 years of follow-up, no correlation was found between CAC score and nadir CD4 cells or zenith viral load at HIV diagnosis. The results of previous studies are contradictory while Volpe et al. [20] and Guaraldi et al. [21] did observe a relationship between CAC progression and low CD4 cells and high viral load; Chow et al. [25] did not observe such association between CD4 cells, viral load, and CAC. These differences may be explained by the age of patients, in fact that our patients were older, and had an increased prevalence of classic CV factors and cardiovascular risk. A long-term follow-up of > 10 years might be useful to determine if the correlation between CAC and HIV factors changed.

A few studies have evaluated CIMT in HIV patients [26]. A meta-analysis in 2019 included 17 studies comparing CIMT between patients with HIV and control patients, and the CIMT of those with HIV was 0.27 mm thicker ($P < 0.027$) [26]. Hsue et al. [3] observed an association between HIV and the progression of CIMT and found that patients with HIV had a higher CIMT than HIV-negative patients, with or without detectable CAC. Other studies have described an increase in CIMT progression after ART initiation, with protease inhibitors or nucleoside reverse transcriptase inhibitors (NRTIs) [27,28]. In the present study, 20% of patients with MDCT findings of low risk (CAC score = 0) exhibited carotid plaques, compared to 82% and 75% of patients with moderate and high risk, respectively. These results suggest that the presence of severe carotid ultrasound findings may be considered a reliable predictor of CVD, as concluded by Spence et al. [10], and a reliable way of identifying high-risk cardiovascular patients, according to the most recent European Guidelines on cardiovascular disease prevention in clinical practice [7]. We found a good correlation between CIMT, MESA risk and SCORE2. However, we did not observe a good correlation between CAC and CIMT. Lester et al. [29] reported this discrepancy in 89 healthy patients with low cardiovascular risk and a CAC score = 0, with the presence of 34% of carotid plaques. Naqvi et al. [30] detected 52% of carotid plaques in 136 asymptomatic patients with low risk and CAC score = 0 [30]. An explanation for these findings may be the limitation of MDCT in detecting non-calcified plaques in the early stages of CVD.

Regarding factors associated with HIV, a moderate correlation was found between CIMT and CD4 T-cell nadir levels < 200 cell/mL and months of nevirapine treatment. These data suggest that CIMT may be a more sensitive technique than CAC (coronary artery calcification) for detecting the relationship between HIV-associated factors and the presence of CVD. Therefore, it would be of interest to conduct further studies in the future with a larger sample size, in which this relationship can be analyzed in more detail.

Concerning inflammation markers, a significant increase was detected in ESR and US-CRP. ESR values increased by 4.7 mm/h ($P = 0.03$), and US-CRP levels increased by 1.6 mg/mL ($P < 0.01$). Several clinical studies have associated elevated ESR levels with an increased risk of mortality from coronary artery disease and the progression of atherosclerosis [31-32]. Erikssen et al. [33] assessed ESR in healthy patients aged 40 to 60 years, and the test was repeated after a 7-year follow-up. ESR was correlated with mortality from coronary artery disease, leading to the conclusion that it may serve as a marker for aggressive forms of coronary artery disease. In contrast, our study did not include patients with established or symptomatic cardiovascular disease, but we still observed an increase in ESR in patients with subclinical cardiovascular disease progression. These find-

ings suggest that ESR determination is a valuable and sensitive test for evaluating inflammation associated with atherosclerosis, and it may provide important short-term prognostic information in the case of subclinical cardiovascular disease and long-term or established cardiovascular disease.

There are several studies that have associated US-CRP levels with the presence of CVD and atherosclerotic development [34], but there is limited research evaluating the ability of US-CRP to determine inflammation associated with CVD in HIV patients. The results of our study suggest that US-CRP may be as useful as ESR in reclassifying low or intermediate-risk patients who have not yet experienced cardiovascular events but may have subclinical CVD and could benefit from medical treatment adjustments.

The present study had several limitations. First, the small sample size decreased our ability to detect associations between CAC and analytical parameters; however, the careful selection of patients without cardiovascular risk factors and non-smoking patients made it possible to eliminate confounding factors. Nevertheless, it would have been useful to analyze clinical outcome as an endpoint in a larger sample, to prove the prognostic and clinical value of subclinical CVD progression. Second, after 6 years of follow-up, the appearance of classic cardiovascular risk factors was significant, which may be a confounding factor relating CAC to HIV-infection parameters. Third, the lack of a control group, or patients without HIV, could be considered a limitation of the present study. However, since the higher incidence of atherosclerosis among patients with HIV has been demonstrated in previous studies [10-12], and our aim was to determine which clinical and analytical parameters related to HIV were associated with the progression of subclinical atherosclerosis, we used the same population of patients with a > 10-year history of HIV specific techniques which are not commonly used in clinical practice to determine whether we were able to detect early. A 6-year follow-up of an HIV-positive cohort allowed us to study the association between clinical and analytical outcomes. In addition, the use of healthy HIV-negative subjects as controls must be weighed against the risk associated with radiation. Moreover, the benefits of MDCT, including cancer screening, must be balanced against the risk of radiation enhancement in HIV patients. However, more extensive follow-up would be desirable to be able to verify the long-term evolution.

CONCLUSIONS

In summary, the probably rapid progression of subclinical CVD in patients with HIV supports the use of MDCT and carotid CIMT to detect increased cardiovascular risk in HIV patients whose SCORE2 index may underestimate it. HIV-infected patients with a SCORE2 index close to a cut-off point for the initiation of treatment may also benefit from MDCT to determine CAC and MESA risk to address early cardiovascular risk-modifying factor management.

Further studies with larger populations and longer follow-up time are needed to assess whether the introduction of new non-invasive techniques such as MCDT and carotid ultrasound will improve the diagnosis of subclinical CVD and endothelial dysfunction in clinical practice in patients with HIV.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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