Prevalence of calcified carotid artery atheromas in panoramic radiographs of HIV-positive patients undergoing antiretroviral treatment: a retrospective study

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Objective. This study investigated the prevalence of calcified carotid artery atheromas (CCAAs) in panoramic radiographs of HIV-positive patients.
Study Design. A retrospective cross-sectional study was performed to evaluate the presence of CCAA in 300 panoramic radiographs. Qualitative variables were compared using the χ^2 test or Fisher exact test, as needed. The Mann-Whitney or Student *t* test was used for the quantitative variables.
Results. In the studied group, 8.2% presented CCAA. Among these patients, most used lopinavir/ritonavir ($P = .0459$), had a greater mean age ($P = .0081$), and displayed a lower nadir CD4 ($P = .0195$). The use of lopinavir/ritonavir increased the chances of CCAA by approximately 2.8-fold compared with those who did not use medication (odds ratio, 2.79; 95% confidence interval, 1.12-6.95; $P = .045$).
Conclusions. The variables that were associated with the identification of CCAA are compatible with the known atherogenic risk factors in patients with HIV. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:67-74)

Several studies have been published correlating images of carotid atheroma (i.e., detected via panoramic radiographs) with risk factors for the development of cerebrovascular accidents.[1-8] These atheromas often appear near the bifurcation of the carotid arteries, which can be observed in the field of panoramic radiography.[9-11] Previous publications suggest that significant stenosis can exist when atheromatous calcifications are observed in panoramic radiographs.[11,12] The identification of significant stenosis of the carotid artery (luminal narrowing of the vessel above 50%) in asymptomatic patients has significant importance in public health, as shown by the results of several studies demonstrating that the treatment of asymptomatic obstructions decreases the risk of stroke and death. Population screenings to identify asymptomatic lesions are not indicated. However, if identified, these injuries require medical monitoring and treatment.[13,14]

Recognizing the potential benefits of calcified carotid artery atheroma (CCAA) identification in panoramic radiographs (performed routinely for dental treatment), the American Dental Association's Council on Scientific Affairs[15] recommended in 2006 that dentists review the radiographs of their patients for such injuries and that they refer relevant patients for a medical assessment.[15]

The prevalence of carotid calcification identified in panoramic radiographs and documented in the literature varies between 3% and 5% of patients without systemic disease[4,6,11,16-18] and between 20% and 38.8% in populations with known risk factors for atherosclerosis (diabetes, menopause, metabolic abnormalities, cardiovascular disease, chronic renal disease, and hypertension).[2,19-25]

The identification of carotid atheroma in panoramic radiographs also represents an important predictive feature. Individuals with these images have a significantly higher risk of vascular events (myocardial infarction, revascularization procedures, transient ischemic attack, and angina) than do control participants with a similar risk of atheroma. According to Cohen et al.,[26] 2.7 years (mean) after the identification of atheroma, 57%

Statement of Clinical Relevance

The premature occurrence of cardiovascular events in HIV-positive patients and the fact that cardiovascular risk scores often fail to identify young patients at risk lead to the need for additional measures. Panoramic radiographs may be helpful in this context.

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of these patients had myocardial infarctions (11%), stroke (7%), death (15%), coronary artery bypass procedures (11%), transient ischemic attack (3%), and angina (10%).[26,27]

Recent scientific evidence identified a new group of patients who could be at an increased risk of cardiovascular diseases: HIV-positive (HIV+) patients receiving highly active antiretroviral therapy (HAART). This risk may be related to the presence of viral infection, the traditional risk factors for cardiovascular disease, or the use of antiretrovirals (ARVs).[28-35]

With the advent in the 1990s of HAART, which associated protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) with the already-used nucleoside reverse transcriptase inhibitors (NRTIs), antiretroviral treatment has reached its primary objective of reducing morbidity and mortality caused by HIV.[36,37] However, several adverse effects, such as nausea, diarrhea, allergic reactions, neuropathy, decreased libido, myalgia, lactic acidosis, kidney diseases, liver diseases, bone metabolism disorders, and changes in the chronology of dental mineralization, have been identified.[36,38-40]

The increased incidence of cardiovascular complications in HIV+ individuals can be related to metabolic changes characterized by abnormal redistribution of body fat and dyslipidemia (lipodystrophy syndrome), in addition to changes in insulin resistance and glucose metabolism.[41-45] Lipodystrophy has been associated with a reduction in the levels of anti-LDLm (an antibody against low-density lipoprotein, modified) in patients with low CD4 T lymphocyte counts and increased serum levels of oxidized low-density lipoprotein in patients using HAART. Moreover, an increase in the intima-media thickness of the carotid or endothelial changes after the beginning of treatment with ARVs has been observed.[29,46-51]

These factors increase the risk of atherosclerosis progression in HIV+ patients.[52] According to some authors, these changes primarily occur when using PIs,[53-56] particularly lopinavir/ritonavir (LPV/r).[57,58]

The comprehensive evaluation of panoramic radiography (a low-cost examination that is widely used by dentists) can be an important tool for detecting the presence of CCAA and risk of vascular stenosis.

This study was a survey of panoramic radiographs and medical records of HIV+ patients of the Special Care Dentistry Center (CAPE) to verify the prevalence of CCAA in panoramic radiographs and the existence of possible variables associated with the presence of these radiopacities.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional prevalence study to evaluate the presence of radiopacities similar to CCAA in HIV+ patients. Among the clinical records of 1701 HIV+ patients registered in the CAPE, 503 had panoramic radiographs, but only 300 were selected, owing to the quality of the images. Radiographs with poor quality (overexposure, underexposure, incorrect patient positioning, or processing errors) or did not include vertebrae C3 and C4 in at least one side of the film were eliminated.

Of the 300 radiographs examined, 22.7% (68/300) were digital, 24.3% (73/300) were conventional with a bilateral image of the cervical spine, and 53% (159/300) were conventional with a one-sided image of the cervical spine.

For the diagnosis of CCAA, previously published criteria were used.[59] The radiographs were examined by 3 professionals, and the evaluations were submitted to κ agreement analysis.

In a Microsoft Excel spreadsheet, information from medical records, such as gender, age, time of HIV seropositivity, use of HAART, time of HAART treatment, type of association used, nadir of lymphocyte T CD4, lymphocyte T CD4 count, viral load, triglycerides, total cholesterol, LDL cholesterol (LDLc), HDL cholesterol (HDLc), glucose, and comorbidities (e.g., cardiovascular diseases, diabetes, hepatitis B and C, hypertension), were recorded. The viral load was established as having a value of 1 when the diagnosis was undetectable, and to facilitate the analysis, these values have been transformed into logarithmic values. The results of the laboratory tests were used if they were performed 6 months before or 6 months after the date of the radiographs.

The type of therapy was classified into 4 categories: NRTI, NRTI + PI, NRTI + NNRTI, and NRTI + NNRTI + PI. Based on a literature review, LPV/r was chosen to determine if there was a significant association between it and the presence of CCAA.

Patients who had not used ARV therapy until radiography or for 2 years or more before radiography were considered to be ARV therapy nonusers. The use of these medicines until the date of the radiography was also recorded in months.

For statistical analysis, the χ^2 test or Fisher exact test and the Student *t* test or Mann-Whitney test were used for the qualitative and quantitative variables, respectively. The odds ratio was calculated with a 95% confidence interval to evaluate the relationship between the variables.

This study was approved by the Research Ethics Committee of the School of Dentistry of the University of São Paulo, Brazil.

RESULTS

The 300 studied radiographs belonged to patients who were HIV+ for a mean of 8.4 years. Most were male (67.8%), and the mean age was 40.53 years.

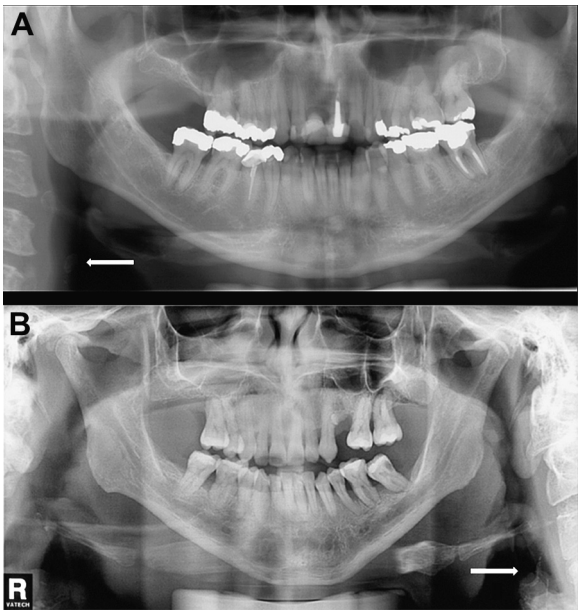

Fig. 1. **A**, The presence of CCAA in an oval shape (*arrow*). **B**, The presence of CCAA in the linear aspect (*arrow*).

Approximately 78.7% were currently using or had used ARVs, and the mean duration of uninterrupted use was greater than 4.5 years. The viral load, CD4 count, and CD4 nadir were 36,697 copies/mL, 470 cells/mm^3, and 214 cells/mm^3, respectively.

Twenty-five radiographs showed images of cervical calcifications (25/300, 8.33%). The prevalence of CCAA was 10.29% (7/68) in the digital radiographs, 9.58% (7/73) in the conventional radiographs examined bilaterally, and 6.91% (11/159) in the conventional panoramic radiographs that only allowed unilateral evaluation (Figure 1).

Data found in the literature show a prevalence of CCAA of 16% to 38.8% in individuals with cardiovascular disease or known predisposing risk factors (Table I) and 2.1% to 5% in patients without cardiovascular risk factors (Table II).

Only the presence or absence of CCAA was investigated; radiography type and the presence of a unilateral or bilateral image were not considered in inferential statistics.

The probability of determining CCAA via panoramic radiography was the same for both genders (odds ratio [OR], 1.02; 95% confidence interval [CI], 0.42-2.45; $P = .85$).

The use of HAART did not increase the chance of CCAA detection in panoramic radiography (OR, 2.09; 95% CI, 0.60-7.21; $P = .35$). There was also no association between the type of ARV combination used and the presence of CCAA (Table III).

Among the patients whose radiographs presented CCAA, a significantly higher proportion had used LPV/r (40.9%) compared with those who did not (19.9%) ($P = .0459$). The use of LPV/r increased the chance of CCAA 2.8-fold compared with those who did not use this medication (OR, 2.79; 95% CI, 1.12-6.95; $P = .045$) (see Table III).

The regression equation [Logit Pi = 2.5649 + (1.0245 X 1)] was used to calculate the probability of occurrence of Y (CCAA) in relation to X (use of LPV/r). For X = 0 (no use of LPV/r), the probability of occurrence of CCAA is 7.14%. For X = 1 (use of LPV/r), the probability of occurrence of CCAA is 17.65%.

No statistically significant relationship between patients with and without CCAA was observed in the laboratory test values for total cholesterol ($P = .9416$), triglycerides ($P = .8099$), HDLc ($P = .3461$), LDLc ($P = .0811$), or glucose ($P = .3316$) (see Table II), as well as for the presence of the comorbidities such as cardiovascular diseases ($P = 1.00$), diabetes ($P = .7137$), hepatitis B and C ($P = 1.00$), and hypertension ($P = .3409$) (Table IV).

Table I. Panoramic radiography studies with a diagnosis of atheroma in patients with systemic diseases

Study (year)	*n*	*Prevalence*	*Age, mean (range) (y)*	*Disease*
Friedlander et al. (1999)[2]	55	22%	60.4	OSA
Friedlander and Maeder (2000)[19]	49	20%	66 (55-81)	Db2
Friedlander and Altman (2001)[20]	52	31%	70	PM
Fridlander et al. (2002)[21]		36%; 24%	68; 62	Db2 id; Db2
Sung et al. (2004)[22]	27	33%	62.3 (56-72)	HCMP
Kansu et al. (2005)[23]	69	16%	44	CKD
Uthman and Al-Saffar (2008)[24]		38.8%	(40-80)	CVD/MS
Pornprasertsuk-Damrongsri et al. (2009)[25]	85	22%	60 (33-75)	MS

OSA, obstructive sleep apnea; *Db2*, type 2 diabetes; *id*, insulin dependent; *PM*, postmenopause; *HCMP*, hypertrophic cardiomyopathy; *MS*, metabolic syndrome; *CVD*, cardiovascular disease; *CKD*, chronic kidney disease.

Table II. Panoramic radiography studies with a diagnosis of atheroma in patients without cardiovascular risks

Study (year)	*n*	*Age (y)*	*Prevalence*
Almog et al. (2002)[11]	778	>55	3.5%
Ohba et al. (2003)[16]	659	>80	5%
Tamura et al. (2005)[17]	2568	50-70	4.13%
Bayram et al. (2006)[4]	4106	>40	2.1%
Pornprasertsuk-Damrongsri and Thanakun (2006)[18]	1370	50-87 (mean, 69)	2.4%
Bayer et al. (2010)[6]	2557	>30 (mean, 66.6)	4.8%

Table III. Inferential statistics for the qualitative variables gender and ARVT in relation to the presence of CCAA

	CCAA				
Variable	*Yes n (%)*	*No n (%)*	*Total n (%)*	*OR (95% CI)*	*P*
Gender					
Male	17 (68.0)	186 (67.6)	203 (67.7)	1.02	.8524*
Female	8 (32.0)	89 (32.4)	97 (32.3)	0.42-2.45	
ARVT					
Yes	22 (88.0)	211 (77.9)	233 (78.7)	2.09	.3524*
No	3 (12.0)	60 (22.1)	63 (21.3)	0.60-7.21	
ARVT with PI					
Yes	17 (77.3)	134 (63.5)	151 (64.8)	1.95	.2928*
No	5 (22.7)	77 (36.5)	82 (35.2)	0.69-5.50	
ARVT with NNRTI					
Yes	10 (45.5)	110 (52.1)	120 (51.5)	0.77	.7097*
No	12 (54.5)	101 (47.9)	113 (48.5)	0.32-1.85	
ARVT with NRTI + PI					
Yes	12 (54.5)	86 (40.8)	98 (42.1)	1.74	.3079*
No	10 (45.5)	125 (59.2)	135 (57.9)	0.72-4.22	
ARVT with NRTI + NNRTI					
Yes	17 (77.3)	149 (70.6)	166 (71.2)	1.41	.6826*
No	5 (22.7)	62 (29.4)	67 (28.8)	0.50-4.00	
ARVT with NRTI + PI + NNRTI					
Yes	5 (22.7)	48 (22.7)	53 (22.7)	1	.7911*
No	17 (77.3)	163 (77.3)	180 (73.7)	0.35-2.85	
ARVT with NRTI					
Yes	-	15 (7.1)	15 (6.4)	NA	.3723**
No	22 (100.0)	196 (92.9)	218 (93.6)		
Use of LPV/r					
Yes	9 (40.9)	42 (19.9)	51 (21.9)	2.79	**.0459**
No	13 (59.1)	169 (80.1)	182 (78.1)	1.12-6.95	

CCAA, calcified carotid artery atheroma; *ARVT*, antiretroviral therapy; *PI*, protease inhibitor; *NRTI*, nucleoside reverse transcriptase inhibitor; *NNRTI*, non-nucleoside reverse transcriptase inhibitor; *LPV/r*, lopinavir/ritonavir; *NA*, not applicable; *OR*, odds ratio; *CI*, confidence interval.
*χ^2 test with Yates correction.
**Fisher exact test.

Table IV. Inferential statistics of the quantitative variables of lipidogram and glucose laboratory values in relation to the presence of CCAA

	CCAA		
Variable	*Yes*	*No*	*P*
Total cholesterol (mg/dL) (median)	181.00	183.50	.9416**
Triglycerides (mg/dL) (median)	104.00	182.00	.8099**
HDLc (mg/dL) (median)	50.00	44.00	.3461**
LDLc (mg/dL) (mean ± SD)	60.50 ± 26.16	105.69 ± 34.46	.0811*
Glucose (mg/dL) (median)	84.00	93.00	.3316**

CCAA, calcified carotid artery atheromas; *HDLc*, HDL cholesterol; *LDLc*, LDL cholesterol; *SD*, standard deviation.
*Student *t* test.
**Mann-Whitney test.

For the parametric variables, a statistically significant difference was found only for age and the CD4 nadir value. Patients with CCAA had a significantly greater mean age ($P = .0081$), and the median CD4 nadir was significantly lower ($P = .0195$) compared with the patients who did not show CCAA (Table V).

Table V. Inferential statistics of the quantitative variables age, viral load, CD4, and CD4 nadir in relation to the presence of CCAA

	CCAA		
Variable	*Yes*	*No*	*P*
Age (y) (mean ± SD)	45.44 ± 8.77	40.08 ± 9.70	**.0081***
HIV time (y) (median)	9.00	7.00	.4325**
ART time (mo) (median)	36.00	36.50	.9545**
CD4 count (median)	464.00	453.00	.8766**
Nadir CD4 (median)	68.00	197.00	**.0195****
Viral load logarithmic value (median)	0.50	0.00	.4079**

CCAA, suspected image of carotid atheroma; *HIV*, human immunodeficiency virus; *ARVT*, antiretroviral therapy; *CD4*, CD4 T lymphocyte count; *Nadir CD4*, lower CD4 count; *SD*, standard deviation.
*Student *t* test.
**Mann-Whitney test.

DISCUSSION

This study used both conventional and digital radiographs. The use of radiograph types did not significantly impact the results; the difference in the

prevalence of CCAA between the 2 types of exams was relatively small (<1%). Beckstrom et al.[60] defended the use of digital radiographs, arguing that digital techniques improve the image and provide an appropriate view of the carotid bifurcation. However, Friedlander et al.[8] concluded that conventional radiographs cover a larger extent of the cervical region and are thus better indicated for carotid atheroma diagnosis. The correct scope of the carotid bifurcation region bilaterally interfered in our results. The identification of the space between C3 and C4 unilaterally decreased the prevalence of CCAA by approximately 40% in the study group. Ertas and Sisman[7] used conventional and digital radiographs and confirmed their radiographic findings using Doppler ultrasound. There was no difference in the accuracy of diagnosis between the 2 modes.

When compared with data found in the literature, the prevalence of CCAA found in the HIV+ patients of this study (8.2%) was lower than in individuals with cardiovascular disease or known predisposing risk factors (see Table I) but higher than in nonspecific population samples (patients without known cardiovascular risks) (see Table II).

It should be noted that the mean age of the patients in this study was 40 years; in many previous studies, one of the criteria for inclusion/exclusion of radiographs was an age older than 50 years. An age above 50 years increased cardiovascular risk even in patients without other cardiovascular risks.[61]

Although the ARVs have been responsible for increasing longevity in HIV-infected patients, this population in Brazil remains young (96% are less than 50 years old).[62] A low mean age in which acute coronary syndromes occur in HIV+ patients has been observed (<45 years), and cardiovascular risk scores used for the general population often fail to identify young patients at risk for myocardial infarction. However, regardless of age, increased cardiovascular risks for HIV+ patients have been demonstrated compared with the seronegative population after adjusting for age groups.[63,64]

It should be noted that comorbidities and the lipidogram were not risk factors for the identification of CCAA in this study; an increase in cholesterol and triglycerides and the presence of diabetes and hypertension are known risk factors for cardiovascular diseases. In HIV+ patients, an increased risk of cardiovascular disease has been associated with adverse effects caused by ARVs (particularly the PIs) that cause metabolic disorders and increase the prevalence of comorbidities.[43,65]

The use of HAART was not associated with the presence of CCAA, but the use of a specific ARV combination, LPV/r, was significantly related. The use of ritonavir aims to saturate the cytochrome p450 enzymes in the liver microsome, decreasing the metabolism of lopinavir, which maintains higher plasma concentrations for a longer period of time. Many studies have reported that this association is one of the most effective viral controls and that more metabolic changes occur.[57,58,66] This drug induces the acceleration of senescence and associated dysfunctions in endothelial cells,[67] causes oxidative stress in the endoplasmic reticulum, and increases the synthesis of inflammatory cytokines, which are released by macrophages in advanced stages of atherosclerosis.[68] Although the mechanism is not fully understood, this drug appears to promote atherosclerotic lesions independent of the presence of dyslipidemia.[69]

In addition to the adverse effects of medication, atherogenesis can also be related to changes in the vascular wall (intima-media thickness) caused by the virus, which occur via the inflammatory reaction caused by the existence of infectious disease and are dependent on the severity of the infection (identified using the nadir CD4 count).[70-72]

In our study, the association between LPV/r and low nadir CD4 count with the presence of CCAA may indicate that HIV infection and its treatment may influence the identification of CCAA. Thus, we believe that the results of this study are in accordance with those of Lorenz et al.,[29] Aberg et al.,[30] Seaberg et al.,[32] and Baker et al.,[33] indicating that both the severity of the infection and the use of HAART are responsible for changes in the vascular wall and in metabolism related to the formation of atheromatous plaques.

This retrospective study conducted with HIV+ patient records sought to test the hypothesis that HAART could contribute to the formation of CCAA. However, cross-sectional studies present clear limitations regarding the temporal relationship of the facts. It is not possible to determine which of the factors are directly related to carotid atheromas. As patients in a more advanced stage of infection (lowest CD4 nadir) are indicated for the use of LPV/r, they may be more susceptible to CCAA, and the medicine may not be the independent variable. The scientific literature could benefit from prospective cohort studies that assess the presence of CCAA in HIV+ patients, following these patients on a regular basis since the beginning of HAART. It would also be appropriate to establish studies investigating the existence or absence of atheroma through the use of other tests such as ultrasound, computed tomography, and nuclear magnetic resonance.

CONCLUSION

On the basis of a higher prevalence of CCAA than that found in the general population, a lower mean age, and

a statistically significant association with known parameters related to atherogenesis in HIV+ patients (nadir CD4 count and use of LPV/r), we recommend the careful examination of panoramic radiographs in these patients. ARV therapy has increased the estimated life of HIV+ patients; advanced age is also one of the primary risk factors for cardiovascular diseases. As this is a preliminary study, the evidence presented herein could serve as a basis for further studies.

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