CLINICAL RESEARCH

Oral Inflammatory Burden and Carotid Atherosclerosis Among Stroke Patients

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ABSTRACT

Introduction: This study aimed to test the hypothesis that oral inflammatory burden (OIB) is independently associated with the carotid atherosclerotic burden (CAB) among individuals with ischemic stroke (IS) or transient ischemic attack (TIA). **Methods:** This cross-sectional observational study included 240 hospital patients with the diagnosis of IS or TIA. The main exposures were apical periodontitis (AP), root canal treatment (RCT), and crestal alveolar (periodontal) bone loss (BL), and the main outcome was the CAB. Exposure and outcome variables were measured through a head and neck multidetector computed tomography angiography and CAB was dichotomized in <50% and ≥50% vessel occlusion. OIB scored as a composite measure of the endodontic and periodontal disease exposure. Hospital health records provided information on sociodemographic and medical covariates. Prevalence ratios (PRs) were calculated through Poisson regression models, estimating the relationship between the oral exposures and CAB, with = 5%. **Results:** Mean age was 62.15 ± 13.1 years, with 56.7% men. Univariate analyses showed that AP ≥2 (PR = 1.83; 95% confidence interval [CI], 1.05–3.17) and endodontic burden (EB) (AP and/or RCT ≥ 2) (PR = 1.98; 95% CI, 1.13–3.47) were associated with CAB ≥50%. Multivariate models, adjusted for sociodemographic and medical covariates, revealed that pooled periodontal and endodontic parameters (OIB = BL ≥ 5 mm and EB ≥ 2) were independently associated with CAB ≥ 50% (PR = 2.47; 95% CI, 1.04–5.87). **Conclusion:** A higher OIB was independently associated with increased levels of CAB among hospital patients with IS or TIA. The combination of endodontic and periodontal parameters strengthened the observed association and should be evaluated in future studies on the relationship between oral health and cardiovascular outcomes. *(J Endod 2022;48:597–605.)*

KEY WORDS

Apical periodontitis; periodontal disease; alveolar bone loss; risk factor; cardiovascular disease

SIGNIFICANCE

A higher oral inflammatory burden (sum of endodontic and periodontal diseases) was independently associated with higher levels of carotid atherosclerotic burden among hospital patients with ischemic stroke. Oral inflammatory diseases may boost the vascular risk in this specific population.

Stroke is characterized as a neurological deficit related to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction or hemorrhage, and is one of the main causes of disability and death worldwide[1]. Ischemic stroke (IS) accounts for 80% of all strokes and occurs after an obstruction in the blood flow to the brain due to a clot or rupture of an atheroma plaque[2].

An atheroma is formed after endothelial damage and is promoted by predisposing factors such as low-grade inflammation, microorganisms and their toxins, hypertension, and cigarette toxins, among others[3]. The traditional cardiovascular disease (CVD) risk factors, such as hypertension, smoking, and dyslipidemia, among others, explain only part of the clinical and epidemiologic features of cardiovascular events[4]. Recent observational studies have provided consistent evidence on the association between oral infections and oral inflammatory diseases, especially periodontitis[5], apical periodontitis (AP)[6], and caries[7], and noncommunicable diseases, notably on outcomes related to atherosclerosis[8]. The biological plausibility that supports this relationship has been previously explored in the literature[9,10].

Considering that both periodontitis and AP have similar microbiota and can modify the serum levels of proinflammatory mediators, it is reasonable to infer that a composite measure of oral inflammatory diseases that includes AP and periodontitis exposure should exhibit a stronger association with CVD than individual assessments alone. However, to date, few studies analyzed the pooled effect of oral inflammatory diseases in relation to CVD or other systemic outcomes[11,12].

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All authors gave their final approval and agree to be accountable for all aspects to work.

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There is compelling evidence from well-designed epidemiological studies regarding the association between periodontal parameters and atherosclerosis in populations with no history of cardiovascular events[13]; however, few studies evaluated the association between oral diseases and atheroma plaque thickness among patients with IS or transient ischemic attack (TIA)[14,15]. Unfortunately, previous studies did not evaluate the combination of periodontitis with other oral parameters such as AP, to analyze the interaction between the different oral inflammatory diseases and atherosclerosis.

Thus, the purpose of this study was to test the hypothesis that oral inflammatory burden (OIB), scored as a composite measure of endodontic and periodontal disease exposure, is independently associated with the carotid atherosclerotic burden (CAB) among individuals with IS or TIA.

METHODS

This observational cross-sectional study was submitted and approved by the Ethics and Research Committee of the Pontifícia Universidade Católica do Rio Grande do Sul (CAAE #66511417.4.1001.5336). This observational study conforms to the STROBE guidelines.

A sample size calculation was carried out considering the data from a previous study[14], in which the means and standard deviations of aortic arch atheroma plaque thickness in patients with low and high periodontitis were 1.6 ± 1.2 mm and 2.9 ± 2.4 mm, respectively. Assuming a power >95% and $\alpha = 5\%$, the calculation yielded in a minimum sample estimate of 126 individuals to identify significant differences.

A total of 418 patients admitted to the São Lucas Hospital (Porto Alegre, Brazil) and diagnosed with IS (an acute ischemic lesion on the brain and/or neurological deficits lasting >24 hours; $n = 324$) or TIA (neurological deficit <24 hours without new ischemic lesions; $n = 94$)[1] between January 2015 and December 2017 were selected for participation. All patients had undergone a head and neck multidetector computed tomography angiography (MDCTA) and a magnetic resonance imaging of the brain before enrollment in this study. A total of 178 patients were excluded from the study because of incomplete acquisition of oral images on MDCTA ($n = 56$) or edentulism ($n = 122$). Therefore, a total of 240 participants were entered into the study and analysis (Fig. 1).

Sociodemographic and medical variables were collected from hospital charts. Sociodemographic and medical variables were collected from hospital charts.

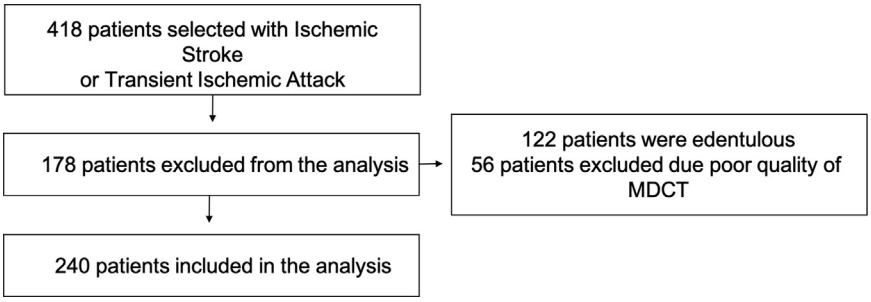

FIGURE 1 – Flowchart of the study sample. MDCT, multidetector computed tomography.

Sociodemographic data included age (dichotomized as <60 or ≥60 years, according to the Brazilian Statute of the Elderly[16], law 10.741/2033[11,17,18]) and sex. The body mass index (BMI) was calculated by dividing the weight by the height squared[19], as recorded by the hospital nutrition department. Diabetes was defined as the use of insulin or hypoglycemic medication, or fasting plasma glucose ≥100 mg/dL, or history of diagnosed diabetes[20]. Low-density lipoprotein cholesterol (LDL-c) was computed from the Friedewald equation[21]. Smoking was dichotomized as never smoker and current/former smoker. Hypertension was defined as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg and classified as hypertension stage 1[22].

The carotid system was explored in transverse and longitudinal scans using MDCTA images. The images were analyzed by an experienced radiologist who was masked regarding the aim of the study. MDCTA was performed with a 64-slice CT scanner (Philips iCT, Amsterdam, Netherlands). All participants had received an iodinated contrast injection (Ultravist 300 (623 mg/mL); Bayer, PharmaAG Berlin, Germany) before imaging. The protocol for image acquisition was as follows: spiral mode, 0.8 rotation time; pitch, 0.8; slice thickness, 0.6–1.0 mm; collimation, 120 × 0.6 mm; acquisition parameters, 110 Kv, 200 mA. The images were visualized using the Arya software (PACS-Aurora v.3.3).

Both common, internal, and external carotid arteries were examined for the presence of atherosclerotic plaque. CAB was classified according to the degree of vessel occlusion: 0%, <50%, 50%–75%, >75%, and 100%[23]. For analytical purposes, and based on the threshold value for vascular therapy[23], CAB was dichotomized as low (CAB <50% in any carotid) or high (CAB ≥50% in any carotid)[24,25].

The oral exposures were evaluated through the MDCTA images. Impacted teeth, deciduous teeth, and third molars were not assessed; hence, participants had a potential of having up to 28 permanent teeth for evaluation. AP and root canal treatment (RCT) were classified as present or absent[26] (Fig. 2*A* and *B*) by an experienced endodontist (T.S.L.) previously calibrated and blinded to the medical variables. Calibration training was performed before the analysis, by 2 examiners who were specialists in endodontics, who independently evaluated 30 MDCTA images twice, with an interval of 30 days. After the second examination, the inter-examiner agreement levels were kappa = 0.869 for AP and kappa = 0.902 for RCT. The intra-examiner agreement levels were kappa = 0.826 for AP and kappa = 0.903 for RCT.

Crestal alveolar bone loss (BL) was measured in mm (± 0.01 mm) from the cementoenamel junction to the alveolar ridge in 4 sites of each tooth (mesial, distal, buccal, and lingual) (Fig. 2*C* and *D*) by a calibrated examiner, who was blinded to the medical variables. The inter-examiner and intra-examiner agreement levels were kappa = 0.811 and kappa = 0.803 respectively. BL was averaged for all measured sites.

For purposes of analysis, both AP and RCT variables were dichotomized as ≤1 or ≥2. Endodontic burden (EB) was calculated as the sum of teeth with AP and/or RCT for each individual and was classified as ≤1 AP and/or RCT or ≥2 AP and/or RCT. Periodontal disease exposure was dichotomized based on the mean BL as present (≥5 mm) or absent (<5 mm). OIB was calculated as a composite score of EB and BL with 4 categories: (1) BL < 5 mm and EB ≤ 1; (2) BL ≥ 5 mm and EB ≤ 1; (3) BL < 5 mm and EB ≥ 2; (4) BL ≥ 5 mm and EB ≥ 2. Presumably, a composite score of 1 (BL < 5 mm and EB ≤ 1) reflects the lowest OIB; whereas, a composite score of 4 (BL ≥ 5 mm and EB ≥ 2) reflects the highest OIB. Composite scores of 2 (BL ≥ 5 mm and EB ≤ 1) and 3 (BL < 5 mm and EB ≥ 2), therefore, would correspondingly reflect intermediate levels of OIB.

Descriptive statistics (frequencies, *N* and %) were calculated according to the CAB. Univariate and multivariate Poisson regressions with robust variance were carried

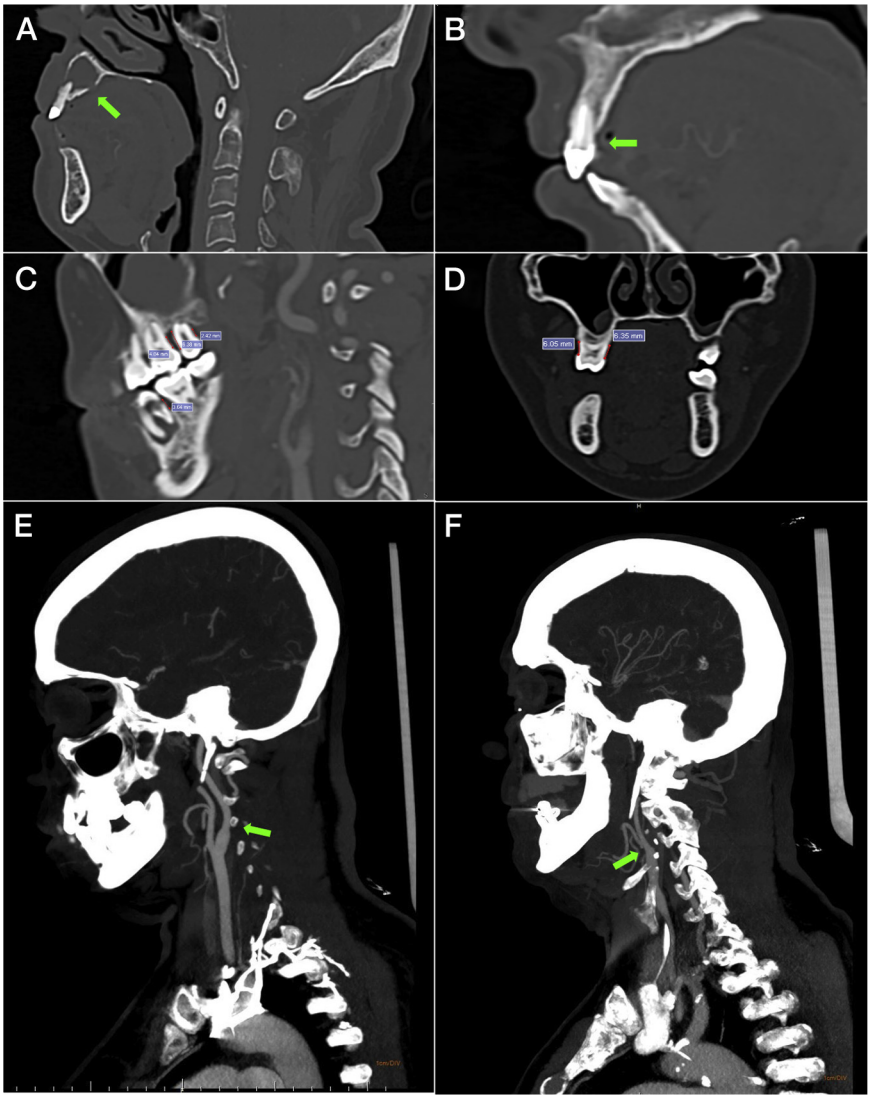

FIGURE 2 – Multidetector computed tomography angiography images showing the presence of apical periodontitis (*arrow* in *A*), root canal treatment (*arrow* in *B*), the methods for the measurement of crestal alveolar bone loss: the distance between the cementoenamel junction and the alveolar ridge in all sides of each tooth (*C*: mesial and distal measurements; and *D*: buccal and lingual measurements) and the absence/presence of atheroma plaque into the carotid artery (*arrow* in *E* and *F*, respectively)

out to estimate the association (prevalence ratios [PRs] and 95% confidence intervals [CI]) between the main oral exposures (AP, RCT, BL, EB, and OIB) and CAB, adjusting for sociodemographic and medical covariables, with $\alpha = 5\%$. Wald χ^2 was calculated to test the strength of the association. Statistical analyses were carried out using SPSS Statistics v.25 (IBM, Chicago, IL).

RESULTS

Table 1 shows the distribution of sociodemographic, medical, and dental variables according to the CAB. The mean age was 62.15 ± 13.1 years (31–91 years), and 56.7% were men. Univariate analysis revealed that age ≥60 years (PR = 2.47; 95% CI, 1.27–4.83), BMI ≥ 25 (PR = 0.53; 95% CI, 0.30–0.92), AP ≥ 2 (PR = 1.83; 95% CI, 1.05–3.17), EB ≥ 2 (PR = 1.98; 95% CI, 1.13–3.47), and OIB BL ≥ 5 mm and EB ≥ 2 (PR = 2.32; 95% CI, 1.06–5.07) were associated with higher levels of CAB. Due to the distribution of the sample, with a low number of observations related to hypertension stage 1 and previous IS or TIA variables, it was not possible to carry out a regression analysis including these variables. Alternatively, a χ^2 test was performed and resulted in a significant association between hypertension stage 1 ($P \leq .01$) and previous IS or TIA ($P = .06$) with CAB.

Table 2 shows the multivariate analysis between AP and CAB. Model 1 is adjusted for sociodemographic variables (age and sex). Model 2 is adjusted for sociodemographic and medical variables (BMI, diabetes, LDL-c, and smoking). Model 3 is adjusted for sociodemographic, medical, and dental variables (BL). In Model 1, AP ≥2 and age ≥60 years were significantly associated with a higher level of CAB ($P = .04$ and $P = .01$, respectively). In Models 2 and 3, only age ≥60 years was independently associated with CAB ≥50% ($P < .01$ for both models).

Table 3 shows the multivariate analysis between EB and CAB. Model 1 is adjusted for sociodemographic variables (age and sex). Model 2 is adjusted for sociodemographic and medical variables (BMI, diabetes, LDL-c, and smoking). Model 3 is adjusted for sociodemographic, medical, and dental variables (BL). In Model 1, EB ≥ 2 and age ≥ 60 years were significantly associated with a higher level of CAB ($P = .03$ and $P = .01$, respectively). In Models 2 and 3, only age ≥ 60 years was independently associated with CAB ≥50% ($P < .01$ in both).

Table 4 shows the multivariate analysis between OIB and CAB. Model 1 is adjusted for sociodemographic variables (age and sex). Model 2 is adjusted for sociodemographic and medical variables (BMI, diabetes, LDL-c, and smoking). In Models 1 and 2, OIB = BL ≥ 5 mm and EB ≥ 2 and age ≥ 60 years were significantly associated with a higher level of CAB (Model 1, $P = .03$ and $P = .01$ and Model 2, $P = .04$ and $P < .01$, respectively).

DISCUSSION

The present study evaluated the association of OIB, scored as a composite measure of endodontic and periodontal disease exposure, and CAB in a specific population of hospital patients with stroke. The results revealed an independent association between OIB and CAB among patients with IS or TIA. Given that survivors of IS or TIA have an increased risk of recurrence of stroke, with a higher chance of mortality and morbidity[1], the present findings may have important clinical implications, reinforcing the history of oral infections as risk indicators for a higher CAB and the occurrence of stroke events.

Although endodontic variables (AP and EB) were associated with CAB in the unadjusted analysis, the results revealed that the combination of endodontic and periodontal variables (OIB) had a synergistic effect and boosted the relation to an independent association linking oral health and atherosclerosis. Thus, our results are following the findings from preceding clinical studies from our group[11,12,27], and suggest that both endodontic and periodontal parameters

TABLE 1 - Sociodemographic, Medical, and Dental Variables in Relation to CAB Among Hospital Patients With Ischemic Stroke, Univariate Poisson Regression With Robust Variance

Variable [*n*]	CAB		PR	*P* value
	< 50% *n* (%)	≥ 50% *n* (%)		
Sociodemographic				
Age, y [239]				
Mean ± SD	60 ± 13.13	69 ± 11.29		
<60	98 (49.2)	10 (25)		
≥60	101 (50.8)	30 (75)	**2.47 (1.27–4.83)**	**.008**
Sex [240]				
Male	112 (56.3)	24 (58.5)		
Female	87 (43.7)	17 (41.5)	0.93 (0.53–1.63)	.791
Medical				
BMI [238]				
Mean ± SD	27 ± 5.58	25 ± 4.8		
<25	64 (32.5)	21 (51.2)		
≥25	133 (67.5)	20 (48.8)	**0.53 (0.30–0.92)**	**.025**
Hypertension stage 1 [240]*				
No	55 (27.6)	2 (4.9)		
Yes	144 (72.4)	39 (95.1)	—	**.002***
Diabetes [240]				
No	162 (81.4)	29 (70.7)		
Yes	37 (18.6)	12 (29.3)	1.61 (0.89–2.92)	.115
LDL-c, mg/dL [204]				
<130	120 (71.9)	24 (64.9)		
≥130	47 (28.1)	13 (35.1)	1.30 (0.71–2.38)	.395
Smoking [240]				
Never	129 (64.8)	21 (51.2)		
Current/Former	70 (35.2)	20 (48.8)	1.59 (0.91–2.76)	.102
Prior IS or TIA [239]				
No	159 (80.3)	38 (92.7)		
Yes	39 (19.7)	4 (7.3)	—	.058*
Dental				
Apical periodontitis (AP) [240]				
AP ≤ 1	141 (70.9)	22 (53.7)		
AP ≥ 2	58 (29.1)	19 (46.3)	**1.83 (1.05–3.17)**	**.032**
Root canal treatment (RCT) [240]				
RCT ≤ 1	173 (86.9)	35 (85.4)		
RCT ≥ 2	26 (13.1)	6 (14.6)	1.11 (0.51–2.44)	.786
Endodontic burden (EB) [240]				
≤1 AP and/or RCT	128 (64.3)	18 (43.9)		
≥2 AP and/or RCT	71 (35.7)	23 (56.1)	**1.98 (1.13–3.47)**	**.016**
Alveolar bone loss (BL), mm [240]				
<5	146 (73.4)	26 (63.4)		
≥5	53 (26.6)	15 (36.6)	1.46 (0.82–2.58)	.194
Oral inflammatory burden (OIB) [240]				
BL < 5 mm and EB ≤ 1	77 (38.7)	11 (26.8)		
BL ≥ 5 mm and EB ≤ 1	31 (15.6)	6 (14.6)	1.30 (0.52–3.25)	.578
BL < 5 mm and EB ≥ 2	69 (34.7)	15 (36.6)	1.43 (0.70–2.93)	.330
BL ≥ 5 mm and EB ≥ 2	22 (11.1)	9 (22)	**2.32 (1.06–5.07)**	**.034**

BMI, body mass index; CAB, carotid atherosclerotic burden; IS, ischemic stroke; LDL-c, low-density lipoprotein cholesterol; PR, prevalence ratio; SD, standard deviation; TIA, transient ischemic attack.

Bold values are statistically significant.

**P* value resulting from the χ^2 test, because a regression could not be carried out for these variables due to the distribution of the sample in relation to CAB.

should be evaluated in future investigations on the relationship between oral diseases and systemic outcomes.

The biological plausibility that supports the association between oral inflammatory diseases and CVD has been extensively studied and is based on the ability of microorganisms from the oral cavity, combined with elevations in serum levels of proinflammatory mediators, to promote early endothelium dysfunction, which enables fat deposition and consequently the formation of atheroma plaques[28,29]. The described mechanisms are the same for endodontic and periodontal infections, and it is possible to infer that both oral diseases can promote endothelial damage. Noteworthy, most studies[30,31] analyzing the relation between

TABLE 2 - Multivariate Regression Analysis for the Association Between AP and CAB Among Hospital Patients With Ischemic Stroke

	Model 1		Model 2		Model 3	
	95% CI		95% CI		95% CI	
Variables [*n*]	**PR**	***P***	**PR**	***P***	**PR**	***P***
AP (240)						
AP (≤1) [163]	1				1	
AP (≥2) [77]	**1.77 (1.02– 3.09)**	**.04**	1.56 (0.88– 2.75)	.13	1.52 (0.87–2.66)	.14
Age (≥60 y) [131]	**2.49 (1.29– 4.80)**	**.01**	**2.95 (1.49– 5.83)**	**<.01**	**2.83 (1.41–5.68)**	**<.01**
Sex (male) [136]	1.01 (0.57- 1.79)	.97	1.23 (0.67–2.26)	.50	1.33 (0.71–2.51)	.37
BMI (≥25) [153]			0.59 (0.33–1.06)	.07	0.56 (0.31–1.02)	.06
Diabetes [49]			1.62 (0.83–3.14)	.16	1.65 (0.84–3.27)	.15
LDL-c (≥130 mg/dL) [60]			1.47 (0.81–2.67)	.20	1.39 (0.77–2.53)	.27
Smoking Current/Former [90]			1.73 (0.98–3.03)	.06	1.61 (0.91–2.84)	.10
Bone loss (≥5 mm) [68]					1.39 (0.73–2.65)	.32

AP, apical periodontitis; BMI, body mass index; CAB, carotid atherosclerotic burden; CI, confidence interval; LDL-c, low-density lipoprotein cholesterol; PR, prevalence ratio.
PR values. Model 1: adjusted for sociodemographic variables; model 2: adjusted for sociodemographic and medical variables; model 3: adjusted for sociodemographic, medical, and dental variables. Bold values are statistically significant.

periodontal parameters and CVD did not control for other potential oral confounders, especially the presence of AP.

Individuals who suffered a lacunar infarct (a subtype of IS that represents nearly 25% of all IS) and were diagnosed with periodontitis presented with elevations in serum markers of systemic inflammation and a disruption of the vascular endothelial function[32]. Patients with stroke are more likely to develop a new episode of CVD, which leads to the recurrence of hospitalization, poorer functional outcomes, and increased mortality[33]. Accordingly, studies evaluating the interaction between oral inflammatory diseases and cardiovascular outcomes in a specific stroke population may reinforce the importance of oral health prevention policies, not only to prevent the occurrence and severity of CVD but also to thwart the recurrence of oral diseases among patients with disability due to the cardiovascular event.

It is usual in epidemiological studies to collect different medical and sociodemographic variables through self-reported measures[31]. Although most of these variables are validated, their accuracy is prone to inconsistencies. In a prior investigation[34], nearly half of the participants selected from a population at high risk for stroke inaccurately self-reported at least 1 cardiovascular risk factor. In our study, all the sociodemographic and medical variables, as well as the diagnosis of IS or TIA, were extracted from hospital charts and based on the routine examinations of the Departments of Neurology and Nutrition, with the support of highly qualified staff, laboratory, and imaging examinations. Thus, a high reliability is expected from all medical variables in the present study. Moreover, the oral variables were measured through high-resolution computed tomography, a method with greater accuracy to detect AP compared with conventional intraoral or panoramic radiographs[26].

Although causal relationships cannot be inferred from observational cross-sectional studies, some Bradford Hill causation criteria[35] can be observed in this study: (1) the *strength of the association* between OIB and CAB ≥50% (PR = 2.5) was similar to age ≥ 60 years, which is an important causal factor to IS; (2) the *biological gradient*, when the different oral inflammatory diseases were combined (OIB), the independent association was confirmed, but when AP and periodontitis were evaluated separately, only the unadjusted analysis was significant; (3) the *coherence of the association and the biological plausibility*, since previous studies have discussed the role of oral microorganisms on the progression of atherosclerosis, as well as the systemic elevation of inflammatory markers and endothelial dysfunction, favoring the formation, maturation, and rupture of atheromatous plaques[36].

Some limitations of the present study must be considered. Because of the distribution of the sample, it was not possible to include hypertension and previous history of IS or TIA in the regression analysis. These are 2 important potential confounding variables; however, the low number of observations precluded meaningful adjustment in the regression analysis. Also, the variables AP, RCT, and EB were dichotomized based on the stratification of a previous study[11], but with slight modifications related to the cutoffs, reflecting the distribution of observations in the present sample. Most importantly, the established cutoffs maintained the concept of oral burden, assessing the cumulative effect of the AP, RCT, and EB, rather than the presence/absence of these conditions. Similarly, a previous study[37] showed that the level of serum inflammatory mediators (interleukin [IL]-6, IL-17, IL-23, and tumor necrosis factor-α) just increased in rats with AP lesions in multiple teeth.

Some epidemiological studies that evaluated the association between oral health and CVD outcomes have larger samples[38], but very few previous studies presented larger samples of patients with stroke[39] than the present investigation. Moreover, in the present study, sample power calculation resulted in power >90%, considering $n = 240$, $\alpha = 5\%$, the proportion of exposed participants with CAB ≥50% (22%), and the proportion of nonexposed with CAB <50% (38.7%).

The methods used to measure the periodontal condition may be another limitation in the present study. The MDCTA examination allowed measurement of BL, which does not reveal the clinical activity of periodontitis. Because of the study design, clinical parameters for periodontitis, such as bleeding on probing, clinical attachment level, and pocket depth, could not be collected, thus precluding assessment of gingival inflammation and hampering assessment of the severity of periodontitis[40]. Furthermore, edentulous participants were excluded from the analysis, because the aim of this study was to test the association between endodontic and periodontal parameters and CAB. Hence, in our analysis, we assume that participants could have the minimum of 1 and

TABLE 3 - Multivariate Regression Analysis for the Association Between EB and CAB Among Hospital Patients With Ischemic Stroke

	Model 1		Model 2		Model 3	
	95% CI		95% CI		95% CI	
Variables [*n*]	**PR**	***P***	**PR**	***P***	**PR**	***P***
EB (240)						
EB (≤1) [146]	1				1	
EB (≥2) [94]	**1.90 (1.08–3.33)**	**.03**	1.68 (0.94–3.02)	.08	1.69 (0.94–3.03)	.08
Age (≥60 y) [131]	**2.45 (1.27–4.75)**	**.01**	**2.86 (1.44–5.70)**	**<.01**	**2.74 (1.36–5.53)**	**<.01**
Sex (male) [136]	1.03 (0.58–1.82)	.93	1.27 (0.69–2.33)	.44	1.39 (0.74–2.64)	.31
BMI (≥25) [153]			0.59 (0.32–1.06)	.08	0.56 (0.31–1.02)	.06
Diabetes [49]			1.63 (0.84–3.16)	.15	1.67 (0.84–3.30)	.14
LDL-c (≥130 mg/dL) [60]			1.48 (0.82–2.68)	.19	1.39 (0.77–2.51)	.27
Smoking Current/Former [90]			1.72 (0.97–3.03)	.06	1.58 (0.89–2.81)	.11
Bone loss (≥5 mm) [68]					1.44 (0.75–2.77)	.27

BMI, body mass index; CAB, carotid atherosclerotic burden; CI, confidence interval; EB, endodontic burden; LDL-c, low-density lipoprotein cholesterol; PR, prevalence ratio.
PR values. Model 1: adjusted for sociodemographic variables; model 2: adjusted for sociodemographic and medical variables; model 3: adjusted for sociodemographic, medical, and dental variables. Bold values are statistically significant.

the maximum of 28 natural teeth. The main reasons for tooth extraction are periodontitis and caries with pulp involvement[41], and tooth loss is a strong surrogate of previous oral inflammatory diseases; however, we decided to exclude edentulous participants to avoid bias, considering that the reasons for tooth extraction could not be accurately determined in this sample.

Caution is recommended in interpreting the results of the analysis of BMI. In the present study, patients with BMI ≥ 25 were less likely to have high CAB. BMI is a validated method to determine nutritional status; however, there are limitations in assessing older populations[42]. The BMI is a predetermined estimate based on the weight in relation to the patient's height, but BMI does not distinguish between fat and muscle. Older people lose muscle mass and generally increase intramuscular fat mass[43], especially with limited physical conditions. Therefore, in the present sample composed of patients with stroke, individuals with BMI < 25 were, in most cases, bedridden and presenting higher levels of disability as a consequence of stroke, and not necessarily those presenting a good nutritional condition. Also, this population is representative of the public health system in South Brazil, and the present results may not be generalizable to populations with different cultural, educational, and economic profiles.

The endodontic parameters are commonly classified as present or absent and quantified according to the number of teeth with periapical lesions or RCT. The number of teeth with AP appears directly related to a higher chance of endothelial damage[44]; however, it is unclear whether the volume of the AP lesion influences the association. Future longitudinal studies are necessary to assess whether the size or volume of the lesions in the OIB are potential risk factors for CVD.

Interestingly, among the traditional cardiovascular risk factors, in the adjusted models only, age ≥60 years was significantly associated with CAB ≥50%. Noteworthy, the present sample composed of unhealthy individuals (all with IS or TIA), and the conventional risk factors for CVD (such as smoking, sex, diabetes, among others) were naturally balanced in the sample. The present findings, showing OIB was independently related to CAB, reinforces the importance of oral condition in this specific population.

TABLE 4 - Multivariate Regression Analysis for the Association Between OIB and CAB Among Hospital Patients With Ischemic Stroke

	Model 1		Model 2	
	95% CI		95% CI	
Variables [*n*]	**PR**	***P***	**PR**	***P***
OIB [240]				
BL < 5 mm and EB ≤ 1 [88]	1		1	
BL ≥ 5 mm and EB ≤ 1 [37]	1.20 (0.46–3.12)	.70	1.15 (0.42–3.12)	.79
BL < 5 mm and EB ≥ 2 [84]	1.57 (0.77–3.20)	.21	1.36 (0.64–2.88)	.42
BL ≥ 5 mm and EB ≥ 2 [31]	**2. 40 (1.07–5.37)**	**.03**	**2.47 (1.04–5.87)**	**.04**
Age (≥60 y) [131]	**2.60 (1.32–5.10)**	**.01**	**2.87 (1.40–5.89)**	**<.01**
Sex (male) [136]	1.07 (0.59–1.96)	.82	1.42 (0.74–2.71)	.29
BMI (≥25) [153]			0.55 (0.30–1.00)	.05
Diabetes [49]			1.67 (0.82–3.41)	.15
LDL-c (≥130 mg/dL) [60]			1.32 (0.71–2.47)	.38
Smoking Current/Former [90]			1.59 (0.89–2.85)	.11

BL, bone loss; BMI, body mass index; CI, confidence interval; EB, endodontic burden; LDL-c, low-density lipoprotein cholesterol; OIB, oral inflammatory burden; PR, prevalence ratio.
PR values. Model 1: adjusted for sociodemographic variables; model 2: adjusted for sociodemographic and medical variables PR values. Bold values are statistically significant.

If a causal relationship between OIB and CAB is confirmed in the future, then the importance of oral health prevention strategies will be strengthened and may contribute to the prevention of recurrence of vascular events. The present results encourage future interventional studies dedicated to evaluate the effect of the treatment of oral inflammatory diseases on the risk of stroke or recurrence of other cardiovascular events in patients with previous CVD.

In conclusion, a higher OIB was independently associated with increased levels of CAB among hospital patients with IS or TIA. The combination of endodontic and periodontal parameters strengthened the observed association and should be evaluated in future studies on the relationship between oral health and cardiovascular outcomes.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Thayana Salgado de Souza Leão: contributed to concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and approval of the final version of the manuscript. Gustavo Henrique Tomasi: contributed to acquisition of data, analysis and interpretation of data, and approval of the final version of the manuscript. Lucas Picolli Conzatti: contributed to acquisition of data, analysis and interpretation of data, and approval of the final version of the manuscript. Luiz Carlos Porcellos Marrone: contributed to concept and design, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. Mark Allan Reynolds: contributed to analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript.

Maximiliano Shünke Gomes: contributed to concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript.

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The authors deny any conflicts of interest related to this study.

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