Elevated Systemic Inflammatory Burden and Cardiovascular Risk in Young Adults with Endodontic Apical Lesions

Mauricio Garrido, DDS,[*] Angélica M. Cárdenas, DDS,[†‡] Jessica Astorga, BSc,[†] Francisca Quinlan, BSc,[†] Macarena Valdés, MSc, PhD,[§] Alejandra Chaparro, MSc, DDS,[¶] Paola Carvajal, MSc, DDS,[*] Pirkko Pussinen, PhD,[‖] Patricia Huamán-Chipana, MSc, DDS,[**] Jorge E. Jalil, MD,[††] and Marcela Hernández, MSc, DDS, PhD[†‡‡]

Abstract

Introduction: The aim of this study was to assess whether apical lesions are associated with inflammatory serum markers of cardiovascular risk, especially high-sensitivity C-reactive protein (hsCRP), in young adults. **Methods:** In this cross-sectional study, otherwise healthy individuals with apical lesions of endodontic origin (ALEOs) and a clinical diagnosis of asymptomatic apical periodontitis and controls aged between 18 and 40 years were included. Patients' sociodemographic characteristics, medical history, and classic cardiovascular risk factors were recorded, and the pathobiological determinants of atherosclerosis in youth score was calculated. Oral clinical and radiographic examinations were performed. Blood samples were collected to determine the lipid profile, glycated hemoglobin, hsCRP, immunoglobulin G, interleukin (IL)-6, IL-10, IL-12p70, matrix metalloproteinase 8, soluble vascular cellular adhesion molecule-1, soluble intercellular adhesion molecule-1, and soluble E-selectin. Bivariate and multivariate analyses adjusting for oral and classic cardiovascular risk factors were performed. **Results:** hsCRP levels were significantly higher in ALEO patients versus controls (median = 2.54 vs 0.78), whereas the pathobiological determinants of atherosclerosis in youth score was comparable among the groups. Also, the levels of IL-6, matrix metalloproteinase 8, and soluble E-selectin were significantly higher in ALEO patients. hsCRP, IL-6, and IL-12 correlated with soluble adhesion molecules. Bivariate analysis based on hsCRP serum concentrations ≥1 mg/L showed an odds ratio (OR) = 6.8, and the risk increased 3.3 times for an additional ALEO. In multivariate analysis, ALEO was significantly associated with hsCRP levels ≥1 mg/L (OR = 5.1–12.8) independently of the adjustment model. ALEO also associated with CRP levels >3 mg/L, which was significant after the adjustment for covariates (OR = 4.0). **Conclusions:** ALEO is associated with the systemic inflammatory burden and cardiovascular risk determined by hsCRP, supporting a mechanistic link for cardiovascular diseases in young adults. *(J Endod 2019;45:111–115)*

Key Words

Cardiovascular diseases, C-reactive protein, E-selectin, interleukin 6, periapical periodontitis

Significance

Available epidemiologic evidence between endodontic infections and cardiovascular diseases requires biologic plausibility. We show that young adults with endodontic apical lesions have an elevated systemic inflammatory burden, providing a clear mechanistic link with moderate-high cardiovascular risk.

Apical periodontitis is an inflammation of the apical periodontium. From a clinical point of view, it is heterogeneous and varies between acute and chronic manifestations depending on the dynamic balance between endodontic bacterial consortia and the host's immune response. The hallmark of its chronic forms is the formation of an osteolytic apical lesion of endodontic origin (ALEO), and the most frequent clinical presentation is asymptomatic apical periodontitis (1–4).

In general terms, low-grade chronic dental infections have been associated with several systemic conditions at different degrees. Recent evidence sustains an epidemiologic link between ALEOs and cardiovascular diseases (CVDs), such as endothelial dysfunction (5), atherosclerosis (6), and coronary heart disease (7, 8), in an analogous fashion to marginal periodontal diseases. This might be especially evident in young adults under 40 years old who do not accumulate other risk factors (9, 10).

From a mechanistic point of view, it is widely accepted that an elevated systemic inflammatory burden significantly influences the development and progression of CVDs (9). Elevated levels of inflammatory bioactive molecules, including acute-phase

From the *Department of Conservative Dentistry and [†]Laboratory of Periodontal Biology, Department of Conservative Dentistry, Faculty of Dentistry and [§]Epidemiology Program, Public Health School, Faculty of Medicine, Universidad de Chile, Santiago, Chile; [‡]Health Sciences Division, Faculty of Dentistry, Universidad Santo Tomás, Bucaramanga, Colombia; [¶]Department of Periodontology, Faculty of Dentistry, Universidad de los Andes, Santiago, Chile; [‖]Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; **Department of Periodontology, Faculty of Dentistry, Universidad Nacional Federico Villarreal, Lima, Perú; [††]Division of Cardiovascular Diseases, School of Medicine, Pontifical Universidad Católica de Chile, Santiago, Chile; and [‡‡]Dentistry Unit, Faculty of Health Sciences, Universidad Autónoma de Chile, Santiago, Chile.

Address requests for reprints to Dr Marcela Hernández, Av Sergio Livingstone 943, Independencia, Santiago, Chile. E-mail address: mhernandezrios@gmail.com

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proteins (high-sensitivity [hs] C-reactive protein [CRP]), cytokines (tumor necrosis factor alpha and interleukin [IL]-1, IL-6, IL-12, and IL-10), matrix metalloproteinases (MMPs [MMP-8 and MMP-9]), and soluble adhesion molecules (soluble [s] E-selectin, vascular cellular adhesion molecule [VCAM]-1, and intercellular adhesion molecule [ICAM]-1), are involved in virtually all steps of atherogenesis and show predictive potential for future vascular events (11–13).

Despite the epidemiologic association, there is still a lack of evidence confirming the biologic plausibility between apical periodontitis and cardiovascular risk. A recent meta-analysis reported limited evidence of higher levels of serum immunoglobulins (Igs) in association with apical periodontitis although other relevant inflammatory markers, such as hsCRP and IL-6, remained inconclusive (9). This is particularly important because hsCRP levels represent the only valid standardized biomarker for predicting cardiovascular risk (13, 14). There are few available studies on this issue, and most of them lack adequate control for classic and nonclassic cardiovascular risk factors, such as marginal chronic periodontitis. They also include clinically heterogeneous forms of apical periodontitis and populations older than the target risk group. We aimed to assess whether ALEO is associated with inflammatory serum markers of cardiovascular risk, especially hsCRP, in young adults.

Methods

Study Participants

A cross-sectional study was conducted adhering to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Patients between 18 and 40 years old consulting at the Clinic of the Faculty of Dentistry, Universidad de Chile, Santiago, Chile, were enrolled between 2012 and 2017 if they had a clinical diagnosis of asymptomatic apical periodontitis (2), no previous endodontic treatment, and no antecedent of current acute or chronic systemic disease. ALEO was defined by the presence of at least 1 radiographic radiolucency (≥3 mm) in teeth with extensive caries and negative clinical tests of pulp sensitivity. Controls met the same criteria and the absence of any tooth with ALEO. Exclusion criteria were the presence of moderate to severe marginal periodontal diseases (15, 16), obesity (body mass index [BMI] ≥30 kg/m^2), anti-inflammatory and/or antibiotic treatment in the previous 3 months, and pregnancy. The protocol was approved by the institutional review board and clearly explained to all study participants in compliance with relevant laws and ethics guidelines; written informed consent forms were signed.

Medical and Oral Examinations

Patients' sociodemographic characteristics and medical history were recorded. Physical examinations and blood samples were performed by trained health care personnel. Classic cardiovascular risk factors were assessed, including age, sex, educational level, current smoking habit, BMI, blood pressure, lipid profile, and glycated hemoglobin. Hypertension was defined as a systolic blood pressure measurement ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Dyslipidemia was defined as total cholesterol ≥200 mg/dL, low-density lipoprotein ≥130 mg/dL, high-density lipoprotein <40 mg/dL, triglycerides ≥150 mg/dL, or a combination thereof. The pathobiological determinants of atherosclerosis in youth (PDAY) score was calculated to estimate cardiovascular risk in young adults as previously reported (17, 18).

Oral clinical examinations were conducted by oral specialists at the clinic. The total periapical radiographic examinations were obtained. Clinical full-mouth recordings, including clinical periapical diagnosis, and the decayed/missing/filled teeth (DMFT) index were performed by 1 calibrated specialist in endodontics (M.G.).

Periodontal clinical parameters were evaluated by a trained periodontist (A.M.C.) at 6 sites in all teeth, including probing depths (PDs), the clinical attachment level, and bleeding on probing at the base of the crevice, excluding third molars. The periodontal assessment was made with a manual periodontal probe (UNC 15; Hu-Friedy, Chicago, IL). Periodontal diseases were defined and classified according to the study by Eke et al (19). A total of 27 patients and 28 controls entered in the protocol and received proper oral care.

Blood Samples and Laboratory Analysis

Fasting blood samples were obtained by venipuncture of the antecubital vein. Blood sample fractions were submitted to the clinical laboratory of the university hospital for determination of glycosylated hemoglobin, lipid profile, and hsCRP (range, 0.1–15 mg/L) and to the Laboratory of Periodontal Biology for further quantitative biomarker analysis.

Serum was obtained by centrifugation and frozen at −80°C for posterior analysis. IgG levels were quantified by a commercial enzyme-linked immunosorbent assay kit according to the manufacturer's recommendations (R&D Systems, Minneapolis, MN). IL-6, IL-10, IL-12p70, MMP-8, sVCAM-1, sICAM-1, and sE-selectin were quantified by multiplex panels (R&D Systems) in a Luminex platform (Magpix, Millipore, St Charles, MO) and analyzed with MILLIPLEX AnalystR software (Viagene Tech, Carlisle, MA) according to the manufacturer's instructions.

Statistical Analysis

Data analysis was performed using STATA v12 software (StataCorp, Collage Station, TX). Only individuals accounting for the whole data set were included in the analysis. P values <.05 were considered statistically significant. Comparisons of quantitative variables between 2 independent groups (ALEO vs controls) were analyzed by the unpaired t test or the nonparametric Mann-Whitney test according to data distribution and the chi-square test for categoric variables. The association between serum markers was evaluated with Spearman rank correlation. The association between apical lesions and cardiovascular risk was determined by hsCRP ≥1.0 mg/L and hsCRP>3.0 mg/L as the primary outcomes (American College of Cardiology Foundation/American Heart Association guidelines 2010). Apical lesions were analyzed as the presence or absence of ≥1 ALEO(s) and the number of lesions. The associations were assessed with bivariate and multivariate logistic regression analyses. Models were constructed by entering covariate adjustment progressively, starting with demographic variables, oral variables, classic cardiovascular risk factors, and stepwise adjustment. The models that resulted in a change of the initial association (odds ratio [OR]) >10% for at least 1 primary outcome were included. An estimated minimum sample size of 18 cases per group was determined with a power of 80% and an alpha level of 5% based on serum IgG levels (9).

Results

Demographic and oral clinical parameters in healthy controls (n = 28) and ALEO patients (n = 27) are shown in Table 1. Demographic parameters including age, sex, educational level, smoking habit, and BMI were similarly distributed. Blood pressure ranged within normal values in most individuals. A few hypertensive cases were identified and equally distributed in the control (n = 2, 7.1%) and ALEO groups (n = 2, 7.4%, P > .05). Oral parameters, including the DMFT index, PDs, and clinical attachment level, were significantly higher in the ALEO group (P < .05). Mild periodontitis was present in 16 patients in the apical lesion group and 11 controls (P < .05).

TABLE 1. Demographic, Clinical, and Laboratory Parameters of Patients with Endodontic Apical Lesions and Controls

Variable	Controls (n = 28)	ALEO (n = 27)	P Value
Age (years, mean ± SD)	24.5 ± 3.9	25.9 ± 5.0	.3
Females (n, %)	12 (43)	11 (41.0)	.9
Educational level (median)	Complete high school	Complete high school	.3
Smokers (%)	10 (35.7)	6 (22.2)	.3
BMI (kg/m^2)	24.4 ± 2.6	25.7 ± 3.1	.1
Systolic pressure (x ± SD)	122.9 ± 14.2	118.3 ± 10.3	.2
Diastolic pressure (x ± SD)	72.6 ± 9.7	73.7 ± 9.1	.7
Hypertension (n, %)	2 (7.1)	2 (7.4)	1.0
DMFT index (median [IQR])	8.5 (2)	11 (5)	<.05
Probing depth (mm, mean ± SD)	1.8 ± 0.3	2.1 ± 0.4	<.05
Clinical attachment level (mm, median [IQR])	1.7 (0.5)	2.0 (0.4)	<.05
Mild periodontitis, n	11	16	<.05
>1 ALEO (n, %)	—	6 (21)	—
Total cholesterol (mg/dL, mean ± SD)	166.1 ± 30.7	169.2 ± 28.7	.7
HDL cholesterol (mg/dL, mean ± SD)	55.7 ± 16.7	52.2 ± 15.1	.4
LDL cholesterol (mg/dL, mean ± SD)	90.6 ± 24.1	92.9 ± 24.0	.7
Triglycerides (mg/dL, median [IQR])	78.0 (59.5)	115.0 (77.0)	.1
Dyslipidemia (n, %)	9 (32.1)	13 (48.1)	.2
HbA1c (%, mean ± SD)	5.1 ± 0.2	5.18 ± 0.3	.6
PDAY score	7.6 (4.0)	9.2 (5.3)	.2

ALEO, apical lesion of endodontic origin; BMI, body mass index; DMFT, decayed/missing/filled teeth; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PDAY, pathobiological determinants of atherosclerosis in youth; SD, standard deviation; x, mean.

Patients had 1 (n = 21, 77.8%) or 2 apical lesions (n = 6, 21%). Clinical laboratory parameters including the lipid profile and glycated hemoglobin were similarly distributed between the groups (>.05). Among them, 9 (32.1%) and 13 (48.1%) individuals from the control and ALEO groups, respectively, had dyslipidemia without significant statistical differences (P > .05). PDAY score calculation resulted in slightly higher values in the apical lesion group compared with the controls (9.2 and 7.6, respectively) with no significant differences (P > .05).

The systemic inflammatory burden is presented in Table 2. Serum hsCRP levels were significantly higher in the ALEO group (median = 2.5, interquartile range = 4.2 mg/L) compared to the controls (median = 0.78, interquartile range = 3.0 mg/L, $P \leq .05$). In keeping with this, the levels of IL-6, MMP-8, and sE-selectin were significantly higher in the ALEO group versus the controls (P = .048, .045, and 0.045, respectively). IgG, IL-10, and IL-12p70 showed no statistically significant differences (P > .05).

Correlations between serum markers in the control and ALEO groups are shown in Table 3. hsCRP, IL-6, and IL-12 positively correlated with soluble adhesion molecules (sVCAM-1, sICAM-1, and/or sE-selectin). Conversely, IL-10 negatively correlated with sICAM-1 in the healthy group. IL-12 positively correlated with IL-6 and -10; sICAM-1 and sE-selectin correlated positively only in the controls. No other statistically significant correlations were found between the markers analyzed (data not shown).

Having 1 or more ALEOs (Table 4) was shown to be associated with the systemic inflammatory burden. Bivariate analysis based on

TABLE 2. The Serum Inflammatory Burden and Soluble Adhesion Molecules in Patients with Endodontic Apical Lesions and Controls

Variable	Controls (n = 28)	ALEO (n = 27)	P Value
IgG (mg/mL, median [IQR])	88.9 (79.0)	82.2 (94.1)	.5
hsCRP (mg/L, median [IQR])	0.78 (3.0)	2.5 (4.2)	<.05
IL-6 (pg/mL, median [IQR])	22.4 (3.7)	23.2 (3.6)	<.05
IL-10 (pg/mL, mean ± SD)	117.1 ± 4.2	117.3 ± 5.5	.5
IL-12p70 (pg/mL, mean ± SD)	542.0 ± 52.0	561.4 ± 53.7	.1
MMP-8 (ng/mL, median [IQR])	3509.0 (2256.0)	4492.0 (4706.0)	<.05
sVCAM-1 median (mg/mL, median [IQR])	686.5 (230.8)	680.10 (29.1)	.8
sICAM-1 median (mg/mL, median [IQR])	1300.0 (900.0)	1400.0 (400.0)	1.0
sE-selectin (mg/mL, mean ± SD)	48.0 ± 19.2	56.4 ± 17.1	<.05

ALEO, apical lesion of endodontic origin; IgG, immunoglobulin G; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; MMP-8, matrix metalloproteinase-8; sE-selectin; soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1.

CRP serum levels ≥1 mg/L showed an OR = 6.8 (95% confidence interval [CI], 2.0–23.3), and the risk increased 3.3 times for an additional ALEO. In multivariate analysis (Table 4), apical lesions were significantly associated with CRP levels ≥1 mg/L, independently of the adjustment model (P < .05), ranging between OR = 5.1 (CI = 1.3–20.4) when including potential oral covariates (DMFT and PD) and 12.8 (CI = 2.4–67.1) when adjusting for classic cardiovascular risk factors (age, sex, smoking habit, educational level, hypertension, BMI, dyslipidemia, and HbA1c). The presence of ALEOs was also significantly associated with CRP levels >3 mg/L when controlling for educational level, hypertension, and PD after stepwise adjustment (OR = 4.0; 95% CI, 1.0–15.7; P = .046).

Discussion

A consistent association between ALEOs and CVDs is sustained by epidemiologic studies, but a mechanistic link is not evident. This might be especially relevant in young adults because of the lack of accumulation of other risk factors that normally occur in older individuals (9, 10, 20). In the present study, we showed that an ALEO is significantly associated with elevated inflammatory serum markers of cardiovascular risk in young adults, especially with hsCRP.

Bivariate analysis showed significantly higher serum levels of hsCRP and IL-6 in ALEO versus control individuals. We showed for the first time that MMP-8 and sE-selectin concentrations are also elevated. The correlation analysis between serum markers suggested positive associations of CRP, IL-6, and IL-12 with soluble adhesion molecules (sVCAM-1, sICAM-1, and/or sE-selectin), especially in ALEO individuals.

The anatomic relation of endodontic ALEOs with the bloodstream can lead to the release of inflammatory mediators, bacterial products (ie, lipopolysaccharide) and/or bacteria, resulting in low-grade systemic inflammation and/or direct vascular damage. In contrast to marginal periodontal infections, no epithelial barrier exists between the necrotic root canal and the highly vascular connective tissue from apical granulomas and cysts. Moreover, extraradicular infection implies

TABLE 3. The Correlation Matrix between Serum Levels of Interleukin (IL)-6 and the Systemic Inflammatory Burden

	hsCRP		IL-6		IL-10		IL-12		sICAM-1	
Marker	C	ALEO	C	ALEO	C	ALEO	C	ALEO	C	ALEO
IL-12	0.2	−0.2	**0.9**	**0.5**	**0.4**	**0.5**	1.0	1.0	—	—
sVCAM-1	**−0.4**	**0.4***	0.1	0.01	**−0.5**	0.2	−0.2	−0.3	−0.2	0.2
sICAM-1	−0.02	0.1	**0.4**	0.1	0.4	0.1	**0.5**	−0.04	1.00	1.0
sE-selectin	0.01	−0.2	**0.8**	**0.7**	0.1	0.2	**0.8**	**0.9**	**0.5**	0.2

ALEO, apical lesion of endodontic origin; C, controls; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; sE-selectin; soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1.

Boldface type indicates $P < .05$.

*$P = .05$.

direct inoculation of endodontic pathogens into the bloodstream (9, 21).

A recent meta-analysis provided evidence, although limited, of higher serum IgG levels in apical periodontitis (9); in contrast, our study failed to identify such a difference. Because the total circulating IgG can be influenced by the extraoral microbiota, its measurement is highly unspecific. On the other hand, significantly higher levels of serum IgG against *Porphyromonas endodontalis* were reported in association with ALEOs, supporting that the presence of this endodontic pathogen in oral biofilms can elicit a humoral adaptive immune response that might contribute to the systemic inflammatory burden and cardiovascular outcome (8). In addition, *Porphyromonas spp* as well as other oral pathogens can contribute to CVD by inducing autoimmune responses through molecular mimicry (22, 23).

Both, sE-selectin and MMP-8 are involved in atherogenesis, and elevated serum levels among apparently healthy men and women have shown predictive potential for future vascular events (11, 12). Elevated levels of both IL-6 and CRP are associated not only with subsequent atherosclerosis but also with the development of type II diabetes, even among individuals with no current evidence of insulin resistance (24).

Emerging reports propose that extrahepatic sources of CRP production may explain the lower and more sustained CRP concentrations that appear to predict cardiovascular risk. Recently, our research group reported that periodontal fibroblasts have low responsiveness to IL-6 (25), whereas enhanced CRP synthesis to IL-6 can be seen in ALEOs via trans-signaling, acting as a potential reservoir of IL-6 and CRP for sustaining a low systemic inflammatory response (26, 27). Although there is no directional association between these entities, experimentally induced apical periodontitis in a rat model supports the hypothesis that ALEOs can induce systemic inflammation and functional impairment in remote organs (28).

CRP is involved in every step of vascular disease by enhancing inflammation, oxidative stress, and coagulation (29). These effects are mediated by several properties of CRP, including its ability to activate complement and up-regulate vascular adhesion molecules, monocyte recruitment into the arterial wall, proinflammatory cytokines (tumor necrosis factor alpha and IL-1), superoxide, myeloperoxidase, and MMPs; it also impairs endothelial vasoreactivity and mediates low-density lipoprotein uptake by endothelial macrophages to form foam cells, among other effects (12, 29, 30).

Until now, hsCRP was the only valid biomarker for predicting cardiovascular risk. hsCRP concentrations ≥1 mg/L represent moderate risk and >3 mg/L high risk (13, 14). In fact, hsCRP measurement is especially recommended because it improves the reclassification of CVD-free subjects at intermediate risk into those with or without need of intervention, particularly among young adults (13, 31).

In this study, the analysis of cardiovascular risk based on CRP serum level concentrations ≥3 mg/L showed a statistically significant association with the presence of at least 1 apical lesion when adjusting for confounders (OR = 4.0). The relationship between ALEOs and CRP ≥1 mg/L showed a robust independent association, with ORs varying from 6.8 (bivariate) to 12.8 (multivariate). In addition, and according to the current findings, this risk increased 3.3 times with the presence of a second ALEO.

Most available mechanistic studies seeking an association between apical periodontitis and the systemic inflammatory burden lack adequate control for confounders. Often, a clinically heterogeneous mixture of acute and chronic forms of apical periodontitis is included, and participants are older than the main risk group, resulting in inconclusive overall evidence for hsCRP (9). Few recent studies accounting for these variables reported early endothelial dysfunction and up-regulation of proinflammatory cytokines, including IL-1, IL-2, IL-6, reactive oxygen species, and asymmetric dimethylarginine in serum from young adults with ALEOs compared with healthy volunteers (5, 32). In our study, we included ALEO ≥3 mm according to the definition of a medium well-defined apical radiolucency (33).

In the current study, the ALEO and control groups came from the same study population and were similar regarding individual classic cardiovascular risk factors, which were mostly controlled by the study design. This was also confirmed by the PDAY score, which determines and predicts coronary atherosclerotic lesions, especially in young individuals, and does not include CRP (17). Accordingly, volunteers' age ranged between 18 and 40 years to target young adults specifically. Oral potential confounders, such as DMFT and chronic periodontitis, were higher in the apical lesion group because they frequently coexist in association with poorer oral health status. Importantly, moderate to

TABLE 4. The Association between Endodontic Apical Lesions (≥1 Lesion) and C-reactive Protein Levels of Cardiovascular Risk

	hsCRP ≥1 mg/L		hsCRP >3 mg/L	
Model	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
AL*	6.8 (2.0–23.3)	<.05	2.4 (0.8–7.5)	.1
AL number	3.3 (1.3– 8.9)	<.05	1.6 (0.69–3.6)	.2
AL†	5.1 (1.3–20.4)	<.05	2.6 (0.7–10.1)	.2
AL‡	12.8 (2.4– 67.1)	<.05	2.7 (0.8–9.5)	.1
AL§	8.5 (2.0–36.9)	<.05	4.0 (1.0–15.7)	<.05

ALEO, ≥1 apical lesion of endodontic origin; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.

*Bivariate.

†Adjusted by the decayed/missing/filled teeth index and probing depth.

‡Adjusted by classic cardiovascular risk factors (age, sex, smoking habit, educational level, hypertension, body mass index, dyslipidemia, and glycated hemoglobin).

§Adjusted by educational level, hypertension, and probing depth.

severe chronic periodontitis was excluded to avoid masking the ALEO effects as an independent, nonclassic cardiovascular risk factor. One drawback of our study was the low number of individuals accounting for the eligibility criteria, but it had enough power to detect the differences between the groups. Finally, despite the different approaches undertaken to control for confounders, potential bias cannot be totally ruled out because it represents a core limitation of observational research that still might partially influence the magnitude of the identified association.

Overall, ALEOs were associated with the systemic inflammatory burden and cardiovascular risk determined by hsCRP, supporting a mechanistic link for cardiovascular diseases in young adults.

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