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Association between apical periodontitis and secondary outcomes of atherosclerotic cardiovascular disease: A case–control study

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Abstract

Aim: To evaluate the association between apical periodontitis (AP) and atherosclerotic cardiovascular disease (ASCDV).

Methodology: A total of 65 periodontally and systemically healthy patients (age ≥ 40 years) were included in the study. Periapical status was assessed through dental examination and periapical radiographs; 33 subjects had AP (AP+), while 32 acted as control (AP−). Moreover, data regarding their periapical index (PAI) score and the Decayed, Missing, and Filled Teeth (DMFT) index were recorded. All subjects underwent echo-colour Doppler assessment of carotid intima-media thickness (CIMT), carotid plaques, degree of stenosis using the North American Symptomatic Carotid Surgery Trial (NASCET) method, maximum diameter of the abdominal aorta (maximum AA) and common iliac arteries (CIA) diameters. Furthermore, peripheral blood flow was also measured using the ankle-brachial index (ABI). Simple and multiple regression analyses were performed.

Results: Among AP+ patients, 57.58% disclosed at least one sign of subclinical carotid atherosclerosis. Multiple regression analysis identified AP as a significant risk indicator for carotid plaques [OR = 4.87 (1.27, 18.98; $p = .021$)] and marked carotid intima-media thickenings (OR = 14.58 [1.22, 176.15], $p = .035$). A significant association was established between AP and other cardiovascular (CV) variables (CIMT, NASCET, and maximum AA). On the contrary, a higher PAI score does not correlate to increased odds of carotid alterations, and the presence of AP did not prove any significant change in CIA and ABI. No significant correlation was established between DMFT and other variables.

Conclusions: Results from the current study highlight that the presence of AP may be regarded as a risk indicator for ASCVD, with AP being associated with 5-fold increased odds of having carotid plaques and 15-fold increased odds of having marked carotid intima-media thickenings. Further studies should be conducted in order to verify whether AP treatment could be beneficial for ASCVD signs.

KEYWORDS
apical periodontitis, cardiovascular diseases, carotid intima-media thickness, carotid stenosis

INTRODUCTION

Apical periodontitis (AP) is an oral inflammatory disease characterized by inflammation and destruction of periradicular tissues (Graunaite et al., 2011) in response to pathogens and their toxins in the root canal system (Cotti & Schirru, 2022). According to a recent systematic review and meta-analyses, the global prevalence of AP accounts for 52% of the adult population worldwide (Tibúrcio-Machado et al., 2021). However, since AP is often not painful and its diagnosis is based on radiographic examinations, its burden is usually underestimated (Berlin-Broner et al., 2017a, 2017b; Tibúrcio-Machado et al., 2021). On the contrary, other clinically visible oral conditions, such as caries and periodontitis, have been intensely studied as contributors to the global burden of diseases (Tibúrcio-Machado et al., 2021).

There is strong evidence that periodontitis is associated with an increased risk for future atherosclerotic cardiovascular disease (ASCVD) (Cotti et al., 2011). Conversely, the potential cardiovascular (CV) consequences of AP remain largely unknown. Despite their different aetiologies and pathogenesis, AP and periodontitis are both polymicrobial infections sharing a common microbiota, often composed of Gram-negative anaerobic bacteria (Sundqvist, 1992), and characterized by an increased systemic level of cytokines (Cotti et al., 2011). Given these similarities, one might assume that also AP could represent a threat to systemic (Segura-Egea et al., 2015) and CV health (Berlin-Broner et al., 2017a, 2017b). Unfortunately, in many trials addressing this issue, the adequate scientific rigorousness was not always applied.

The potential connection between endodontic infections and CV risk has been discussed only in recent years producing controversial results, with some studies not supporting the hypothesis (Frisk, 2007; Frisk et al., 2003), others being inconclusive (Joshipura et al., 2006) and others in favour of a positive correlation (Chauhan et al., 2019; Costa et al., 2014; Petersen et al., 2014). An effective screening tool used for atherosclerotic disease monitoring is carotid intima-media thickness (CIMT). According to a recent study, every 0.1 mm increase in CIMT raises by 10% to 15% the risk of myocardial infarction (MI) (Lorenz et al., 2007; Naqvi & Lee, 2014). Recently, a cross-sectional study measured the possible association between periapical lesions and ASCVD using flow-mediated dilatation (FMD) and CIMT as parameters of risk, demonstrating that patients with AP have more significant subclinical signs of atherosclerosis compared to subjects without AP (Chauhan et al., 2019). However, recent evidence suggests that carotid plaque appears to be a more powerful predictor of CV risk compared with CIMT alone (Naqvi & Lee, 2014).

Nonetheless, to the best of the authors' knowledge, no previous studies have evaluated carotid alterations in AP patients combining CIMT with carotid plaques and degree of stenosis using the NASCET method. Moreover, no data are present regarding the impact of AP on clinical and subclinical signs of peripheral artery disease (PAD) and abdominal aortic aneurysm (AAA).

The hypothesis that we would like to figure out with this case–control design is that there is an epidemiological association between the presence of periapical lesions and the presence of subclinical signs of atherosclerosis. Therefore, the aim of the present case–control study was to investigate the association between AP and surrogate measures of ASCVD.

MATERIALS AND METHODS

Study design

The present observational study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Von Elm et al., 2008). The research protocol was approved by the local Ethics Committee (protocol number: 22967/2020) and received the registration number on Clinicaltrials.gov (NCT05792787).

Setting and participants

Study subjects were recruited from the pool of patients in the Unit of Endodontics and Conservative Dentistry of the Department of Medical Biotechnologies, University of Siena (Siena, Italy) from January 2022 to February 2023.

The inclusion criteria of the study were:

- age above 40 years old;
- presence of at least 24 teeth;
- ability and willingness to give informed consent.

The exclusion criteria were:

- systemic diseases;
- administration of antibiotics in the last 6 months;

- administration of antiaggregant, antiplatelet, and antihypertensive medications;
- existing sign of cardiovascular diseases (CVD);
- smoking habits (daily smoking);
- diabetes;
- obesity [body mass index (BMI) ≥ 30 kg/m^2];
- arterial hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg);
- dyslipidaemia;
- periodontitis (Page & Eke, 2007);
- non endodontic lesions in maxilla/mandible (Chauhan et al., 2019);
- pregnancy or lactation;
- inability to communicate effectively in Italian;
- inability or unwillingness to give informed consent.

Subjects fulfilling the previously described criteria were enrolled from the outpatient department and allocated into two distinct groups (Figure 1). One group was composed of patients affected by AP (AP+), and the other group was composed of pair-matched healthy controls (AP−). AP cases were defined as those patients having at least 1 tooth exhibiting radiographic evidence of apical radiolucency exceeding twice the width of the periodontal ligament space (Bornstein et al., 2011; Low et al., 2008) and having PAI >2 (Costa et al., 2014) (Figure 2a). Healthy individuals were defined as those patients free from clinical and radiographic evidence of AP with PAI ≤2 (Costa et al., 2014) (Figure 2b).

The study was conducted in accordance with the Declaration of Helsinki. Before being included in the study, written informed consent was signed by all the study participants after reading a patient information sheet.

Variables

Risk factor assessment

Subjects were interviewed regarding sociodemographic characteristics (age, gender, smoking habits, alcohol consumption and pregnancy status), CV risk factors, other medical conditions, and medications using standardized questions from the Centers for Disease Control and Prevention Behavioural Risk Factor Surveillance System (Desvarieux et al., 2005). Diabetes mellitus was defined by self-report of physician-diagnosed diabetes. Smoking was assessed categorically (yes/no), and only intermittent and social smokers (smoking on a non-daily basis) were enrolled in the study. Moreover, the body mass index (BMI) was computed as weight (kg)/height (m^2). Also, data on alcohol consumption were recorded and categorized as "below suggested intake" (≤1 drink/day for women and 1 to 2 drinks/day for men) and "above suggested intake" (>1 drink/day for women and 1 to 2 drinks/day for men) (O'Keefe et al., 2018).

Oral examination

All patients received extra- and intra-oral examinations. The periapical status was investigated by palpation, percussion, thermal cold testing along with panoramic radiographs. Furthermore, teeth that exhibited deep carious lesions, deep restorations, absence of response to pulp testing, or painful response to biting and/or percussion or palpation were considered suspected of AP (American Association of Endodontists, 2013) and underwent further periapical radiograph using the long cone paralleling technique with film holder (Duncan et al., 2023).

The following parameters were recorded:

- number of Decayed, Missing and Filled teeth (DMFT) index;
- number of teeth present;
- Periapical Index Score (PAI) to evaluate the periapical status;
- presence of AP;
- periodontal status through periodontogram;
- lesions other than endodontic aetiology of maxilla and mandible (Chauhan et al., 2019).

The PAI score (Ørstavik et al., 1986) was determined by visually examining the periapical area and assigning a numerical value based on the extent and severity of the inflammation. The scores range from 0 to 5 based on radiographic images of the apical region (Costa et al., 2014):

1. Normal periapical structures;
2. Small changes in bone structure;
3. Changes in bone structure with light mineral loss;
4. Periodontitis with circumscribed bone and well-defined halo of bone sclerosis;
5. Severe periodontitis with major bone loss and a diffuse radiolucent image.

Scores 1 and 2 represent apical periodontal health; scores 3, 4, and 5 represent AP. The selection of the applied score was based on previously validated guidelines (Ørstavik et al., 1986). Two examiners (G.M., C.M.) underwent a calibration process involving 100 standard radiographs that the index developers had already scored. Any discrepancies in their evaluations were resolved through

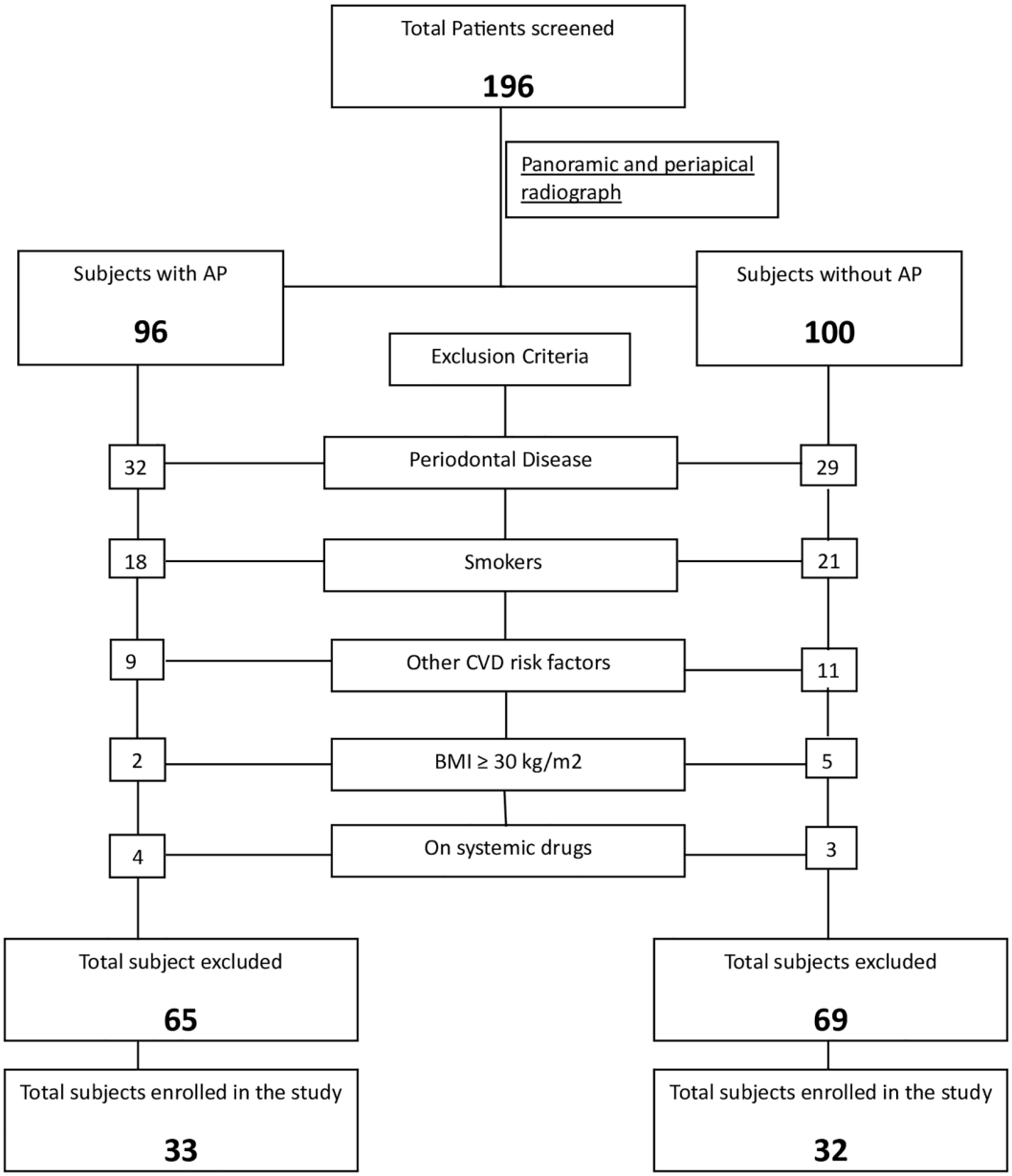

FIGURE 1 Flow chart for selection of subjects.

discussion. This calibration procedure was repeated twice within a two-week interval to ensure consistency, and both inter- and intra-observer agreements were quantified using kappa values. Following the calibration procedure, both examiners independently evaluated periapical radiographs of the teeth being studied under standardized conditions. The highest PAI score among the individual roots was considered for multirooted teeth. In cases where uncertainty arose, they reached a consensus and selected the higher scores. Importantly, during case assessment, the examiners were blinded to the identities and clinical conditions of the patients. Kappa statistics were used to assess intra- and inter-observer agreement (Landis & Koch, 1977).

Cardiovascular examination protocol

All the participants received a CV evaluation of the carotid axis, common iliac arteries (CIA), and abdominal aorta (AA) in the Unit of Vascular Surgery of the Department of Medicine, Surgery and Neuroscience, University Siena (Siena, Italy) by a single experienced operator (M.A.L.) blinded to the periapical status of participants. The CV assessment included physical examination, blood pressure measurement (brachial and tibial), past medical history, and echo colour Doppler ultrasounds.

CIMT measurements were taken from the right and left internal carotid artery (ICA) using a high-resolution Doppler ultrasound device system (LOGIQ S8 XDclear,

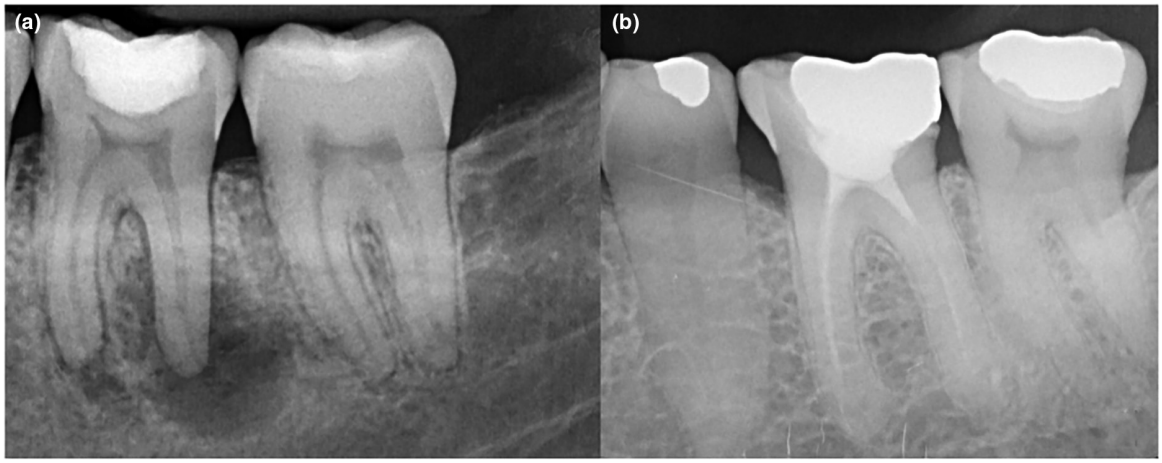

FIGURE 2 The figure shows two periapical radiographs. (a) AP+ patients with a well-defined radiolucent area and exacerbating features (PAI 5). (b) AP− patient with an endodontically treated tooth but with normal periapical bone structure.

General Electrics, Boston, MA, USA) with a linear transducer (frequency 7 MHz) (Touboul et al., 2007). The patient was lying supine with his neck hyperextended and tilted 45° to the left for the right ICA measurement and to the right for the left one. The CIMT was measured in the longitudinal plane, perpendicular to the ultrasound beam, along a minimum of 10 mm length of the distal ICA, displaying both the near and far arterial walls (Touboul et al., 2007).

CIMT values were regarded as continuous variables, and the maximum and mean CIMT values between the two arteries were considered. CIMT values were categorized according to the CIMT burden as none (CIMT ≤ 0.9 mm), mild (1 < CIMT ≤ 1.2), moderate (1.2 < CIMT ≤ 1.5), or marked (IMT > 1.5) carotid intima-media thickenings (Chambless et al., 1997).

Along with these CIMT recordings, the presence or absence of atherosclerotic plaques was assessed (Pinho et al., 2013) in both the left and right ICA for each patient (Figure 3). Plaque is defined as a focal area that encroaches into the arterial lumen between the lumen-intima and media-adventitia boundary (Biswas et al., 2021) and it was simply dichotomized as either "yes" or "no" according to whether carotid plaque was present or absent in one of the two arteries. For those patients displaying carotid plaques, the percent of stenosis in the carotid artery was also calculated using the NASCET method, which allows to distinguish between mild (0–50%), medium (50–69%), and severe grade of stenosis (≥70%) (Lian et al., 2012) (Figure 3).

To monitor the presence of an abdominal aortic aneurysm (AAA), the AA was located with the ultrasound probe (5 MHz), and its diameter was measured at its widest point (maximum AA).

Furthermore, the diameters of the right and left CIAs were also assessed to screen for peripheral artery disease (PAD), AAA or isolated iliac aneurism. A CIA > 18 mm in men and >15 mm in women is considered aneurismal

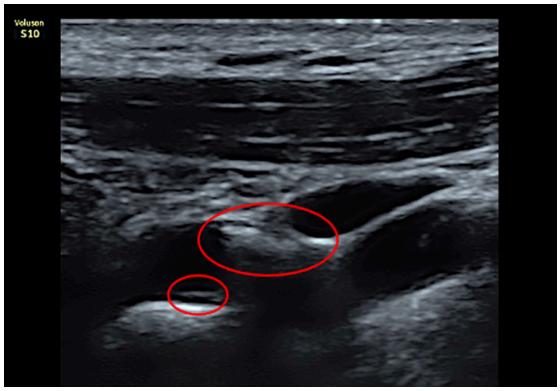

FIGURE 3 An ultrasound image of the carotid bulb (AP+ group) displaying atherosclerotic plaques (red circles) and a mild grade of stenosis.

(Speziale et al., 2022). Only the mean and maximal values between the right and left CIA measurements were used in the analysis. The abdominal vascular assessment protocols were conducted following previously validated guidelines (Georges & Moreno, 2022).

Ankle brachial index (ABI) calculation was also performed. ABI was obtained as the ratio between the systolic blood pressure of the lower extremity (i.e., the ankle) and the upper extremity (Peltonen et al., 2022). An ABI <0.9 is indicative of atherosclerosis (Price et al., 2007).

Statistical analysis

Sample size calculation was carried out on the basis of the CIMT values in patients with and without AP reported in a previous study (Chauhan et al., 2019). Results from sample size calculation showed that 24 subjects would be required

in each group to reach the power of 95%, given an alpha error of .05. Moreover, considering a drop-out rate of around 30%, a total of 65 participants were included in the study (33 and 32 patients, respectively, for AP+ and AP− groups).

Statistical analysis was performed with the statistical software STATA BE (version 17.1, StataCorp LP, Texas, USA), setting the level of significance at $\alpha = .05$. Continuous variables were reported as mean and standard deviation, while categorical variables were expressed as number of observations (proportions). After verification of data distribution (Shapiro–Wilk test $n \leq 50$), the Mann–Whitney U test was used to compare the central tendency measures of two independent groups. The association between categorical variables was assessed using Fisher' exact test.

Simple and multiple logistic/linear regression models were built to independently evaluate the crude and adjusted estimates of association between oral health-related variables (AP− AP+ vs. AP−, PAI—PAI score 0/1 vs. 2, PAI score 0/1 vs. 3, PAI score 0/1 vs. 4, PAI score 0/1 vs. 5, DMFT—continuous, and number of teeth—continuous) as exposures and the surrogate measures of ASCVD as outcomes. Multiple models were adjusted for age, gender, BMI, and alcohol consumption. Finally, to assess the possible presence of a dose–response relationship, sensitivity analyses were performed using the five different categories of PAI as exposure, using PAI 0 as the reference category. Results were expressed as difference in Means (MD) or Odds Ratio (ORs) with 95% Confidence Intervals (95% CI).

RESULTS

Participants characteristics

A total of 65 subjects were enrolled in the study and allocated to the AP+ [$N = 33$] and AP− [$N = 32$] groups. One participant consented to participate but did not show up to the data collection appointment. All individuals satisfying the eligibility criteria accepted to participate and were included in the analysis. Participant characteristics overall and by periapical status are reported in Table 1. The intra-examiner agreement for the PAI score

TABLE 1 Demographic characteristics of the population, overall and by group.

Characteristics	Overall (n = 65)	Cases (AP+)	Controls (AP−)	*p*-Value
Age (years), mean (SD)	56.45 ± 9.10	55.61 ± 9.10	57.31 ± 9.83	.581
Gender, *N* (%)				
Males	23 (35.38%)	14 (42.42%)	9 (28.12%)	.301
Females	42 (64.62%)	19 (57.58%)	23 (71.88%)	
BMI, mean (SD)	24.54 ± 2.70	24.48 ± 2.89	24.61 ± 2.52	.778
Smoking, *N* (%)				.492
Non-smokers	63 (96.92%)	31 (93.94%)	32 (100%)	
Smokers	2 (3.08%)	2 (6.06%)	0 (0%)	
Cigarettes/day, mean (SD)	0.062 ± 0.39	0.12 ± 0.55	0.00 ± 0.00	.16
Alcohol intake, *N* (%)				***.015****
Below suggested intake	46 (70.77%)	28 (84.85%)	18 (56.26%)	
Above suggested intake	19 (29.23%)	5 (15.15%)	14 (43.75%)	
PAI score, *N* (%)				
0	32 (49.23%)	0 (0%)	32 (100%)	***.00*****
1	0 (0%)	0 (0%)	0 (0%)	
2	0 (0%)	0 (0%)	0 (0%)	
3	17 (26.25%)	17 (51.52%)	0 (0%)	
4	12 (18.46%)	12 (36.36%)	0 (0%)	
5	4 (6.15%)	4 (12.12%)	0 (0%)	
DMFT, mean (SD)	10.86 ± 4.99	11.76 ± 5.27	9.93 ± 4.57	.175
No. teeth, mean (SD)	26.29 ± 3.92	26.58 ± 2.08	26.00 ± 5.20	.65

Note: Results of continuous variables are reported as mean [95% confidence interval]; results of binary and categorical variables are expressed as number of observations (proportion). Significance levels for estimates in bold and italics: *$p < .05$; **$p < .01$; ***$p < .001$.

Abbreviations: BMI, body mass index; DMFT, decayed missing filled teeth; *N* (%), number of observation (proportion); No, number; PAI, periapical index; SD, standard deviation.

resulted in kappa = .76 (95% CI: 0.69–0.79; $p < .05$) for the first examiner and kappa = .79 (95% CI: 0.71–0.84; $p < .05$) for the second examiner; inter-examiner agreement resulted to be substantial (kappa = .74, 95% CI: 0.69–0.81; $p < .05$). The mean age was 56.45 ± 9.10 years, with a proportion of 35.38% of males and 64.62% of females; the mean BMI was 24.54 ± 2.70. There were no significant differences between the 2 groups in relation to age, number of teeth present, and DMFT. Among the AP+ group, 17 patients displayed a PAI 3 (51.52%); 12 patients presented a PAI 4 (18.46%), while only 4 patients displayed PAI 5 (6.15%). Moreover, significant differences were reported as to alcohol consumption between the two groups.

Outcome data

AP and cardiovascular variables

Data from Doppler ultrasound measurements are shown in Table 2. The presence of periapical lesions (exposure) in the AP+ group is significantly associated with higher CIMT values (outcomes) compared to healthy controls (1.39 ± 0.22 mm, and 1.15 ± 0.21, $p = .000$, respectively) (Figure 4a). Results of the linear/logistic regression analysis are presented in Table 3. From the multivariate linear regression emerged that the presence of periapical lesions is associated with higher CIMT values (Coeff = .21 [0.20–0.31], $p > .001$) also after adjusting for age, sex, smoking habits, and alcohol consumption.

The prevalence of carotid plaques and maximum CIMT values (outcomes) differ significantly between AP+ (exposures) and AP− patients [18 (54.55%) versus 5 (15.62%), $p = .002$ and 1.51 ± 0.23 mm versus 1.26 ± 0.25 mm, $p = .021$, respectively] (Figure 4b).

Among AP+ patients, 57.58% reported at least one sign of subclinical carotid atherosclerosis between carotid plaques and maximum CIMT>1.5 mm, with the difference being statistically significant between the two groups ($p = .012$). The presence of periapical lesions increased the odds of having either plaques or maximum CIMT>1.5 (OR = 4.07 [1.42, 11.71]; $p < .01$) but not after adjusting for confounders. A significant correlation was established between AP and maximum CIMT (mm) (Coeff = .25 [0.13, 0.37] $p < .01$), also in the adjusted analysis.

AP was associated with higher odds of carotid plaque occurrence also after adjustments (OR = 4.87 [1.27, 18.98] $p < .05$). In crude analysis, periapical lesions were significantly associated with increased odds of marked carotid thickenings (OR = 3.79 [1.29, 11.19]; $p < .05$), but not after adjustments. Maximum NASCET values were also reported to be significantly increased in individuals with AP compared to controls (Figure 4c).

Around 3% of AP+ patients reported measurements of maximum CIMT within normal ranges (CIMT≤0.9 mm), while around 52% displayed marked carotid thickenings.

TABLE 2 Prevalence of atheroma and CVD variables in cases versus controls.

Characteristics	Overall (*N*=)	Cases (AP+)	Controls (AP−)	*p*-Value
CIMT (mm), mean (SD)[a]	1.28 ± 0.25	1.39 ± 0.22	1.15 ± 0.21	***.000*****
CIMT>1.5 mm/Atheroma, *N* (%)	27 (41.54%)	19 (57.58%)	8 (25%)	***.012****
Maximum CIMT (mm), mean (SD)[b]	1.39 ± 0.27	1.51 ± 0.23	1.26 ± 0.25	***.021****
Maximum CIMT>1.5 mm, *N* (%)[b]	24 (36.92%)	17 (51.52%)	7 (21.88%)	***.02****
Atheroma, *N* (%)[b]	23 (35.38%)	18 (54.55%)	5 (15.62%)	***.002****
Maximum thickening, *N* (%)[b]				***.006****
None (CIMT ≤ 1)	8 (12.31%)	1 (3.03%)	7 (21.88%)	
Mild (1 < CIMT ≤ 1.2)	19 (29.23%)	6 (18.18%)	13 (40.62%)	
Moderate (1.2 < CIMT ≤ 1.5)	14 (21.54%)	9 (27.27%)	5 (15.62%)	
Marked (CIMT > 1.5)	24 (36.92%)	17 (51.52%)	7 (21.88%)	
Maximum NASCET, %, mean (SD)[b]	0.073 ± 0.11	0.12 ± 0.12	0.03 ± 0.07	***.001****
Maximum AA, mean (SD)	17.14 ± 3.26	18.14 ± 3.04	16.10 ± 3.18	***.011****
CIA (mm), mean (SD)[a]	10.90 ± 1.55	11.16 ± 1.57	10.63 ± 1.51	.16
Maximum CIA (mm), mean (SD)[b]	11.34 ± 1.76	11.66 ± 1.77	11.01 ± 1.71	.15

Abbreviations: AA, abdominal aorta; CIA, common iliac artery; IMT, Intima medial thickness; MD, mean deviation; NASCET, north American symptomatic carotid endarterectomy trial. Significance levels for estimates in bold and italics: *$p < .05$; **$p < .01$; ***$p < .001$.

[a]Right and left artery mean outcome.

[b]Right or left artery maximum outcome.

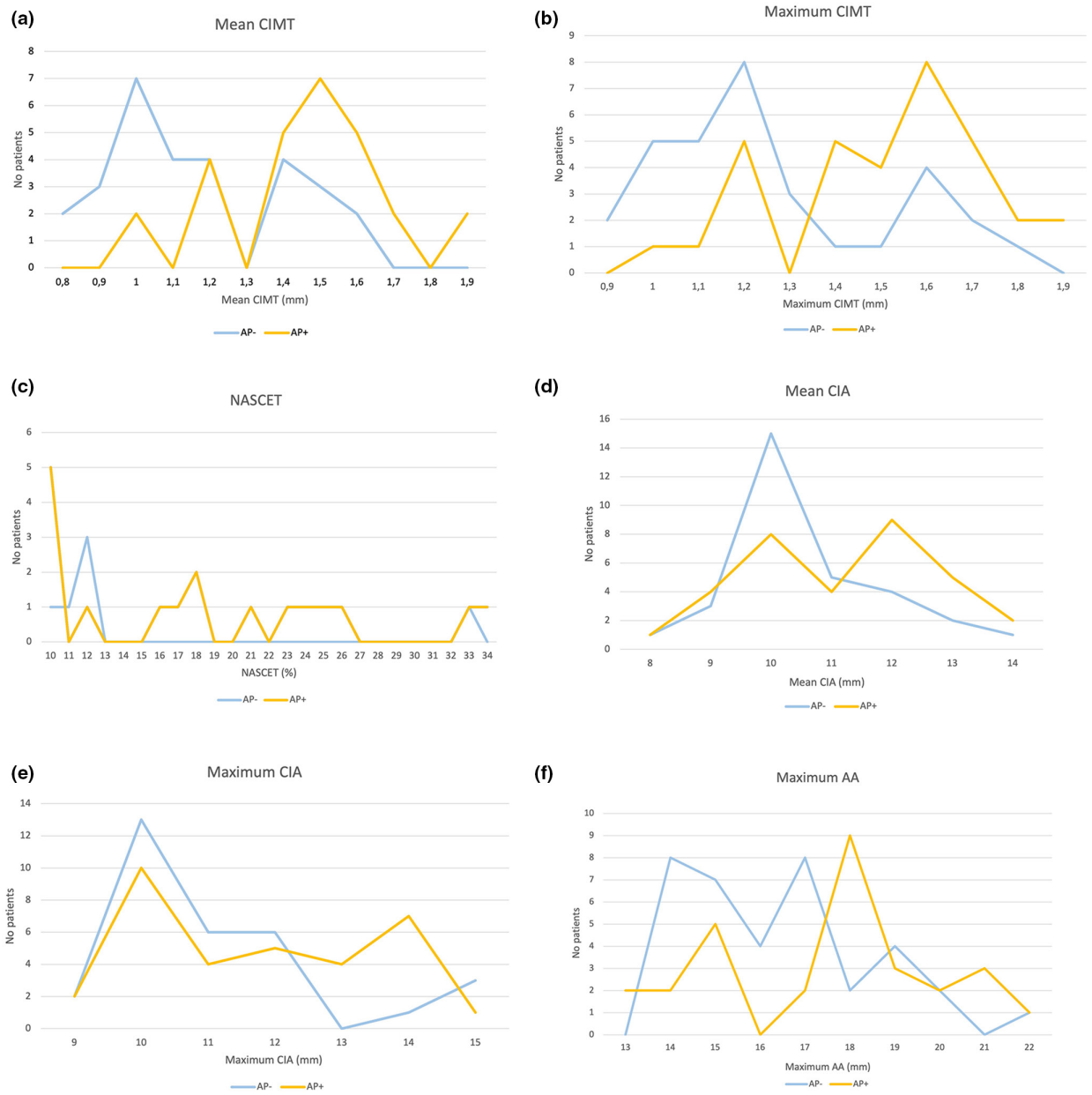

FIGURE 4 Distribution of CV variables by periapical status (AP+/AP−): (a) Mean CIMT; (b) Maximum CIMT; (c) NASCET; (d) Maximum AA; (e) Mean CIA; (f) Maximum CIA. maximum AA, abdominal aorta maximum diameter; maximum CIA, maximum value common iliac artery; maximum CIMT, maximum value carotid intima-media thickness; Mean CIA, mean value common iliac artery; mean CIMT, mean value carotid intima-media thickness; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

The prevalence of marked, moderate, and mild maximum CIMT was significantly higher in the AP group when compared to controls ($p = .006$). AP resulted in a significantly positive adjusted OR for maximum CIMT>1.5 mm (OR = 14.58 [1.22, 176.15], $p > .05$).

Among the study participants, those who disclosed carotid plaques [23 (35.38%)] reported a mild degree of stenosis and a mean percent of stenosis of 7.3%. In addition, a linear relationship between AP and NASCET was disclosed (Coeff = .66 [0.17, 0.14]) also after adjusting for confounders.

A significant correlation was established between AP and maximum AA diameter also following adjustments (Coeff = 2.06 [0.36, 3.75]). In contrast, no significant correlation was established between AP and other variables (CIA and ABI index). Precisely, differences observed in the CIA mean diameter between the two groups resulted to be non-significant (11.16 ± 1.57 and 10.63 ± 1.51, $p = .16$, respectively) (Figure 4e). 100% of patients obtained an ABI index between normal ranges.

TABLE 3 Crude and adjusted linear/logistic regression models. Exposures are expressed in different columns, outcomes in different rows. Only outcomes maximum/Right or Left values.

	Exposure variables							
		PAI score						
Outcomes	**AP+ (vs. AP−)**	**0/1**	**2 (vs. 0/1)**	**3 (vs. 0/1)**	**4 (vs. 0/1)**	**5 (vs. 0/1)**	**DMFT**	**No. of teeth**
CIMT, MD (95% CI)[b]		Ref.						
Crude	***0.25 (0.139–0.35)*****	Ref.	-	***0.311 (0.19–0.44)*****	***0.16 (0.02–0.31)****	0.21 (−0.012–0.44)	***0.01 (0.00–0.02)****	0.00 (−0.01–0.02)
Adjusted[a]	***0.21 (0.20–0.31)*****	Ref.	-	***0.25 (0.12–0.38)*****	0.12 (−0.018–0.27)	***0.27 (0.06–0.48)****	0.01 (−0.01–0.02)	0.00 (−0.011–0.2)
CIMT>1.5 mm/ Atheroma, yes, OR (95% CI)[c]								
Crude	***4.07 (1.42–11.71)*****	Ref.	-	***7.2 (1.93–26.81)*****	3 (0.75–11.99)	1 (0.09–11.03)	1.09 (0.98–1.21)	1.07 (0.9–1.27)
Adjusted[a]	2.58 (0.76–8.76)	Ref.	-	3.53 (0.81–15.48)	2.12 (0.44–10.20)	1.24 (0.085–18.17)	1.04 (0.93–1.18)	1.10 (0.85–1.44)
Maximum CIMT, MD (95% CI)[c]								
Crude	***0.25 (0.13–0.37)*****	Ref.	-	***0.32 (0.18–0.47)*****	***0.17 (0.00–0.32)****	0.19 (−0.06–0.44)	***0.013 (0.00–0.27)****	0.01 (−0.01–0.03)
Adjusted[a]	***0.21 (0.09–0.34)*****	Ref.	-	***0.27 (0.12–0.42)*****	0.13 (−0.03–0.29)	***0.25 (0.01–0.50)****	0.01 (−0.01–0.02)	0.01 (−0.01–0.025)
Atheroma, yes, OR (95% CI)[c]								
Crude	***6.48 (2.00–20.98)*****	Ref.	-	***9.9 (2.49–39.29)*****	***5.4 (1.23–23.72)****	1.8 (0.15–20.99)	***1.13 (1.01–1.26)****	1.03 (0.89–1.19)
Adjusted[a]	***4.87 (1.27–18.70)****	Ref.	-	***5.83 (1.23–27.60)****	4.78 (0.89–25.82)	2.48 (0.17–35.50)	1.085 (0.96–1.23)	1.03 (0.85–1.24)
Maximum thickening, MD (95% CI)[c]								
Crude			-	-	-	-	-	-
None (CIMT ≤1)		Ref.	-	-	-	-	-	-
Mild (1 < CIMT ≤1.2)	3.23 (0.32–32.48)	Ref.	-	***0.098 (0.017–0.57)****	1.62 (0.14–18.58)	0.54 (0.029–9.99)	-	-
Moderate (1.2 < CIMT ≤1.5)	***12.6 (1.19–133.89)****	Ref.	-	0.51 (0.10–2.57)	4.2 (0.332–53.129)	2.8 (0.20–40.06)	-	-
Marked (CIMT >1.5)	***17 (1.75–164.99)****	Ref.		-	5 (0.45–1.16)	-	-	-
Adjusted[a]								
None (CIMT ≤1)		Ref.	-	-	-	-	-	-
Mild (1 < CIMT ≤1.2)	3.15 (0.28–35.90)	Ref.	-	0.18 (0.02–1.26)	1.52 (0.10–22.80)	0.40 (0.01–18.95)	-	-
Moderate (1.2 < CIMT ≤1.5)	10.06 (0.81–124.46)	Ref.	-	0.60 (0.07–5.45)	2.75 (0.16–45.99)	5.79 (0.17–198.53)	-	-
Marked (CIMT >1.5)	***14.58 (1.22–176.15)****	Ref.	-	-	3.54 (0.23–54.12)	-	-	-
Maximum NASCET, MD (95% CI)[c]								
Crude	***0.86 (0.04–0.14)****	Ref.	-	***0.10 (0.036–0.156)*****	***0.09 (0.02–0.16)*****	0.03 (−0.07–0.14)	***0.01 (0.00–0.012)****	0.00 (−0.01–0.01)
Adjusted[a]	***0.66 (0.17–0.12)****	Ref.	-	***0.06 (−0.00–0.123)****	***0.08 (0.013–0.14)****	0.05 (−0.044–0.15)	0.00 (−0.00–0.01)	0.00 (−0.02–0.01)
Maximum AA, MD (95% CI)[c]								

(Continues)

TABLE 3 (Continued)

	Exposure variables							
		PAI score						
Outcomes	**AP+ (vs. AP−)**	**0/1**	**2 (vs. 0/1)**	**3 (vs. 0/1)**	**4 (vs. 0/1)**	**5 (vs. 0/1)**	**DMFT**	**No. of teeth**
Crude	***2.05 (0.51–3.59)*****	Ref.	-	***2.29 (0.41–4.18)****	1.45 (−0.68–3.57)	2.84 (−0.50–6.17)	0.12 (−0.042–0.28)	−0.17 (−0.37–0.39)
Adjusted[a]	***2.06 (0.36–3.75)****	Ref.	-	1.96 (−0.17–4.09)	1.66 (−0.60–3.9)	3.23 (−0.14–6.61)	0.073 (−0.10–0.25)	−0.16 (−0.38–0.69)
Mean CIA, MD (95% CI)[b]								
Crude	0.53 (−0.23–1.30)	Ref.	-	0.63 (−0.30–1.57)	0.28 (−0.77–1.33)	0.90 (−0.74–2.56)	0.07 (−0.01–0.15)	- 0. 15 (−0.25 to −0.06)
Adjusted[a]	0.091 (−0.11–0.29)	Ref.	-	0.17 (−0.77–1.12)	0.12 (−0.90–1.14)	1.00 (−0.52–2.53)	0.032 (−0.043–0.11)	−0.13 (−0.23 to −0.04)
Maximum CIA, MD (95% CI)[c]								
Crude	0.65 (−0.22–1.51)	Ref.	-	0.74 (−0.31–1.80)	0.33 (−0.86–1.52)	1.20 (−0.67–3.05)	0.08 (−0.01–0.16)	−0.17 (−0.27 to −0.06)
Adjusted[a]	0.11 (−0.11–0.33)	Ref.	-	0.09 (−0.94–1.12)	0.15 (−0.96–1.26)	1.28 (−0.38–2.95)	0.03 (−0.05–0.12)	***−0.15 (−0.25 to −0.04)****

Abbreviations: AA, abdominal aorta; CIA common iliac artery; CIMT, carotid intima medial thickness; MD, mean deviation; NASCET, north American symptomatic carotid surgery trial. Significance levels for estimates in bold and italics: *$p < .05$; $p < .01$; $p < .001$.

[a]Adjusted for age, BMI, gender, smoking, and alcohol intake.

[b]Right and left artery mean outcome.

[c]Right or left artery maximum outcome.

PAI and cardiovascular variables

Multiple regression models (Table 3) indicated that the odds of atheroma, CIMT>1.5 mm, and the combination of both (CIMT>1.5 mm/Atheroma) decreases when shifting from the reference group (PAI 0/1) to PAI 3 (OR = 5.83, OR = 5.11 and OR = 3.53 respectively), PAI 4 (OR = 4.78, OR = 2.24 and OR = 2.12, respectively), reaching the lowest ORs for PAI 5 (OR = 2.48, OR = 2.08, and OR = 1.24, respectively).

DMFT and cardiovascular variables

The DMFT seems to significantly affect only CIMT, Maximum CIMT, Atheroma, and Maximum NASCET but not after adjustment. No significant correlation was established between DMFT and other variables.

Number of teeth and cardiovascular variables

A significant inverse correlation was observed between the number of teeth and Maximum CIA. No significant correlation was established between teeth number and other variables.

DISCUSSION

The findings from the present case–control study showed a significant association between AP and subclinical signs of ASCVD, demonstrating the occurrence of significant carotid changes (carotid plaques and marked carotid intima-media thickenings) in patients with AP compared to controls. The final regression model revealed how the presence of AP led to 5-times and 15-times increased odds of carotid plaques and marked carotid intima-media thickenings, respectively. Additionally, the results of this study reveal the existence of a significant relationship between AP and other ASCVD risk parameters (mean and maximum CIMT, maximum NASCET and maximum AA).

The aim of the current case–control study was to investigate whether AP (exposure) can be identified as a separate risk factor for ASCVD (outcome) using non-invasive parameters of risk. Our data confirmed an association between AP and certain CV risk markers, as documented in previous publications, where the OR of having CVD in patients with AP was found to be 5.3 (An et al., 2016) and 2.79 (Costa et al., 2014). In these studies, the inclusion of individuals with CVD-related systemic diseases might have influenced the results; discrepancies with our findings are probably caused by different criteria for patients' selection, parameters for ASCVD risk assessment, as well as diagnostic methods to detect atherosclerotic changes (Chauhan et al., 2019).

From our results, a linear relationship between the presence of AP and CIMT (both mean and maximum measurements) emerged even after adjustments for confounders. These findings are consistent with a recently published cross-sectional study showing a statistically significant difference in CIMT between patients affected by AP and controls (Chauhan et al., 2019). Furthermore, it was demonstrated that every 0.1-mm increment of CIMT is associated with an increased risk of MI by 10% to 15% (Lorenz et al., 2007; Naqvi & Lee, 2014). Therefore, it can be speculated that AP+ patients may have a higher risk of CV events compared to healthy controls. However, it is equally plausible that high CV risk factors could contribute to the development of AP. The complex interplay between AP and CV risk warrants further investigation to disentangle the direction of this relationship and better understand the underlying mechanisms.

According to our logistic regression model, AP was associated with 5 times higher odds of carotid plaque occurrence, even after adjustments. Furthermore, 57.58% of patients displayed at least one sign of subclinical atherosclerosis (either marked CIMT or carotid plaques) in one of the two carotid arteries. Accordingly, it is possible to hypothesize that the presence of periapical lesions could amplify the vascular inflammation pathognomonic of atherosclerosis. Notably, a recently published systematic review demonstrated that AP is associated with increased levels of IL-1, IL-2, IL-6, immunoglobulins (IgA, IgG, and IgM), and C-reactive protein (CRP) (Gomes et al., 2013). These chronic inflammatory mediators may be carried via the circulation to various areas in the body (Berlin-Broner et al., 2017a, 2017b).

CIMT values from the present report are higher compared to those from a previous study (Chauhan et al., 2019). These results may be due to the different target populations investigated in both studies. The former enrolled younger individuals (18–40 years old), while the current report selected patients above 40 years of age. A higher mean age of study participants could represent an important confounder which might have a role in the controversial results across other studies (Chauhan et al., 2019; Costa et al., 2014; Frisk et al., 2003; Joshipura et al., 2006). However, CIMT is a marker of carotid atherosclerosis that can be tracked in young patients, while carotid plaque occurs later in life (Naqvi & Lee, 2014). Therefore, to assess the power of AP in predicting atherosclerotic plaque occurrence, we increased the mean age of the population. Through the use of a pair-matched design and conditional logistic

regression, we were able to control for variables that could have affected the study outcomes (age, gender, BMI, smoking, alcohol intake) (An et al., 2016).

Unlike other studies, in the present report, CIMT measurements were taken from the ICA (Chauhan et al., 2019; Pinho et al., 2013). It was recently demonstrated that the presence of an increased CIMT in the ICA corresponds to a higher relative risk of incident CVD compared to the same value in the common carotid artery (CCA), therefore representing a better predictor for future ASCVD (Cao et al., 2007; Naqvi & Lee, 2014). Additionally, to improve reproducibility, we used the combined values of the right and left ICAs, while in a previous study, CIMT was measured only from the right CCA (Chauhan et al., 2019).

There is controversy regarding what CIMT values should be considered abnormal, with different arbitrary cut-off points used to predict atherosclerotic risk (Naqvi & Lee, 2014). The relationship between CIMT and CV risk is continuous, and determining a threshold CIMT could be incorrect. However, the latest ESH/ESC hypertension guidelines (2013) have reconfirmed that CIMT >0.9 mm is a marker of asymptomatic organ damage. Nevertheless, it has been proven that in middle-aged and elderly patients, the threshold values indicating high CV risk are higher, in accordance with our findings (Goff et al., 2014).

In this study, we also evaluated the degree of carotid stenosis using the NASCET method. Around 55% of AP+ patients displayed carotid plaques and a mild degree of stenosis (below 29%). Moreover, a linear relationship between AP and NASCET values of stenosis was also found.

There are no studies in the literature that have analysed the CV risk profile in patients with AP using ABI, AA, and CIA diameters as secondary outcomes. Although a previous meta-analysis supports a significant relationship between periodontitis and PAD (Yang et al., 2018), in the current study, both groups featured a lack of clinical and preclinical PAD, as evidenced by normal diameters of CIA (Figure 4d,e) and values of ABI. However, from our results emerged that maximum AA diameters were significantly higher in AP subjects, and a significant correlation between AP and an increase in maximum AA diameters was also demonstrated (Figure 4f). Therefore, patients with periapical lesions are at an increased risk for AAA compared to healthy subjects.

In the present study, the relationship between the level of exposure (AP), quantified with PAI score, and the increase in CV risk was also evaluated. Previous studies have attempted to establish a possible association between the severity of periapical bone destruction with the incidence of acute coronary events (Oikarinen et al., 2009) and CV mortality (Liljestrand et al., 2021). However, to the best of our knowledge, this is the first study formulating the hypothesis of a significant association between a higher PAI score and surrogate measures of ASCVD. The model showed that the association of PAI with carotid alterations was not cumulative, and a higher PAI score does not correlate to increased odds of carotid plaques, atheroma, and the combination of both.

The purpose of the study was to investigate the epidemiological association between AP and ASCVD. Participants with any systemic disease, including periodontitis, were ruled out to increase internal validity. Although there is evidence of a significant correlation between periodontitis and carotid plaques occurrence, there are no data on AP. Not all the studies using CIMT as CV outcome also include atherosclerotic plaque in the CIMT measurements (Chauhan et al., 2019), but carotid plaque assessment appears to be a more powerful predictor of future events of ASCVD compared to CIMT alone (Mohamed et al., 2022).

Our findings show that the two groups differ significantly as to alcohol consumption, with over 40% of AP− patients exceeding the recommended intake. The significant difference may be attributed to subtle variations in age and gender between the two groups. Despite known differences in alcohol use by age and gender (Auchincloss et al., 2022; Veerbeek et al., 2019), our data contradicts recent findings that underscore the repercussion of alcohol on system inflammation (Dukić et al., 2023). Indeed, alcohol is recognized as a significant contributor to early-onset CVD (O'Keefe et al., 2018) and preclinical studies have reported that its chronic consumption enhances inflammation and osteoclastogenesis on induced periapical lesions in rats (Dal-Fabbro et al., 2019; Pinto et al., 2020). However, further research is needed to advance knowledge on this association in humans. To better isolate the true relationship between the exposure and the outcome, adjustments for alcohol consumption were made across multiple models.

While we have focused on the impact of AP on the CV risk profile, it is equally important to investigate the potential influence of atherosclerosis on periapical health. Evidence suggests a connection involving Angiotensin II, a key component of the renin-angiotensin system (Martins et al., 2016). This molecule has been observed to up-regulate RANKL expression causing osteoclasts activation leading to periapical bone destruction (Martins et al., 2016). It is well established that angiotensin II has atherogenic effects and may play a role in this bidirectional relationship (Poznyak et al., 2021). Nevertheless, a definitive biological mechanism by which ASCVD could lead to an increased risk for AP remains unclear. However, a large body of evidence associates atherosclerosis with periodontitis (Abraham et al., 2019). Despite differences in aetiology and pathogenesis, periodontitis and AP exhibit similarities (Cotti et al., 2011; Sundqvist, 1992). Therefore, it is plausible to hypothesize that the effect of ASCVD

on AP may also be possible. However, further research is needed to comprehensively understand the bidirectional relationship between these conditions.

The current study presents some limitations. First, given the observational study design, it is impossible to establish the cause-effect relationship between the exposure and the outcome. In addition, reverse causality could not be excluded. Randomized controlled trials would provide the highest level of evidence; however, for ethical reasons, they cannot be applied to AP cases since prompt treatment is necessary upon diagnosis. Hence, we must rely on observational studies. Secondly, our study did not include any microbiological or immunological analysis; therefore, no possible theory regarding the CVD-AP relationship can be confirmed. Thirdly, even though the major confounding factors were considered in the multiple models, the risk of residual confounding cannot be ruled out. Fourthly, the sample size calculation was performed based on the primary outcome; therefore, it cannot be ruled out that some estimates related to secondary outcomes may have large CIs due to a decrease in statistical power for those estimates. Furthermore, despite periapical X-ray represents the most used radiograph in clinical practice to diagnose AP, their ability to detect changes in periapical bone is limited, and their interpretation can lead to underdiagnosis (An et al., 2016). Cone-beam computed tomography (CBCT) is currently the gold standard to ensure early and reliable detection of all periapical lesions (Cotti & Schirru, 2022).

CONCLUSIONS

Results from the current study highlight that the presence of AP may be regarded as a risk indicator for ASCVD, with AP being associated with 5-fold increased odds of having carotid plaques and 15-fold increased odds of having marked carotid intima-media thickening. Further studies should be conducted in order to verify whether AP treatment could be beneficial for ASCVD signs. These results may lay the groundwork in order to develop synergistic preventive approaches to tackle both oral and systemic conditions.

AUTHOR CONTRIBUTIONS

Giulia Malvicini (Formal Analysis, Data curation, Methodology, Writing—original draft), Crystal Marruganti (Formal Analysis, Investigation, Writing—original draft), Mustafa Abu Leil (Data curation, Investigation), Marco Martignoni (Supervision, Writing—review and editing), Edoardo Pasqui (Conceptualization, Methodology), Gianmarco de Donato (Supervision, Methodology, Writing—review and editing), Simone Grandini (Data curation, Methodology), Carlo Gaeta (Supervision, Data curation).

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT AND DOCUMENT

Approved by the University Hospital of Siena Ethics Committee (Siena, Italy), Area Vasta Toscana Sud Est, protocol number 22967/2020.

PATIENT CONSENT STATEMENT

All enrolled patients were informed about the study protocol and were asked to read and sign the informed consent. The present study was conducted according to the declaration of Helsinki.

RELEVANT REPORTING GUIDELINES PAPERWORK

The present observational study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

CLINICAL TRIAL REGISTRATION

The present case–control study was registered on Clinicaltrials.gov and received the following registration number: NCT05792787.

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