Association between intracranial carotid artery calcifications and periodontitis. Cone-beam computed tomography (CBCT) study.

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3) Disclaimers:

The authors do not have any financial interests in any of the products mentioned in this article.

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5) Word Count and number of figures and references.

Number of words in the Abstract: 247

Number of words in the manuscript: 3067

Number of references: 34

Number of figures: 2

Number of tables: 4

6) Short running title:

Presence of intracranial carotid artery calcifications

7) Key summary:

A nearly half (45%) of the subjects displayed intracranial carotid artery calcifications on the CBCT

images, and these calcifications were significantly related to the presence of chronic periodontitis, age,

gender, and CVDs.

8) Authors contribution statement.

All authors have contributed to the conception and protocol development of this study. AA, PW, and YH have conducted data collection and analysis. All authors have been involved in drafting and revising the manuscript critically, and have approved the final version for publication.

Abstract

Background: Intracranial carotid artery calcifications (ICACs) are one type of calcification that may be detected as incidental findings in cone-beam computed tomography (CBCT). This retrospective study aimed to examine the prevalence of ICACs on CBCT images and their associations among age, gender, chronic periodontitis, and patient-reported cardiovascular diseases (CVDs).

Methods: A total of 303 CBCT scans were reviewed and a total of 208 patients met the inclusion criteria. The presence or absence of ICACs was evaluated in the ophthalmic and cavernous segments of each scan. Patient demographic data, including age, gender, and medical history, specifically focused on CVDs were recorded. The presence or absence of periodontitis was recorded from each subject with full mouth radiographs and clinical measurements. Odds ratios (ORs) were calculated as part of the logistic regression analysis.

Results: Overall, ICACs were found in 93 subjects (45%). The bilateral ICACs were found in 43 subjects (21% of the total subjects, 46% of the subjects with ICACs). There were statistically significant associations between presence of ICACs and periodontitis (OR = 4.55), hypertension (OR = 3.02), hyperlipidemia (OR = 2.87), increasing age (OR = 2.24), and the male gender (OR = 1.85). Smoking status was not significantly correlated with ICACs.

Conclusion: This study revealed that nearly half (45%) of the subjects displayed ICACs on the CBCT images. ICACs are significantly related to the status of chronic periodontitis, age, gender, and CVDs. A more careful review of CBCT scans is highly recommended to detect these calcifications and refer patients for further medical evaluation.

Key Words:

Cardiovascular disease(s), Periodontitis, Radiology, Imaging,

1. Introduction

Periodontitis is a common multifactorial disease characterized by clinical attachment loss and bone loss and may result in tooth loss, if not treated effectively.[1] Periodontitis occurs in most age groups, but it is most prevalent among adults over the age of 30, affecting 42% of the US adult population, of which 7% have severe periodontitis.[2] Over the last 40 years, numerous studies have demonstrated an association between periodontal disease and several chronic diseases.[3-5] These studies have reported an association among periodontal disease and diabetes mellitus, osteoporosis, rheumatoid arthritis, chronic obstructive pulmonary disease, and cardiovascular diseases (CVDs).[6-8] Several case-control and cross-sectional studies have discussed the relationship between periodontal diseases and coronary heart disease (CHD).[9-11] These studies indicated that patients with periodontitis have a 1.14 times higher relative risk of developing coronary heart disease and a 25% increased risk compared with control subjects.[11, 12] In addition, several studies have suggested that atherosclerosis may be exacerbated by periodontitis. [13-15] Chronic periodontal infections may stimulate endothelial dysfunction through systemic inflammation that is exacerbated by elevated levels of interleukin-6 and fibrinogen. Moreover, bacterial products from *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, including gingipains and soluble bacterial components, can induce endothelial dysfunction.[16] Inflammation plays a role in the

entire pathogenesis with atherosclerosis, starting from the expression of the endothelial adhesion molecules, including intercellular adhesion molecule I and vascular cell adhesion molecule I. These molecules are expressed in response to soluble inflammatory mediators, such as interleukin 1 and 6, in the bloodstream, leading to endothelial permeability, leukocyte migration, and adhesion. Fatty streaks and calcifications become phagocytosed within macrophages, resulting in the increasing release of pro-inflammatory cytokines (e.g., interleukin-1, interleukin-6 and tumor necrosis factor alpha). The disintegrated endothelial layer leads to the production of thrombin from prothrombin and the formation of fibrin to fibrinogen that can result in thrombosis and, consequently, to cerebrovascular accidents or myocardial infarction.[7, 17] According to a polymerase chain reaction study on samples taken from carotid endarterectomies, 44% of atheromas were found positive for at least one periodontal bacteria and *P. gingivalis* and *Tannerella forsythia* were observed in 26% and 30%, respectively, of the surgical specimens. These periodontal pathogens are strongly related to bleeding on probing and deep pocket depths.[10, 18] Extracranial carotid artery calcifications (ECACs) may be visualized in panoramic radiographs beneath the mandibular angle proximal to the cervical vertebrae at the C3 and C4 levels. These calcifications were detected among 10%–12% of male patients and 10%–16% of female patients, either unilaterally or bilaterally.[19] Regarding the accuracy of panoramic radiographs for detection of ECACs, one study compared ultrasonography with conventional panoramic radiographs. The authors found that the panoramic radiographs had a sensitivity of 66.6%, and a positive predictive value of 45% was found for the detection of carotid artery calcifications in patients whose angiograms confirmed the presence of coronary artery disease and a sensitivity of 50% in patients with a normal angiogram. [20] However, the sensitivity and specificity reached 76% and 98% in digital panoramic X-rays, respectively, in the portrayal of carotid artery calcifications.[21] In addition, a statistically significant association was

found between the presence of ECACs in panoramic radiographs and the percentage of alveolar bone loss in patients with periodontitis.[19]

Intracranial carotid artery calcifications (ICACs) are one type of calcification that may be detected as incidental findings in cone-beam computed tomography (CBCT). A cross-sectional study by Khosropanah and co-workers compared the prevalence of intracranial and extracranial artery calcifications in 705 CBCT scans. They reported that more than 60% of the scans were positive for ICACs and 39.9% were positive for ECACs. The findings also showed that there was a correlation between ICACs and ECACs [22] and another study by de Weert reported that ICACs were independently associated with smoking, hypercholesterolemia, and history of cardiac and/or ischemic cerebrovascular diseases. [23] A dental practitioner who prescribes CBCT imaging is responsible for the interpretation of the entire scanned volume. This interpretation is based on a thorough knowledge of the anatomical structures, variations, and abnormalities on radiographic images. It is crucial to examine the entire volume systematically, which may include paranasal sinuses, airway spaces, the base of the skull, the cervical spine, and temporomandibular joints. To the best of the current authors' knowledge, no research has examined the association between internal carotid artery calcifications and periodontitis. Therefore, this retrospective study aimed to examine the prevalence of ICACs on CBCT images and their associations among age, gender, chronic periodontitis, and patient-reported CVDs.

2. Materials and Methods

Prior to the initiation of this study, Indiana University Institutional Review Board approved this protocol. (#1904630905). Due to the nature of retrospective study and minimal risk, the informed consents and HIPAA authorization forms were not obtained. This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. The scans of 303 subjects were reviewed for

the presence of ICACs. The included samples consist of scans taken between March 1, 2012 to March 29, 2018 at the Indiana University School of Dentistry Cone Beam Imaging Facility. All scans were taken with an iCAT$^\parallel$ with Field of View (FOV: diameter of 16 cm, height of 13 cm), voxel size of 0.3 mm, exposure time of 8.9 seconds, and 120 kVp. All CBCT scans were prescribed by different departments, including periodontics, oral surgery, oral pathology, prosthodontics, as well as private practitioners. The CBCT scans were exposed for multiple indications, and no patients had a scan exposed solely for the purpose of this study.

Inclusion criteria:

- Patients aged 30 years and above.
- Large or medium field-of-view (FOV) CBCT scans that included the maxilla only or the maxilla and mandible
- A confirmed periodontal diagnosis in the electronic dental record (EDR) that was approved by a faculty member of the department of periodontology at Indiana University School of Dentistry

Exclusion criteria:

- Edentulous patients
- Patients with limited FOV scans
- Scans with motion artifacts.

2.1 Data Collection

The patients' charts in the EDR were reviewed, including the subjects' demographic data, age, gender, and date of the scan. All subject related information was extracted from Axium¶ data base. Information about the subjects' medical history, specifically on CVDs were recorded. CVDs included hypertension

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$^\parallel$ Imaging Sciences, Hatfield, USA

¶ Axium Software: Deltek $^\copyright$, Herndon, VA, United States

(HTN), history of myocardial infarction, atrial fibrillation, angina pectoris, chronic heart failure, any history of ischemic cerebrovascular disease, and hyperlipidemia (HDL). The self-reported smoking status was classified as a current smoker and non-smoker. The presence or absence of a periodontal diagnosis was documented and approved by the faculty members of the department of periodontology. These faculty members received monthly calibration sessions for diagnosis and treatment planning within the department. All periodontal diagnoses were made with a combination of intra-oral complete series of radiographs and periodontal charts including probing depth, gingival recession, clinical attachment loss, bleeding on probing and plaque scores. CBCT data was not used for periodontal diagnoses in this study. All periodontal diagnoses were determined based on the previous classification because all the data were retrieved between March 1, 2012, to March 29, 2018.[24] The access to research data was limited only to the researchers who have a user ID and password to ensure that subjects' identification data are secured.

Image evaluation:

Two oral and maxillofacial radiologists from author's group (AS and PW) evaluated the scans for the presence or absence of ICACs. The examiners were blinded to the patients' medical and dental history. All DICOM data were transferred to CS imaging software[#] for image analysis. The images were evaluated, and ICACs were considered present when there is radiodensity at the ascending part of the petrous segment up to the cavernous segment in the axial, coronal, and sagittal planes based on the reported criteria [22]. Cohen's kappa statistics were used to evaluate intra-examiner repeatability and inter-examiner agreement [25]. A total of 10 scans were chosen randomly for this calibration. Both AS and PW evaluated for presence or absence of ICAC. Regarding intra-examiner calibration, the same scans were

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[#] CS imaging Software: Carestream Health, Inc, Rochester, NY, United States

reviewed ten days after the initial review. Intra-examiner repeatability and inter-examiner agreement were performed until the kappa score reached >0.9.

2.2 Statistical analysis:

Logistic regression was used to examine the relationships among periodontitis, age, gender, CVD, HTN, HDL, and smoking status with the presence of ICACs. Each factor was first examined individually, followed by a multivariable analysis. Because of the collinearity issue among the factors, a model including all factors was inappropriate. Instead, a stepwise variable selection procedure was used to select a limited set of significant factors. Odds ratios (ORs) along with their 95% confidence intervals were calculated as part of the logistic regression analysis. The significance level of the study was determined as 5%. Analyses were performed using SAS version 9.4[**].

Results

A total of 303 subjects were screened for inclusion in the study. 208 subjects with ages ranging from 33 to 95 years old (mean age 62±13 years) met the inclusion criteria. ICACs were found in 93 subjects, and bilateral ICACs were found in 43 subjects (21% of the total subjects, 46% of the subjects with ICACs). Out of the total subjects, 111 subjects had periodontitis, 109 subjects had CVD, 84 subjects had HTN, and 42 subjects had HDL (Table 1). Out of the total subjects who had ICACs, 53 subjects were male and 40 were female (Figure 1A). Of all the subjects, 68 subjects who had ICACs also had periodontitis, and 67 subjects had CVD (Figure 1B and 1C). When CVD was sub-classified into HTN and HDL, 51 subjects and 28 subjects had HTN and HDL, respectively, and 28 subjects who had ICACs were smokers. (Figure 1 D–F). This study revealed that aging is also associated with a higher prevalence of

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[**] SAS version 9.4: SAS Institute Inc., Cary, NC, USA

the presence of the calcifications. The odds ratio of age for the existence of ICACs was 2.24, and this represented for a 10-year increase in age. When each characteristic was evaluated individually, all characteristics except smoking status were significantly associated with the presence of ICACs (Table 2). Using a stepwise variable selection procedure, age, periodontitis, and CVD were included in the multivariable model as significantly associated with ICACs (Table 3). When analyzing ICACs as a three-level outcome (bilateral ICACs, unilateral ICACs, and no ICACs: Figure 2A-B), the generalized logistic model provides comparisons for bilateral ICACs vs. unilateral ICACs, bilateral ICACs vs. no ICACs, and unilateral ICACs vs. no ICACs. The advantages of separating bilateral and unilateral ICACs are that the analysis can then test bilateral ICACs vs. unilateral ICACs and examine the differences in how bilateral and unilateral ICACs are compared with no ICACs. There was no statistically significant difference between bilateral and unilateral ICACs in age, gender, presence of periodontitis, CVD, HTN, HLD, and smoking status. However, when a comparison between bilateral ICACs and no ICACs was made, the findings revealed a statistically significant difference in age, gender, presence of periodontitis, CVD, HTN, but not significant different with smoking status. In addition, when a comparison was made between unilateral ICACs and no ICACs, unilateral ICACs have statistically significant associations with age, presence of periodontitis, CVD and HDL. (Table 4).

Discussion

To the best of the authors' knowledge, this retrospective study is the first study to examine the association between the presence of ICACs and periodontitis using CBCT datasets. The findings of the study revealed a correlation between the presence of ICACs with age, gender, and CVD Moreover, ICACs were found in 61% of the subjects who have periodontitis, and no difference was found between the presence of these calcifications bilaterally or unilaterally with periodontitis, age, and CVD. We

examined the CBCT from the ascending part of the petrous segment up to the cavernous segment for ICACs, as Damaskos, da Silveira, and Berkhout found that 92% of internal carotid artery calcifications were found in this segment.[26] These calcifications play a significant role in the development of the atherosclerotic process, and may be used as a reliable marker for intracranial atherosclerosis as they occur in up to 90% of atheromatous lesions.[27] Furthermore, a six-year cohort multidetector computed tomography (MDCT) study reported that ICACs contributed to 75% of incidence of strokes.[27, 28]

It has been hypothesized that periodontopathic bacteria identified in atherosclerotic plaque specimens may play a role in the entire development and progression of atherosclerosis, inducing fatty streaks after the elevation of inflammatory mediators, such as IL-1, IL-6, TNF-α, and C-reactive protein. The sustained increased levels of these mediators are highly correlated with atherosclerosis.[29] However, the calcification mechanism of atherosclerotic lesions is complex and not fully understood.[27] Previous studies have investigated the association between ECACs in panoramic radiographs and periodontitis. These studies found a positive association between the presence of these calcifications and chronic periodontitis.[30, 31] However, the diagnosis of bone loss was determined using panoramic radiographs. A study reported that the underestimation of bone loss may reach up to 32% with panoramic images[32], and the accuracy of determining the presence of crestal bone loss was not precise. Nevertheless, periodontitis is defined as the percent of alveolar bone loss with panoramic radiographs without any clinical parameters.[19] [30] In this study, the periodontal diagnosis was utilized from the patients data, based on a periodontal examination including probing depths, gingival recession, clinical attachment level, and radiographic bone loss from a full-mouth set of intraoral radiographs. However, one of the limitations of the current study included that the severity, extent, and activity of periodontitis were not analyzed with associated with the presence or absence of ICACs. Due to the nature of this retrospective cross-sectional

study, further details of the relationship between ICACs and periodontal conditions, such as the duration of periodontitis, were not evaluated in this study.

The findings of the study revealed that male gender and increasing age are correlated with the presence of ICACs. These findings are consistent with those of previous CBCT and MDCT studies. [22, 23] Due to the high resolution of images and small voxel sizes, the detection of calcification was comparable between CBCT and MDCT.[33] In addition, in the CBCT study by Damaskos et al., the prevalence of ICACs was 15% higher than the findings of this study. This finding might be due to the greater number of CBCT scans reviewed by Damaskos (705 vs. 208 in the present study).[22] Studies have demonstrated that elevated blood pressure, HDL, and smoking habit are highly associated with stroke, and the presence of calcified atherosclerotic lesions has been radiographically associated with stroke.[34, 35] Although few CBCT studies have investigated the association between the presence of ICACs and CVDs, several MDCT studies found a positive association of the presence of ICACs with HTN, HDL, and smoking. [23, 28, 36] The results of the current study are consistent with the aforementioned findings. However, we did not find an association between the presence of ICACs and smoking status in this study, but smoking status was self-reported by the study participants. The results may have been different if the patient's smoking status was classified based on detailed information such as smoking intensity and duration of smoking history.[37] A limitation of using CBCT images for ICACs detection is that while most atherosclerotic lesions are calcified, some atheroma are not calcified and cannot be visualized using CBCT imaging. In other words, patients who did not present with ICACs in CBCT imaging may still have atherosclerotic lesions. Therefore, CBCT cannot make a definitive diagnosis for atherosclerosis. In CBCT images, clinicians need to be aware that intracranial calcifications would be from different diseases such as tuberous sclerosis, lipoma, or any neoplasm related conditions.[38]

Needless to say, due to the small sample size and the nature of the retrospective study, this study cannot

make clear correlations between intracranial carotid artery calcifications and periodontitis. Future prospective clinical trials using other advanced imaging modalities, such as B-mode ultrasonography and computed tomography angiography, may provide more evidence on the significance between ICACs and chronic periodontitis.

Conclusion

This study revealed that nearly half (45%) of the subjects displayed ICACs on the CBCT images. The findings showed that these calcifications were significantly related to the presence of chronic periodontitis, age, gender, and CVDs. As CBCT imaging is more widely used in the diagnostic and treatment planning methods in periodontics and implant dentistry, a thorough interpretation of CBCT scans is highly recommended by an oral and maxillofacial radiologist to detect these calcifications and refer patients for further medical evaluation, particularly for patients who are unaware of their cardiovascular condition.

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Figure legends:

Figure 1 (A–F): Correlation of ICACs with gender, periodontitis, CVD, HTN, HDL, and smoking.

A: Correlation of ICACs with gender

B: Correlation of ICACs with periodontitis

C: Correlation of ICACs with CVD

D: Correlation of ICACs with HTN

E: Correlation of ICACs with HDL

F: Correlation of ICACs with smoking

Figure 2-A: Axial, coronal, and sagittal views of the CBCT demonstrating bilateral radiodensity (arrow) in the cavernous segment suggestive of ICACs.

Figure 2-B: Axial, coronal, and sagittal views of the CBCT demonstrating unilateral radiodensity(arrow) in the cavernous segment suggestive of ICACs

CBCT: cone-beam computed tomography

ICACs: intracranial carotid artery calcification

Tables:

Table 1. Demographic data, subjects with ICAC, periodontitis, CVD, HTN, HDL, and smoking.

SD: Standard deviation; ICACs: intracranial carotid artery calcification; CVD: cardiovascular disease; HTN: hypertension; HDL: hyperlipidemia.

Table 2: Odds ratio and p-values of patients with ICACs under different characteristics

^Odds ratio for age represents the odds ratio for a 10-year increase in age.

ICAC: intracranial carotid artery calcification; CVD: cardiovascular disease; HTN: hypertension; HDL: hyperlipidemia.

Table 3: Odds ratio and p-values of patients with ICACs under different characteristics using a stepwise variable selection procedure. (CVD: cardiovascular disease)

Table 4: Analyzing ICACs as a three-level outcome (bilateral ICACs, unilateral ICACs, no ICACs) under different characteristics using generalized logit model

^ Odds ratio for age represents the odds ratio for a 10-year increase in age.

ICACs: intracranial carotid artery calcification; CVD: cardiovascular disease; HTN: hypertension; HDL: hyperlipidemia.