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Research Article

Characterization of Soft Tissue Calcifications in Persons with Diabetes

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Abstract

CBCT offers an opportunity to detect and localize soft-tissue calcifications by evaluating the scan's multiplanar representation. Diabetes mellitus is a chronic metabolic condition resulting in hyperglycemia, which we believe is associated with different soft-tissue presentations. This study aims to evaluate the presence, anatomical location, type, and size of calcifications in persons with diabetes mellitus. We hypothesize that the prevalence of specific calcifications may be associated with diabetes mellitus. This retrospective case-control study was completed by evaluating 92 large volume CBCT images of Penn Dental Medicine (PDM) patients with and without diabetes mellitus, matched for age and gender, to assess the presence, anatomical location, type, size, and distribution of calcifications. All large field of view (FOV) CBCT scans for dental patients attending PDM clinics between 2015 and 2022 were utilized. Craniofacial calcifications, including vascular, pulpal, soft tissue, ligament, and pathological calcifications, were evaluated and documented using CBCT imaging. Comparisons of categorical variables was done using the Fisher's Exact test. A high prevalence of vascular calcifications was noticed; extracranial internal carotid artery calcification (EICAC) 29% and intracranial internal carotid artery calcification (IICAC) of the internal carotid arteries (41%), tonsiloliths (34%) and pulp calcifications (54%) were discovered. There was no statistically significant difference in race ($p = 0.09$), periodontal disease status ($p = 0.58$), or presence of hypertension (0.38) between the two groups, but the known group with diabetes was more likely to have cholesterolemia (72% vs 41%, $p < 0.001$). This study demonstrates a high prevalence of vascular calcifications, tonsiloliths and pulp calcification in the study sample. Further analysis to identify the cause of such calcifications and the association of the calcifications with underlying systemic conditions is needed in the future. Detecting radiographic biomarkers for diabetes will aid early institution of preventive measures to reduce morbidity and mortality, ultimately reducing the global burden of diabetes.

Keywords: *Carotid Artery Atherosclerosis; Digital Imaging; Radiology; Oral-Systemic Disease(s); Evidence-Based Dentistry; Intracranial Internal Carotid Artery Calcification (IICAC); Extracranial Internal Carotid Artery Calcification (EICAC); Health Care*

Introduction

The introduction of cone beam computed tomography (CBCT) in dentistry has transformed imaging diagnostics by providing a cost-efficient and low dose volumetric imaging alternative [11]. Incidental findings (IF) are frequently noted on CBCT imaging, with variability in their occurrence and characteristics. Theodoridis., *et al*. reported that when including various anatomical variations, 99.5% of the CBCT examinations analyzed in their retrospective study revealed at least one incidental finding [22]. Soft tissue calcifications are commonly observed and may either be physiological or arise from a variety of pathological conditions. Their appearance on radiographic imaging can serve as an indicator, aiding in the establishment of a specific diagnosis [5]. The possibility of their presence being a signal or predisposition to chronic systemic conditions should not be overlooked. Understanding the prevalence and characteristics of these calcifications is essential for accurately interpreting dental radiographic examinations. The presence of vascular calcification has been used by medical radiologists to determine the severity and prognosis of various systemic diseases such as hyperparathyroidism [7] coronary artery disease and diabetes [1]. Furthermore, the detection of various types of calcifications and the pattern of presentation among persons living with diabetes, both Type I and Type II, can be an early diagnostic indicator.

The World Health Organization's (WHO) 2030 Agenda for Sustainable Development (SDG target 3.4) aims to reduce by one-third premature mortality from noncommunicable diseases (NCDs) through prevention and treatment [19,23]. While diabetes mellitus is often diagnosed through clinical symptoms, patient testimony and blood testing, the ability to objectively diagnose diabetes through imaging findings may have significant impact, since more persons will visit the dentist relative to identified patients with systemic conditions being managed by medical specialists. This study aims to identify the prevalence of specific calcifications among patients with diabetes mellitus and pinpoint those that could be used as early diagnostic markers. The key criteria for diagnosing soft tissue calcifications include their anatomical location, distribution, quantity, size, and shape. The ability to identify systemic conditions like diabetes early on through radiographic imaging will aid early institution of preventive measures, significantly helping dentists adjust treatment plans to best personalize patient care and ultimately reduce the global burden of the condition.

Methods

This retrospective study was completed by evaluating 92 large volume CBCT scans of groups with and without diabetes and conformed to the STROBE protocol. The participants included patients attending the PENN Dental Medicine (PDM) clinic between 2015 and 2022. All radiographs were obtained through a database from PDM's records in the MiPACS Dental Enterprise Viewer® 4.3.0.68. 46. Participants each for groups with and without diabetes were matched for gender and age (+/- 5 years). The scans were evaluated for the presence, anatomical location, type, size, and distribution of calcifications. IRB approval number #849252. All large FOV CBCT scans exceeding or equal to 8 cm x 8 cm encompassing the base of the skull and covering the area of the Sella turcica were included. Cases were patients with Type I and Type II diabetes and controls were patients without diabetes. Using Anatomage® *in vivo* advanced 3-D imaging software (Anatomage® 6.0, San Jose, CA, USA), scan evaluation was carried out by two reviewers, an Oral and Maxillofacial Radiology specialist with four years' experience and a second-year dental student who had been calibrated. Craniofacial calcifications were evaluated from CBCT imaging and documented. These calcifications were physiological or pathological, including vascular, pulpal, soft tissue, and ligament. The cervical, cavernous and ophthalmic segments of the ICA were examined in the 3D software to identify linear or circumferential patterns of calcification (MAC) in the three anatomic planes (axial, coronal and sagittal) using the thin slice (0.1 mm grayscale slice thickness) multi-planer tools. All images with these characteristics were documented as positive for MAC. Data from records of the control group of patients was also reported. This served as a data bank for statistical analysis such as diagnostic indicators for underlying systemic diseases such as diabetes. Biostatistical analysis was carried out to determine the occurrence of specific calcifications, as seen on CBCT, in patients with and without diabetes mellitus. Results were based on the resultant data as analyzed. We expected to see the prevalence of specific calcifications associated with diabetes mellitus.

Results

The CBCT scans were evaluated for evidence of the presence, type, size and distribution of calcifications. There was no statistically significant difference in race ($p = 0.09$), periodontal disease status ($p = 0.58$), or presence of hypertension (0.38) between the two groups, but the individuals with diabetes were more likely to have cholesterolemia (72% vs 41%, $p < 0.001$). Tooth related calcifications as seen in the two groups is provided in table 1 and the prevalence of calcifications as seen generally among the research participants is documented in table 3. Calcifications noted include IICAC, tritecious calcifications, tonsilloliths and pineal gland calcification (Figure 2) among others. Table 2 highlights calcifications with a statistically significant difference among the control group. Comparisons of categorical variables were done using the Fisher's Exact test. The only two calcifications with a statistically significant difference between the two groups occurred at a higher rate in the matched subjects than in the group with diabetes: Pineal gland calcification (24% vs 7%, $p = 0.04$) and dystrophic calcification (20% vs 4%, $p = 0.05$).

Calcification Type	Group with Diabetes	Matched Subjects	p-value
Presence of pulp stones	6 (13%)	7 (15%)	1.0
Presence of ≥ 1 pulp calcification	28 (61%)	22 (48%)	0.30
Mean # of pulps calcified (s.d.)	2.8 (3.3)	3.1 (4.5)	0.71
> 8 teeth missing	30 (65%)	26 (57%)	0.52
Mean # teeth missing (s.d.)	15.0 (16.3)	13.3 (9.5)	0.61

Table 1: *Tooth related calcifications.*

Calcification Type	Group with Diabetes	Matched Subjects	p-value
Pineal gland calcification present	3 (7%)	11 (24%)	0.04
Dystrophic calcification present	2 (4%)	9 (20%)	0.05

Table 2: *Calcifications with statistically significant associations among controls.*

Calcification Type	Prevalence
Ossification of stylo-hyoid ligament	11%
Presence of pulp stones	14%
Presence of tonsilloliths (Figure 2)	34%
Petroclinal ligament calcification	11%
Presence of sialoliths	2%
Presence of ≥ 1 pulp calcification	54%
Pineal gland calcification	15%
Calcification of tritecious cartilage (Figure 2)	7%
Thyroid cartilage calcification	11%
Dystrophic calcification	12%
Intracranial internal carotid artery calcification (IICAC) (Figure 2)	41%
Extracranial internal carotid artery calcification (EICAC)	29%

Table 3: *Prevalence of Calcifications among participants.*

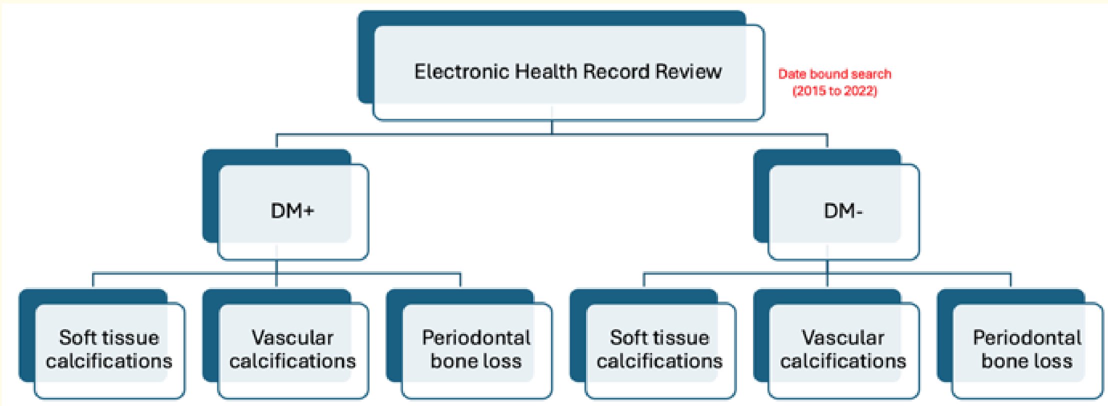

Figure 1: *Schema for methods. Participants divided into cases (diabetic) and controls (non-diabetic). Each group is then evaluated for soft tissue and vascular calcifications and periodontal bone loss.*

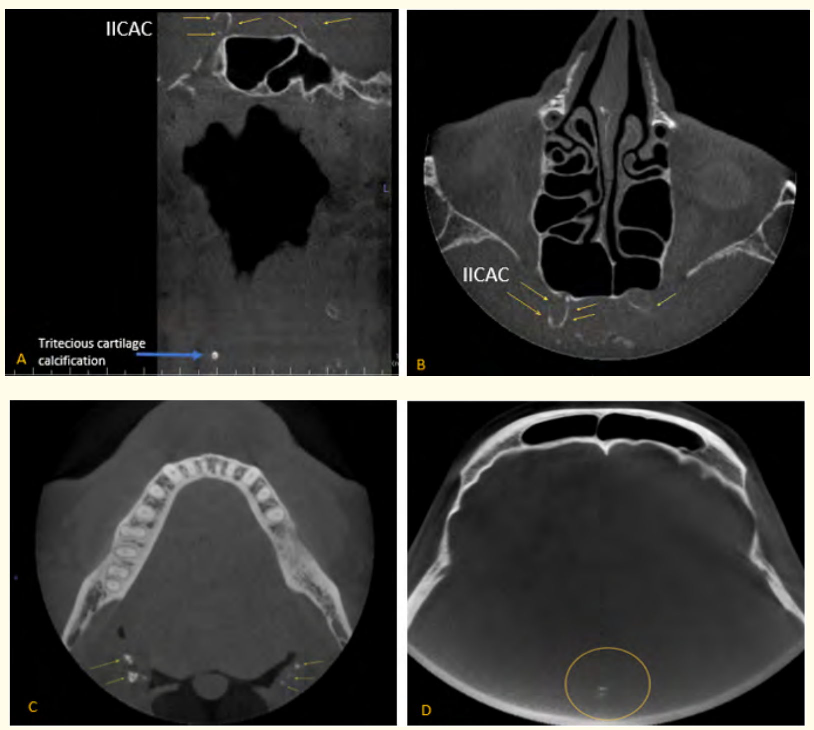

Figure 2: *CBCT sections. A) Coronal section: Yellow fine arrows in the Sella turcica region, point to the intracranial internal carotid artery calcification (IICAC), while the blue arrow in the soft tissue lateral to the right side of the oropharynx point to the calcified tritecious cartilage. B) Axial section, yellow fine arrows in the Sella turcica region, point to the intracranial internal carotid artery calcification (IICAC). C and D are axial sections with the yellow fine arrows in the oropharynx pointing to multiple, irregular shaped calcified structures bilaterally distributed in the oropharynx consistent with tonsilloliths and yellow ring encircling the pineal gland calcification respectively.*

Discussion

The use of CBCT in the dental setting has increased [8] and its application spans all dental specialties making these scans a minefield for data collation. IFs in CBCT scans are prevalent [10,15] and yet there is no extensive research into how such findings can identify bio sensitive markers that can be used in clinical practice to improve patient outcomes. These incidental findings relate to paranasal sinuses, dentition, temporomandibular joints (TMJs) and localized manifestations of diseases. The study conducted by Barghan., *et al*. [2] showed that large FOV CBCT studies may demonstrate a relatively high prevalence of IFs in the head and neck region and outside of the maxillofacial skeleton, which may or may not require referral to medical practitioners, follow-up with advance imaging or other diagnostic tests, and/or surgical or nonsurgical intervention [2]. It is important to keep diagnostic radiology skills current for dentists so they can correctly identify IFs that need further investigation [2,13]. It is also important to carefully evaluate the use of CBCT following the As Low As Reasonably Achievable (ALARA) principle, to weigh the risk of undetected incidental findings against radiation exposure [13].

In our study, a total of 12 different types of calcifications were noted. Among the noted calcifications, tonsiloliths (34%, figure 2C), pulp calcifications (54%) and vascular calcifications (IICAC (41%, figure 2A and 2B) and EICAC (29%) were the most prevalent. Our study did not report the presence of any calcifications to be significant to the cohort with diabetes. The high prevalence of tonsiloliths, pulp calcifications and carotid artery calcifications is supported by literature. Srivastava., *et al*. in their study, reported a high prevalence of pulp stones in the cardiovascular group followed by the group with diabetes in a Saudi Arabian population [21], this reinforces the need for more research into soft tissue calcifications and how it is associated with systemic conditions. Exploration into the pathophysiology of calcification may provide answers to why certain systemic conditions present a high prevalence of calcifications. Another study investigating the association between carotid artery calcification (CAC) detected incidentally on dental CBCT scans and positive diabetes status reported that 68 out of 288 patients with CAC had diabetes [16]. Whereas Yalcin., *et al*. reported that tonsiloliths (18.8%) were the most prevalent soft tissue calcification in their analysis of 1557 CBCT images [24].

Studies have shown the association between pulp stones and cardiovascular disease [9,17]. A high prevalence of pulp calcifications was observed in our study population with no statistical difference across the groups, this can be attributed to our patient sample consisting of predominantly older population. Bernick., *et al*. studied the pulp of noncarious teeth from individuals aged 15 to 75 years and noted that there is a progressive deposition of calcified masses that originate in the pulp in the aging process [4], indicating that increasing age is a factor in the pulp calcification process. Other studies have found hypercalcemia, gout and increase incidence of end-stage renal disease as pre-disposing factors to pulp calcification [20].

Interestingly, dystrophic calcifications were high in the control group of our study. Dystrophic soft-tissue calcifications occur in damaged or necrotic tissue. Zazzeroni., *et al*. report that dystrophic calcification has an inflammatory nature and is influenced by traditional cardiovascular risk factors [25]. Diabetes and cardiovascular disease share many risk factors including inflammation; therefore, it is important to study the prevalence of dystrophic calcifications in a larger sample size to explore its association with diabetes further. Another type of soft-tissue calcification observed to be higher in the control group was pineal gland calcification (Figure 2D). A systematic review and meta-analysis conducted by Belay and Worku studied the pooled prevalence of pineal gland calcification, stating that an increase in age, male sex, and white ethnicity increased the prevalence of pineal gland calcification [3]. Analyzing the prevalence of pineal gland calcification in relation to age within our study sample may provide valuable insights into similar associations. More research in this field is needed to identify similarities within patients presenting with pineal gland calcification.

Diabetes mellitus is a chronic metabolic condition resulting in hyperglycemia. Complications such as cardiovascular disease, impaired vision, kidney disease and diabetic angiopathy are associated with diabetes. Specifically, diabetes mellitus may also showcase other nonspecific symptoms including abnormal weight loss and fatigue [12]. The more information we have about individuals with diabetes, the more efficient and precise the evidence based medical care they can be offered. Among the US population overall in 2021, 29.7 million people of all ages had diabetes, 38.0% had prediabetes, and 22.8% had not received a diagnosis [6]. The population with pre-diabetes and undiagnosed diabetes will benefit from detection of sensitive biomarkers that can identify diabetic status prior to symptoms, as this will allow for implementation of preventive measures such as lifestyle changes earlier on in the disease process. Studies have shown positive correlation between presence of diabetes and calcifications [12,16,21], however, it is important to distinguish at this point that medial arterial calcification (MAC) is physiologically distinct from atherosclerosis and it is this variant that is reported with an association to diabetes, how be it in late complications of diabetes and end stage renal disease (ESRD). A study by Jennison., *et al*. comparing patients with and without diabetes demonstrated that vascular calcification in both the anterior and posterior blood vessels of the ankle is over 90% predictive of a diagnosis of diabetes [12]. There is a possibility of identifying calcifications that may have a statistically significant relationship with persons living with diabetes. Further studies need to be conducted to assess the potential of having radiographic biomarkers for early detection of diabetes which will subsequently aid to reduce the global burden by implementing preventive measures early.

Early diagnosis helps with the application of preventative measures such as lifestyle interventions and glucose lowering therapies to improve glycemic control and prevent complications [21]. CBCT, with 3-dimensional viewing and elimination of superimposed anatomical structures, provides a superior alternative to the diagnostic analysis while maintaining high resolution [16]. Soft tissue calcifications can be detected with panoramic radiographs; however, the 2-dimensional nature restricts localization, and evaluation of the bucco-lingual aspect and impact on vital structures. Contrastingly, CBCT can more accurately depict the anatomy of the head and neck with the ability for volumetric evaluation, which makes it preferable to be used in diagnosis [14]. CBCT capture of the maxilla, mandible and cranium for dental treatment planning such as implant placement, surgical dis-impaction, orthodontic analysis and more makes the prescribing physician liable for all anatomical regions captured within the field of view. Hence, detecting calcifications in such areas as the base of the skull is inevitable.

Our study analyzed medium to large CBCT scans of patients of PDM to evaluate for soft tissue calcifications, periodontal status, existing dental treatments, and bone and soft-tissue pathologies. We reported a high prevalence of tonsiloliths, pulp calcifications and vascular calcifications among our sample. The amount of pulp calcifications reported in the cohort with diabetes was higher (61%). Ultimately, a calcified pulp may become necrotic resulting in apical infection needing endodontic treatment or extraction. Further analysis to identify the association and cause of such calcifications is needed.

The limitations to our study include a small sample size. An analysis of a larger sample is needed to identify associations between underlying systemic conditions and the presence of soft-tissue calcifications. Further, our study only utilized CBCT scans obtained at PDM which have specific patient demographics.

A possible avenue for future research could involve categorizing subjects by calcification conditions and analyzing the prevalence of diabetes within each group to identify radiographic indicators of the disease. Potential associations between demographics, lifestyle factors such as smoking, alcohol consumption, and sedentary behavior as well as underlying medical conditions that may predispose individuals to soft-tissue calcifications should be explored in future studies. It is essential for dental clinicians to have strong radiographic diagnostic skills to detect IFs and make informed decisions regarding referrals to primary care providers or dental specialists; when in doubt, referral to the radiologist is advised. Moreover, staying up to date with literature on diabetes and related conditions is crucial to identifying sensitive radiographic markers for systematic disease conditions that may aid implementation of early preventative measures, thereby ultimately improving patient care and outcomes.

Conclusion

Our study demonstrated that vascular calcifications, tonsiloliths, and pulp calcifications are prevalent overall upon analysis of CBCT images taken in a dental setting. The prevalence of extracranial and intracranial internal carotid artery calcification was high among the study participants. Further analysis is needed to identify the association and cause of such calcifications. Identifying radiographic indicators for diabetes can facilitate the early implementation of preventive measures, thereby lowering morbidity and mortality rates and ultimately alleviating the global impact of this condition.

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Authors Contribution

Adeyinka F. Dayo: Contributed to conception and design of study, acquisition, analysis, and interpretation of data, drafted manuscript, critically revised manuscript and overall supervision.

Pankti Rana: Contributed acquisition, analysis, and interpretation of data, drafted manuscript, and critically revised manuscript.

Michael Mader: Contributed to design of study, analysis, and interpretation of data, and critically revised manuscript.

All authors gave their final approval and agreed to be accountable for all aspects of the work.

Conflict of Interest

Pankti Rana, Michael Mader and Adeyinka F. Dayo declare that there is no conflict of interest.

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Strobe Checklist

This study conforms to STROBE protocol.

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