RESEARCH ARTICLE

Association between extra- and intracranial calcifications of the internal carotid artery: a CBCT imaging study

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Objectives: This study aimed to evaluate the association between the extracranial and intracranial calcification depiction of the internal carotid artery (ICA), incidentally found in CBCT examinations in adults, and to discuss the conspicuous clinical implications.

Methods: Out of a series of 1085 CBCT examinations, 705 CBCT scans were selected according to pre-defined criteria. The extra- and intracranial calcifications depicted along the course of the ICA were documented according to a comprehensive set of descriptive criteria.

Results: In total, 799 findings were detected, 60.1% ($n = 480$) were intracranially and 39.9% ($n = 319$) were extracranially allocated. The χ^2 test showed associations between all variables ($p < 0.001$). Also, most of the combinations of variables showed statistically significant results in the McNemar's test ($p < 0.001$).

Conclusions: We found that a significant correlation exists between extra- and intracranial calcifications of the ICA. It is clear that in cases of the presence of a calcification in the ICA extracranially, the artery's intracranial portion has an increased risk of showing the same findings. CBCT imaging is widely used as a diagnostic tool, thus, our results contribute to the identification of a subgroup of patients who should undergo further medical evaluation of the atherosclerosis of the ICAs.

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Introduction

It is well documented that mural calcifications of the major arteries can be easily detected, and calcium deposits may be used as a marker of atherosclerosis.^{1–3} Its presence, in the form of calcified carotid plaque, was found to be an independent predictor of ischaemic cerebrovascular and cardiac events.⁴ Eventually, these mural calcifications easily appear in non-enhanced CT images.^{5–9}

The image quality of the visualization of atherosclerosis of the carotids, by CT, does not differ from those

of CBCT, although the overall subjective image quality is considered higher.^{10,11}

A plethora of studies in the dental literature documents the ability of commonly used dental radiographs—panoramic, cephalometric and CBCT—in depicting calcified carotid artery atherosclerosis. Yet, only few studies described and evaluated the ability of CBCT to depict the presence of these calcifications in both the extra- and intracranial course of the internal carotid artery (ICA).^{12–15}

Given that CBCT depicts these findings, it is useful to determine the association between the presence of extra- and intracranial calcifications within the ICA's course. Such a correlation, could highlight the clinical significance

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of the presence of arterial calcifications within the field of views commonly produced by CBCT, to determine whether similar findings coexist intracranially and, thus, to reduce the potential risk in dental patients. In our previous study, we found significant calcification frequencies in either the extra- or intracranial course of the ICA in CBCT scans.¹⁵ Therefore, we decided to conduct a new study with CBCT data of patients of a larger cohort, which could provide firm statistical support for the presence of correlation between the extra- and intracranial calcifications. We also based our premise on data showing that the presence of calcium within a vascular bed is indicative of a more extensive atherosclerotic burden.^{7,16,17} Consequently, this study aimed to evaluate the association between the extra- and intracranial calcification depiction of ICA that are incidentally found in CBCT examinations in adults and to discuss the conspicuous clinical implications.

Methods and materials

Subjects

In this study, subjects comprised a series of 1085 CBCT examinations recruited from the database of an imaging centre in Athens, Greece. These examinations were performed from October 2011 until October 2012 and pertained to adults primarily referred by oral and maxillofacial surgeons for (a) orthognathic surgery, (b) facial trauma, (c) placement of implants (complex cases, evaluated for both maxilla and mandible) and (d) control because of malignancy in their medical history records.

The following inclusion criteria were met: (a) subjects should be 40 years of age or older, (b) CBCT examinations had to be performed according to the maxillofacial protocol mode (full volume or large field of view) and (c) scans should be without movement and/or stripe artefacts. 35.0% ($n = 380$ out of 1085) of the examinations were excluded. In total, 705 CBCT data sets were finally enrolled, which were 65.0% of all the initially included subjects. Table 1 presents the selection criteria applied for the study's initial cohort. The age and gender of the samples were recorded; also, the identity of the patients was protected by codification.

Ethics

The Ethics and Research Committee of the National and Kapodistrian University of Athens, School of Dentistry,

Athens, Greece, approved our study's protocol (Ref.216/26.08.2013).

CBCT imaging

All the CBCT volumetric data sets were acquired with a NewTom™ VGi CBCT imaging unit (QR Srl, Verona, Italy), in 110 kV; 3.6 s; average, 19.1 mAs per patient. The volumetric reconstructions of these data sets (15×15 cm; voxel size of 0.3 mm) were created by using the manufacturer's proprietary software NewTom cone beam three-dimensional imaging, NNT v. 3.10 (QR Srl).

Image evaluation

The examiners evaluating the images were blinded with regard to the patients' social, medical and dental history data (clinical, histological and radiographic), since no prior individual information was obtained that might bias the examiners' opinion. The retrospective coevaluation of the volumetric data sets was performed by two (SD and KT) experienced oral and maxillofacial radiologists (OMFRs) by consensus. This was based on a series of criteria regarding the image analysis procedure, the consistency of findings within the image acquisition and the characteristics of the presence of these calcifications.

Specifically, the image analysis was standardized and performed by evaluating all the multiplanar reconstructions of each of the volume's data. The maximum intensity projection protocol was also used to assist the three-dimensional location and the extension of the findings.

A calcification was considered to be present when it was evident on a series of at least three sequential slices (axial and/or coronal and/or sagittal), that is, three times the axial slice thickness (3.0×0.3 mm = 0.9 mm), so that any false-positive finding, as a result of image noise or artefacts, could be avoided.

Radio-opacities depicted within the cervical portion of the artery, from the carotid bifurcation area until its entrance into the carotid canal, were considered to be extracranial calcifications of the ICA (usually referred as CACs). In more detail, in axial projections, they present as single or multiple "rice grains" with a homogeneous opacity and a linear or curvilinear shape. They are most commonly located in the cervical soft tissue, approximately 0–10 mm anterolaterally to the anterior tubercle of the transverse process; lateral or more often lateroposterior to the greater cornu of the hyoid bone; and always posterolateral to the pharyngeal airway space.¹⁸ In coronal projections, CAC depiction appears lateral to the anterior tubercle of the

Table 1 Selection criteria of subjects

Gender	Age		FoV		Presence of artefacts	Total
	≥ 40 years	< 40 years	Large	Other		
Male	417	99	321	96	6	315
Female	516	53	401	115	11	390

FoV, field of view.

The number of subjects in the "large FoV column" were the selected subjects from the " ≥ 40 years" group with a large FoV CBCT scan. The "Total" column represents the remaining subjects with a large FoV scan without artefacts.

cervical vertebrae. On the sagittal sections, CACs are identified medial and inferior to the angle of the mandible, lateral and mostly anterior to the cervical tubercle with their vertical position varying from C3 to C5¹⁸ (Figures 1 and 2).

Any similar radio-opacity depicted along the artery's intracranial course (from the ascending part of the petrous portion up to the cavernous portion) was recorded as an ICA calcification (ICAC). The aforementioned anatomical area of the ICA's intracranial course was thoroughly evaluated. This evaluation was performed by the use of multiplanar reconstructions along the petrous portion of the carotid canal in the temporal bone to the lacerum segment. This continued along the adjacent cavernous portion, where the artery is ascending towards the posterior clinoid process passage by the side of the body of the sphenoid bone, and again, curving upwards on the medial side of the anterior clinoid process.^{6,14} The S-shaped curve of the cavernous segment is called the "carotid siphon". Owing to its course, ICAC is shown as a characteristic oblique ring-like structure or "figure eight" (8)-shaped radio-opacity in coronal projections¹⁵ (Figures 1 and 2).

Statistical analysis

The presence or absence of the aforementioned findings was recorded, and the results (data) were primarily

evaluated with descriptive statistics. This was applied to our study cohort that was subdivided into five decade-based age categories, that is, 40–49, 50–59, 60–69, 70–79 and 80–90 years of age, for each gender. Additionally, the association of the presence of CACs and ICACs within the same CBCT data set in the total group was assessed with the use of the χ^2 and the McNemar's tests (SPSS® Statistics for Windows v. 20.0; IBM Corporation, Armonk, NY).

Results

In total, 705 CBCT data sets were evaluated retrospectively (390 females and 315 males). The patients' ages ranged from 40 to 90 years (mean, 60.22 years; standard deviation, 10.2 years).

A total of 799 calcifications were recorded, 480 (60.1%) were ICACs and 319 (39.9%) were CACs. The ICAC findings were either only left ($n = 44$) or only right ($n = 42$) sided, or bilaterally ($n = 197$) present. Accordingly, 59 CACs were found to be only left sided, 68 only right sided and 96 bilateral. The exact findings distribution within both genders and age categories is shown in Table 2.

We found an association between all variables, as shown by the χ^2 tests (all $p < 0.001$). The aforementioned association connotes that, when a CAC is evident, a strong

Figure 1 Extracranial internal carotid artery calcification (CAC) and intracranial internal carotid artery calcification (ICAC) of the internal carotid artery. (a) Axial projection: an oblique tubular/linear structure, extending laterally to the left anterior clinoid process present (arrow) and a "rice grain" appearance calcification laterally to the right posterior clinoid process (dotted arrow). (b) Coronal projection: extreme, linear, homogeneous radio-opacity, depicted medioposteriorly to the lower surface of the left and right anterior clinoid process (arrows). Right and left anterior clinoid process (dotted arrows). (c) Sagittal projection: "rice grain"-shaped and curvilinear masses depicted along the course of the internal carotid artery in the carotid siphon area (arrow). (d) Axial projection: multiple "rice grains", curvilinear (right) and linear (left), homogeneous radio-opacity-CAC (arrows). (e) Para-sagittal projection of the same patient; the radio-opacities are sited lateral to the C3–C4 vertebrae (arrow). (f) Para-coronal projection of the CAC (arrow). Note the proximity with calcified superior cornu of the thyroid cartilage to the CAC being posteroinferior. (g) Maximum intensity protocol three-dimensional reconstructed image (oblique rear projection) of the same patient disclosing the ICAC and CAC (arrows). Calcification of the pineal gland and habenula (dotted arrow).

possibility for an ICAC presence in the same data set exists. Also, most combinations of variables showed statistically significant results of the McNemar's test ($p < 0.001$), which indicates a difference in the proportion of CAC/L and ICAC/L; CAC/L and ICAC/R; CAC/R and ICAC/L; and CAC/R and ICAC/R. This means that for most combinations of variables the relative number of cases presented with calcification is not equal. Two of the combinations of variables showed no statistically significant results for the McNemar's test, that is, ICAC/L and ICAC/R, and CAC/L and CAC/R. This indicates an equal distribution of the presence of calcifications on the left and on the right side in the evaluated data sets. A summary of the outcomes of the statistical analysis is presented in Table 3.

Discussion

We aimed to evaluate the association between the extra- and intracranial depictions of the ICA calcifications

found in the CBCT examinations in adult patients and to discuss the apparent clinical implications. To the authors' knowledge, the association of both extra- and intracranial calcifications of the ICA, using CBCT data, has never been investigated before. The results of our study showed strong statistical evidence for the presence of ICACs in cases of CAC depiction (χ^2 tests; all p -value's < 0.001). This means that reasonable grounds exist for suspecting the presence of ICA calcifications intracranially in cases of analogous findings extracranially.

This connotes the significance to the OMFR profession of our results in adult patients, as these calcifications (mostly the extracranials) may fall within either the CBCT's field of view or in any other extraoral imaging modality that has been selected by an OMFR and/or a dentist.

To some extent, because the dental literature lacks similar studies, it is only possible to compare our results with those based on other imaging methods than CBCT. Furthermore, it was recently shown that the

Figure 2 The interrelatedness of the intracranial internal carotid artery calcification (ICAC) presence with the extracranial internal carotid artery calcification (CAC) depiction. (a) Axial projection: an oblique tubular structure (arrows) is shown, extending mediolateral to the anterior clinoid process. (b) Coronal projection: multiple, curvilinear, homogeneous radio-opacities (arrow). Note the characteristic oblique ring-like or “eight-shaped” radiopacity depicted lateroposteriorly to the lower surface of the anterior clinoid process (dotted arrow) and lateroanteriorly to the upper part of the “figure 8” more medioanteriorly (arrow). (c) Sagittal projection: “figure 8”-like and linear masses depicted along the course of the internal carotid artery (arrow). (d) Axial projection: a curvilinear (left), and a “rice grain”, curvilinear (right) homogeneous radio-opacity-CAC (arrows). (e) Parasagittal projection of the same patient; the radiopacities-CAC are located proximal to the C4 vertebrae (arrow). ICAC is also depicted (dotted arrow); (f) Maximum intensity protocol three-dimensional reconstructed image of the same patient disclosing the CAC (arrows) and ICAC (dotted arrows).

Table 2 The gender and age distribution of extra- and intracranial findings in this study's cohort

		Extracranial internal carotid artery calcification			Intracranial internal carotid artery calcification			
Age category (years)	Cases (n)	Only left	Only right	Bilateral	Only left	Only right	Bilateral	Total findings
Male								
40–49	51	2 (3.92%)	2 (3.92%)	2 (3.92%)	2 (3.92%)	1 (1.96%)	3 (5.88%)	17
50–59	100	10 (10.00%)	10 (10.00%)	12 (12.00%)	4 (4.00%)	10 (10.00%)	21 (21.00%)	100
60–69	111	14 (12.61%)	16 (14.41%)	26 (23.42%)	8 (7.20%)	7 (6.30%)	56 (50.45%)	209
70–79	40	5 (12.50%)	5 (12.50%)	15 (37.50%)	0 (0.00%)	2 (5.00%)	26 (65.00%)	94
80–90	13	1 (7.69%)	3 (23.07%)	6 (46.15%)	1 (7.69%)	1 (7.69%)	10 (76.92%)	38
Total	315 (44.68%)	32 (6.98%)	36 (7.86%)	61 (13.31%)	15 (3.27%)	21 (4.58%)	116 (25.32%)	458
Female								
40–49	61	1 (1.61%)	1 (1.61%)	0 (0.00%)	2 (3.27%)	0 (0.00%)	2 (3.27%)	8
50–59	129	7 (5.42%)	5 (3.87%)	6 (4.65%)	7 (5.42%)	9 (6.97%)	17 (13.17%)	74
60–69	122	8 (6.55%)	14 (11.47%)	9 (7.37%)	13 (10.65%)	6 (4.91%)	26 (21.31%)	111
70–79	65	7 (10.76%)	10 (15.38%)	16 (24.61%)	4 (6.15%)	6 (9.23%)	29 (44.61%)	117
80–90	13	4 (30.76%)	2 (15.38%)	4 (30.76%)	3 (23.07%)	0 (0.00%)	7 (53.84%)	31
Total	390 (55.32%)	27 (7.91%)	32 (9.38%)	35 (10.26%)	29 (8.50%)	21 (6.15%)	81 (23.75%)	341
Subtotals ^{M+F}		59 (7.38%)	68 (8.51%)	96 (12.01%)	44 (5.50%)	42 (5.25%)	197 (24.65%)	
Total ^{M+F}	705	319 (39.92%)			480 (60.07%)			799

M+F, number in males and/or females.

The percentages listed after the number of findings for each row in Table 2 refer to the number of findings per number of cases in that gender or age category.

presence of calcium in the thoracic aorta or carotid arteries is indicative of a more extensive atherosclerotic burden and may therefore be associated with the highest risk of morbidity and mortality.⁷ Furthermore, in a case–control autopsy study, patients with intracranial plaques presented more often with coronary atherosclerosis (plaques or stenosis), lacunar infarction and multilacunes, than did patients with stroke, but without intracranial plaques.¹⁶ Also, a meta-analysis of prospective studies gave evidence of an association between the presence of calcifications in any arterial wall and a three- to four-fold higher risk for cardiovascular events and death.¹⁷ Our results are considered similar to those provided by the literature, regarding the association of “fingerprint” of the extra- and intracranial ICA atherosclerosis presence, to that of different vascular beds.

The presence of arterial calcifications in an individual, either extra- or intracranially, is similar for both the left and right ICAs, as the results of the McNemar test showed. This connotes that the presence of CAC and/or ICAC in our study's cohort is a rather symmetrical finding. Our findings are similar to those of a study that suggested atherosclerosis of the human carotid arteries is generally a bilaterally symmetrical disease.⁹

One may argue that no correlation data concerning the age and gender parameters are provided in this study; but, the adequate data, regarding the influence of the age and gender in CBCT depiction, were examined in our previous study.¹⁵ Thus, we consider that our methodology, regarding the exclusive determination of association between the extra- and intracranial depiction of the ICA calcifications found in CBCT examinations in adult patients, was relevant.

The importance of CAC depiction was recently restated by a consortium of OMFRs and medical radiologists.¹⁹ Also more recently, the severity of the presence of ICAC—even as incidental finding—resulted in the highest recommendation for further evaluation.^{14,15,20} We believe that the results of our study contribute to this effort. In either case, the presence of a CAC or an ICAC on an image under evaluation represents the “tip of the iceberg” and a later manifestation of an already mature atheroma has been associated with a high risk of cerebral emboli. Their presence is also indicative for an existing underlying pathology, as this is often associated with coexisting risk factors in the at-risk population, such as patients presented with Type 2 diabetes, hypertension, smoking, hypercholesterolaemia, metabolic syndrome, history of cardiovascular disease, history of neck radiotherapy, menopause and advanced age.^{21–23}

Table 3 Synopsis of the statistical results of the variables

Combination of the variables	χ^2	df	p-value	McNemar test p-value
CAC ^{Left} /ICAC ^{Left}	111.247	1	<0.001	<0.001
CAC ^{Left} /ICAC ^{Right}	113.151	1	<0.001	<0.001
CAC ^{Right} /ICAC ^{Left}	110.509	1	<0.001	<0.001
CAC ^{Right} /ICAC ^{Right}	120.593	1	<0.001	<0.001
CAC ^{Left} /CAC ^{Right}	172.061	1	<0.001	0.474
ICAC ^{Left} /ICAC ^{Right}	379.801	1	<0.001	0.913

CAC, extracranial internal carotid artery calcification; df, degrees of freedom; ICAC, intracranial internal carotid artery calcification.

Their presence primarily delineates the diagnostic task in cases of a calcification presence within the lumen of ICA. It was recently confirmed that carotid siphon calcifications, along with advanced age and hypertension, represent risk factors for lacunar infarctions and that the degree of these calcifications may be used to predict future lacunar infarctions.²⁴ Given that the presence of extensive vascular calcification in the distal ICA on CT scans with “bone-level” windows suggests an intracranial stenosis >50%,² the ability of CBCT to disclose this kind of images with regard to their clinical significance is crucial.

However, the CBCT’s sensitivity, specificity, and positive- and negative-predictive values in the diagnosis of atherosclerosis remain to be investigated in future studies. Accordingly, the intra- and interobservers agreement regarding this calcification detection needs further evaluation. Unluckily, we evaluated the images acquisition by consensus, thus, such information is not provided in this study.

Our results depend only on the interpretation that outlines the borders between the calcifications and the skull. This implies the need to eliminate the “contamination” of bone attenuation on CBCT images produced by other calcified structures or pathological conditions. Based on this perspective, one might argue that these findings seem underestimated. However, CBCT is

inherently insufficient to provide quantitative calcium scores,^{18,25} and thus, it is not likely that it can provide the most accurate results, in contrast to the results of multidetector CT or electron-beam CT.^{2,3,21,24,25}

Conclusions

Our study documents a significant correlation between extra- and intracranial calcifications of ICA, as these are depicted in CBCT scans. We support that in cases of the presence of an extracranial calcification in the ICA, the intracranial portion is more likely to also show similar findings. As CBCT imaging is widely used as a diagnostic tool for the pre- and/or post-surgical assessment and evaluation of dental patients, our study indicates that the identification of these calcifications in CBCT volumes is essential. It may add to the early diagnosis of patients at risk, because dental patients form a subgroup that is completely different from patients usually seen by cardiologists or other medical specialists.

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