RESEARCH ARTICLE

Association of calcified carotid artery plaque in panoramic images and diagonal earlobe crease

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Objectives: Brazilians who are free of traditional atherogenic risk factors frequently suffer myocardial infarctions (MI). Calcified carotid artery plaque (CCAP) on panoramic images (PIs) has been shown to be a validated “risk indicator” of future MIs. The diagonal earlobe crease (DELC) is likewise a validated “risk indicator” of future MI. We sought to determine the prevalence of DELC+ among patients having CCAP+ on their PIs.

Methods: In a masked cross-sectional study, three dentists evaluated PIs of patients ($N = 481$) over age 55 for presence of CCAP+. Among the CCAP+ cohort, the presence of DELC+ was determined by two additional dentists masked to the presence of CCAP+ on PIs. A control group (CCAP-) comprised of individuals with PIs devoid of plaque was similarly evaluated for evidence of DELC+.

Results: A mixed-gender group (8.6%) of patients ($N = 41$; mean age 67.5 ± 6.8) evidenced CCAP+ on their PIs and approximately 88% of these individuals ($N = 36$) had concomitant DELC+. Among members of the control group ($N = 41$), 17 patients were DELC+. Our results demonstrated that among the full mixed-gender cohort ($N = 82$), the association between CCAP+ and DELC+ was statistically significant ($p = 0.0001$). However, when adjusting for gender, only the CCAP+ men were significantly ($p = 0.00011$) more likely to evidence DELC+ on clinical examination.

Conclusions: Males with atherosclerosis of their carotid arteries as evidenced by PIs displaying calcified atheromas are significantly more likely to evidence a DELC+ than those without an imaged atheroma.

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Introduction

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Atherosclerosis of the coronary and carotid arteries resulting in fatal myocardial infarctions (MIs) and strokes is a major public health problem in industrialized countries.¹ Many of these adverse events occur

Figure 1 A 70-year-old female patient with bilateral diagonal earlobe creases (DELC). Note the oblique wrinkle in the lobule portion of both auricles (arrows).

in individuals free of prodromal signs, symptoms and classical risk factors (*e.g.* hypertension and diabetes). This “detection gap” has spurred clinicians to assess specific extravascular physical findings (*e.g.* identification of xanthelasmas on the eyelid),² as well as routinely obtained diagnostic tests used for other purposes [*e.g.* identification of carotid artery atherosclerosis on panoramic and cone-beam computer tomography (CBCT)]^{3,4} in order to help identify persons with occult disease who would benefit from early diagnosis and therapeutic intervention.

Addressing this issue, an American pulmonologist (Sanders T. Frank) described how a number of patients in his practice manifested premature atherosclerosis of the coronary arteries while simultaneously displaying a deep diagonal ear lobe crease (DELC: Frank’s sign; Figure 1).⁵ DELC runs anteriorly-posteriorly from the tragus, diagonally backward to the edge of the auricle of the ear at approximately 45 degrees. Biopsy specimens of the furrow demonstrate pre-arteriolar wall thickening, degeneration of elastin, and tears in elastic fibers; a histopathologic display similar to that seen in ischemic coronary vessels.^{6–8}

Confirmation of this hypothesis was elaborated upon by Tranchesi *et al.*, a Brazilian cardiologist, who demonstrated that the prevalence of DELC was significantly higher in patients (irrespective of gender) with $\geq 70\%$ coronary artery stenosis identified by angiography, than among controls.⁹ The clinical correlate of these findings were demonstrated by Danish cardiologists who, for 35 years, followed almost 11,000 individuals initially free of ischemic heart disease (IHD).¹⁰ At the study’s termination it was determined that patients ($N = 1,465$), irrespective of gender, with DELC were at significantly increased risk of developing IHD (fatal or non-fatal MI, angina pectoris, need for revascularization procedure) independent of chronological age and well-known cardiovascular risk factors. Shrestha *et al.*, a Japanese neurologist, studied preoperatively screened carotid

Figure 2 The panoramic image of the same 70-year-old female patient (as in Figure 1) with a calcified carotid artery atheroma (arrow) visible below the right angle of the mandible. The atheroma appears on the image to be anterior to the interspace between C₃ and C₄ and posterior to the greater horn of the hyoid bone.

artery Doppler ultrasound studies obtained for patients with a prior history of cardiovascular/cerebrovascular disease noting that only male patients evidenced a significant correlation between DELC and atherosclerotic plaque.¹¹ Confirmation of the relationship between DELC and MI and stroke has been corroborated by clinical studies (enrolling a mixed-gender or predominantly male cohort) conducted in Finland,¹² Denmark,¹³ Japan,¹⁴ United Kingdom,¹⁵ Turkey,¹⁶ Sweden,¹⁷ China,¹⁸ Canada¹⁹ and by meta-analysis of 37 studies comprising almost 32,000 subjects which denoted that DELC is associated with cardiovascular disease having a sensitivity of 62% [95% CI (0.56–0.67)], specificity of 67% [95% CI (0.61–0.73)] and a diagnostic odds ratio of 3.27 [95% CI (2.47–4.32)].²⁰

These reports prompted an American oral and maxillofacial surgeon to conduct a pilot observational study which demonstrated that 9 of 10 consecutive neurologically asymptomatic patients (mean age 65) with calcified carotid artery plaque (CCAP) (Figure 2) on their PI manifested DELC (8 bilateral and 1 unilateral) upon clinical examination.²¹ The clinical correlate to this finding was established earlier by this same surgeon in collaboration with a neurologist by their study. They demonstrated that dental patients with CCAP on their PI were significantly more likely than vascular risk-matched controls, devoid of such lesions, to manifest an adverse cardiovascular event within a 3-year period of time.²²

Many Brazilians die from MI because of occult coronary artery disease.²³ The early identification and treatment of such individuals are crucial. Up until this point in time, only a rudimentary association between CCAP and DELC has been established, namely by the Friedlander *et al.* uncontrolled study, of which the results were reported in a Letter to the Editor²¹ and a short abstract²⁴ with a paucity of detail. Given these scientific shortcomings, we were prompted to design a prospective study to determine the prevalence rates of DELC among a cohort of both male and female Brazilian patients with atheromas on their (PIs). We hypothesized that the study would demonstrate that the prevalence

of DELC is significantly higher among individuals evidencing CCAP on their PIs than among a control group having an imaging study devoid of atheromas.

Methods and materials

The study was approved by the Ethical Committee of the School of Dentistry at the Pontifícia Universidade Católica do Paraná (PUCPR), and by the National Council of Ethics in Research, Brazil. During the study period (March 1, 2015–May 24, 2018) the Oral Radiology section of PUCPR examined 502 PIs of patients aged 55 and older. Of these, 481 qualified for enrollment based on meeting the study's PI quality criteria (not over or under exposed and extended bilaterally 2.5 cm inferior and 2.5 cm posterior to the cortical rim of the midpoint of the mandibular angle) (Figure 2). The senior author and two additional oral medicine specialists, trained and calibrated, reviewed all PIs. The final diagnosis of CCAP was established when at least two of the three examiners agreed. Confounding radiopacities frequently imaged in the area (that is, hyoid bone, epiglottis, stylomandibular ligament, stylohyoid ligament, calcified lymph nodes and triticeous cartilage, submandibular gland sialoliths, and phleboliths) were assessed and accounted for.²⁵ Individuals diagnosed with either unilateral or bilateral CCAP were assigned a designation of CCAP+. All PIs were taken using Orthopantomograph™ OP200D, 2,5 mm Al 85kV, (Instrumentarium Dental, Tuusula, Finland).

Subjects (CCAP+) were then referred to the Department of Stomatology for a clinical examination in order to determine the presence or absence of DELC by two additional oral medicine specialists, masked to the presence of CCAP. A control group of 41 patients whose PIs did not demonstrate atheromas (CCAP–) was likewise evaluated for the presence of DELC. The patients were examined in a dental chair positioned at an angle of least 45 degrees to avoid artefact.²⁶ To avoid misinterpretation of artifactual creases, patients with piercings in the lobule were excluded. The DELC was considered

present if there was an oblique (at approximately 45°) crease in the lobular portion of the auricle that extended 80% or more of the earlobe length and it measured ≥1 mm in depth^{27,28} (Figure 1). Individuals diagnosed with either unilateral or bilateral DELC were assigned a designation of DELC+.

Chi-square test was utilized to determine the significance of the relationship between CCAP and DELC. Given administrative and financial constraints, no other atherogenic risk data was collected.

Results

The screening population consisted of 481 individuals over age 55 having a technically adequate PI. There were 217 (45.1%) males (mean age 65 ± 7.1) and 264 (54.9%) females (mean age 63.1 ± 6.7). The study group (*N* = 41) comprised of CCAP+ individuals consisted of 28 males and 13 females. The control group (*N* = 41) comprised of CCAP– individuals consisted of 25 males and 16 females.

As can be seen in the Table 1, the mixed-gender study group of individuals (28 CCAP+ males and 13 CCAP+ females) were significantly (*p* = 0.00011) more likely to evidence DELC on clinical examination than those in the control group (25 CCAP– males and 16 CCAP– females). However, when the study group was subdivided by gender, only CCAP+ males were significantly (*p* = 0.00001) more likely to evidence DELC on clinical examination.

Discussion

The results of our study conducted among a mixed-gender cohort of community-residing Brazilian patients attending a dental school clinic demonstrated that a significant number of those individuals concurrently harbored two validated “risk indicators” of a future MI: one radiographic (CCAP+) the other dermatologic (DELC+). However, further analysis determined that

Table 1 Relationship between Calcified Carotid Artery Plaque (CCAP) and Prevalence of Diagonal Earlobe Crease (DELC)

Mixed gender (^a <i>N</i> = 82)	^a <i>N</i> (%)	^b DELC+ (%)	<i>p</i> value
‘CCAP+	41 (50.0%)	36 (87.8%)	0.00011
‘CCAP–	41 (50.0%)	17 (41.5%)	
Males (^a <i>N</i> = 53)			
‘CCAP+	28 (52.8%)	26 (92.9%)	0.00001
‘CCAP–	25 (27.2%)	9 (36.0%)	
Females (^a <i>N</i> = 29)			
‘CCAP+	13 (44.8%)	10 (76.9%)	0.13728
‘CCAP–	16 (55.2%)	8 (50.0%)	

^a*N* is subject count

^bDELC+, Positive for diagonal earlobe crease.

‘Study Group: CCAP+, positive for calcified carotid artery plaque.

‘Control Group: CCAP–, negative for calcified carotid artery plaque

only males with CCAP+ were significantly more likely to evidence DELC+ on clinical examination.

We hypothesize that the rationale behind the high prevalence rate of DELC in CCAP+ patients is due to the underlying principle that atherosclerosis is a systemic disease. Histopathologic evaluations of biopsied DELC tissue, when compared to carotid artery endarterectomy specimens obtained from patients evidencing CCAP on their PIs,²⁹ similarly evidenced atherosclerotic-like changes.⁶⁻⁸

In this cross-sectional study of older Brazilian male and female patients, the primary outcome was the significant association between CCAP+ on PIs and DELC, a cutaneous “risk indicator” of adverse vascular events. The present study thereby confirms the linkage of these two “risk indicators” as described in Friedlander’s study which was conducted among an exclusively North American Caucasian male cohort and demonstrated that 90% of individuals with CCAP+ on their PI manifested DELC.²¹ Further substantiation of this linkage was provided by other American oral and maxillofacial surgeons who, in a controlled study, reported that 60% of patients (gender specific data not provided) with CCAP on either their PI or on CBCT evidenced DELC, whereas in the control group this dermatologic sign was not observed.²⁴

Prior research studies have separately validated the construct that the presence of CCAP on a PI and DELC on clinical examination herald future adverse cardiovascular events. Specifically, a dentist and a neurologist in an earlier controlled cohort study followed a group ($N = 46$) of male patients (mean age 68) with CCAP on their PI for an average follow up period of 3.6 years.²² During this time period, they reported that adverse vascular events from coronary artery and carotid artery atherosclerosis became clinically evident including angina requiring hospitalization, need for coronary artery revascularization surgery, non-fatal MI, stroke and transient ischemic attack. These occurrences were significantly more common among the study patients than among controls. Similarly, in another prospective clinical study of newly admitted hospitalized patients ($N = 108$), matched for sex, race, and age, with at least one DELC but free of known coronary artery atherosclerosis, were followed for an 8- to 10-year period. The

authors reported that cardiac event rates (cardiac death, nonfatal MI, need for coronary artery by-pass surgery) for those with DELC were significantly higher (10.4 events per 100 patients-years) than for those without DELC (1.4 events per 100 patients-years).³⁰

Our study had strengths and weaknesses. Specifically, to the best of our knowledge, this study is the first to report the association between PIs demonstrating CCAP and DELC, the dermatologic predictor of future MI in a South American population. This is uniquely consequential given that 50% of males and 64% of females die of sudden adverse cardiovascular events without having prior classical symptoms or established traditional risk factors, which would have identified them as being a member of a high-risk group.³¹⁻³³ However, our study does have certain limitations. It evaluated a small sample size in a single center, which may not reflect the general population given that we did not obtain nor record ethnic data from our cohort, whereas prior research efforts have demonstrated that racial identity influences DELC prevalence rates.³¹ We do however concede that while more research in this area is indicated, our results confirms the ability of dental healthcare professionals to identify individuals harboring validated high “risk indicators” of future adverse cardiovascular events. An assessment that is easily accomplished during initial evaluation by concurrently reviewing the patient’s panoramic imaging for CCAP and their earlobes for DELC.

Conclusion

We conclude that DELC is more often seen in male patients evidencing CCAP on their PI than in those free of observed atheromatous disease, which should alert providers of their associated significant risk for future adverse cardiovascular events. This finding is consistent with the systemic effects of atherosclerosis, more acutely seen in males rather than in females. While the clinical significance of the simultaneous appearance of these two signs requires further substantiation in large multi-center trials, it remains prudent to refer individuals (of either gender) with one or both of these previously validated “risk indicators” (CCAP+ or DELC+) for further medical evaluation.

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