Prevalence of calcified carotid artery atheromas on the panoramic images of patients with syndrome Z, coexisting obstructive sleep apnea, and metabolic syndrome

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Objectives. The objective of this study was to compare the prevalence of calcified carotid artery atheromas (CCAAs) on panoramic images of individuals (n = 31) with obstructive sleep apnea (OSA) with individuals (n = 117) with syndrome Z (SZ: OSA with concomitant metabolic syndrome [MetS]).
Study design. Images of patients with OSA or SZ referred from the Sleep Service to Dentistry were evaluated. Descriptive statistics and *t* tests (Bonferroni correction) were conducted to determine significant differences between atheroma prevalence and proatherogenic factors (age, apnea-hypopnea index, body mass index, lipid profile, blood pressure, glucose) between OSA and SZ groups.
Results. Individuals with OSA had an atheroma prevalence of 35% and those with SZ 42% ($P = .52$). Individuals with SZ also had significantly more severe atherogenic profiles (obesity, dyslipidemia, hyperglycemia) than OSA patients ($P \leq .05$). Greatest CCAA prevalence (63%) was evidenced by SZ patients with severe OSA and moderate MetS.
Conclusion. Individuals with SZ have significantly greater atherogenic burden and slightly higher prevalence of CCAAs when compared with individuals with OSA. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:134-141)

The obesity epidemic sweeping the United States has resulted in a significant number of these obese individuals developing obstructive sleep apnea (OSA).[1] The disorder is most often seen in persons with an upper airway narrowed by parapharyngeal fat deposits and is characterized by recurrent episodes of absent (apnea) or diminished airflow (hypopnea) owing to loss of pharyngeal tone, resulting in obstruction during sleep despite persistent respiratory effort. Approximately 20% of American adults have mild OSA, defined as 5 or more apneas plus hypopneas per hour of sleep (i.e., the apnea-hypopnea index [AHI] ≥5) and 7% have moderate to severe OSA (AHI ≥15).[2]

The obesity epidemic has also resulted in the development of metabolic syndrome (MetS). MetS is the concurrence of multiple metabolic abnormalities associated with the development and progression of atherosclerosis. It is typified by the clustering of 3 to 5 quantitatively defined risk markers that include obesity signified by increased body mass index (BMI), dyslipidemia, hypertension, and hyperglycemia. The prevalence rates of MetS among men and women (ages ≥20 years) are 33.7% and 35.4%, respectively.[3]

Individuals having either OSA or MetS are at high risk of suffering an adverse cardiovascular event because of the associated proatherogenic elements. Contemporaneous epidemiologic studies have noted that these illnesses are responsible for more than 38,000 yearly deaths from myocardial infarction (MI) and stroke.[4-6] Recently it has been determined that an unknown number of Americans simultaneously have both diseases, with the illness termed Syndrome Z (SZ).[7] The proatherogenic elements harbored by individuals having these combined illnesses places them at even

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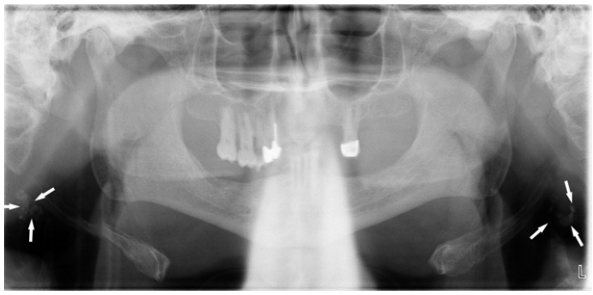

Fig. 1. A panoramic radiograph digitally enhanced with the manufacturer provided software evidencing bilateral carotid artery atheromas (*arrows*). Note the globular and vertical opacities on the patient's right just inferior to the greater horn of the hyoid bone, and in a similar location on the left note the semicircular opacity. The patient, a 63-year-old man, was diagnosed with moderate OSA and mild MetS (SZ) by the Sleep Medicine Service using overnight polysomnography (AHI = 20.2), clinical examination, and laboratory data (BMI = 36.2).

greater risk of succumbing to adverse cardiovascular events.[8]

In 2010, the American Academy of Sleep Medicine issued a Practice Parameters statement, which concluded that certain groups of patients with OSA who were intolerant to positive airway pressure could be effectively treated by fabrication of oral appliances or maxilla-mandibular advancement.[9] Diagnostic procedures to determine how best to perform these dental interventions almost always require obtaining a panoramic radiograph. These images also have the capability of demonstrating calcified atherosclerotic lesions (atheromas) of the carotid artery (Figure 1).[10,11] Medical and dental researchers have previously demonstrated that these atheromas are surrogate markers of coronary artery atherosclerosis and an independent sign heralding future myocardial infarction and stroke.[12-14]

A previous study evaluated the panoramic radiographs (analogue) of 54 patients with OSA for the presence of atheromas and noted a 22% prevalence[15]; however, it was conducted before the use of digital radiography with image-enhancing capabilities (i.e., altering brightness, contrast, and magnification) and before the medical profession's recognition that some of these individuals may have had occult MetS also and therefore in fact had SZ.[16,17] It was decided to revisit this issue by segregating patients solely with OSA from those with SZ and determining the prevalence rates of calcified carotid artery atheromas (CCAAs) on the digital images of each group of individuals. The hypothesis was that those with SZ would have a greater prevalence of CCAAs on their images compared with those with OSA alone.

MATERIALS AND METHODS

Patients studied

After receiving institutional review board approval for the study, the Medical Center's comprehensive electronic medical record system was queried and the chart of every patient referred to the dental service for treatment of OSA by the Sleep Medicine service between July 1, 2007, and June 30, 2010, was retrieved, yielding a total of 490 patients. Each of these charts was reviewed by one of the authors (J.T.) to determine the patient's eligibility to be enrolled into the study. Inclusion criteria were the following: (1) a diagnosis of OSA by the Sleep Medicine Service in which the AHI was 5 or more events per hour of electroencephalographic sleep based on either a full, attended, overnight sleep study in the Veterans Affairs sleep laboratory using polysomnography or a multichannel home sleep test and a patient complaint of excessive daytime sleepiness[18]; (2) a digital panoramic image of diagnostic quality. Exclusion criteria included: (1) being of female gender given the paucity of such individuals in the Veterans Affairs system, (2) individuals diagnosed as having OSA at another institution, (3) laboratory data that were not recorded within 1 year before the sleep study, (4) evidence of calcified submandibular or cervical lymphadenopathy on which single or multiple nodes were described on palpation as being "hard and movable" on either the head and neck component of the physician's physical examination or the dentist's maxillofacial examination. Based on these criteria, the final analytical sample consisted of 216 patients.

For each patient in the analytical sample, the following data elements were abstracted from the medical record: age, AHI, BMI, triglycerides, high-density lipoprotein (HDL), blood pressure (BP) readings, and fasting serum glucose values.

The data were first analyzed to classify patients into OSA severity levels based on the AHI as follows: (1) mild: AHI 5 to 14, (2) moderate: AHI 15 to 30, and (3) severe: AHI of 31 or higher.[19] Apnea was defined as the complete cessation of airflow, and hypopnea was defined as a discernable reduction in airflow for 10 seconds or more accompanied by a decrease in oxygen saturation of at least 4%.

Criteria for diagnosing MetS in the analytical sample were based on recommendations proposed by the Adult Treatment Panel III (ATPIII),[20] with later modification of the serum glucose level by the American Heart Association.[21] The diagnosis was established when 3 of the 5 following risk markers or medications to control them were evidenced: (1) BMI of 30 kg/m^2 or higher, (2) triglycerides of 150 mg/dL or higher, (3) HDL 40 mg/dL or lower, (4) hypertension: systolic BP of 130 mm Hg or higher or diastolic BP of 85 mm Hg or

higher, (5) insulin resistance defined as fasting serum glucose of 100 mg/dL or higher. The severity of each patient's MetS was categorized by summing the number of risk markers evidenced. The presence of 3 risk markers was deemed mild MetS, 4 was deemed moderate MetS, and 5 was termed severe MetS.[22] Note that we replaced the ATPIII recommended waist circumference measurement of 102 cm or larger with a BMI value based on the recommendations of the World Health Organization[23] and the American Association of Endocrinologists[24] because of its ready clinical availability and simplicity as well as studies showing that using BMI has the same identification and prognostic values as waist circumference.[25,26] Those individuals having 3 or more metabolic risk markers and an AHI greater than 5 were assigned a diagnosis of SZ.

Of the 216 patients initially enrolled, there were 148 panoramic images that were of satisfactory quality (not over- or underexposed) and demonstrated an area of interest that extended 2.5 cm inferior and 2.5 cm posterior to the cortical rim of the midpoint of the mandibular angle. The senior author (A.H.F.) reviewed each radiograph by altering the brightness, contrast, and magnification to determine the presence or absence of atheroma(s) in this area of interest using previously published criteria.[27] Confounding radiopacities frequently imaged in the area (i.e., hyoid bone, epiglottis, stylomandibular ligament, stylohyoid ligament, calcified triticeous cartilage, submandibular gland sialoliths, and phleboliths) were excluded by their appearance. Individuals identified with atheroma(s) were assigned a designation of "present" as opposed to "absent." This investigator was masked as to which cohort (OSA vs SZ) each digital image belonged (Figure 1).

Table I. Patient characteristics (n = 148)

	OSA (n = 31)	*Syndrome Z (n = 117)*	*P value (Bonferroni)*
Age, y			.2707
± SD	56 ± 12	61 ± 12	
Range	30–82	26–91	
Body mass index (kg/m^2)			.0003
± SD	28 ± 3	32 ± 6	
Range	22–39	21–50	
Apnea-hypopnea index, events/h			1.0000
± SD	26 ± 19	26 ± 18	
Range	5–81	5–101	
Triglycerides, mg/dL*			.0440
± SD	113 ± 67	169 ± 106	
Range	39–298	39–677	
HDL-C, mg/dL*			.0369
± SD	45 ± 13	38 ± 11	
Range	22–75	20–92	
Systolic blood pressure (mm Hg)†			1.0000
± SD	126 ± 14	125 ± 14	
Range	105–176	94–186	
Diastolic blood pressure, mm Hg†			1.0000
± SD	76 ± 9	74 ± 10	
Range	56–91	42–99	
Fasting glucose (mg/dL)‡			.0130
± SD range	96 ± 23	124 ± 46	
Range	53–175	78–366	

OSA, obstructive sleep apnea; *HDL-C*, high-density lipoprotein-cholesterol.
*Results acquired while individuals were receiving dyslipidemic medications.
†Results acquired while individuals were receiving antihypertensive medications.
‡Results acquired while individuals were receiving antihyperglycemic medications.

Data analysis

De-identified data were entered into an electronic spreadsheet and checked for accuracy before importing the file into statistical software for analysis. Descriptive statistics were run to assess univariate measures of central tendency and dispersion of age and the clinical variables for the sample as a whole, and by OSA versus SZ groupings. To determine whether age and the clinical variables were significantly different between individuals with OSA and individuals with SZ, *t* tests for independent groups, corrected for multiple tests (Bonferroni; SAS procedure MULTTEST), were used. Chi-square analysis was used to evaluate the relationship between atheromas and presence of OSA and SZ. Cross tabulations and chi-square analyses were conducted to determine the prevalence of atheromas by OSA severity levels. Finally, cross-tabulations were run to assess the distribution of atheromas by OSA severity and number of metabolic syndrome risk markers. Analyses were conducted using PASW Statistics version 18 (release 18.0.0 2009, IBM Corporation, Somers, NY) and SAS version 9.1 (SAS version 9.1. SAS Institute Inc., Cary, NC).

RESULTS

The study group consisted of 31 individuals with OSA and 117 with SZ (Table I). Those with SZ were approximately 5 years older ($P = .27$) and evidenced significantly greater obesity, dyslipidemia, and hyperglycemia than those with OSA. Individuals with SZ evidenced atheromas (Figure 2) on their panoramic images more frequently (49/117, 42%) than individuals with OSA (11/31, 35%); however, this difference was not statistically significant ($P = .52$).

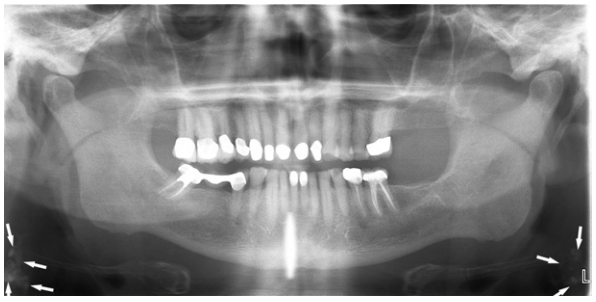

Fig. 2. A panoramic radiograph digitally enhanced with the manufacturer provided software evidencing bilateral carotid artery atheromas (*arrows*). Note the multiple globular contiguous opacities that lie adjacent to and for the most part inferior to the greater horn of the hyoid bone. The patient, a 68-year-old man, was diagnosed with severe OSA and moderate MetS (SZ) by the Sleep Medicine Service using overnight polysomnography (AHI = 48.8), clinical examination, and laboratory data (BMI = 33.4).

Individuals with OSA were equally distributed among severity levels (Table II). Counterintuitively, and without ready explanation, those with mild OSA manifested the highest prevalence (55%) of CCAA on their images, but this difference was not statistically significant ($P = .19$).

Among the individuals with SZ, most (57%; 67/117) had mild MetS irrespective of OSA severity level (Table III). The largest group (n = 29) of patients had both mild OSA and mild MetS. In this group of patients, 10 (35%) of the 29 had CCAA. As the severity of OSA increased among individuals with mild MetS, the prevalence of CCAAs increased linearly from 35% to 50%. Individuals having the severe form of OSA and concomitant moderate MetS manifested the highest prevalence (63%) of atheromas.

DISCUSSION

In the United States, the first and third most common causes of death (myocardial infarction and ischemic stroke, respectively) are almost always the result of atherosclerosis and thus explains the relevance of our findings.[28] Specifically, in this study we determined that (1) individuals having comorbid OSA and MetS, that is SZ, have a greater prevalence of calcified carotid artery atherosclerotic lesions on their panoramic images than individuals solely with OSA; (2) individuals with SZ have significantly more severe atherogenic profiles (obesity, dyslipidemia, hyperglycemia) than individuals solely with OSA; and (3) more than half of individuals with SZ having both severe OSA and moderate MetS have CCAAs on their panoramic images. These findings are consistent with a study by Drager et al.,[29] who, using ultrasound to evaluate the carotid artery in the bifurcation region, noted that individuals with SZ had a prevalence of atherosclerotic plaque that was almost twice (10.0% vs 19.6%) as common as those having solely MetS. Drager et al.'s observations,[29] like those in our study, likely result from the additive proatherogenic effect present in individuals having both OSA and MetS.

Table II. Distribution by severity level of individuals (n = 31) with OSA and of calcified carotid artery atheromas on the panoramic images

Severity of OSA	*No. of individuals*	*Prevalence of atheromas*
Mild (AHI 5-14)	11	6*/11† (55%‡)
Moderate (AHI 15-30)	10	2*/10† (20%‡)
Severe (AHI ≥31)	10	3*/10† (30%‡)

OSA, obstructive sleep apnea; *AHI*, apnea-hypopnea index.
*Number of individuals classified as having atheroma(s).
†Total number of individuals within OSA severity level.
‡Proportion of individuals with atheroma within OSA severity level.

In earlier studies of patient populations with OSA, calcified atheromas have been visualized in the carotid artery on cephalometric radiographs[30] and also in the coronary artery on electron beam computerized tomography[31] and 3-dimensional intravascular ultrasound.[32] Given the medical profession's relatively recent understanding of the relationship between OSA and MetS, however, it may be assumed that some of the individuals enrolled in the 3 previously cited studies had the combined entity, namely SZ.

OSA and associated atherogenic mechanisms

Chronic intermittent hypoxia (IH) (decrement in blood oxygen saturation) caused by OSA-associated apneic and hypopneic events stimulates carotid chemoreceptors to activate the sympathetic nervous system (SNS) and release norepinephrine.[33] The norepinephrine causes vasoconstriction in the peripheral vascular bed, resulting in a surge in blood pressure, which causes hypertension that damages the blood vessel's lining and walls fostering atheroma formation.[34] The repetitive process of IH alternating with rapid reoxygenation/reperfusion is responsible for the excessive production of reactive oxygen species (ROS; oxidative stress) that react negatively with nitric oxide produced by vascular endothelium, preventing the expected homeostatic dilatation response and thereby furthering vessel wall damage and atheroma development.[35,36]

ROS also increase expression of transcription factors, such as nuclear factor kappa, which upregulate the production of proinflammatory cytokines, such as C-reactive protein.[37,38] Synergistically, the transcription factors and cytokines upregulate the production of chemoattractant protein and adhesion molecules that facilitate the recruitment and accumulation of monocytes

Table III. Distribution of calcified carotid artery atheromas on the panoramic images of patients with syndrome Z (n = 117) relative to severity level of OSA and MetS

	Severity of metabolic syndrome by number of RMs		
Severity of OSA	*Mild (RM 3) (n = 67)*	*Moderate (RM 4) (n = 35)*	*Severe (RM 5) (n = 15)*
Mild (AHI 5-14) (n = 39)	10[a]/29* (35%†)	3‡/6* (50 %†)	2‡/4* (50%†)
Moderate (AHI 15-30) (n = 37)	8‡/22* (36%†)	5‡/13* (39%†)	0‡/2* (0 %†)
Severe (AHI ≥31) (n = 41)	8‡/16* (50%†)	10[a]/16* (63%†)	3‡/9* (33%†)

OSA, obstructive sleep apnea; *MetS*, metabolic syndrome; *RM*, risk marker; *AHI*, apnea-hypopnea index.
*Total number of individuals within OSA / MetS severity level.
†Proportion of individuals with atheroma within OSA/MetS severity level.
‡Number of individuals with atheroma(s).

and platelets onto the endothelial surface.[39-41] Adherence of the monocytes to the damaged and dysfunctional endothelium enables their entrance into the vessel wall where they are transformed into macrophages. The macrophages then take up the oxidized (promoted by ROS) low-density lipoprotein (LDL), leading to foam cell formation. Simultaneously, platelet-derived growth factor causes hypertrophy of vascular smooth muscle cells, which likewise accumulate oxidized lipids.[42] These noted processes result in the development of atherosclerotic lesions in the carotid artery and often even more advanced lesions in the coronary arteries.[43]

Atherogenic mechanisms associated with MetS in conjunction with OSA (SZ)

Hyperglycemia, one of the key elements in MetS, arises in part from insulin resistance, which is defined as insulin producing less than the expected biological effect. This hyperglycemic state is worsened by the OSA hypoxia activation of the SNS resulting in the release of catecholamines that increase glycogen breakdown, induce gluconeogenesis, decrease insulin sensitivity, and reduce insulin-mediated glucose uptake. The previously formed ROS elicit release of tumor necrosis factor alpha, which inhibits glucose uptake and the storage of free fatty acids (FFA) by the adipocytes within the abdominal adipose tissues.[44] Thus hampered, the adipocytes release large amounts of FFA into the systemic circulation.[45] Muscle cells take up much (but not all) of the FFA, but as they become glutted with FFAs, they also become insulin resistant. With the muscle cells unable to adequately uptake glucose, hyperglycemia is further exacerbated and, in response, the beta cells of the pancreases are stimulated and produce additional insulin (hyperinsulinemia).[46] The residual FFA that was unable to be absorbed by the muscle cells is diverted to the liver via the portal vein where it stimulates the synthesis, assembly, and secretion of lipoproteins that promote atherogenesis (raised triglycerides, low concentrations of HDL cholesterol, and small, dense LDL cholesterol).[47-49] Hypertension is now reinforced in the SZ state by a number of other mechanisms, including hyperinsulinemia stimulation of SNS,[50] overabundance of FFAs that exert a constrictive effect on blood vessels,[51] and impairment of insulin's usual vasodilatory effect.[52] Furthermore, as previously noted, hypertension disrupts the integrity of the endothelial lining of the coronary and carotid blood vessels, permitting ingress of elements associated with atheroma development.[53]

DENTAL IMPLICATIONS

The results of our study suggest that dentists should carefully review panoramic images for the presence of CCAA when patients present for treatment of OSA. This effort is critically important because in a previous study of neurologically asymptomatic males older than 50 without SZ, 23% of individuals with ultrasound-confirmed CCAAs had hemodynamically (≥50%) significant stenosis in the carotid bulb or internal carotid artery.[54] In addition to the stroke-causing potential of hemodynamically significant lesions, the mere presence of any-sized calcified atheroma on panoramic images has great prognostic significance. Specifically, in another previous control study it was demonstrated that CCAAs were true independent markers of elevated vascular risk often heralding near-term (<3 years) MI, need for coronary artery revascularization surgery, hospitalization for intractable angina, transient ischemic attack, and stroke.[14]

The prognostic implications of carotid artery atherosclerotic plaques on panoramic images established by these earlier investigations are consistent with a number of B-mode ultrasound studies that have likewise shown that these plaques are a very strong predictor of future adverse cardiovascular/cerebrovascular events. The Tromsø Study conducted among 6179 Norwegians (mean age 60) demonstrated that the adjusted relative risk (RR; 95% confidence interval [CI]) for first-ever MI between the highest carotid plaque tertile versus no plaque was 1.56 (1.04-2.36) in men and 3.95 (2.16-7.19) in women.[55] The CAFES-CAVE study conducted among 10000 Italians

(6055 males, 3945 females; mean age 53.2) substantiated that the presence of both nonstenotic and stenotic plaques in the carotid bifurcation identified subjects at moderate and high risk of future nonfatal and fatal cardiovascular events.[56] Similarly, the Kuopio, Finland, Ischemic Heart Disease study of 1288 men (between ages 42 and 60) demonstrated that carotid bulb plaque was a major risk factor for nonfatal and fatal MI in men with nonstenotic and stenotic plaque 4.15 (95% CI, 1.51-11.47; $P < .01$) and 6.71 (95% CI, 1.33-33.91; $P < .01$), respectively, when compared with men free of any structural changes in the carotid wall.[57] Likewise, the Northern Manhattan carotid artery ultrasound study of 1118 stroke-free multiethnic subjects (59% women, mean age 68) substantiated the fact that those with calcified carotid artery plaque in comparison with those without, had a significantly increased risk of combined adverse vascular outcome (ischemic stroke, MI, or vascular death) (hazard ratio 2.5, 95% CI, 1.0-5.8).[58]

Several methodological issues should be considered in the interpretation of our study results. First, the data were collected retrospectively rather than prospectively. Second, we had to adapt the ATPIII definition of the MetS to the data elements available in our local medical center's records. Specifically, we used obesity as defined by BMI as a proxy for central obesity, which is classically identified by waist measurement. This alteration may have classified some patients with obesity who did not have abdominal obesity, or missed some patients with central obesity, as this is not always captured by a high BMI. In addition, our findings are based on a male population in one Veterans Affairs health care system and cannot be generalized to the US population or to women. Finally, although the sample size for the OSA group was limited, post hoc power analysis of the primary variables related to classically identified major atherogenic risk factors yielded power of 71% to 99% to detect a change of 30% in fasting glucose level, 20% change in BMI, a 20% decrease in HDL, and 15% changes in blood pressure.[59] For triglycerides, a change from 113 to 180 (59%) would yield a power of 71%. These power estimates were made using alpha levels corrected for multiple comparisons.

In summary, our research has identified a very high prevalence of atherosclerotic lesions on the panoramic images of a cadre of patients presenting for dental treatment of OSA. A large number of these individuals also had MetS, qualifying them for a diagnosis of SZ. This latter group of individuals had an even greater prevalence of CCAAs on their images. CCAAs have previously been shown to herald adverse cardiovascular and cerebrovascular events, and, therefore, the findings in this most recent study are consistent with epidemiologic studies that have shown that this group of individuals is at uniquely high risk of future MI and stroke.

In conclusion, the dental profession must be prepared to assist in the management of a new cadre of high-risk patients and recognize that one of its most frequently used diagnostic tools may identify a preclinical indicator of future adverse cardiovascular events. It is therefore incumbent on the profession to be uniquely vigilant for the presence of CCAAs when evaluating the panoramic images of patients with sleep-disordered breathing and if a lesion is identified, refer the individual back to his or her physician with a detailed note describing the findings.

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