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內文：

Objectives.

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])

Introduction

A significant number of obese individuals developing obstructive sleep apnea (OSA).

1. Upper airway narrowed by parapharyngeal fat deposits
2. Recurrent episodes of absent (apnea) or diminished airflow (hypopnea)
3. Approximately 20% of American adults have mild OSA ([AHI] >5)
   7% have moderate to severe OSA (AHI >15).

[AHI]the apnea-hypopnea index

The obesity epidemic has also resulted in the development of metabolic syndrome (MetS).

[MetS] --concurrence of multiple metabolic abnormalities associated with the development and progression of atherosclerosis

increased body mass index (BMI)

dyslipidemia,

hypertension, and hyperglycemia

Individuals having either OSA or MetS are at high risk of suffering an adverse cardiovascular event.

Recently it has been determined that an unknown number of Americans simultaneously have both diseases, with the illness termed Syndrome Z (SZ).

In 2010, the American Academy of Sleep Medicine

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

Diagnostic procedures→ panoramic radiograph→ demonstrating calcified atherosclerotic lesions

(atheromas) of the carotid artery

atheromas→ coronary artery atherosclerosis+ (future) myocardial infarction and stroke

A previous panoramic radiograph study: 22% of 54 patients with OSA have presence of atheromas
…but some of these individuals may have had occult MetS also and therefore in fact had SZ
→prevalence rates of calcified carotid artery atheromas (CCAAs)

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
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

● Inclusion criteria :
1. a diagnosis of OSA 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 sleepiness18;
2. a digital panoramic image of diagnostic quality.

● Exclusion criteria included:
1. being of female gender given the paucity of such individuals in theVeterans 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.

●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.

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

● Criteria for diagnosing MetS in the analytical sample were based on recommendations proposed by the Adult Treatment Panel III (ATPIII), (3 of the 5)
1. BMI of 30 kg/m2 or higher,
2. triglycerides of 150 mg/dL or higher,
3. HDL 40mg/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.

(3 risk factor→: mild MetS,
4 risk factor → moderate MetS,
5 risk factor → severe MetS)

● 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

Data analysis

1. De-identified data
2. statistical software for analysis
3. OSA versus SZ groupings
4. 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)
5. Chisquare analysis(卡方檢定) was used to evaluate the relationship between atheromas and presence of OSA and SZ.
6. Cross tabulations and chi-square analyses were conducted to determine the prevalence of atheromas by OSA severity levels
7. cross-tabulations were run to assess the distribution of atheromas by OSA severity and number of metabolic syndrome risk markers

using PASW Statistics version 18 & SAS version 9.1

RESULTS

The study group consisted of 31 individuals with OSA and 117 with SZ

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	

SZ→5 years older, significantly greater obesity, dyslipidemia, and hyperglycemia than OSA group

Atheromas? SZ → more frequently (49/117, 42%) than individuals with OSA (11/31, 35%); however, this difference was not statistically significant (*P=0* .52).

1. Individuals with OSA were equally distributed among severity levels
2. As the severity of OSA increased among individuals with mild MetS, the prevalence of CCAAs increased linearly from 35% to 50%.
3. 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

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
3. more than half (63%) of individuals with SZ having both severe OSA and moderate MetS have CCAAs on their panoramic images

Drager et al.: used ultrasound to evaluate the carotid artery in the bifurcation region,→ 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→likely result from the additive proatherogenic effect present in individuals having both OSA and

MetS

OSA and associated atherogenic mechanisms

1. OSA-associated apneic and hypopneic → Chronic intermittent hypoxia (IH) →stimulates carotid chemoreceptors → activate the sympathetic nervous system (SNS) release norepinephrine →causes vasoconstrictionin the peripheral vascular bed→ a surge in blood pressure (hypertension) →damages the blood vessel's lining and walls→fostering atheroma formation.
2. The repetitive process of IH alternating with rapid reoxygenation/reperfusion →excessive production of reactive oxygen species (ROS; oxidative stress)→ react negatively with nitric oxide produced by vascular endothelium→ preventing the expected homeostatic dilatation response →thereby furthering vessel wall damage and atheroma development.

ROS also increase expression of transcription factors, such as nuclear factor kappa→ upregulate the production of proinflammatory cytokines, such as C-reactive protein → upregulate the production of chemoattractant protein and adhesion molecules that facilitate the recruitment and accumulation of monocytes and platelets onto the endothelial surface. → 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.

These noted processes result in the development of atherosclerotic lesions in the carotid artery and ofteneven more advanced lesions in the coronary arteries.

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

Hyperglycemia, one of the key elements in MetS, arises insulin resistance→This hyperglycemic state is worsened by the OSA hypoxia activation of the SNS→ release of catecholamines(兒茶酚胺) that increase glycogen breakdown →gluconeogenesis, decrease insulin sensitivity, and reduce insulin-mediated glucose uptake.
The previously formed ROS elicit release of tumor necrosis factor alpha→ inhibits glucose uptake and the storage of free fatty acids (FFA) by the adipocytes within the abdominal adipose tissues→
the adipocytes release large amounts of FFA into the systemic circulation.(Muscle cells take up much of the FFA(but not all))→ they become glutted with FFAs, they also become insulin resistant. →muscle cells unable to adequately uptake glucose→ hyperglycemia→beta cells of the pancreases are stimulated and produce additional insulin (hyperinsulinemia)→ The residual FFA is diverted to the liver→stimulates the synthesis, assembly, and secretion of lipoproteins that promote atherogenesis (raised triglycerides ,low concentrations of HDL cholesterol, and small, dense LDL cholesterol)

Hypertension is now reinforced in the SZ state by a number of other mechanisms

1. reinforced hyperinsulinemia stimulation of SNS

2. overabundance of FFAs that exert a constrictive effect on blood vessels
3. impairment of insulin's usual vasodilatory effect.
4. 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.

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.

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.

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.

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.

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).

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.