Evaluation of association between obstructive sleep apnea and coronary risk scores predicted by tomographic coronary calcium scoring in asymptomatic patients

Asemptomatik hastalarda tomografik koroner kalsiyum skorlaması ile öngörülen koroner risk skorları ve obstrüktif uyku apnesi arasında ilişkinin değerlendirilmesi

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ABSTRACT

Objective: This cross-sectional observational study is designed to evaluate direct effects of obstructive sleep apnea syndrome (OSA) on presence and extent of coronary atherosclerosis by using tomographic coronary calcification scoring on a population asymptomatic for coronary artery disease.
Methods: Ninety-seven consecutive patients (49.17±0.86 years) who were evaluated with sleep study for the suspicion of obstructive sleep apnea syndrome underwent tomographic coronary calcium scoring test. Cardiovascular risk factors, current medications and sleep study recordings of all patients were recorded. Patients were classified into 4 groups according to the apnea-hypopnea index (AHI). Linear and logistic regression analyses were used for assessment of association between variables.
Results: Coronary risk scores of patients, assessed by tomographic coronary calcium scoring, were observed to increase linearly from simple snoring group to severe OSA groups (p=0.046). When patients were classified according to their gender, AHI and parameters reflecting severity of OSA-related hypoxia were found to correlate significantly with coronary risk scores of women but not with scores of men. Linear regression analysis revealed age as the only independent associated variable with cardiovascular risk scores assessed by tomographic coronary calcification scoring (Beta coefficient: 0.27, 95% CI 0.007-0.087, p=0.018). Binary logistic regression analysis also revealed age as the only variable which independently predicted the presence of coronary calcification (OR:1.11, 95% CI 1.039-1.188, p=0.002).
Conclusion: These results suggest that presence of OSA may contribute to coronary artery disease risk of patients in association with its severity; however, association between OSA and subclinical atherosclerosis seems to be primarily dependent on age.
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Key words: Coronary atherosclerosis, obstructive sleep apnea, hypoxia, tomographic coronary calcium scoring, regression analysis

ÖZET

Amaç: Obstrüktif uyku apnesi sendromu (OSA) solunumla ilgili uyku bozuklukları içinde incelenen ve vücuttaki birçok sistemi ilgilendiren önemli bir sağlık sorunudur. Koroner arter hastalığı için asemptomatik olup, OSA varlığından şüphe edilen hastalar kullanılarak yapılan bu kesitsel gözlem çalışması, obstrüktif uyku apnesi sendromu ile koroner ateroskleroz varlığı ve yaygınlığı arasındaki ilişkiyi doğrudan araştırmak için planlanmıştır.
Yöntemler: Çeşitli nedenler ile uyku laboratuvarında uyku testi yapılan 97 hastaya (yaş: 49.17±0.86) tomografik koroner kalsiyum skorlaması tetkiki yapıldı. Tüm hastaların kardiyovasküler risk faktörleri, kullanmakta oldukları ilaçlar ile uyku testi sonuçları kaydedildi. Hastalar uyku testinde saptanan apne-hipopne indeksleri (AHİ) kullanılarak obstrüktif uyku apnesi şiddetine göre 4 gruba ayrıldı. Değişkenler arasında ilişkilerin değerlendirilmesinde lineer ve lojistik regresyon analizleri kullanıldı.
Bulgular: Gruplar arasında basit horlama grubundan ağır OUAS grubuna gidildikçe tomografik koroner kalsiyum skorlaması ile öngörülen kardiyovasküler risk skorlarının doğrusal olarak anlamlı derecede arttığı görüldü (p=0.046). Hastalar cinsiyete göre ayrıldıklarında, AHİ ve uyku

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apnesi ile ilişkili hipoksiyi yansıtan parametrelerin esas olarak bayanlarda koroner risk skorları ile ilişkili olduğu saptandı. Lineer regresyon analizinde yalnız yaşın kardiyovasküler risk skorları ile bağımsız ilişkili olduğu görüldü (Beta katsayısı: 0.27, %95 GA 0.007-0.087, p=0.018). Binary lojistik regresyon analizinde de sadece yaşın koroner arter kalsifikasyonu varlığının bağımsız öngörücüsü olduğu saptandı (OO:1.11, %95 GA 1.039-1.188, p=0.002).

Sonuç: Bu sonuçlar asemptomatik hastalarda, OSA şiddeti arttıkça kardiyovasküler riskin arttığını fakat risk artışından esas olarak artan yaşın sorumlu olduğunu düşündürmektedir. *(Anadolu Kardiyol Derg 2011; 11: 428-35)*

Anahtar kelimeler: Koroner ateroskleroz, obstrüktif uyku apnesi, hipoksi, tomografik koroner kalsiyum skorlaması, regresyon analizi

Introduction

Obstructive sleep apnea syndrome (OSA) is a highly prevalent sleep-related disorder characterized by repeated partial or complete closure of the pharynx, gasping episodes, sleep fragmentation and daytime sleepiness (1). The physiologic consequences of these episodes are repetitive bursts of sympathetic activity, hypoxia, hypercapnia, increased left ventricular after load, acute hypertension and endothelial dysfunction (2). These events give rise to the clinical complication of this syndrome and contribute to the association between OSA and cardiovascular complications as chronic hypertension, coronary artery disease, arrhythmia, congestive heart failure and stroke (3, 4).

The association between obstructive sleep apnea and coronary artery disease is a complex issue to investigate. Theoretically, OSA and related consequences create proinflammatory state that facilitates atherosclerosis formation and progression (5). However, severity of OSA in humans is highly variable and the clinical syndrome typically evolves over many years. As such, there is high degree of variation regarding the duration of exposure to the adverse effects of OSA at the time of diagnosis. Besides, patients with OSA usually have coexisting risk factors such as hypertension, obesity and insulin resistance, which precludes definitive conclusion regarding the independent effect of OSA on atherosclerosis progression.

Arterial calcium development is intimately associated with vascular injury and atherosclerotic plaque (6). Coronary artery calcification is an active process and can be seen at all stages of atherosclerotic plaque development. Various tomographic techniques permit quantification of coronary artery calcification, which reflects amount of coronary atherosclerosis burden and is associated with coronary events and asymptomatic myocardial ischemia. Tomographic coronary calcium scoring is increasingly being used for risk stratification of asymptomatic patients and is especially useful for patients who are at intermediate risk for cardiovascular event development according to Framingham scoring system (6).

Recently, two studies have reported contradictory data regarding the association between OSA and coronary artery calcification in patients asymptomatic for coronary artery disease. Sorajja et al. (7) found that the presence and severity of OSA was significantly associated with presence and extent of coronary artery calcification independent of co-existing risk factors. In contrast with the observations of former study, Kim et al. (8) reported that they did not observe any independent association between severity of OSA and coronary artery calcification after adjusting their data for body mass index (BMI) in a population of middle-aged Asian males.

The aim of the present study is to evaluate the direct association between OSA and presence and extent of coronary atherosclerosis by using tomographic coronary calcification scoring on a population who had been referred to polysomnography for clinically suspected OSA and asymptomatic for coronary artery disease.

Methods

Study design and patients

Study was designed as to be a cross-sectional observational study and 110 consecutive patients (age: 48.0±9.5 years, 72 male) who had been referred to sleep laboratory of Department of Chest Diseases, Faculty of Medicine, Hacettepe University for polysomnography with complaints suggestive of OSA constituted study population. Exclusion criteria were defined as:

1- Previous history of acute coronary syndrome and/or coronary artery disease diagnosed by coronary angiography and /or revascularization ,
2- Findings suggestive of active cardiac ischemia [typical chest pain during exercise or rest, electrocardiographic (ECG) changes suggestive of ischemia and/or regional motion abnormalities observed during echocardiographic study].

After exclusion of patients according to exclusion criteria, 97 patients (64 male, 33 female; age: 49.17±0.86) asymptomatic and free of any history of coronary artery disease were left and all these patients underwent computed tomography study for tomographic coronary calcification scoring.

A detailed medical story, physical examination, 12 lead electrocardiography, complete blood count and serum biochemistry were obtained from all patients. Presence of classic cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking habitus were assessed. Based on the criteria used previously in similar studies (7-9), diabetes mellitus was diagnosed when patients were taking hypoglycemic medications or when, in the absence of treatment, fasting blood glucose levels were higher than 126 mg/dl in two consecutive determinations. Hyperlipidemia was defined as fasting total serum cholesterol more than 200 mg/dl and/or when patients were taking an oral lipid-lowering agent. Subjects currently taking antihypertensive drugs or showing a systolic blood pressure of 140 mm Hg or more and/or a diastolic blood pressure of 90 mmHg or more, based on the average of two or more readings taken in the sitting position at different days before investigation,

were defined as hypertensive. Patients smoking at least one cigarette daily for 1 year within the last 5 year were considered smokers.

The study was approved by Hacettepe University Faculty of Medicine, Medical, Surgical and Pharmaceutical Research's Ethics Committee (protocol No: HEK 06/10) and written informed consent was obtained from all patients.

Polysomnography

Overnight polysomnography was performed by a computerized system (Somnologica software, Medcare Flaga, Reykjavik, Iceland) and included the following variables: electrooculogram, electroencephalogram, electromyogram of submental muscles, electromyogram of the anterior tibialis muscle of both legs, electrocardiogram and airflow (with an oronasal thermistor). Chest and abdominal efforts were recorded using inductive plethysmography and arterial oxyhemoglobin saturation by pulse oximetry with a finger probe. Sleep stages were scored according to the standard criteria of Rechtschaffen et al. (10). Arousals were scored according to accepted definitions. Apneas were defined as complete cessation of airflow ≥10 seconds. Hypopnea was defined as reduction of >50% in one of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, or with a fall of ≥3% in oxygen saturation or an arousal. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The deep desaturation index was defined as the number of events in which oxygen saturation falls below 90% per hour of sleep.

All patients' AHI, deep desaturation index, basal oxygen saturation and average oxygen saturation values during sleep were recorded and used in the analysis. Patients with AHI <5 were included in the simple snoring group (Group 1). Subjects with AHI ≥5 were considered as OSA and classified according to their AHI as mild (AHI ≥5 and AHI <15) (Group 2), moderate (AHI ≥15 and AHI <30) (Group 3) and severe (AHI ≥30) OSA groups (Group 4).

Tomographic coronary calcification scoring

All subjects in the study population underwent non-enhanced multi-slice computed tomography (MSCT) with retrospective ECG-gating. All subjects were in sinus rhythm throughout the scan. All of the examinations were performed with a 16-MDCT scanner (Sensation 16, Siemens Medical Solutions, Erlangen, Germany). The area between carina to apex of the heart was scanned in craniocaudal direction. Calcium scoring parameters were tube voltage 120 kV, an effective tube current-time product of 133 mAseff, a collimation of 12x0.75 mm, a table feed of 2.8 mm per rotation, and a tube rotation time of 420 ms. No tube current modulation has been applied. In each patient, 60% of the R-R reconstruction was prepared at 512x512 reconstruction matrix and a medium smooth convolution kernel (B35f). All reconstructed images were transferred to an external workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany) for coronary calcium scoring (Syngo Calcium Scoring CT, Siemens, Germany). Coronary calcium score was determined by applying the method described by Agatston et al. (11), using a threshold of 130 HU. All examinations were analyzed by an experienced radiologist. Data analysis included calcium volume, calcium mass, Agatston score and number of lesions.

Coronary risk of patients was assessed by a scoring system which uses coronary calcification score percentiles according to age and gender. Accordingly, 1 point was assigned to the patients with calcification scores between 0 and 25th percentiles; 2 points were assigned to patients between 26 and 50th percentiles; 3 points were assigned to patients between 51 and 75th percentiles; 4 points were assigned to patients between 76 and 90th percentiles and 5 points were assigned to patients with calcification scores equal or over 91st percentile.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA). Distribution of data was assessed by using one-sample Kolmogorov-Smirnov test. Values displaying normal distribution were expressed as the mean±SD and values not displaying normal distribution were expressed as median (interquartile range). For comparison of categorical variables or percentages, we used Chi-square test. Differences between numeric variables of two groups were tested with independent samples Student's t-test for continuous variables displaying normal distribution and Mann-Whitney U test for continuous variables not displaying normal distribution. Significance of differences between more than two groups was assessed by using one-way ANOVA, followed by Sheffe post-hoc test for continuous variables displaying normal distribution and Kruskal-Wallis test followed by Bonferroni corrected Mann-Whitney U post-hoc test for continuous variables not displaying normal distribution. The significance of linear change of numeric variables across multiple (more than two) groups was tested with Jonckheere-Terpstra test, and the significance of linear change of categorical variables across multiple groups was tested with Mantel-Haenszel Chi-square test. Correlation was tested by Pearson or Spearman's correlation tests where appropriate. Multivariate linear regression analysis was used to test independent contribution of following potential predictors for coronary risk scores based on tomographic coronary calcification scores: age, body-mass index, apnea-hypopnea index, deep oxygen desaturation index and nocturnal average oxygen saturation. Binary logistic regression analysis was performed to evaluate independent predictive values of following potential variables for the presence of coronary calcification: age, gender, presence of hypertension, presence of hyperlipidemia, presence of diabetes, presence of smoking habitus, BMI, AHI, deep oxygen desaturation index and nocturnal average oxygen saturation. A significance level was set at $p<0.05$.

Results

Clinical characteristics of patients with OSA

Patients with OSA were sub-grouped according to AHI values as simple snoring group (Group 1, n=17), mild OSA group (Group 2, n=22), moderate OSA group (Group 3, n=21) and severe OSA groups (Group 4, n=37).

BMI values of patients were observed to significantly increase from simple snoring group to severe OSA groups (p<0.001). There were also significant differences between groups regarding basal oxygen saturation; nocturnal average oxygen saturation and deep oxygen desaturation index values and oxygen saturations were observed to decrease significantly in association with OSA severity. There were no significant differences between groups regarding age, gender and prevalence of other cardiovascular risk factors as diabetes, hypertension, hyperlipidemia, and smoking (Table 1).

Study population's medications are shown in Table 2. Only frequency of statin usage was significantly different between groups.

Coronary calcification scores in patients with OSA

There were no significant differences regarding tomographic coronary calcification scores between OSA groups (p>0.05). The percentiles of tomographic coronary calcification scores according to gender and age are shown in Table 3. Coronary risk scores of patients assessed by tomographic coronary calcium scoring were observed to increase linearly from simple snoring group to severe OSA groups (p=0.046) (Table 4, Fig.1). Patients were sub-classified according to their tomographic calcification scores, as such patients with calcification scores between 0 and 50th percentile were grouped as 'Group A' and patients with calcification scores ≥51st percentile were grouped as 'Group B'. Age, BMI, AHI, deep desaturation index values were significantly higher and basal oxygen saturation values were significantly lower in patients of high risk group (Group B) compared with the ones of low risk group (Group A). In addition, hypertension was more prevalent in high risk group (Table 5).

Clinical correlates and determinants of coronary calcification in patients with OSA

Univariate correlation analysis revealed that age, AHI, presence of hypertension and oxygen saturation related parameters recorded during polysomnography were significantly correlated (p<0.05) with coronary risk scores assessed by coronary calcium scoring in the whole population. Gender specific analysis revealed that parameters related with the severity of OSA and related hypoxia were all associated with coronary risk scores of

Table 1. Demographic characteristics and risk factors of patients classified according to severity of OSA

Variables	Group 1 (n=17)	Group 2 (n=22)	Group 3 (n=21)	Group 4 (n=37)	αF and Chi-square for trend	αp
Age, years	46.60±4.59	46.56±9.54	52.17±7.20	49.85±10.60	0.674	0.413
Gender, n (%)						
Male	10 (58.8)	16 (72.7)	16 (76.2)	22 (59.5)	2.48	0.479
Female	7 (41.2)	6 (27.3)	5 (23.8)	15 (40.5)		
Body-mass index, kg/m^2*	28.25±4.04	27.61±3.09	29.18±3.28	30.99±4.43	4.09	0.009
Basal oxygen saturation, %**	94.34±1.32	94.45±1.53	93.58±1.41	92.38±2.48	6.98	<0.001
Nocturnal average oxygen saturation, %***	94.30±1.20	94.12±1.63	93.04±1.20	91.20±3.40	12.20	<0.001
Deep oxygen desaturation index, n/hour****	0.00 (1.00)	2.00 (2.25)	4.00 (7.00)	13.00 (24.75)	49.88	<0.001
Diabetes, n (%)	2 (11.8)	2 (9.1)	2 (9.5)	7 (18.9)	----	0.652
Hypertension, n (%)	4 (23.5)	7 (31.8)	7 (33.3)	15 (40.5)	----	0.222
Hyperlipidemia, n (%)	2 (12.5)	6 (27.3)	5 (23.8)	11 (29.7)	----	0.271
Smoking, n (%)	6 (35.3)	7 (31.8)	9 (42.9)	10 (27.0)	----	0.603
Plasma HDL, mg/dl	54.14±9.0	50.88±12.20	51.30±12.280	52.42±12.54	0.19	0.903
Plasma LDL, mg/dl	120.86±24.49	110.03±37.11	117.98±29.74	106.55±37.32	0.72	0.542
Plasma triglyceride, mg/dl	139.00 (83.0)	142.00 (106.00)	139.50 (101.50)	129.50 (86.25)	0.38	0.998

Group 1-simple snoring, Group 2-mild OSA, Group 3-moderate OSA, Group 4-severe OSA
Data are presented as mean±SD, median (interquartile range) and number (percentage)
αOne-way ANOVA, followed by Sheffe post-hoc test, Kruskal-Wallis test followed by Bonferroni corrected Mann-Whitney U post-hoc test and Chi-square test
*BMI- p=0.019 for comparison of Group 2 vs Group 4
** Basal oxygen saturation: p: 0.009 for comparison of Group 1 vs Group 4; p: 0.002 for comparison of Group 2 vs Group 4
***Nocturnal average oxygen saturation (%): p<0.001 for comparison of Group 1 vs Group 4; p<0.001 for comparison of Group 2 vs Group 4; p<0.001 for comparison of Group 3 vs Group 4
****Deep oxygen desaturation index: p<0.001 for comparison of Group 1 vs other groups; p =0.06 for comparison of Group 2 vs Group 3; p<0.001 for comparison of Group 2 vs Group 4; p=0.001 for comparison of Group 3 vs Group 4
HDL - high density lipoprotein, LDL - low-density lipoprotein, OSA - obstructive sleep apnea

women (p<0.05), but only deep saturation index was significantly associated with risk scores of men (p<0.05). Out of classical risk factors, only age and presence of hypertension were found to be correlated with coronary risk scores of both men and women (Table 6).

Regarding severe OSA patients, the ratio of women with calcification scores over 50th percentile was 60.0%; whereas the ratio of men with calcification scores over 50th percentile was 40.9% (p=0.210). There were no significant differences between men and women regarding prevalence of hypertension, prevalence of hyperlipidemia and prevalence of diabetes. Men were smoking more however; women were more obese than men. There were also no significant differences regarding parameters related to OSA and related hypoxia between men and women (Table 7).

Independent association of OSA with coronary risk scores assessed by tomographic coronary calcium scoring was evaluated with linear multivariate regression analysis and effects of age, BMI, apnea-hypopnea index and parameters related with nocturnal hypoxia (deep oxygen desaturation index and nocturnal average oxygen saturation) were included in the model. Only age was found to be independently associated with cardiovascular risk scores assessed by tomographic coronary calcification scoring (Beta coefficient: 0.28, 95% CI 0.012-0.086, p=0.01). Binary logistic regression analysis also revealed age as the only variable independently associated with the presence of coronary artery calcification (OR: 1.11, 95 CI 1.039-1.188, p=0.002).

Table 2. Medications received by study population at the time of enrollment into study

Variables	Group 1 (n=17)	Group 2 (n=22)	Group 3 (n=21)	Group 4 (n=37)	*p
Aspirin, n (%)	0	5 (22.7)	5 (23.8)	9 (24.3)	0.147
Beta-blocker, n (%)	0	4 (18.1)	3 (14.2)	4 (10.8)	0.268
RAS-blockers, n (%)	1 (5.8)	6 (27.2)	6 (28.5)	14 (37.8)	0.102
Diuretics, n (%)	0	4 (18.1)	3 (14.2)	6 (16.2)	0.290
Alfa-blocker, n (%)	1 (5.8)	0	0	2 (5.0)	-
Statin, n (%)	0	2 (9.0)	2 (9.0)	10 (27.0)	0.040
Fibrate, n (%)	0	1 (4.0)	0	0	-
Oral antidiabetics, n (%)	1 (5.8)	2 (9.0)	1 (4.7)	4 (10.8)	0.834
Insulin, n (%)	0	0	0	1 (.7)	-

Data are presented as number (percentage)
*Chi-square test
RAS - renin-angiotensin system

Table 3. Percentiles for tomographic coronary calcification scores according to gender and age

	Age intervals		
	<50 years	50-59 years	≥60 years
Men (64), n	38	16	10
25 percentile, AU*	0.0	0.0	0.0
50 percentile, AU	0.0	0.0	112.35
75 percentile, AU	0.12	37.07	267.17
90 percentile, AU	29.70	132.59	1077.49
Women (33), n	16	12	5
25 percentile, AU	0.0	0.0	0.0
50 percentile, AU	0.0	2.45	8.80
75 percentile, AU	0.750	12.22	55.65
90 percentile, AU	15.93	77.81	-

*AU - Agatston units

Discussion

The principle finding of the present study is that coronary risk scores of asymptomatic patients assessed by tomographic coronary calcium scoring increase in association with the severity of OSA. However, much of this association was observed to be related with age, which was the only independently associated variable with both the presence and extent of coronary calcification.

The association between OSA and cardiovascular risk factors such as obesity and hypertension has been well documented (12, 13). Body-mass index values were observed to increase significantly from simple snoring group to severe OSA group in our study which is in agreement with previous studies (p=0.009). There were no significant differences between groups

Table 4. Tomographic coronary calcium scores and coronary risk scores of patients classified according to severity of OSA

Variables	Group 1 (n=17)	Group 2 (n=22)	Group 3 (n=21)	Group 4 (n=37)	*Chi-square for trend	p
Tomographic coronary calcification score (Agatston units)*	4.61±13.29 0.00 (0.00)	58.23±175.23 0.00 (7.42)	32.40±63.46 0.00 (38.90)	53.22±196.24 0.60 (20.05)	5.62	0.132
Cardiovascular risk score assessed by calcification scoring*	1.52 ± 1.17 1.00 (0.00)	2.04 ± 1.55 1.00 (2.25)	2.14 ± 1.55 1.00 (2.50)	2.43 ± 1.50 2.00 (3.00)	5.23	0.150
Cardiovascular risk score assessed by calcification scoring**	1.52 ± 1.17 1.00 (0.00)	2.04 ± 1.55 1.00 (2.25)	2.14 ± 1.55 1.00 (2.50)	2.43 ± 1.50 2.00 (3.00)	-	0.046

Group 1-simple snoring, Group 2-mild OSA, Group 3-moderate OSA, Group 4-severe OSA
Data are presented as mean± SD and median (interquartile range)
* Kruskal-Wallis test
**The significance of linear change of cardiovascular risk sores across 4 groups was tested with Jonckheere-Terpstra test
OSA - obstructive sleep apnea

regarding age and hypertension prevalence; however hypertension was significantly more prevalent in group with higher cardiovascular risk according to calcification scores (p=0.021). In addition, patients of higher risk group were significantly older compared with the ones of lower risk (p=0.002). There were also significant correlations between OSA related nocturnal hypoxia parameters and hypertension. While some studies have reported the association between OSA and coronary events, there are limited data regarding the association between OSA and subclinical coronary disease. The mechanism of association between OSA and coronary artery disease may be related to deleterious effects of hypoxia on endothelial functions, hyperadrenergic state and the effects of highly prevalent co-existing risk factors (13). Nocturnal desaturation and reoxygenation episodes observed in these patients have been suggested to result in oxidative stress which facilitates the metabolic cascade associated with increased inflammatory response and development of atherosclerosis (14).

Table 5. Comparison of classical cardiovascular risk factors and OSA-related hypoxia parameters of patients with tomographic coronary calcification scores between 0 and 50th percentile (Group A) and coronary calcification scores above 51st percentile (Group B)

Variables	Group A (n=62)	Group B (n=35)	p
Age, years	47.19±8.48	52.68±7.54	0.002
Diabetes, n (%)	6 (9.7)	7 (20.0)	0.131
Hypertension, n (%)	16 (25.8)	18 (51.4)	0.021
Smoking, n (%)	21 (33.9)	11(31.4)	0.495
Hyperlipidemia, n (%)	16 (26.2)	8 (22.9)	0.456
Body-mass index, kg/m^2	28.75±3.55	30.39±4.66	0.05
Apnea-hypopnea index, n/hour	19.00 (28.75)	29.85 (40.27)	0.019
Basal oxygen saturation,%	93.78±2.09	92.89±1.94	0.041
Nocturnal average oxygen saturation, %	93.19±2.39	92.16±3.06	0.097
Deep oxygen desaturation index, n/hour	2.0 (5.45)	6.15 (11.25)	0.003

Group A-tomographic coronary calcification scores between 0 and 50th percentile
Group B-tomographic coronary calcification scores ≥51st percentile
Data are presented as mean±SD, median (interquartile range) and number (percentage)
*Independent samples Student's t-test, Mann-Whitney U test and Chi-square test
OSA - obstructive sleep apnea

Many of the studies investigating the influence of OSA on presence and severity of atherosclerosis have studied the association of OSA and carotid intima-media thickness as a marker of systemic atherosclerosis in various populations (15-19). Although there are variations regarding the designs and populations of these studies, general finding is that OSA patients have higher carotid intima-media thickness values in association with disease severity. However, high prevalence of co-existing cardiovascular risk factors and the variations regarding the methodology of these studies complicate the conclusion regarding independent effects of OSA and related hypoxic, autonomic and hemodynamic alterations on atherosclerosis pathophysiology.

The issue of 'subclinical coronary artery disease' in otherwise healthy obstructive sleep apnea patients is hardly debated in the literature. Tomographic coronary calcium scoring is known to be a quantitative indicator for atherosclerotic burden of coronary arteries and is especially valuable for risk stratification of asymptomatic patients (6). Coronary artery calcification score is not a normally distributed value and the amount of calcium varies greatly among subjects of different ages and gender. For this reason, we developed a cardiovascular risk scoring system using percentiles defined for age and gender for standardization of coronary risk based on coronary calcification scores. We found significant univariate correlations between coronary risk scores and age, AHI, basal oxygen saturation, nocturnal average oxygen saturation and deep oxygen desaturation index values. Out of classical risk factors only hypertension was associated with coronary risk scores in our study. However,

Table 6. Univariate correlation analysis between potential variables and coronary risk scores assessed by tomographic coronary calcification scoring

Variables	All patients (n=97)		Men (n=64)		Women (n=33)	
	r	p	r	p	r	p
Age	0.375	<0.001	0.392	<0.001	0.306	0.084
Apnea-hypopnea index (AHI)	0.247	0.015	0.119	0.349	0.476	0.005
Basal oxygen saturation	-0.222	0.030	-0.151	0.235	-0.366	0.039
Nocturnal average oxygen saturation	-0.234	0.022	-0.159	0.208	-0.393	0.026
Deep oxygen desaturation index	0.308	0.002	0.272	0.033	0.354	0.047
Hypertension	0.300	0.003	0.265	0.034	0.345	0.049
Diabetes	0.143	0.161	0.176	0.165	0.067	0.710
Smoking	-0.038	0.710	-0.019	0.883	-0.019	0.916
Hyperlipidemia	0.054	0.605	0.088	0.493	-0.030	0.869
Body-mass index	0.135	0.192	0.046	0.718	0.265	0.143

*Pearson and Spearman's correlation tests

on multivariate analysis only age was found to be independently associated with coronary risk score based on tomographic coronary calcification scores. Thus, it may be suggested that the mechanism between OSA and coronary atherosclerosis is primarily dependent on increasing age. Recently, two studies have reported the data on the association between OSA and coronary artery calcification in patients asymptomatic for coronary artery disease. Sorajja et al. (7) found that the presence and severity of OSA was significantly associated with presence and extent of coronary artery calcification independent of co-existing risk factors. However, Kim et al. (8) reported that they didn't observe any association between OSA and coronary artery calcification after adjusting for BMI in a multivariate model including co-existing cardiovascular risk factors in a population of middle aged Asian males. The authors suggested that the cause of discrepancy between the findings of these studies may be due to different clinical characteristics of populations as former study recruited patients with higher prevalence of hypertension or diabetes. Our study population is similar to the population of Sorajja et al. (7) as participants were recruited from patients who had referred for polysomnography due to a suspected sleep disorder. Distinct from the results of Sorajja et al. (7) we didn't observe any independent association between coronary risk scores and AHI or OSA-related hypoxia parameters. These parameters were also not independently predictive for the presence of coronary calcification. The cause of inconsistency regarding the results of these studies is not clear, however relatively small population size of our study may be a contributing factor. In addition, all three studies are cross-sectional studies and there may be wide variation between subjects regarding the time of exposure to untoward effects of OSA. Ethnicity may also be a concern since studies conducted for different ethnic groups have shown a broad range in the coronary artery calcification scores of asymptomatic subjects (20).

Surprisingly, our subgroup analysis revealed that AHI and all OSA-related hypoxia parameters were associated with coronary risk scores in women but only deep saturation index was associated with risk scores of men. There were no significant differences between men and women regarding age, apnea-hypopnea index, OSA related hypoxia parameters and prevalence of hypertension, diabetes and hyperlipidemia. Women were significantly more obese; however, prevalence of smoking was more frequent in men (Table 7). Gender-specific issues in ischemic heart disease presentation, evaluation, and outcomes have been extensively studied in 'Women's Ischemia Syndrome Evaluation (WISE)' study (21). It has been suggested that vascular dysfunction is generally more prevalent in women as compared to men and is manifest by more frequent symptoms and evidence of provocative ischemia or altered metabolism in the absence of obstructive disease due to sex hormone differences. Thus, it may be hypothesized that there may be inter-gender difference regarding susceptibility to the effects of OSA and related hypoxia. Further large scale, prospective studies are warranted for definitive conclusion regarding independent association between OSA and coronary atherosclerosis and gender specific issues should also be considered as well.

Table 7. Comparison of cardiovascular risk factors and OSA-related parameters of men and women enrolled in the study

Variables	Men (n=64)	Women (n=33)	*p
Age, years	48.54 (11.00)	50.39 (13.50)	0.248
Hypertension, n (%)	18 (28.1)	15 (45.5)	0.088
Hyperlipidemia, n (%)	14 (22.2)	10 (30.3)	0.385
Diabetes, n (%)	25 (39.1)	11 (33.3)	0.580
Smoking, n (%)	27 (42.2)	5 (15.2)	0.007
Body-mass index, kg/m^2	28.58±3.87	30.78±3.99	0.011
Apnea-hypopnea index, n/hour	21.30 (30.50)	22.00 (34.60)	0.864
Basal oxygen saturation, %	93.34±1.89	93.70±2.41	0.429
Nocturnal average oxygen saturation, %	92.87±1.50	92.73±2.50	0.812
Deep oxygen desaturation index	4.00 (8.50)	3.00 (9.97)	0.987

Data are presented as mean±SD, median (interquartile range) and number (percentage)
*Independent samples Student's t-test, Mann- Whitney U test and Chi-square test
OSA - obstructive sleep apnea

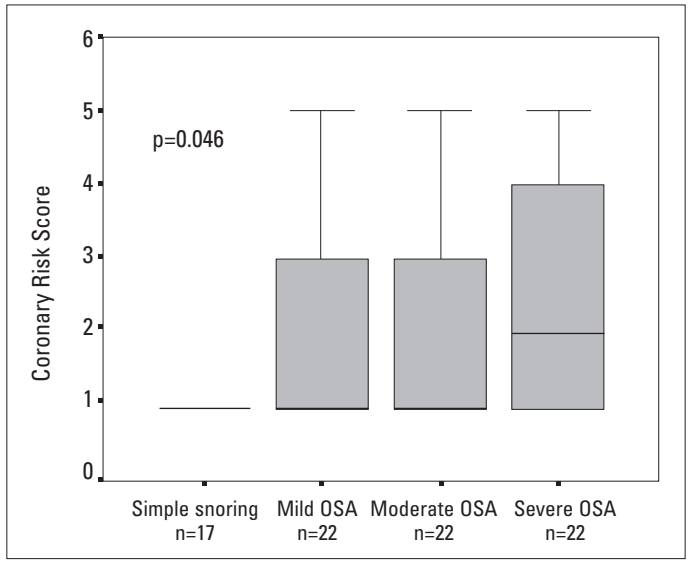

Figure 1. Coronary risk scores of patients classified according to AHI values as simple snoring, mild OSA, moderate OSA and severe OSA groups
AHI - apnea-hypopnea index, OSA - obstructive sleep apnea

Study limitations

Small sample size is main limitation of this study. In addition, our study was a cross-sectional study, which can not identify causal or temporal relationships between OSA and subclinical coronary artery calcification. We did not perform blood gas analysis. We also did not study the parameters reflecting the autonomic balance and chronic inflammatory process.

Conclusion

We could not find any significant differences regarding tomographic coronary calcification scores between OSA groups. However, coronary risk scores of patients assessed by tomographic coronary calcium scoring were observed to increase linearly from simple snoring group to severe OSA groups. Patients with higher coronary risk had higher AHI and OSA-related hypoxia parameters compared with the patients with low risk. However, only age was independently associated with presence and extent of coronary calcification.

Conflict of interest: None declared.

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