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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Obstructive sleep apnea is a risk factor for osteoarthritis

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SUMMARY

Obstructive sleep apnea is a risk factor for osteoarthritis

Introduction: *Obstructive sleep apnea (OSA) syndrome is closely associated with cardiovascular and metabolic disorders. Recent studies reported that osteoarthritis (OA) is associated with cardiovascular disease as well as inflammation defined as "metabolic disorder". Due to the strong association of metabolic*

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disorders with both OA and OSA, we aimed to investigate the association between severity of OSA and osteoarthritis grade based on X-Ray.

Materials and Methods: *Patients who underwent polysomnography due to suspicion of OSA were recruited in a cross-sectional study. Included patients were grouped according to apnea-hypopnea index (AHI) as mild (AHI between 5 and 14.9), moderately (AHI between 15 and 29.9), and severe OSA (AHI ≥ 30). Patients with AHI < 5 served as the control group. Kellgren-Lawrence scoring system was used to express OA severity, which was graded as Grade 0, 1, 2, 3 and 4.*

Results: *One hundred twenty patients were enrolled into the study. Mean age was 52.4 ± 11.5 years and 56% (68/120) of the patients were male. A strong correlation was present between severity of OSA and severity of OA. Among those with Grade 4 OA group (33 patients), all patients had severe OSA and this association was independent from body-mass index. In the Grade 1 OA group, none of the patients had severe OSA (p< 0.05). A positive correlation was also seen between severity of OSA, OA and hs-CRP.*

Conclusion: *There is a strong association between OSA and OA. OSA might be a novel risk factor for the development OA. Further studies should evaluate the effect of OSA treatment on OA.*

Key words: *Osteoarthritis; obstructive sleep apnea; inflammation*

ÖZET

Obstrüktif uyku apnesi osteoartrit için risk faktörüdür

Giriş: *Obstrüktif uyku apne ile kardiyovasküler hastalıklar ve metabolik bozukluklar arasında sıkı ilişki vardır. Yapılan araştırmalar osteoartrit ile kardiyovasküler hastalık ve inflamasyon arasında da ilişki olduğunu göstermiştir. Bu çalışmada direkt grafi ile sınıflandırılmış osteoartrit ile obstrüktif uyku apnenin ağırlığı arasındaki ilişki araştırılmıştır.*

Materyal ve Metod: *Bu kesitsel çalışmaya obstrüktif uyku apne şüphesi ile polisomnografi yapılan hastalar dahil edildi. Apne hipopne indeksi (AHİ)'ne göre hastalar hafif (AHİ= 5-14.9), orta (AHİ= 15-29.9), ağır (AHİ ≥ 30) ve kontrol (AHİ < 5) grubu olarak sınıflandırıldı. Osteoartrit ağırlığı Kellgren-Lawrence skorlama sitemi kullanılarak evre 1, 2, 3 ve 4 olarak sınıflandırıldı.*

Gereç ve Yöntem: *Çalışmaya 120 hasta dahil edildi. Hastaların ortalama yaşı 52.4 ± 11.5 yıl olup; hastaların %56 (68/120)'sı erkek olarak tespit edildi. Obstrüktif uyku apnenin ciddiyeti ile osteoartritin ciddiyeti arasında sıkı bir ilişki saptandı. Ağır osteoartriti (evre 4) olan tüm hastaların (33 hasta) ağır obstrüktif uyku apne hastalığı olduğu ve bu ilişkinin beden kitle indeksinden bağımsız olduğu tespit edildi. Hafif evre osteoartrit olan hastaların hiçbirinde obstrüktif uyku apne hastalığı olmadığı saptandı (p< 0.05). Osteoartrit, obstrüktif uyku apne hastalığı ve C-reaktif protein (CRP) arasında sıkı ilişki gözlendi.*

Bulgular: *Obstrüktif uyku apne osteoartrit gelişmesi için bir risk faktörü olabilir. Obstrüktik uyku apne hastalığı tedavisinin osteoartrit üzerine etkisi ile ilgili yeni çalışmalara ihtiyaç vardır.*

Anahtar kelimeler: *Obstrüktif uyku apne; osteoartrit; inflamasyon*

INTRODUCTION

Osteoarthritis is a major health problem with significant morbidity and disability that is associated with arthritis of the knees and hip joints. It has resulted in a total of 71.1 million years lived with disability in the twentieth century (1). It is estimated that in the next decade, 20 to 30% of the world's population will have some type of osteoarthritis, which is most frequently found in the population over 60 years of age (2). Therefore, understanding the role of modifiable risk factors for osteoarthritis is important for improving prevention. Currently, evidence supports a relationship between osteoarthritis and metabolic syndrome, independent of obesity (3,4). High body mass index (BMI) and large waist circumference are widely recognized as the most important modifiable risk factors for knee osteoarthritis (5). Furthermore, individual risk factors that make up metabolic syndrome, including central obesity, diabetes, high blood pressure, dyslipidemia, and insulin resistance, have been shown to be independently associated with degenerative joint disease (6). The link between metabolic syndrome and osteoarthritis has been explained by metabolic syndrome-associated atheromatous vascular disease, small vessel occlusion, and venous stasis, which might predispose patients to subchondral bone ischaemia, leading to poor nutrient and gas exchange in the articular cartilage (7). In addition to increased BMI, inflammation is another important risk factor for the high prevalence of osteoarthritis in the metabolic syndrome. It appears that inflammation plays a key role between osteoarthritis and metabolic syndrome (8).

Obstructive sleep apnea (OSA) is an underdiagnosed condition characterized by recurrent episodes of obstruction of the upper airways leading to sleep

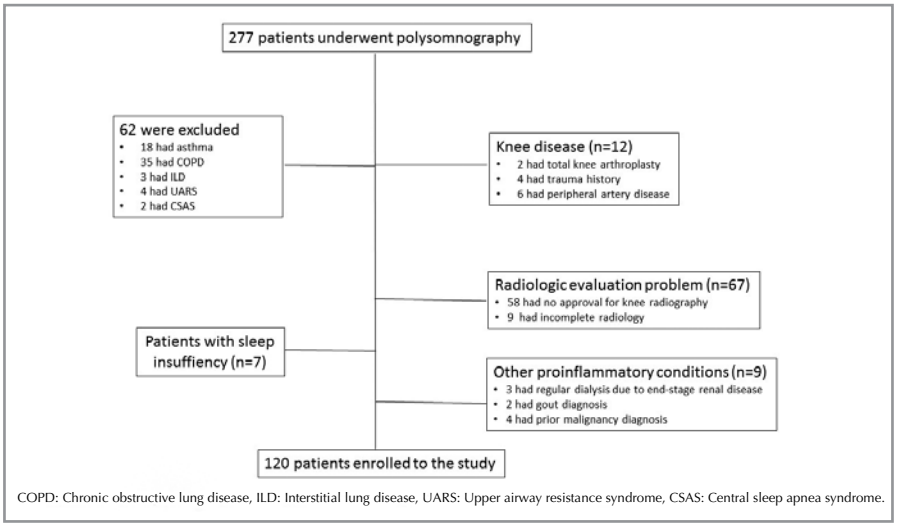

Figure 1. Flow diagram of the study.

fragmentation and intermittent hypoxia during sleep (9). It is well known that obesity can predispose to the development of OSA (10). The prevalence of OSA is increasing worldwide secondary to the ongoing epidemic of obesity (10). Recent evidence has shown that surrogate markers of cardiovascular risk, including sympathetic activation, systemic inflammation, and endothelial dysfunction, are significantly increased in patients with OSA, independent of BMI (11,12).

Although a strong relationship can be found among inflammation and osteoarthritis on the one hand, and inflammation and OSA on the other hand, no previous studies have investigated the effect of OSA on osteoarthritis. With this background in mind, we aimed to investigate the association between severity of OSA and osteoarthritis grade based on X-Ray.

MATERIALS and METHODS

This cross-sectional study was conducted at Istanbul Medeniyet University School of Medicine, Department of Pulmonary Medicine, Sleep Disorders Center. The study protocol was approved by the Istanbul Medeniyet University Clinical Research Ethics Committee (IMU/0093). All patients were included in the study after signing informed consent form.

Study Population

Patients who underwent a polysomnography due to suspicion of OSA were included in our study between May 2014 and April 2015. Subjects younger than 18 years, patients with central sleep apnea syndrome, upper airway resistance syndrome, those with active infections, malignancy, interstitial lung disease and bronchial asthma were excluded. In addition, patients with chronic kidney disease, peripheral vascular disease, rheumatic disease, total knee arthroplasty, incomplete radiography, and acute trauma of the knees were also excluded from the study. 277 patients underwent to polysomnography study during the study period and 120 participants included to the final analysis. The flow diagram of the study is shown in Figure 1. Patients with an apnea hypopnea index (AHI) < 5 were recruited as a control group. The AHI cut-offs for mild, moderate, and severe OSA were 5 to 14.9, ≥ 15 to 29.9, and ≥ 30 events per hour of sleep, respectively.

Demographic characteristics, including age, gender, history of previously diagnosed diabetes mellitus or hypertension, and smoking status, were recorded for each study participant. BMI was calculated as weight in kilograms (measured by a scale) divided by the square of height. Routine blood chemistry, including lipid profile, HbA1c and high-sensitivity C-reactive protein (hsCRP) were obtained.

Sleep Study

All participants underwent a standard overnight polysomnography (Alice 6, Anne Deneubourg, Germany and Grass Technologies, Medical Devices, CA, USA). As described in our previous study, the sleep study included electrooculography (two channels), electroencephalography (six channels), electromyography of

the submental muscles (one channel) and of bilateral anterior tibialis muscles (two channels), electrocardiography, airflow measurements (with an oronasal thermistor and nasal cannula pressure transducer), body position during sleep, and snoring vibrations (snore sensor) (13). Chest and abdominal effort (two channels) were recorded using piezoelectric belts, while arterial oxyhemoglobin saturation (one channel) was measured by pulse oximetry. The recordings were scored according to the standard criteria of the AASM. Apnea was defined as a ≥ 90% decrease in the air flow persisting for at least 10 seconds relative to the baseline amplitude. Hypopnea was defined as a ≥ 3% oxygen desaturation or event is associated with an arousal, all sustaining for at least 10 seconds. Arousals were scored according to accepted definitions (14). The AHI was calculated as the number of apneas plus hypopneas per hour of sleep. Patients with an AHI ≥ 5 events/hour were diagnosed as having OSA. The oxygen desaturation index (ODI) was defined as the total number of measurements of oxyhemoglobin desaturation of ≥ 3% within ≥ 10 seconds - < 3 minutes from the immediate baseline, divided by the total sleep time (14). Sleep efficiency is defined as the ratio of time spent asleep (total sleep time, TST) to the amount of time spent in bed (TIB).

Evaluation of Osteoarthritis in Knee Joints

Radiographic examination of the knee: Experienced radiologic technicians took weight bearing and anterior-posterior radiographs of both knees before polysomnography. The Kellgren-Lawrence (KL) scoring system was used to evaluate osteoarthritis from grade 0 to 4 by an expert physical therapy and rehabilitation physician who was blinded to the results of the polysomnographic study (15).

Western Ontario and Mcmaster Universities arthritis index: The Western Ontario and McMaster Universities Arthritis (WOMAC) Index is a set of standardized questionnaires used to evaluate the condition of patients with osteoarthritis of the knee, including pain, stiffness, and physical functioning of the joints. The WOMAC measures are pain (score range 0-20), stiffness (score range 0-8), and functional limitation (16).

Statistical Analysis

Statistical analysis was performed using SPSS software, version 16. Fishers' exact test was used to compare variables in different groups. Descriptive analyses were presented as the means and standard deviations. The Kruskal-Wallis test was used to compare parameters between groups. For comparison of the AHI scores among osteoarthritis stages, the Bonferroni procedure was used to correct the Mann-Whitney U test. Linear regression analysis was used to identify factors independently associated with logarithmically converted pain, stiffness and limitation scores. The magnitude of the association is expressed in ORs and 95% CIs.

RESULTS

Main Characteristics of the Patients Included in the Study

In total, 120 patients with osteoarthritis were included; mean age was 52.4 ± 11.5 years, 68 (56%) patients were male, 63 (53%) hypertension, 37 (30%) had diabetes and 30 (25%) had cardiovascular disease. Additionally, 7 (5%) patients had grade 1 osteoarthritis, 20 (16%) patients had grade 2 osteoarthritis, 60 (50%) patients had grade 3 osteoarthritis, and 33 (29%) patients had grade 4 osteoarthritis. Mean AHI score was 32.7 ± 23.3/h. The comparative laboratory and demographic characteristics of the study population based on osteoarthritis stage are shown in Table 1. The sleep study (polysomnography) measurements of the study population based on osteoarthritis stage are shown in Table 2. As shown in Table 2, the AHI score increased progressively from osteoarthritis stage 1 to osteoarthritis stage 4 (Figure 2). Post hoc analysis showed that the AHI scores differed between grades 1 and 3 osteoarthritis ($p< 0.0001$), grades 1 and 4 osteoarthritis ($p< 0.0001$), grades 2 and 3 osteoarthritis ($p< 0.0001$), grades 2 and 4 osteoarthritis ($p< 0.0001$) and even between grades 3 and 4 osteoarthritis ($p= 0.006$).

As the severity of osteoarthritis increased, the prevalence of diabetes, cardiovascular disease and hypertension, BMI, the AHI score and age increased as well (Table 1 and 2, $p< 0.005$). In addition, there were no patients with severe OSA in the grade 1 or grade 2 osteoarthritis group, whereas all patients with grade 3 and 4 osteoarthritis had moderate to severe OSA (Table 1, $p= 0.001$). There was a positive correlation between the AHI and hsCRP ($r= 0.49$, $p< 0.0001$).

Association of Osteoarthritis With Polysomnographic Variables

Osteoarthritis stages were significantly correlated with the AHI (Kendal tau= 0.520, $p< 0.0001$), the oxygen desaturation index (Kendal tau= 0.406, p<

Table 1. The laboratory and demographic characteristics of the study population based on osteoarthritis stage

	Osteoarthritis (grade 1) (n= 7)	Osteoarthritis (grade 2) (n= 20)	Osteoarthritis (grade 3) (n= 60)	Osteoarthritis (grade 4) (n= 33)	p
Age (years)	41.3 ± 4.8	48.4 ± 12.8	53.7 ± 11.4	54.6 ± 19.3	0.007*
Female (n,%)	4 (57.1)	6 (30)	24 (40)	18 (54.5)	0.267**
Hypertension (n,%)	0 (0)	4 20)	35 (58.3)	24 (72.7)	< 0.0001**
Type 2 diabetes (n,%)	2 (28.6)	3 (15)	18 (30)	14 (42.4)	0.215**
CVD (n,%)	1 (14.3)	1 (5)	17 (28.3)	11 (33.3)	0.001**
BMI (kg/m^2)	31.0 ± 7.0	29.6 ± 5.2	32.6 ± 5.8	35.2 ± 5.3	0.003*
Office systolic BP (mmHg)	108.4 ± 10.5	123.2 ± 11.5	137.1 ± 10.3	142.8 ± 6.7	< 0.0001*
Office diastolic BP (mmHg)	70.3 ± 6.2	80.5 ± 9.0	94.2 ± 9.2	98.1 ± 7.5	< 0.0001*
Fasting Blood Glucose (mg/dL)	97.1 ± 16.1	93.8 ± 16.4	113.1 ± 32.6	108.3 ± 25.0	0.039*
Hemoglobin (g/dL)	13.5 ± 0.99	13.6 ± 1.02	16.2 ± 19.5	13.6 ± 1.43	0.916*
HDL-cholesterol (mg/dL)	40.3 ± 8.0	40.3 ± 7.9	37.8 ± 9.2	40.6 ± 10.3	0.280*
LDL- cholesterol (mg/dL)	105.0 ± 17.2	100.5 ± 22.7	116.8 ± 32.0	121.4 ± 26.5	0.048*
Trigylceride (mg/dL)	126.0 ± 47.8	157.6 ± 83.6	208.1 ± 158.2	139.1 ± 63.9	0.036*
HbA1c (%)	6.13 ± 1.93	5.07 ± 0.71	5.99 ± 1.25	6.11 ± 1.59	0.001*
Hs-CRP (mg/L)	0.62 ± 0.78	0.37 ± 0.26	0.71 ± 0.55	0.66 ± 0.59	0.045*
OSA group					
Control group (n,%) (AHI < 5 events/h)	5 (71.4)	6 (30)	1 (1.7)	0	0.001*
Mild OSA group (n,%) (AHI, 5 to 14.9 events/h)	2 (28.6)	10 (50)	9 (15)	0	
Moderate OSA group (n,%) (AHI, ≥ 15 to 29.9 events/h)	0	4 (20)	15 (25)	2 (6.1)	
Severe OSA group (n,%) (AHI > 30 events/h)	0	0	35 (58.3)	31 (93.9)	

* p value is based on Kruskal-Wallis test,
** Fisher's exact test.
CVD: Cardiovascular disease, BMI: Body mass index, BP: Blood pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, Hs-CRP: High sensitivity C-reactive protein, OSA: Obstructive sleep apnea, AHI: Apnea hypopnea index.

Table 2. Polysomnographic variables according to osteoarthritis stage

	Osteoarthritis (grade 1) (n= 7)	Osteoarthritis (grade 2) (n= 20)	Osteoarthritis (grade 3) (n= 60)	Osteoarthritis (grade 4) (n= 33)	p
AHI (/hour)	6.36 ± 2.96	8.82 ± 7.48	35.7 ± 21.4	47.2 ± 19.9	< 0.001*
Oxygen desaturation < 90 % index (%)	0.30 ± 0.48	0.18 ± 0.28	5.41 ± 12.4	7.21 ± 9.63	< 0.0001*
Oxygen desaturation index (/hour)	2.6 ± 1.39	4.64 ± 4.10	24.67 ± 21.79	35.56 ± 23.46	< 0.0001*
Mean SaO_2 (%)	96.9 ± 1.46	95.7 ± 1.35	95.0 ± 2.55	95.6 ± 1.34	0.07*
Minimum SaO_2 (%)	84.3 ± 10.9	87.9 ± 4.47	79.2 ± 13.2	75.2 ± 9.93	< 0.0001*

*p value is based on Kruskal-Wallis test. AHI: Apnea hypopnea index, REM: Rapid eye movement.

0.0001), minimum oxygen saturation (Kendal tau= -0.359, p< 0.0001), and mean oxygen saturation (Kendal tau= -0.215, p= 0.004).

Multivariate Linear Regression Analysis

Multiple linear regression analyses were performed to determine the association between the independent variables, including the AHI score, age, gender, BMI, diabetes, hypertension, presence of cardiovascular disease, hsCRP and the Kellgren-Lawrence (KL) scores of pain, stiffness and limitation. Results of these analyses are shown in Tables 3,4 and 5. The AHI score was independently associated with the pain, stiffness and limitation scores (Table 3, 4 and 5). Lastly, we made linear regression analysis to define independent variables (including OA grade, age, gender, BMI, hypertension, diabetes, cardiovascular

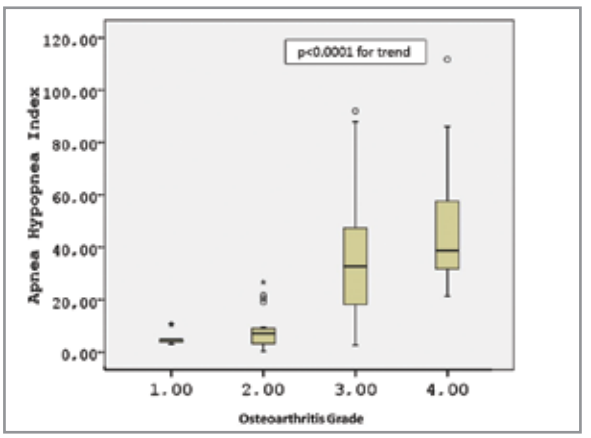

Figure 2. Apnea hypopnea scores according to the severity of osteoarthritis.

Table 3. Linear regression analysis with the Western Ontario and McMaster Universities Arthritis (WOMAC) Index pain score

	β	CI for β	Beta	p
Gender	0.345	0.208-0.482	0.486	< 0.0001
Age	0.017	0.010-0.024	0.458	< 0.0001
BMI	0.004	-0.009-0.018	0.072	0.512
Diabetes	0.076	-0.059-0.211	0.103	0.265
Hypertension	0.032	-0.112-0.177	0.044	0.659
CVD	-0.050	-0.192-0.092	-0.65	0.484
hs-CRP	0.152	0.0276-0.027	0.242	0.018
AHI	0.006	0.003-0.009	0.400	< 0.0001

β: Partial regression coefficient, CI: Confidence interval, Beta: Partial correlation coefficient, CVD: Cardiovascular disease, BMI: Body mass index, Hs-CRP: High sensitivity C-reactive protein, AHI: Apnea hypopnea index.

Table 4. Linear regression analysis with the Western Ontario and McMaster Universities Arthritis (WOMAC) Index stiffness score

	β	CI for β	Beta	p
Gender	0.156	0.086-0.226	0.314	< 0.0001
Age	0.018	0.014-0.021	0.750	< 0.0001
BMI	0.004	-0.003-0.011	0.102	0.220
Diabetes	-0.011	-0.083-0.061	-0.021	0.762
Hypertension	-0.036	-0.112-0.040	0.072	0.347
CVD	-0.066	-0.142-0.011	0.118	0.093
hs-CRP	0.062	0.006-0.130	0.138	0.073
AHI	0.002	0.001-0.003	0.161	0.040

β: Partial regression coefficient, CI: Confidence interval, Beta: Partial correlation coefficient, CVD: Cardiovascular disease, BMI: Body mass index, Hs-CRP: High sensitivity C-reactive protein, AHI: Apnea hypopnea index.

Table 5. Linear regression analysis with Western Ontario and McMaster Universities Arthritis (WOMAC) Index limitation score

	β	CI for β	Beta	p
Gender	0.354	0.234-0.474	0.386	< 0.0001
Age	0.027	0.021-0.032	0.628	< 0.0001
BMI	0.006	-0.005-0.018	0.083	0.270
Diabetes	0.019	-0.105-0.142	0.019	0.767
Hypertension	0.105	-0.021-0.230	0.114	0.102
CVD	-0.108	-0.239-0.023	-0.105	0.104
hs-CRP	0.120	0.003-0.238	0.143	0.045
AHI	0.005	0.002-0.008	0.248	0.001

β: Partial regression coefficient, CI: Confidence interval, Beta: Partial correlation coefficient, CVD: Cardiovascular disease, BMI: Body mass index, Hs-CRP: High sensitivity C-reactive protein, AHI: Apnea hypopnea index.

Table 6. Linear regression analysis with apnea hypopnea index

	β	CI for β	Beta	p
Osteoarthritis grade	0.343	0.270-0.416	0.640	0.0001
Gender	-0.079	-0.205-0.46	-0.085	0.212
Age	-0.006	-0.012-(-)0.001	-0.160	0.022
BMI	0.006	-0.006-0.018	0.074	0.337
Diabetes	-0.046	-0.181-0.089	-0.046	0.499
Hypertension	0.099	-038-0.235	0.106	0.154
CVD	-0.051	-0.195-0.092	-0.048	0.480
hs-CRP	0.185	0.068-0.302	0.217	0.002

β: Partial regression coefficient, CI: Confidence interval, Beta: Partial correlation coefficient, CVD: Cardiovascular disease, BMI: Body mass index, Hs-CRP: High sensitivity C-reactive protein, AHI: Apnea hypopnea index.

disease, hsCRP) related with logarithmically converted AHI score. Age, OA grade and hsCRP were independently related with AHI (Table 6).

DISCUSSION

The present study reveals a strong relationship between OSA and osteoarthritis. The prevalence of osteoarthritis is significantly high in OSA patients compared with subjects without OSA. In addition, we also showed that the severity of OSA is independently associated with the severity of osteoarthritis. As far as we know, this is the first study in the literature that shows such a strong association.

Obesity is a well-established risk factor for osteoarthritis of weight bearing joints, such as the hips and knees, with mechanical overload being the causative link (17,18). However, overweight and obese people also have an increased risk of osteoarthritis in their hands, which are not weight-bearing, implicating systemic factors in the obesity-osteoarthritis connection (19). Studies have also identified obesity as a predictor of osteoarthritis in non-weight bearing joints, supporting the influence of a systemic metabolic effect whereby adipose tissue secretes inflammatory mediators, which directly cause cartilage degeneration (18,20). In our study, the possible explanations for the increased prevalence and severity of osteoarthritis in OSA patients are age and BMI, both of which are higher and are independent risk factors for osteoarthritis in OSA patients compared with patients without OSA (17,21). However, although age and BMI were similar among the mild, moderate and severe OSA groups, the prevalence and severity of osteoarthritis were significantly higher in the moderate and severe OSA groups. This association was independent of other risk factors for osteoarthritis, including increased BMI. Therefore, we speculate that OSA may be a risk factor for the development of osteoarthritis.

The pathogenesis of osteoarthritis involves abnormalities in common metabolic intermediates, including glucose, hormones, several growth factors, transcription factors, nitric oxide and reactive oxygen species (22). Assessment of the role of inflammatory mediators in intervertebral disc degeneration has consistently shown that cytokines, such as tumour necrosis factor-α, interleukin-6, and nitric oxide, are present in higher concentrations in degenerative discs and likely play a role in disease progression (23). In addition, previous studies showed that degenerative disc disease is believed to be mediated through atherosclerosis, insufficient blood supply and high blood pressure (24). It is well known that OSA significantly increases the aforementioned inflammatory mediators and is also an independent risk factor for increased blood pressure and insufficient blood supply to organs (12,25,26). In addition, OSA exacerbates hypoxia at the tissue level, which also triggers chronic inflammation, macrophage infiltration, reduction of adiponectin level, elevation of leptin level, adipocyte death, endoplasmic reticulum stress, and mitochondrial dysfunction, all of which may play a role in the development of osteoarthritis (11,27). Additionally, we also found a strong positive correlation between OSA and inflammation, which was defined by hs-CRP. In light of the previous studies and our findings, we speculate that in addition to other risk factors, increased inflammation seen in OSA could be important predisposing risk factors for the development and severity of osteoarthritis.

The current study has limitations. First, a cause and effect relationship cannot be drawn in such a study due to its design and observational nature. Second, temporal relationships cannot be assumed, and it would be more prudent to prospectively determine whether the presence of OSA would translate into worse outcomes in osteoarthritis. Third, the selected patients were from a single center, and generalizability is limited. Finally, the number of patients with grade 1 and 2 osteoarthritis was low.

In conclusion, we have demonstrated that there is a strong relationship between OSA and OA. OSA might a novel risk factor for osteoarthritis. Further studies are warranted to elucidate the underlying mechanisms for this, and randomized-controlled trials with a larger sample-size are needed to determine causality in addition to the effect of treatment of OSA on the severity and progression of osteoarthritis.

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