Original Research Article

Is the radiological stage of knee osteoarthritis associated with the risk of obstructive sleep apnea or insomnia severity?

Arzu Dinç Yavaş[1]*, Ayşe Serap Akgün[2]

[1]İstanbul Aydın University, School of Medicine PMR, İstanbul, Turkey
[2]İstanbul Medipol University, School of Medicine Radiology, İstanbul, Turkey

*Correspondence:
Dr. Arzu Dinç Yavaş,
E-mail: arzudinc0111@gmail.com

ABSTRACT

Background: Aim was to investigate the relationship between knee osteoarthritis severity and obstructive sleep apnea risk and insomnia severity

Methods: A total of 127 patients with knee osteoarthritis were included in this prospective cross-sectional study. The relationship between Kellgren-Lawrence classification, Western Ontario and McMaster University Osteoarthritis Index score, Berlin questionnaire score, Insomnia Severity Index score, age, sex, and body-mass index was evaluated with univariate and multivariate analyses.

Results: The mean age of the radiological stage 1 group was significantly lower compared to the other group (p<0.001). 84.3% of all patients were female, and there was no significant sex difference between the groups (p=0.327). The median WOMAC scores of the stage 2, 3 and 4 groups were significantly higher than that of the stage 1 group (p<0.001). The median WOMAC pain subscore of the stage 3 and 4 groups were significantly higher than that of the stage 2 and the stage 1 group (p<0.001). Multiple logistic regression analysis revealed that high BMI (p=0.005) was the only factor independently associated with greater OSA risk. Multiple linear regression analysis revealed that sex (p=0.008) and WOMAC score (p=0.001) were independently associated with greater insomnia severity.

Conclusions: In multivariable analysis, high BMI was determined as the only independent risk factor associated with higher OSA likelihood, while advanced age and high WOMAC total score were determined as independent risk factors for greater insomnia severity. The WOMAC score can be used to predict the severity of osteoarthritis and insomnia, and could be valuable for management.

Keywords: Osteoarthritis, Insomnia, Apnea

INTRODUCTION

Osteoarthritis is the most common musculoskeletal disease and is one of the most common chronic health problems among adults.[1,2] It is characterized by progressive destruction of articular cartilage and changes in the structural parts of the joint, including bone, ligaments, muscles, capsule, meniscus, and synovial membrane. It causes joint pain, movement restriction, and poor quality of life.[2,3] Chronic pain and poor quality of life as a result of osteoarthritis can bring along various sleep disturbances which may worsen pain and pain-related adversities.[2,4-6] To break this vicious cycle, it is important to understand the impact of osteoarthritis on sleep and its relationship to common sleep disorders.[1] Obstructive sleep apnea (OSA) is a chronic sleep-related respiratory disorder. It is thought that the increase in the proportion of the elderly population and the incidence of obesity play an important role in the increasing incidence of OSA.[2,7,8] The same factors are also associated with an increased incidence of osteoarthritis.[1,9,10]

In one study, it was argued that OSA and osteoarthritis are risk factors for each other with various common molecular and physical mechanisms, and common treatment modalities for the two diseases were investigated.[2] Insomnia is another common sleep disturbance that is defined as insufficient sleep related to deficiencies in starting or maintaining sleep.[1,4] In one study, the incidence of insomnia in patients with symptomatic osteoarthritis was reported to be 62.9%.[1]

In a cluster-randomized controlled trial, it was reported that 76% of patients with osteoarthritis had OSA and/or insomnia.[4] This positive feedback cycle associated with obesity, pain, age, and sleep problems has encouraged many researchers to examine the relationship between osteoarthritis, OSA and insomnia. However, there are few studies examining the risk of OSA and the severity of insomnia in patients with osteoarthritis.[11] This is an important gap in knowledge since the severity of osteoarthritis may impact the severity of OSA or insomnia, as well as their likelihood.

Aim and objectives

Therefore, our primary aim with this study was to investigate whether the radiological stage of knee osteoarthritis was associated with OSA risk and insomnia severity. Our secondary aims were to determine risk factors associated with these two sleep disorders in patients with knee osteoarthritis and to assess the relationship between radiological knee osteoarthritis stage and severity of pain and disability.

METHODS

Study design

The study was conducted at the department of physical medicine and rehabilitation and department of radiology, of Medipol University Hospital between September 2019 and December 2020 in compliance with the 1964 Helsinki declaration and its later amendments. Written informed consent was acquired from all participants.

Study population

Patients whose information were incomplete and whose questionnaires were not filled, patients with known psychiatric disorders, cases with metabolic bone disease, patients consuming alcohol and/or using opioids and/or abusing substances, patients with known OSAS using active positive airway pressure therapy, those who had concurrent rheumatic or knee disorders, subjects with severe comorbidities, and those receiving cancer therapy for active cancer were excluded from the study. Patients who did not meet the exclusion criteria, which were mentioned above, were first categorized according to their radiological stages. A total of 127 patients with symptomatic knee osteoarthritis at various stages based on radiographic evidence were included in the study.[12]

Data and instruments used

Sociodemographic data such as age and sex of the patients were recorded, height and weight measurements were made and body mass indexes (BMI) were calculated as weight/height^2 (kg/m^2).

Knee osteoarthritis diagnosis and staging

Patients with knee osteoarthritis were diagnosed according to the diagnostic criteria of the American college of rheumatology.[13] The grade of knee osteoarthritis was determined according to the Kellgren-Lawrence Classification using anteroposterior and mediolateral knee radiography.[12] In this staging system, 5 stages are determined according to the severity of osteophytes, joint space, sclerosis and deformity of bony ends. Stage 0 indicates the absence of osteoarthritis and stage 4 indicates severe osteoarthritis. According to this classification, there were 31 patients in the stage 1 group, 32 patients in the stage 2 group, 33 patients in the stage 3 group, and 31 patients in the stage 4 group.

Western Ontario and McMaster University Osteoarthritis Index (WOMAC)

The WOMAC Osteoarthritis Index is one of the most commonly used, patient-filled osteoarthritis severity scoring systems for patients with lower extremity osteoarthritis.[14] The questionnaire contains 24 items covering three dimensions: pain (5 items), stiffness (2 items) and physical function (17 items). The questions in each item are scored by the patient according to the last 2 weeks with a score between 0-4 relating to increasing severity. Then scoring in percentages is calculated with the following formula:[15]

$$Percentage = (total\ score \div 96) \times 100$$

The pain subscore of the WOMAC index was used to determine the severity of pain. The scores between 0 and 4 for each of the 5 items were summed, so that a minimum of 0 and a maximum of 20 points were obtained to quantify pain.

Berlin questionnaire

The Berlin questionnaire was developed as a tool for OSA screening. It classifies patients as high or low risk for OSA based on self-reports of snoring, wake-time sleepiness or fatigue, hypertension and obesity.[16,17] The questionnaire consists of a total of 10 questions, 5 in category 1 (related to snoring and dyspnea), 4 in category 2 (related to fatigue, weakness and driving problems), and 1 in category 3 related to the presence of hypertension or obesity (BMI >30 kg/m^2).

The presence of two or more symptoms in categories 1 and 2, and one or more symptoms in category 3 was considered significant for each of the categories separately. Patients

with 2 or more significant categories were classified as high risk and others as low risk for OSA.[17]

Insomnia severity index (ISI)

The Insomnia Severity Index is a system consisting of 5 questions about sleep problems. Since the first question has 3 subgroups, it is evaluated over 7 questions in total. Each question was answered by the patient with an increasing score from 0 to 4. Scores range from a minimum of 0 points (clinically insignificant insomnia) and a maximum of 28 points (severe insomnia).[18]

Outcomes

The primary outcome of this study was to examine whether the radiological stage of knee osteoarthritis was associated with OSA risk and insomnia severity, and the secondary outcomes were to identify risk factors associated with insomnia severity and OSA risk in patients with knee osteoarthritis and to demonstrate the relationship between the radiological stage of osteoarthritis and symptom severity and other factors.

Statistical analysis

All analyses, with a significance threshold of p < 0.05, were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test the normality of distribution of continuous variables. For continuous data, summary values are given as mean ± standard deviation or median (1st to 3rd quartiles) according to normal or non-normal distribution, respectively. Absolute and relative frequency (percentage) values were used to summarize categorical variables. Normally distributed continuous variables were analyzed with the one-way analysis of variances (ANOVA). Non-normally distributed continuous variables were analyzed with the Kruskal-Wallis test. Categorical variables were analyzed with the chi-square test or Fisher-Freeman-Halton test. Pairwise comparisons were adjusted by Bonferroni correction method. Logistic regression analyses were performed to determine significant factors independently associated with high risk of OSA. Linear regression analyses were performed to determine significant factors independently associated with high insomnia severity. Variables were analyzed with univariable regression analysis and statistically significant variables were included into multivariable analysis.

RESULTS

Overall mean age was 56.8±11.2 years. While the mean age of the stage 1 group (46.3±11.2) was significantly lower compared to the other groups, mean ages were similar for the other three groups (57.9±8.3 vs. 60.0±7.8 vs. 62.6±10.2, respectively) (p<0.001). The great majority

of patients were females in all four groups, and the groups were similar with regard to sex distribution (p=0.327).

The stage 4 group's median BMI was significantly higher than the those in stage 2, and the stage 2 group's median BMI was significantly higher than those in stage 1 (p<0.001).

Table 1: Summary of all patients' demographic characteristics and other variables.

Parameters	N (%)
Mean age±SD	56.80±11.20
Sex	
Female	107 (84.3%)
Male	20 (15.7%)
Body mass index	31.6 (28.4-35.7)
Osteoarthritis	
Stage 1	31 (24.4%)
Stage 2	32 (25.2%)
Stage 3	33 (26.0%)
Stage 4	31 (24.4%)
WOMAC score, % (range)	52.08 (29.16-69.79)
WOMAC pain score, % (range)	8 (4-12)
Berlin questionnaire score (%)	
Low risk	50 (39.4)
High risk	77 (60.6)
Insomnia Severity Index score, % (range)	9 (4-15)

Data are given as mean±SD or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

The median WOMAC scores of the stage 2, 3 and 4 groups were similar and significantly higher than that of the stage 1 group (p<0.001). The median WOMAC pain subscore of the stage 3 and 4 groups were similar to each other and significantly higher than that of the stage 2 group, while the median WOMAC pain subscore of the stage 2 group was found to be significantly higher than that of the stage 1 group (p<0.001). The percentage of patients with high risk according to the Berlin questionnaire in the stage 4 group was significantly higher than that of the stage 1 group (p=0.003); whereas the stage 2 and stage 3 groups had similar results with other groups.

The summary data of participants according to osteoarthritis stage are presented in (Table 1-2). Multiple logistic regression analysis revealed that high BMI (p = 0.005) was the only factor independently associated with high risk of OSA (as determined by Berlin score) (Table 3). Multiple linear regression analysis revealed that sex (p=0.008) and WOMAC score (p=0.001) were independently associated with high insomnia severity (according to ISI score). We found male patients had lower ISI score than female patients, while higher WOMAC score was associated with higher ISI score (Table 4).

Table 2: Summary of variables and analysis results with regard to osteoarthritis stage.

Parameters	Osteoarthritis				P value
	Stage 1 (N=31)	Stage 2 (N=32)	Stage 3 (N=33)	Stage 4 (N=31)	
Age	46.32±11.19[a]	57.97±8.26[b]	60.03±7.83[b]	62.61±10.21[b]	<0.001
Sex (%)					
Female	26 (83.9)	30 (93.8)	26 (78.8)	25 (80.6)	0.327
Male	5 (16.1)	2 (6.3)	7 (21.2)	6 (19.4)	
Body mass index	28.1 (26.2-31.0)[a]	31.2 (28.8-34.75)[b]	32.4 (29.7-35.6)[b,c]	38.5 (31.6-41.0)[c]	<0.001
WOMAC score, % (range)	22.91 (6.25-44.79)[a]	52.08 (33.00-65.10)[b]	59.37 (39.58-71.87)[b]	62.50 (51.04-72.90)[b]	<0.001
WOMAC pain score, % (range)	3 (1-4)[a]	6 (4-8)[b]	11.5 (8.5-14)[c]	12 (11-15)[c]	<0.001
Berlin Questionnaire score (%)					
Low risk	20 (64.5)	13 (40.6)	11 (33.3)	6 (19.4)	0.003
High risk	11 (35.5) [a]	19 (59.4)[ab]	22 (66.7)[a.b]	25 (80.6)[b]	
Insomnia Severity Index score	8 (2-14)	8 (5-17)	7 (4-13)	12 (6-17)	0.414

Data are given as mean±SD or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Same letters denote the lack of statistically significant difference between groups.

Table 3: Significant factors independently associated with high risk of sleep apnea syndrome, logistic regression analysis results.

Parameters	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.031 (0.998-1.065)	0.068	-	-
Sex, Male	0.759 (0.290-1.990)	0.575	-	-
Body mass index	1.190 (1.093-1.297)	<0.001	1.150 (1.044-1.267)	0.005
Osteoarthritis				
Stage 2	2.657 (0.959-7.364)	0.060	0.795 (0.227-2.787)	0.719
Stage 3	3.636 (1.296-10.207)	0.014	0.427 (0.056-3.246)	0.411
Stage 4	7.576 (2.386-24.058)	0.001	0.477 (0.045-5.055)	0.539
WOMAC score	1.036 (1.019-1.053)	<0.001	1.013 (0.984-1.043)	0.379
WOMAC pain score	1.217 (1.111-1.334)	<0.001	1.166 (0.892-1.525)	0.261
Nagelkerke R^2	-		0.323	

Table 4: Significant factors independently associated with greater insomnia severity, linear regression analysis results.

Parameters	Univariable			Multivariable		
	Unstandardized coefficients (95% CI)	Standardized coefficients	P value	Unstandardized coefficients (95% CI)	Standardized coefficients	P value
Age	-0.007 (-0.115-0.102)	-0.011	0.906	-	-	-
Sex, Male	-5.366 (-8.552-2.180)	-0.286	0.001	-4.308 (-7.492-1.125)	-0.225	0.008
Body mass index	-0.003 (-0.184-0.178)	-0.003	0.975	-	-	-
Osteoarthritis						
Stage 2	1.877 (-1.547-5.301)	0.119	0.280	-	-	-
Stage 3	-0.148 (-3.546-3.251)	-0.009	0.932	-	-	-
Stage 4	2.258 (-1.193-5.709)	0.142	0.198	-	-	-
WOMAC score	0.098 (0.054-0.142)	0.369	<0.001	0.113 (0.046-0.180)	0.422	0.001
WOMAC pain score	0.287 (0.029-0.544)	0.194	0.029	-0.186 (-0.550-0.179)	-0.126	0.315
Adjusted R^2	-			0.178		
Regression model	-			F=10.025, p<0.001		

DISCUSSION

The number of studies investigating the relationship between the radiological stage of knee osteoarthritis and the risk of OSA and the severity of insomnia is quite limited. In the present study, it was observed that the risk of OSA increased with higher osteoarthritis stage. In addition, mean age, median BMI, median WOMAC total score and pain subscore were significantly higher in patients with more advanced radiological stage of osteoarthritis. However, BMI was the only independent risk factor associated with greater risk of OSA in patients with osteoarthritis. The risk factors independently associated with greater severity of insomnia in patients with osteoarthritis were female sex and high WOMAC total score.

Osteoarthritis and OSA may seem like two unrelated diseases, but have many common features, including aging and metabolic disorders (obesity, molecular mechanisms, cardio-metabolic disorders, sleep deprivation and depression etc.).[2,11] The multivariable results of this study did not identify osteoarthritis stage as a factor independently associated with greater OSA risk. However, in univariate analysis, the percentage of patients with high OSA risk in the stage 4 group (80.6%) was found to be significantly higher than those in stage 1 (35.5%).

The higher BMI of high-stage patients may have been effective in the formation of these results. In a cluster-randomized controlled study, similarly, high BMI was cited as one of the risk factors associated with an increased risk of OSA.[4] Contrarily, in a study investigating the relationship between the severity of OSA determined by polysomnography and the severity of osteoarthritis determined by the Kellgren-Lawrence scoring system, a strong positive correlation was found between the severity of the two diseases, independent of BMI, and it was concluded that OSA could be an important novel risk factor for osteoarthritis.[11]

Interestingly, Diaz et al reported that osteoarthritis increased the risk of new-onset OSA in the elderly, but was not associated with chronic OSA.[19] In another study, although more than one-third of patients were at high risk for OSA, being at high risk did not yield a significant influence on risk.[20] However, in the comprehensive analysis of Gaspar et al it was concluded that both diseases may be risk factors for each other. As a rationale, it has been shown that the hallmark features of OSA increase pain perception, fatigue and depression, which in turn decreases sleep quality and quality of life and increases osteoarthritis-related depression in osteoarthritis patients with OSA. They also noted that chronic pain in osteoarthritis patients causes loss of movement, sedentary lifestyle, and sleep disturbance, which may contribute to obesity thereby increasing OSA risk.[2] Although clinical data appears to be somewhat supportive of possible relationships between the two diseases, clarifying common molecular and physical mechanisms between the two diseases and solving the obesity problem (by considering it as both a cause and a result), can benefit management, especially among people with both diseases. Moreover, identification of these common mechanisms could lead to medical treatments that can be effective in both diseases.

Insomnia is another common sleep disturbance, so its association with osteoarthritis is worth investigating, and many researchers have done so.[1,21,22] While no significant relationship was found between the severity of insomnia and the severity of the radiological stage of osteoarthritis in the current study, a high WOMAC total score, which is an indicator of the clinical severity of osteoarthritis, was found to be an independent risk factor associated with greater severity of insomnia. Female sex was found as another risk factor for insomnia severity. In a population-based study investigating sleep problems, it was noted that symptomatic hip or knee osteoarthritis was independently associated with an increased likelihood of reporting sleep problems, insomnia, and insufficient sleep.[1] The increased pain and decreased physical function in osteoarthritis are likely to be related to insomnia. It is thought that insomnia caused by pain contributes to the disruption of central pain modulatory processes, and thus exacerbating insomnia.[22,23-25] Smith et al. investigated the possibility of treating insomnia to improve these centrally-regulated features of osteoarthritis pain and achieved positive results.[21] A cluster-randomized controlled trial indicated that the factors associated with insomnia severity in patients with osteoarthritis were older age, post-traumatic stress disorder diagnosis, high WOMAC pain score, and presence of depressive symptoms.[4] Contrary to this highly probable relationship between osteoarthritis pain and insomnia, the current study's multivariable analysis did not reveal a significant relationship between insomnia severity and pain score. On the other hand, the significant effects of total WOMAC score and female sex on the severity of insomnia could indicate other mechanisms (in addition to pain) that could elevate the risk of insomnia in osteoarthritis. Consistent with the results of this study, in a community cohort with hip/knee osteoarthritis, higher WOMAC score was shown as an independent risk factor for poor sleep.[26] The association of WOMAC score with sleep disorders has been replicated in other studies.[27,28] In addition, while there was no significant relationship between the radiological staging of osteoarthritis and insomnia, the significant relationship between total WOMAC score and insomnia could indicate that WOMAC score might be a more effective indicator in evaluating the severity of osteoarthritis-related sleep problems. Consistent with the literature the higher number of female patients with osteoarthritis in this study may have been effective in this effect of sex on sleep disturbance.[29,30] Additionally, the effect of hormonal changes and/or menopausal status on sleep and mood may be another reason for obtaining these results. We think that the clarification of these relationships with more comprehensive studies may contribute to the management of these two frequently co-occurring diseases.

In this study, we also examined the relationship with osteoarthritis radiological stage and age, sex, BMI, osteoarthritis clinical severity and osteoarthritis-related pain severity. We found that advanced age, high BMI, high WOMAC total score and pain subscore were positively associated with the radiological stage of osteoarthritis. Allen et al. found that patients with symptomatic osteoarthritis had significantly higher BMI and age compared to non-symptomatic patients, but surprisingly, obesity was not found to be associated with sleep problems.[1] It has been well-established that advanced age and obesity are risk factors for osteoarthritis.[2,10,31,32] Although the incidence of osteoarthritis increases with age, secondary osteoarthritis cases that occur as a result of joint injury are common among young individuals.[2,33] It is thought that advanced age contributes to the formation of osteoarthritis through multiple mechanisms, including increased adiposity, loss of skeletal muscle mass, alteration of circadian rhythm, and changes in age-related markers.[2,9,34-37] The relationship between obesity and osteoarthritis is explained with mechanical stress, increased adipocytes, and increased pro-inflammatory macrophages in adipose tissue.[2] Since osteoarthritis is a disease with joint degeneration, pathologies such as joint pain, stiffness and physical dysfunction are expected. WOMAC is used to determine the severity of these three domains and therefore, WOMAC scores could correlate with radiological stage of osteoarthritis.[27] While Cubukcu et al. found a significant relationship between the Kellgren-Lawrence rating scale and age or disease duration, they did not find any of the WOMAC subscores to be associated with the Kellgren-Lawrence rating scale, contrary to our results.[29] Some other studies also support these findings.[38,39] In another study, a significant relationship between radiological scoring and WOMAC score was mentioned.[40] One reason for the differences among studies may be that the WOMAC scoring is a self-reported scoring system, which may have the potential to affect the results. Another reason may be that, although the radiological classification is based on objective findings, there are likely to be observational differences among classifiers. Therefore, until the relationship between radiological and clinical severity assessment methods is clarified, it seems more logical to interpret the results of these two methods together.

The fact that this is a single-center study limits our ability to generalize the results. If there was a control group in the comparison of some parameters, the results might have been more valuable in terms of advanced interpretations. The lack of some factors that may affect the results of the instruments used in the study, such as poor overall health, psychological distress, social support, education, socioeconomic status, menopausal status, laboratory disorders and the drugs used, also appear to limit the conclusions.[14,20,26,41] Polysomnography, which is the gold standard of assessment, could not be used to assess OSA due to the difficulty of implementation, difficulty in patient acceptance, and ethical problems. Instead, the Berlin questionnaire, which only performs OSA risk classification, was used. However, the place of the Berlin questionnaire in the diagnosis of OSA is controversial.[16] Many of the instruments are self-reported and the lack of more objective tools may have affected the reliability of the results. Although regression analysis minimizes confounding effects caused by differences in age, BMI and other factors, these factors may have influenced outcomes.

CONCLUSION

In conclusion, our univariate analyses showed that advanced age, high BMI, high WOMAC total score, high WOMAC pain subscore, and high OSA risk were associated with greater radiological stage of knee osteoarthritis. In multivariable analysis, high BMI was determined as the only independent risk factor associated with higher OSA likelihood, while advanced age and high WOMAC total score were determined as independent risk factors for greater insomnia severity. Patients with a high BMI have an increased risk of OSA; therefore, weight loss therapy may be beneficial for osteoarthritis patients with higher BMI. Patients with a high WOMAC score can be expected to have higher radiological osteoarthritis stage and insomnia severity. Therefore, the WOMAC score can be used to predict the severity of osteoarthritis and insomnia and to develop management modalities for them. Given the risk of sleep problems exacerbating pain and disability from osteoarthritis, we recommend taking additional precautions for both insomnia and OSA among these subjects. However, more comprehensive studies are needed to investigate and manage osteoarthritis-specific sleep disorders, with the inclusion of various factors associated with sleep health.

REFERENCES

1. Allen KD, Renner JB, Devellis B, Helmick CG, Jordan JM. Osteoarthritis and sleep: the Johnston County Osteoarthritis Project. J Rheumatol. 2008;35(6):1102-7.
2. Gaspar LS, Sousa C, Álvaro AR, Cavadas C, Mendes AF. Common risk factors and therapeutic targets in obstructive sleep apnea and osteoarthritis: An unexpected link? Pharmacol Res. 2021;164:105369.
3. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393(10182):1745-59.
4. Taylor SS, Hughes JM, Coffman CJ, Jeffreys AS, Ulmer CS, Oddone EZ, et al. Prevalence of and characteristics associated with insomnia and obstructive sleep apnea among veterans with knee and hip osteoarthritis. BMC. 2018;19(1):79.
5. Smith MT, Quartana PJ, Okonkwo RM, Nasir A. Mechanisms by which sleep disturbance contributes

to osteoarthritis pain: a conceptual model. Curr Pain Headache Rep. 2009;13(6):447-54.

6. Power JD, Perruccio AV, Badley EM. Pain as a mediator of sleep problems in arthritis and other chronic conditions. Arthr Rheumat. 2005;53(6):911-9.

7. Darien I. International classification of sleep disorders. Am Acad Sleep Med. 2014.

8. Peppard PE, Hagen EW. The Last 25 Years of Obstructive Sleep Apnea Epidemiology-and the Next 25? Am J Resp Critical Care Med. 2018;197(3):310-2.

9. Xie J, Wang Y, Lu L, Liu L, Yu X, Pei F. Cellular senescence in knee osteoarthritis: molecular mechanisms and therapeutic implications. Age Res Rev. 2021;70:101413.

10. Raud B, Gay C, Guiguet-Auclair C, Bonnin A, Gerbaud L, Pereira B, et al. Level of obesity is directly associated with the clinical and functional consequences of knee osteoarthritis. Sci Rep. 2020; 10(1):3601.

11. Kanbay A, Köktürk O, Pıhtılı A, Ceylan E, Tulu S, Madenci E, et al. Obstructive sleep apnea is a risk factor for osteoarthritis. Tuberkuloz Ve Toraks. 2018; 66(4):304-11.

12. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheumat Dis. 1957;16(4):494-502.

13. Bonnin A. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthr Rheumat. 2000;43(9):1905-15.

14. Walker LC, Clement ND, Deehan DJ. Predicting the Outcome of Total Knee Arthroplasty Using the WOMAC Score: A Review of the Literature. J Knee Surg. 2019;32(8):736-41.

15. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumat. 1988;15(12):1833-40.

16. Ng SS, Tam W, Chan TO, To KW, Ngai J, Chan KKP, et al. Use of Berlin questionnaire in comparison to polysomnography and home sleep study in patients with obstructive sleep apnea. Resp Res. 2019;20(1):40.

17. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Int Med. 1999;131(7):485-91.

18. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297-307.

19. Diaz K, Faverio P, Hospenthal A, Restrepo MI, Amuan ME, Pugh MJ. Obstructive sleep apnea is associated with higher healthcare utilization in elderly patients. Ann Thorac Med. 2014;9(2):92-8.

20. Taylor-Gjevre RM, Gjevre JA, Nair B, Skomro R, Lim HJ. Components of sleep quality and sleep fragmentation in rheumatoid arthritis and osteoarthritis. Musculoskelet Care. 2011;9(3):152-9.

21. Smith MT, Finan PH, Buenaver LF, Robinson M, Haque U, Quain A, et al. Cognitive-behavioral therapy for insomnia in knee osteoarthritis: a randomized, double-blind, active placebo-controlled clinical trial. Arthr Rheumat. 2015;67(5):1221-33.

22. Petrov ME, Goodin BR, Cruz-Almeida Y, King C, Glover TL, Bulls HW, et al. Disrupted sleep is associated with altered pain processing by sex and ethnicity in knee osteoarthritis. J Pain. 2015;16(5):478-90.

23. Lee YC, Lu B, Edwards RR, Wasan AD, Nassikas NJ, Clauw DJ, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. Arthr Rheumat. 2013;65(1):59-68.

24. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep. 2007;30(4):494-505.

25. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. Arthr Rheumat. 2013;65(2):363-72.

26. Hawker GA, French MR, Waugh EJ, Gignac MA, Cheung C, Murray BJ. The multidimensionality of sleep quality and its relationship to fatigue in older adults with painful osteoarthritis. Osteoarthr Cartil. 2010;18(11):1365-71.

27. Silva A, Mello MT, Serrão PR, Luz RP, Ruiz F, Bittencourt LR, et al. Influence of Obstructive Sleep Apnea in the Functional Aspects of Patients With Osteoarthritis. JCSM. 2018;14(2):265-70.

28. Parimi N, Blackwell T, Stone KL, Lui LY, Ancoli-Israel S, Tranah GJ, et al. Hip pain while using lower extremity joints and sleep disturbances in elderly white women: results from a cross-sectional analysis. Arthr Care Res. 2012;64(7):1070-8.

29. Cubukcu D, Sarsan A, Alkan H. Relationships between Pain, Function and Radiographic Findings in Osteoarthritis of the Knee: A Cross-Sectional Study. Arthritis. 2012;2012:984060.

30. Hussain S, Cicuttini F, Alyousef B, Wang Y. Female hormonal factors and osteoarthritis of the knee, hip and hand: a narrative review. Climacteric. 2018;21(2):132-9.

31. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthr Cartil. 2015;23(4):507-15.

32. Wang T, He C. Pro-inflammatory cytokines: The link between obesity and osteoarthritis. Cytokine & growth factor reviews. Arthr Rheumat. 2018;44:38-50.

33. Riordan EA, Little C, Hunter D. Pathogenesis of post-traumatic OA with a view to intervention. Best Pract Res Clin Rheumatol. 2014;28(1):17-30.

34. Tchkonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, Scrable H, et al. Fat tissue, aging, and cellular senescence. Aging cell. 2010; 9(5):667-84.
35. Marzetti E, Hwang AC, Tosato M, Peng LN, Calvani R, Picca A, et al. Age-related changes of skeletal muscle mass and strength among Italian and Taiwanese older people: Results from the Milan EXPO 2015 survey and the I-Lan Longitudinal Aging Study. Experiment Gerontol. 2018;102:76-80.
36. Sato S, Solanas G, Peixoto FO, Bee L, Symeonidi A, Schmidt MS, et al. Circadian reprogramming in the liver identifies metabolic pathways of aging. Cell. 2017;170(4):664-77. e11.
37. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6): 1194-217.
38. Rupprecht T, Oczipka F, Lüring C, Pennekamp P, Grifka J. Is there a correlation between the clinical, radiological and intrasurgical findings of osteoarthritis of the knee? A prospective study on 103 patients. Zeitschrift fur Orthopad Unfallchir. 2007;145(4):430-5.
39. Külcü DG, Yanık B, Atalar H, Gülşen G. Associated factors with pain and disability in patients with knee osteoarthritis. Arch Rheumatol. 2010;25(2):077-81.
40. Szebenyi B, Hollander AP, Dieppe P, Quilty B, Duddy J, Clarke S, et al. Associations between pain, function, and radiographic features in osteoarthritis of the knee. Arthr Rheumat. 2006;54(1):230-5.
41. Wilcox S, Brenes GA, Levine D, Sevick MA, Shumaker SA, Craven T. Factors related to sleep disturbance in older adults experiencing knee pain or knee pain with radiographic evidence of knee osteoarthritis. J Am Geriatr Soc. 2000;48(10):1241-51.