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The Relationship between Disability due to Osteoarthritis and Subclinical Atherosclerosis: A Case-Control Study

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ABSTRACT

Objectives: This study aims to evaluate the association between the disability of due to osteoarthritis (OA) and subclinical atherosclerosis.

Methods: The disability level of the OA patients attributable to OA was assessed based on the Australian Canadian Osteoarthritis Hand Index (AUSCAN) and the Western Ontario and McMaster Universities Arthritis Index. Subclinical atherosclerosis was assessed based on the results of carotid intima media thickness (CIMT), arterial stiffness index-β (ASI-β), carotid femoral pulse wave velocity (CFPWV), aortic distensibility and echocardiographic calcification (echo-CCS) assessments.

Results: A total of 160 (%100.0) patients were divided into hand OA 40 (25.0%), knee OA 40 (25.0%), hip OA 40 (25.0%) and one control group 40 (25.0%). There was a relationship between the Kellgren-Lawrence stage of OA and CIMT, ASI-β, CFPWV, echo-CCS in the hand OA group (r=0.540 and p=0.042; r=0.530 and p=0.044; r=0.720 and p=0.001; r=0.580 and p=0.035, respectively). In addition, a statistically significant positive correlation between the AUSCAN score and CIMT, ASI-β, echo-CCS of the patients in the hand OA group (r=0.460 and p=0.025; r=0.390 and p=0.033; r=0.550 and p=0.010, respectively).

Conclusion: The disability level attributable to hand OA may reflect the severity of subclinical atherosclerosis. In primary care, physicians' awareness on the association between hand OA and subclinical atherosclerosis may be beneficial in the care of asymptomatic patients.

Keywords: Osteoarthritis, atherosclerosis, synovial membrane, synovitis

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INTRODUCTION

Osteoarthritis (OA) is a degenerative disorder of the joints, characterized by progressive cartilage destruction, osteophyte formation and subchondral sclerosis.[1] OA results from a variety of biochemical and morphological changes in the joints that may be attributable to genetic, mechanical and biochemical factors.[1,2] OA is the most common joint disease in the world, affecting approximately 10% of men and 18% of women over the age of 60.[3]

Atherosclerosis is a progressive, chronic and inflammatory disease of the arteries that may persist and progress in the long-term, but without clinical symptoms.[4] Carotid intima media thickness (CIMT), arterial stiffness index-β (ASI-β), carotid femoral pulse-wave velocity (CFPWV), aortic distensibility (AD) and the newly introduced echocardiographic calcification scoring (echo-CCS) assessments may all be performed as non-invasive approaches to the detection of subclinical atherosclerosis (SAS).[4,5] Progressive increments in the CIMT between

sequent echocardiographic measurements are an independent indicator of an increased risk of coronary artery disease and stroke in asymptomatic patients during long-term follow-up.[4-6] The ASI-β can indicate atherosclerosis, which develops as a result of the thickening of the arterial wall and a loss of elasticity. Increased ASI-β is not only an indicator of vascular reclination, but also a predictor of target organ damage and increased cardiovascular events.[7] The CFPWV approach to the evaluation of arterial stiffness is the most simple, reliable, non-invasive and highly reproducible method, and is currently considered the optimum approach to the evaluation of arterial stiffness. Epidemiological CFPWV findings are an independent predictor of cardiovascular events while echo-CCS assessments are an independent predictor of coronary artery disease and increased all-cause mortality in patients at high cardiovascular risk.[8-11]

OA is one of the most diagnosed joint pathologies in primary health care. As the population ages, primary health care physicians can be expected to encounter more and more patients suffering from OA.[1,3] Medical literature contains several studies investigating the association between the OA and SAS. Most of these studies report a substantial association between hand, knee or hip OA and SAS. As SAS may progress in the long term without clinical symptoms, primary health care physicians may take a more comprehensive approach to their patients given the possible association between OA and SAS.[12-17]

Although the association between OA and SAS has already been demonstrated in medical literature, to the best of our knowledge, there has been no study to date investigating the relationship between the disability level of the patients associated with OA, and SAS determined by a relatively large number of parameters, such as CIMT, ASI-β, CFPWV, AD, and echo-CCS. This study aims to evaluate the association between the disability of due to OA and SAS.

METHOD

The single-center, prospective and single-blind study was carried out between January 2019 and December 2019. Patients admitted to the orthopedics and traumatology outpatient clinic and diagnosed with hand, knee or hip OA according to the American College of Rheumatology (ACR) classification criteria for OA of the hand, knee and hip were included to the study.[18-20] The patients diagnosed with OA underwent a routine X-ray examination of the associated joints to confirm the diagnosis of OA. Patients below the age of 40 and over the age of 65 years, and those with known rheumatic or non-rheumatic valve disease, non-sinus rhythm, known coronary artery disease, congenital heart disease, malignancy, chronic obstructive pulmonary disease, previous ischemic stroke, known carotid and/or peripheral arterial disease, chronic inflammatory disease, chronic kidney disease (glomerular filtration rate less than 30 ml/min), uncontrolled hypertension, traumatic arthritis, rheumatoid arthritis or any kind of inflammatory arthritis were excluded from the study. The patients were divided into three OA groups, being those with hand OA, knee OA and hip OA. The roentgenograms of the patients were examined and evaluated according to the Kellgren-Lawrence classification for the assessment of the degree of OA.[21] The patients in the hand OA group were requested to fill out the Australian Canadian Osteoarthritis Hand Index (AUSCAN) questionnaire, while those in the knee and hip OA groups were requested to fill out the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire, to evaluate the disability level of the patients associated with the OA.[22,23] The control group comprised 40 volunteers aged 40–65 years who were admitted to the orthopedics and traumatology clinic with a traumatic injury to an extremity, and who were not diagnosed with OA of the hand, knee or hip. The patients in the control group did not undergo a routine X-ray examination of the hand, knee or hip for the exclusion of OA, but may have undergone an X-ray to rule out fractures of the extremity. Diagnoses excluding OA were based on patient history and a clinical examination of the associated joints according to the ACR classification criteria for OA of the hand, knee and hip.[18-20] The flow chart of the study is shown in Figure 1.

The clinical examination of the patients, the diagnosis of the presence or absence of OA, the classification of the degree of OA, and the evaluation of the disability level of the patients associated with OA were made by the same investigator. The investigator was blinded to the SAS examination results of the patients in the hand, knee and hip OA groups, and the control group. The patients in the hand, knee and hip OA groups, and the control groups were taken for routine blood samples to determine serum glucose, serum creatinine, C- reactive peptide, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol levels.

The patients in the hand, knee and hip OA groups, and the control group were taken for SAS examination, and then underwent CIMT, ASI-β, CFPWV, AD and echo-CCS assessments, as mentioned. SAS was evaluated by CIMT, ASI-β, CFPWV, AD and echo-CCS. The SAS examinations were performed by the same investigator, who was blinded to the results of the OA evaluation of the patients.

CIMT measurements: The right and left carotid arteries were visualized using an ultrasound device (EPIQ 7, Phil-

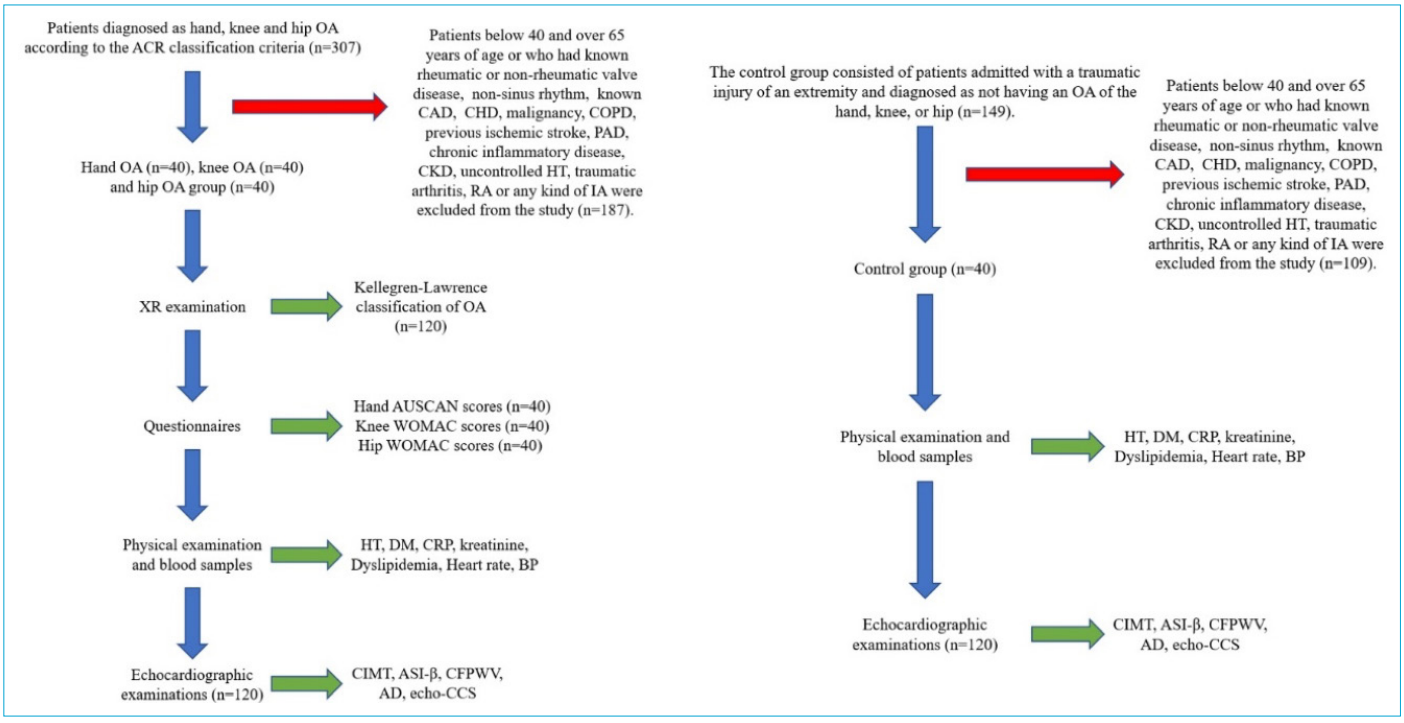

Figure 1. The flow chart of the study.

AD: Aortic distensibility; ASI- β: Aortic stiffness index-β; AUSCAN: Australian Canadian osteoarthritis hand index; CAD: Coronary artery disease; CFPWV: Carotid-femoral pulse wave velocity; CHD: Congenital heart disease; CIMT: Carotid intima-media thickness; COPD: Chronic obstructive heart disease; CKD: Chronic kidney disease; echo-CCS: Echocardiographic calcification score; HT: Hypertension; OA: Osteoarthritis; PAD: Peripheral artery disease; RA: Romatoid arthritis; IA: Inflammatory arthritis; WOMAC: Western Ontario and McMaster Universities arthritis index.

Blue arrow: The cascade of the performed examinations on the patients. Red arrow: The patients excluded from the study. Green arrow: The results used in the statistical analyses.

ips Healthcare, Andover, Massachusetts) with a 13 MHz linear probe. A 1 cm segment was detected within the distal first 2 cm region from the main carotid artery bulb. The highest and average CIMT values of the segments were determined based on the far edge measurement method, with measurements performed for both main carotid arteries, and the values were then evaluated separately and averaged.

CFPWV measurements: CFPWV assessments were performed using a SphygmoCor® device (AtCor Medical, Sydney, Australia). The patients' height and weight were measured, and their body mass index (BMI) was calculated. The right common carotid artery and right femoral artery were used for the CFPWV measurements. The distance between the waves of the carotid and femoral artery (ΔL) was adapted to the surface area of the patient, and the distance between the point at which the waves were recorded and the time between the waves of the carotid and femoral artery (Δt) were measured. The calculation was made according to the following formula: PWV=ΔL (meters)/Δt (seconds).[8]

Evaluation of ASI-β and AD: A two-dimensional transthoracic echocardiography (TTE) was performed using a 3.5-MHz transducer (EPIQ 7, Philips Healthcare, Andover, Massachusetts). Systolic aortic diameter and diastolic aortic diameter were determined in M-Mode 3–4 cm above the aortic valve in the transthoracic parasternal long-axis cross-section. Measurements were taken at peak anterior movement and QRS peak, respectively. Systolic and diastolic blood pressures were obtained after resting for 10 minutes. The evaluations were made automatically by the echocardiography device, using the following formulae:[7,15]

- Aortic strain=(Systolic aortic diameter–Diastolic aortic diameter)/Diastolic aortic diameter
- ASI-β=Log (Systolic blood pressure/Diastolic blood pressure)/Aortic strain
- AD=(2 x Aortic strain)/(Systolic blood pressure/Diastolic blood pressure)

Evaluation of echo-CCS: A two-dimensional transthoracic echocardiography (TTE) was performed using a 3.5-MHz transducer (EPIQ 7, Philips Healthcare, Andover, Massachusetts), in accordance with the with American Echocardiog-

raphy criteria. The parasternal short and long axes, and apical two, three, four and five cavity images were used in all examinations. The anatomical structures of the heart were evaluated with an eco-CCS. Calcification was defined as the presence of a bright echocardiographic intensity when compared to the areas adjacent to the same structure. The possible maximum score was 13.

The statistical analysis was performed using IBM SPSS Statistics (Version 23.0). The Kolmogorov–Smirnov test was used to measure the distribution of variables. Frequency, percentage, mean, standard deviation were used as descriptive statistical methods. Independent sample t test was used to compare the mean examination scores of the two groups. Pearson's correlation analysis was used for correlation analysis. Chi-square test for categorical variables were used. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 160 (%100.0) patients were divided into hand OA 40 (25.0%), knee OA 40 (25.0%), hip OA 40 (25.0%) and control group 40 (25.0%). Sociodemographic and clinical features of patients with hand, knee and hip OA patients and control group are summarized in Table 1.

The mean AUSCAN score of the hand OA group was 37.1±7.0; the mean WOMAC score of the knee OA group was 60.8±15.6; and the mean WOMAC score of the hip OA group was 62.2±16.0. The SAS parameters in the patient and control groups are summarized in Table 2.

There was a relationship between the Kellgren-Lawrence stage of OA and CIMT, ASI-β, CFPWV, echo-CCS in the hand OA group (r=0.540 and p=0.042; r=0.530 and p=0.044; r=0.720 and p=0.001; r=0.580 and p=0.035, respectively).

There was a statistically significant positive correlation between the AUSCAN scores of the patients and the CIMT, ASI-β, AD and echo-CCS parameters in the hand OA group (p=0.025, p=0.033, p=0.034 and p=0.010, respectively). In addition, a significant relationship between the WOMAC scores of the patients and the AD and echo-CCS parameter in the knee OA group (p=0.040 and p=0.040 respectively). The relationship subclinical atherosclerosis parameters between AUSCAN and WOMAC scores are summarized in Table 3.

DISCUSSION

This study aims to evaluate the association between the disability of due to OA and SAS. The echo-CCS score was

Table 1. Sociodemographic and clinical features of patients with hand, knee and hip osteoarthritis patients and control group

	Hand			Knee			Hip		
	OA (n=40)	Control (n=40)	p	OA (n=40)	Control (n=40)	p	OA (n=40)	Control (n=40)	p
Age (years)	56.4±5.3	56.5±5.5	0.930*	55.0±6.3	56.5±5.5	0.243*	56.1±5.7	56.5±5.5	0.720*
Gender									
Female	22 (55.0)	22 (55.0)	1.000†	20 (50.0)	22 (55.0)	0.820†	21 (52.5)	22 (55.0)	1.000†
Male	18 (45.0)	18 (45.0)		20 (50.0)	18 (45.0)		19 (47.5)	18 (45.0)	
BMI (kg/m^2)	24.3±1.5	24.2±1.4	0.764*	24.2±1.5	24.2±1.4	0.990*	24.1±1.6	24.2±1.4	0.822*
Smokers	11 (27.5)	10 (25.0)	0.845†	10 (25.0)	10 (25.0)	1.000†	11 (27.5)	10 (25.0)	0.845†
Heart rate (beats/min)	76.8±13.0	75.2±12.7	0.588*	73.3±12.0	75.2±12.7	0.502*	75.1±12.8	75.2±12.7	0.970*
SBP (mmHg)	122.6±10.6	122.7±8.7	0.950*	123.6±8.2	122.7±8.7	0.641*	123.0±9.6	122.7±8.7	0.875*
DBP (mmHg)	74.2±8.3	73.4±7.5	0.640*	74.4±7.1	73.4±7.5	0.556*	74.8±8.2	73.4±7.5	0.436*
HT	12 (30.0)	10 (25.0)	0.788†	11 (27.5)	10 (25.0)	0.848†	9 (22.5)	10 (25.0)	0.931†
DM	12 (30.0)	11 (27.5)	0.917†	12 (30.0)	11 (27.5)	0.912†	13 (32.5)	11 (27.5)	0.815†
Dyslipidemia	11 (27.5)	10 (25.0)	0.842†	9 (22.5)	10 (25.0)	0.935†	11 (27.5)	10 (25.0)	0.849†
Serum creatinine (mg/dL)	1.1±0.1	1.1±0.1	0.641*	1.1±0.1	1.1±0.1	0.452*	1.1±0.1	1.1±0.1	0.377*
CRP (mg/L)	3.4±0.8	3.4±1.1	0.704*	3.4±0.9	3.4±1.1	0.843*	3.4±0.8	3.4±1.1	0.670*

BMI: Body mass index; CRP: C-reactive protein; DBP: Diastolic blood pressure; DM: Diabetes mellitus; HT: Hypertension; OA: Osteoarthritis; SBP: Systolic blood pressure.

Data is presented as mean±standard deviation and n (%).

*Independent sample t test, †Chi-square test.

Table 2. The subclinical atherosclerosis parameters in the patient and control groups

	Hand			Knee			Hip		
	OA (n=40)	Control (n=40)	p	OA (n=40)	Control (n=40)	p	OA (n=40)	Control (n=40)	p
CIMT (mm)	0.8±0.1	0.7±0.2	0.038	0.7±0.2	0.7±0.2	0.782	0.7±0.2	0.7±0.2	0.402
ASI-β	3.9±0.6	4.0±0.7	0.141	4.0±0.7	4.0±0.7	0.802	4.0±0.7	4.0±0.7	0.370
CFPWV (m/s)	9.9±1.0	9.4±1.1	0.020	9.4±1.1	9.4±1.1	0.610	9.5±1.1	9.4±1.1	0.163
AD	4.1±0.2	4.2±0.3	0.049	4.2±0.3	4.2±0.3	0.610	4.2±0.3	4.2±0.3	0.347
Echo-CCS (points)	4.4±1.4	3.5±1.3	0.008	4.6±1.2	3.5±1.3	0.002	4.5±1.3	3.5±1.3	0.008

AD: Aortic distensibility; ASI-β: Aortic stiffness index-β; CFPWV: Carotid-femoral pulse wave velocity; CIMT: Carotid intima media thickness; echo-CCS: Echocardiographic calcification score; OA: Osteoarthritis.

Data is presented as mean±standard deviation.

Independent sample t test.

Table 3. The relationship subclinical atherosclerosis parameters between AUSCAN and WOMAC scores

	AUSCAN*		WOMAC†		WOMAC‡	
	r	p	r	p	r	p
echo-CCS	0.550	0.010	-0.100	0.554	0.330	0.040
CFPWV	0.360	0.124	-0.030	0.891	0.330	0.040
ASI- β	0.390	0.033	0.020	0.834	0.300	0.160
AD	-0.370	0.034	-0.080	0.783	-0.200	0.480
CIMT	0.460	0.025	-0.010	0.913	0.140	0.510

AD: Aortic distensibility; ASI- β: Aortic stiffness index-β; AUSCAN: Australian Canadian osteoarthritis hand index; CFPWV: Carotid-femoral pulse wave velocity; CIMT: Carotid intima-media thickness; echo-CCS: Echocardiographic calcification score; OA: Osteoarthritis; WOMAC: Western Ontario and McMaster Universities arthritis index.

*Patients with hand OA, †Patients with hip OA, ‡Patients with knee OA.

Pearson correlation test.

found higher in all OA groups than in the control group in this study. The echo-CCS scores were higher in the hand, knee and hip OA groups than in the control group. To the best of our knowledge, the present study is the first to use the echo-CCS parameter for the evaluation of SAS in OA patients in the medical literature. The echo-CCS demonstrated its value as an independent predictor of cardiovascular disease and all-cause mortality in individuals at high risk for cardiovascular disease.[11] Proteases and cytokines are common factors in the etiopathogenesis of OA and heart/valve calcifications. Metalloproteinase 1-2-3-9, interleukin 1-6, tumor growth factor beta-1, insulin growth factor-1, tumor necrosis factor alpha, and other mediators such as nitric oxide, fetuin a, osteopontin and osteoprotegerin are known to be mediators of the common pathways in both OA, and valve and annular calcifications.[11] In the present study, a significant association was noted between the echo-CCS and the hand, knee and hip OA that could be attributed to these common OA pathways and the valve and annular calcifications.

Another result of this study, the CIMT, CFPWV and echo-CCS parameters were significantly higher, and AD was significantly lower in the hand OA group than in the control group, which is implying a significant association between SAS and hand OA. There have been several studies reporting a substantial association between the OA and SAS determined by CIMT measurements.[13,17] Carotid and coronary atherosclerosis with clinical symptoms were also seen more commonly in patients with hand OA than in those without.[17] Why SAS is more common in patients with hand OA than in patients without is a subject of many hypotheses. Advanced age, chronic inflammatory state, sudden decrease in estrogen levels in the postmenopausal period and some gene defects (The KLOTHO Gen) can be listed as common etiologies of hand OA and SAS together although the exact mechanism behind the higher prevalence of SAS in hand OA patients is still not clear.[13,17]

Other results of this study, a significant correlation was noted between the AUSCAN scores in the hand OA group, which reflects the disability level of the patients related to hand OA, and the AD and echo-CCS parameters. In addition, it was observed that as the radiological stage of the hand OA increased, the parameters reflecting SAS increased. Based on these results, it can be claimed that as the disability level of patients related to hand OA increases, the severity of SAS and the likelihood of having SAS are increased. The mechanisms by which OA initiates and progresses are still unclear, although several have been put forward as suggested etiopathogenesis of OA, among which can be counted genetic predisposition, mechanical loading, proteases, cytokines, nitric oxide, calcium crystals, sex hormones and aging, as the main ones.[24-27] Another mechanism blamed for the onset of OA is atherosclerotic vascular disease, which causes subchondral bone ischemia and subsequent hypercoagulation in the synovium.[26] The articular cartilage relies on synovial fluid for gas exchange and nutrition, and atherosclerosis, whether subclinical or clinical, may lead to localized hypoxia and neoangiogenesis, which and may have a detrimental effect on the chondrocytes.[28] Localized hypoxia may also result in a hypercoagulable state in the synovium and cause venous stasis, which deepens the hypoxic state in the cartilage and subchondral bone. Furthermore, venous stasis may also result in a ruined interstitial fluid flow and a relatively high concentration of waste products, which has a deleterious effect on the chondrocytes.[29] All of these factors may collectively be detrimental to the joint cartilage and may play a role in the initiation and progression of OA, as suggested by Conaghan et al., stating that OA may be an atheromatous vascular disease.[17,24] The strong association between SAS and hand OA may also result from chronic inflammation which is known to play an active role in both OA and atherosclerosis. The glycation end products that accumulate in the cartilage and vascular system due to oxidative stress are known to play a role in the etiopathogenesis of both diseases.[21] It may be claimed that the pain caused by OA leads to obesity, and that the subsequent inflammation attributable to metabolic processes results in SAS. However, some prospective studies have shown that SAS may predict the initiation of knee OA on long-term follow-up.[17,28,30] Vascular pathologies such as atherosclerosis in rodents were found to be significantly involved in the initiation and progression of OA in animal studies.[31,32] Based on these findings, it can be accepted that SAS is on the causal pathway of OA initiation and progression, despite the definite role of chronic inflammation in the etiopathogenesis of both OA and atherosclerosis. However, more studies are needed to identify the exact role of the SAS in the onset and progress of the OA. The association between hand OA and SAS seems to be causative although the exact molecular mechanism is still far away to manifest clearly. It is also still a matter of debate whether the treatment of SAS in the early period of the disease can decrease the prevalence and progression of OA.[28]

There are a few limitations to the present study. First, the number of OA patients in the study groups was far from sufficient to reveal a strong relationship between OA and SAS. Second, the comorbidities of the patients in the study groups e.g., diabetes or hypertension, may affect both atherosclerosis and OA progression, and so the association between OA and SAS might be greater or lower than identified in the present study.

CONCLUSION

There was a relationship between SAS and hand OA was identified in the present study, with some of the SAS parameters being correlated with the AUSCAN scores of the hand OA patients, reflecting the disability level of the patients associated with hand OA.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare no conflict of interest.

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Ethics Committee Approval: The present study was approved by the Nigde Omer Halisdemir University Ethics Committee (Approval date: Feb 12, 2019, and Approval number:02/2019). In addition, written informed consent forms were obtained from all patients.

Authorship Contributions: Concept – H.A., A.S.S.; Design – H.A.; Supervision – H.A., A.S.S.; Materials – H.A., A.S.S.; Data collection &/or processing – H.A., A.S.S.; Analysis and/or interpretation – H.A., A.S.S.; Literature search – H.A., A.S.S.; Writing – A.S.S.; Critical review – H.A., A.S.S.

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