JKKI: Jurnal Kedokteran dan Kesehatan Indonesia
Indonesian Journal of Medicine and Health
Journal homepage: https://journal.uii.ac.id/JKKI
P-ISSN 2085-4145 | E-ISSN 2527-2950

Radiographic findings and body mass index in elderly patients with knee osteoarthritis: A cross-sectional study

Yose Steven Lie,[1*] Sulistyani Kusumaningrum,[2] Fatichati Budiningsih,[3] Bayu Basuki Wijaya[3]

[1]Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia
[2]Radiology Department, Regional Public Hospital Dr. Moewardi, Surakarta, Indonesia
[3]Geriatric Department, Regional Public Hospital Dr. Moewardi, Surakarta, Indonesia

Article Info:

Keywords: osteoarthritis, Kellgren dan Lawrence, body mass index

Article History:

Received: February 19, 2024
Accepted: September 6, 2024
Online: December 27, 2024

***Corresponding author:**
yosesteven20@gmail.com

DOI: 10.20885/JKKI.Vol15.Iss3.art3

Original Article

ABSTRACT

Background: Osteoarthritis (OA) is a chronic condition characterized by the gradual wearing down of joint cartilage. Its prevalence is increasing due to aging populations and obesity rates. The Kellgren and Lawrence classification system is commonly used to assess OA severity based on radiologic findings.
Objective: This study aims to determine the relationship between body mass index (BMI) and the radiological severity of knee OA as classified by the Kellgren and Lawrence system, in elderly patients.
Methods: We conducted a cross-sectional analysis of outpatients diagnosed with knee OA at Dr. Moewardi Regional Public Hospital from January 2020 to August 2023. Patient records and knee X-rays graded by the Kellgren and Lawrence system were reviewed. Two radiologists independently assessed the X-rays to ensure accuracy. BMI was calculated using the formula weight (kg) divided by squared height (m^2), with weight and height measured using calibrated instruments. Spearman's rho bivariate correlation analysis was performed to analyze the data.
Results: A total of 96 patients were analyzed, with the majority being female (62.50%) and aged 60-69 years (59.30%). The most prevalent OA severity was grade 3 (46.89%), and the most common OA location was bilateral (73.96%). There was a significant moderate correlation between Kellgren & Lawrence and BMI (p=0.000; rho=0.401).
Conclusion: A moderate correlation exists between the severity of knee OA and BMI in elderly patients. Those with a higher BMI tend to present with more severe OA.

INTRODUCTION

Osteoarthritis (OA) leads to the thinning of joint cartilage, resulting in stiffness, pain, and limited mobility as bones begin to rub together. It is a common cause of joint pain and is the most widespread form of arthritis, affecting approximately 302 million individuals worldwide. OA can significantly contribute to disability, particularly among the elderly population.[1] Several risk factors, such as obesity, lack of physical activity, and joint injuries, have contributed to the increasing prevalence of OA.[2] Additionally, aging plays a critical role in OA development, as joints structures experience wear, and their regulatory function deteriorate over time.

According to data from the Indonesian Central Bureau of Statistics, the number of elderly individuals increased from 18 million (7.60%) in 2010 to 27 million (10.00%) in 2020, with projections indicating a rise to 40 million (13.80%) soon. Improvements in basic services, such as healthcare, have contributed to the population's increasing life expectancy. However, this rise in life expectancy brings new challenges, such as the health complications associated with aging. Elderly individuals naturally experience declines in body function, physical and cognitive abilities, and an increased risk of diseases that can lead to disability or death.[3] OA is one such condition heavily influenced by aging. As people age, articular cartilage undergoes significant

changes. Joint aging occurs when there is thinning and discoloration of the cartilage which was originally white and shiny to a dull yellow, and its mechanical properties also deteriorate. These changes occur due to the aging of chondrocytes, the cells responsible for maintaining cartilage homeostasis. In older individuals, chondrocytes show impaired synthetic activity, leading to smaller, irregular protein synthesis. This imbalance in anabolic and catabolic processes, involving factors such as Insulin-like Growth Factor-1 (IGF-1), Osteogenic protein-1, and Transforming Growth Factor-β (TGF-β), contributes to cartilage degeneration and the progression of OA. The depletion of proteoglycans, an early sign of cartilage loss, further accelerates this degeneration. Collagen, too, becomes stiffer with age, making cartilage more prone to mechanical failure. Accumulation of reactive oxygen species (ROS) in aging chondrocytes lead to Deoxyribonucleic Acid (DNA) damage, telomere shortening, loss of anabolic activity, increased proinflammatory cytokines and matrix metalloproteinases, ultimetaley chondrocyte senescence, and apoptosis.[4]

OA is influenced by combination of systemic factors (age, gender, genetics, diet, and obesity) and local biomechanical factors (trauma, joint loading, neuromuscular issues, and bone structure). These risk factors contribute to both the severity and location of OA. Systemic and biomechanical factors damage chondrocytes, stimulating the release of matrix metalloproteinases (MMPs), which degrade collagen and proteoglycans, leading to an imbalance in cartilage synthesis and breakdown.[4] The degradation of these components triggers the loss of articular cartilage, which is a hallmark of OA progression. In Central Java, the 2018 Basic Health Research report revealed that joint disease increases with age, from 13.9% in individuals aged 65-74 years to 16.03% in those aged 75 and above.[5] These statistics highlight the growing risk of OA as people age.

Radiography is commonly used as the gold standard for diagnosing OA, although it is limited in detecting early-stage OA or monitoring disease progression.[6] The Kellgren and Lawrence's classification, introduced in 1957, evaluates OA severity based on radiological features. It is the most widely used system to assess OA severity, with grades ranging from 0 (no OA) to 4 (severe OA). The World Health Organization (WHO) endorsed this classification in 1961 for epidemiological studies of OA.[7]

Body mass index (BMI) is commonly used to classify individuals based on their weight. It's calculated by dividing a person's weight (kg) by the square of their height (m^2). According to Indonesian's 2014 National Nutrition Guidelines, a BMI between 25-27 kg/m^2 is classified as overweight, while a BMI greather than 27 kg/m^2 is considered obese. Central Java Province ranks 20^{th} among provinces in terms of adult's obesity (aged ≥18).[8] The city of Surakarta ranks 16^{th}, with 4.13% of its population classified as obese. Obesity is a significant risk factor for OA and influences its pathophysiology through both mechanical and metabolic processes. Mechanically, increased body weight places additional stress on joints, while obesity-related metabolic processes contribute to joint inflammation. Adipokines, signaling molecules produced by adipose tissue, play a critical role in joint destruction and remodeling. Hormones such as leptin and adiponectin, produced by adipokines, are known to affect joint health. For example, leptin has been shown to increase the activity of degenerative enzymes and promote proinflammatory cytokine production, accelerating the development of OA. This study aims to explore the potential relationship between BMI and the severity of knee OA in elderly patients, focusing on how obesity impacts OA progression.

METHODS

Research design

This study employed a cross-sectional analytic observational design. No interventions or treatments were applied to the variables, and statistical analysis was conducted to explore how and why the phenomenon occurs. Data collection was carried out simultaneously at a single point.

Research location

This research was conducted in the outpatient clinic, medical records room, and the picture

archiving and communication system room at Dr. Moewardi Regional Public Hospital, Surakarta from May to August 2023.

Research subject

The study population consisted of outpatients diagnosed with knee OA at Dr. Moewardi Regional Public Hospital, Surakarta, between January 2020 andAugust 2023. The patient had to meet specific inclusion and exclusion criteria. The inclusion criteria were described as follows: patients aged 60 years and older, patients who had undergone knee x-ray examinations, and patients diagnosed with knee OA. Exclusion criteria included incomplete medical record (e.g. missing data on weight, height, or knee X-rays), and patients on bed rest who could not undergo weight and height measurements.

Sample size determination

The required sample size (n) was determined using the following formula:

$$n = \frac{z_{\alpha}^2 PQ}{d^2}$$

with:

n : minimum sample size

z_{α}: error rate in research (5% = 1.96)

P : proportion of knee osteoarthritis = 0.5 or 50% because the previous proportion is unknown

Q : 1-P

D : desired level of absolute accuracy (set by the researcher at 10%)

Based on this formula, it was obtained the number of samples was:

$$n = \frac{1{,}96^2 \times 0{,}50 \times (1-0{,}50)}{0{,}10^2} \qquad n = 96$$

Based on the results of the formula calculation, the minimum sample size was 96 patients with a diagnosis of knee OA.

Data collection

Data collection was performed using patient medical records that met the inclusion and exclusion criteria, along with knee X-rays. Radiological grading was determined using the Kellgren and Lawrence classification, which grades osteoarthritis from 0 to IV, as described in Table 1.

Table 1. Interpretation of Kellgren and Lawrence

Grade	Radiologic Findings
0	No radiological findings of osteoarthritis
I	There were no radiological indications of osteoarthritis.
II	Narrowing of joint space is uncertain and there may be osteophytic lipping present.
III	There are definite osteophytes and potential joint space narrowing.
IV	Multiple osteophytes are moderate, joint space narrowing is definite, there are small pseudocystic areas with sclerotic walls, and potential bone contour deformity.

From the classification in Table 1, we assessed grade 0 if the X ray showed no radiological evidence of osteoarthritis. Grade I indicated questionable findings of osteoarthritis. Grade II was assessed if it revealed the presence of osteophytes and joint space narrowing. Grade was assessed if III shows multiple osteophytes, joint space narrowing, and sclerosis. Grade IV was assessed if it indicated large osteophytes, severe sclerosis, and joint deformity.[9] Radiological images were

interpreted by at least two radiologists independently evaluate each image and reach a consensus on the interpretation through an interobserver agreement assessment. This process ensured accuracy and reliability in the findings by confirming that multiple experts agreed on the results. Body mass index was calculated by dividing the patient's weight (in kilograms) by the square of their height (in meters). Weight was measured using a GEA ZT 120 scale (China) in kilograms, and height in was measured using a GEA SH2A stadiometer (China) in meters. Both instruments were calibrated for accurate measurement. These methods were designed to enhance the precision and reliability of the research findings.

Statistical methods

After data collection, statistical analyses were conducted using IBM SPSS Statistics for Windows Version 23.00. The Kolmogorov-Smirnov test was used to assess the normality of the data. If the significant value was greater than 0.05, the data were considered normally distributed. Spearman's rho bivariate correlation analysis was used to examine the relationship between the radiological grade according to Kellgren and Lawrence and BMI. A significant value of less than 0.05 indicated a correlation.

Ethics

Ethical clearance with the number of 652/IV/HREC/2023 was obtained from the Dr. Moewardi Regional Public Hospital's Health Research Ethics Commission.

RESULTS

This study was conducted on a sample of 96 participants. The majority were female, with 60 participants (62.5%), and the most common age group was 60-69 years, accounting for 57 participants (59.3%). According to the Kellgren & Lawrence classification, the highest degree of OA was Grade 3, observed in 45 participants (46.89%). Additionally, the most common location of OA was bilateral (both knee), seen in 71 participants (73.96%) (Table 2).

Tabel 2. Characteristics of Research Subjects

Characteristic	Frequency (n=96)	Percentage (%)
Gender		
Man	36	37.50%
Woman	60	62.50%
Age		
60-69 years old	57	59.38%
70-79 years old	36	37.50%
≥ 80 years old	3	3.12%
Degree of OA		
Grade 1	1	1.03%
Grade 2	41	42.71%
Grade 3	45	46.89%
Grade 4	9	9.37%
Location of knee OA		
Right	10	10.41%
Left	15	15.63%
Bilateral (Both)	71	73.96%

Figure 1 presents radiological images showcasing examples of knee OA across the four Kellgren & Lawrence grades. In addition to grade classifications, large osteophytes and bone sclerosis are evident. Grade 1 displays slight narrowing of the joint space and the potential formation of osteophytes. Grade 2 shows the initial osteophytes formation. Grade 3 features visible narrowing of the joint space, moderate osteophyte formation, bone sclerosis, and potential bone deformity. The most severe form of OA is grade 4, where there is a deformity of the ends of the bones with a clash between the bones due to very narrow joint space.

Figure 1. Radiological examination. (A) Example of grade 1 knee osteoarthritis (OA), the deformity is still not clearly visible, with slightly narrowing of joint space (dark red), (B) Example of grade 2 knee OA, osteophyte (green arrow), (C) Example of grade 3 knee OA, clear joint space narrowing (yellow arrow), osteophyte (orange arrow), and bone sclerosis are visible (red arrow), (D) Example of grade 4, significant narrowing of the joint (light blue arrow), bone end deformity (brown arrow), big osteophyte (purple arrow), and bone sclerosis (dark blue arrow).

The study's results indicated a significant positive correlation between the Kellgren & Lawrence general X-ray images and BMI, with a moderate level of correlation (Table 3).[10] Higher BMI was associated with a more severe radiological degree of knee OA as measured by Kellgren & Lawrence classification. A significant positive correlation value was observed in the correlation analysis.

Table 3. Relationship between Kellgren and Lawrence and independent variables

	Spearman's rho Correlation (r)	Sig (2-tailed)	95% Confidence Interval Lower	Upper
KL vs BMI	0.401	0.000*	0.182	0.562
KL vs Gender	0.085	0.410	-0.128	0.277
KL vs Location of knee OA	0.007	0.943	-0.198	0.200
KL vs Age	0.029	0.778	-0.194	0.242

KL: Kellgren and Lawrence classification, BMI: Body Mass Index, OA: Osteoarthritis, *significant ($p < 0.05$)

In addition to the correlation analysis, a multiple regression analysis was performed (Table 4).[10] The results confirmed that BMI was the only independent variable showing a significant relationship with the Kellgren & Lawrence classification. Other variables such as age, location of knee OA, and gender did not exhibit significant results in the multiple regression analysis.

Table 4. Multiple regression between Kellgren and Lawrence and independent variables

Model (Dependent Variable: KL)	Standardized Coefficients Beta	Sig.
BMI (Group)	0.449	0.000*
Gender	- 0.016	0.877
Location of knee OA	- 0.032	0.748
Age	0.064	0.523

KL: Kellgren and Lawrence classification, BMI: Body Mass Index, OA: Osteoarthritis, * significant (p < .05)

DISCUSSION

This study involved 96 participants, with 62.5% being female, likely due to women's increased susceptiblity to OA, particularly after menopause. Most participants were aged 60-69 years, as this group is more likely to remain mobile and seek medical care, while only three participants were over 80, possibly due to reduced mobility or mortality. Grade 3 OA was the most common, as mild OA (grade 1) often presents few clinical symptoms, leading patients not to seek care. Grades 2 and 3 had similar frequencies, as symptoms typically begin at these stages. Grade 4 OA was less common, potentially due to patients being unable to seek care or having undergone total knee replacement. The most common OA location was bilateral, likely due to both knees bearing similar loads, leading to simultaneous OA development.

The study found that BMI was the only variable significantly correlated with the radiological severity of osteoarthritis (OA), consistent with findings by Johnston et al.[11] and supported by meta-analysis by Zheng and Chen.[12] However, other studies, such as Widhiyanto's, found no significant relationship between BMI and OA, suggesting that factors beyond BMI, such as comorbidities and physical activity, may also play a role.[13]

People who are overweight have a higher degree of OA, namely 88.9%, while those with low body weight have a lower degree of OA as well, as much as 88.3%.[14] Study of 1,859 individuals found that a change in average life expectancy of 6 years and a body mass index of 41% in pre-industrial and post-industrial samples had an effect on the incidence of OA, increasing the risk of developing OA by 2.1 times.[15] Research has shown that for every 5-point increase in BMI, the risk of developing OA in the knee increases by 35%. This underscores the significant impact of obesity on both the occurrence and progression of OA, particularly in the knee. In fact, obesity is a leading factor in knee arthroplasty, which can lead to complications after surgery. Obesity-related OA is caused by an increase in joint loading and dysregulation of cytokines. Overuse of joints increases the mechanical loading of joints. Some populations with occupations involving excessive joint use also exhibit OA symptoms, for example, people who work in mines tend to have predisposing factors for hip OA and people who work in book printing shops tend to have OA in their fingers.[16] Increasing levels of leptin, Interleukin-1 (IL-1), Tumor Necrosis Factor (TNF), and IL-6 which are inflammatory cytokines in the body produced by white adipose tissue, cause OA in metabolic pathways.[17]

Although BMI is commonly used in population-level studies, it does not accurately distinguish between muscle and fat mass. So, because of these calculations a person may experience central obesity which is a condition of excess visceral fat but has a normal BMI. In addition, the opposite can occur, such as in athletes, one of which is bodybuilders, in bodybuilders a BMI that exceeds normal cannot be categorized as obesity, because a high BMI is caused by a lot of muscle mass, compared to fat mass. The BMI also does not account for sex differences in the distribution of body fat or age-related decline in muscle mass. With age, body fat increases and muscle mass decreases, height and weight change. Therefore, in measuring BMI there are many considerations that must be considered.[18]

To improve obesity assessment, alternative methods such as skinfold thickness, BIA, or dual-energy x-ray absorption could be used. However, these methods can be costly, inconvenient, and not widely available or standardized across different examiners or machines. Moreover, some of these techniques may not be practical for routine clinical use due to their technical complexity and reliance on specialized equipment. In contrast, waist circumference can provide a simple way to assess fat distribution. According to the International Diabetes Federation's

guidelines, a waist circumference of over 90 cm in men and over 80 cm in women (or lower thresholds for some Asian populations, including Indonesians) may be indicative of obesity.[19]

Individuals who are 65 years or older are at a 3.56 times higher risk of developing moderate to severe OA in comparison to those under the age of 65.[20] Gender differences can also play a role in the development of OA, as women tend to experience more severe symptoms and disability, as well as higher grades of the condition. These sex differences become more apparent in individuals who are 55 years old or older.[21] Additionally, low levels of estrogen hormone in post-menopausal women, which have been linked to OA progression, can contribute to the disease's progression by causing loss of muscle mass, impairing muscle function, leading to joint instability, uneven joints, and eventually resulting in cartilage damage. Furthermore, osteoporosis can be caused by a deficiency in estrogen. Overall, sex hormones play a significant role in the development of OA, particularly about their effects on muscles and bones. The impact of anatomical and biomechanical loads should also be considered when examining the discrepancies in OA prevalence between the sexes. In women, the anatomical strain induced by dynamic deformation of the lower limb in a varus direction increases the stress placed on the medial compartment of the knee joint, leading to cartilage deterioration.[22] Studies have shown that patients who developed knee OA in one knee were more likely to experience it in the opposite knee as well. This suggests that the existence of OA in one knee does not necessarily mean that the other knee is OA-free, as the disease can progress and eventually lead to bilateral knee OA.[23]

A limitation of this study is its unicentric design, with data collected from a single hospital. Future research with larger, multicentric cohorts is needed to validate these findings. Additionally, other factors such as comorbidities and trauma history should be considered in future studies. In conclusion, this study emphasizes the importance of maintaining a healthy BMI to prevent the progression of knee OA. Clinicians should educate patients on weight management as part of OA treatment and prevention strategies.

CONCLUSION

There is a moderate correlation between the severity of knee osteoarthritis (OA) and body mass index (BMI) in elderly patients. Those with a higher BMI tend to have more severe OA. Future research should involve larger sample sizes from diverse sources and explore additional factors such as age, gender, and comorbidities to provide a more comprehensive understanding of the relationship with knee OA severity.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to disclose.

ACKNOWLEDGMENTS

While compiling my research, the author received valuable help and support from various individuals. The author would like to express my sincere thanks to Samuel Ferdinand Wadoe, Marsa Zaidan, and Jessica Vivian Purnomo for their assistance and support throughout this endeavor.

AUTHORS CONTRIBUTION

YSL played a central role in developing the concept and defining the intellectual content, conducting literature searches, acquiring and analyzing data, and preparing the manuscript. SK served as the primary supervisor, providing guidance and direction throughout the research process. In addition, FB and BBW served as supporting supervisors, contributing to manuscript editing and review.

LIST OF ABBREVIATIONS

OA: Osteoarthritis, BMI: Body Mass Index, KL: Kellgren & Lawrence, IGF-1: Insulin-like Growth Factor 1, TGF-β: Transforming Growth Factor β, DNA: Deoxyribonucleic Acid, IL-1: Interleukin 1, TNF: Tumor Necrosis Factor, IL-6: Interleukin 6, BIA: Body Impedance Analysis

REFERENCES

1. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2020;72(2):149–62. DOI:10.1002/acr.24131.
2. Hawker GA. Osteoarthritis is a serious disease. Clin Exp Rheumatol. 2019;37 Suppl 120(5):3–6. https://pubmed.ncbi.nlm.nih.gov/31621562/.
3. Kementerian Kesehatan RI. Infodatin lansia 2016. Report. 2016. p. 8.
4. Blom, A, Warwick, D, Whitehouse M. System of orthopaedics and trauma. In: Apley & Solomons system of orthopaedics and trauma. 10th Ed. New York: CRC Press; 2018. p. 433.
5. Riskesdas Jawa Tengah. Laporan Provinsi Jawa Tengah riskesdas 2018. Kementerian Kesehatan RI. 2018. 88–94 p.
6. Li Q, Amano K, Link TM, Ma CB. Advanced imaging in osteoarthritis. Sports Health. 2016;8(5):418–28. DOI:10.1177/1941738116663922.
7. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. Clin Orthop Relat Res. 2016;474(8):1886–93. DOI:10.1007/s11999-016-4732-4.
8. Kemenkes RI. Hasil riset kesehatan dasar tahun 2018. Kementrian Kesehatan RI. 2018;53(9):1689–99.
9. Audrey HX, Bin Abd Razak HR, Andrew THC. The truth behind subchondral cysts in osteoarthritis of the knee. Open Orthop J. 2014;8(1):7–10. DOI:10.2174/1874325001408010007.
10. Schober P, Boer C, Schwarte LA. Correlation coefficients: Appropriate use and interpretation. Anesthesia & Analgesia. 2018;126(5):1763–8. DOI:10.1213/ANE.0000000000002864.
11. Johnston SS, Ammann E, Scamuffa R, Samuels J, Stokes A, Fegelman E, et al. Association of body mass index and osteoarthritis with healthcare expenditures and utilization. Obes Sci Pract. 2020;6(2):139–51. DOI:10.1002/osp4.398.
12. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: Systematic review and meta-analysis of prospective studies. BMJ Open. 2015;5(12):e007568. DOI:10.1136/bmjopen-2014-007568.
13. Widhiyanto L, Desnantyo AT, Djuari L, Kharismansha M. Correlation between knee osteoarthritis (OA) grade and body mass index (BMI) in outpatients of orthopaedic and traumatology department RSUD Dr. Soetomo. Journal Orthopaedi and Traumatology Surabaya. 2019;6(2):71. DOI:10.20473/joints.v6i2.2017.71-79.
14. Mutiwara E, Najirman N, Afriwardi A. Hubungan indeks massa tubuh dengan derajat kerusakan sendi pada pasien osteoartritis lutut di RSUP Dr. M. Djamil Padang. Jurnal Kesehatan Andalas. 2016;5(2):376–80. DOI:10.25077/jka.v5i2.525.
15. Wallace IJ, Worthington S, Felson DT, Jurmain RD, Wren KT, Maijanen H, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. Proc Natl Acad Sci USA. 2017;114(35):9332–6. DOI:10.1073/pnas.1703856114.
16. Swastini NP, Ismunandar H, Wintoko R, Hadibrata E, Djausal AN. Faktor resiko osteoarthritis. Medical Profession Journal of Lampung. 2022;12(1):49–54. DOI:10.53089/medula.v12i1.329.
17. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? Br Med Bull. 2015;115(1):111–21. DOI:10.1093/bmb/ldv028.
18. Gurunathan U, Myles PS. Limitations of body mass index as an obesity measure of perioperative risk. Br J Anaesth. 2016;116(3):319–21. DOI:10.1093/bja/aev541.
19. Zhu L, Spence C, Yang WJ, Ma GX. The IDF definition is better suited for screening metabolic syndrome and estimating risks of diabetes in Asian American adults: Evidence from NHANES 2011–2016. J Clin Med. 2020;9(12):3871. DOI:10.3390/jcm9123871.
20. Mustari MN, Massi MN, Usman MA, Fikry A, Bukhari A, Idris I, et al. Dynamic interaction of obesity, age, MCP-1 level, and ACE-1 gene with the severity of knee osteoarthritis: A cross-

sectional study. Ann Med Surg (London). 2023;85(8):3845–51. DOI:10.1097/MS9.0000000000000973.
21. Migliore A, Picarelli G. Is osteoarthritis a gender-specific disease? Ital J Gender-Specific Med. 2018;4(1):13–20. DOI:10.1723/2968.29765.
22. Tschon M, Contartese D, Pagani S, Borsari V, Fini M. Gender and sex are key determinants in osteoarthritis not only confounding variables. A systematic review of clinical data. J Clin Med. 2021;10(14):3178. DOI:10.3390/jcm10143178.
23. Metcalfe AJ, Andersson M Le, Goodfellow R, Thorstensson CA. Is knee osteoarthritis a symmetrical disease? Analysis of a 12 year prospective cohort study. BMC Musculoskelet Disord. 2012;13(1):153. DOI:10.1186/1471-2474-13-153.