Original Article

Factors associated with osteoarthritis in menopausal women: A registry study of osteoporosis sarcopenia and osteoarthritis

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Abstract

Background: Bone and muscle mass decline after menopause. The risk of osteoarthritis (OA), sarcopenia, and osteoporosis increases in later life. Our objective aimed to assess the possible factors affecting osteoarthritis in menopausal women. **Methods:** This is a registry study of osteoporosis, sarcopenia, and osteoarthritis. All subjects accepted bone mineral density (BMD) and body composition studies, and X-rays of both knees were performed. A medical history was taken and biochemical data were recorded. Logistic regression analyses were used to examine the associations between the presence of osteoarthritis and BMD, muscle mass, and other parameters. **Results:** A total of 139 patients were enrolled. The mean age of the patients was 73.86 ± 5.83 years in the osteoarthritis group and 74.53 ± 9.90 in the non-osteoarthritis group ($p = 0.663$). The mean body mass index (BMI) was 24.36 ± 3.64 kg/m^2 in the osteoarthritis group, compared with 23.78 ± 3.61 in the non-osteoarthritis group ($p = 0.366$). The lumbar spine T score was -2.06 ± 1.33 g/cm^2 in the osteoarthritis group, and -1.25 ± 1.76 in the non-osteoarthritis group ($p = 0.006$). There were no significant differences in smoking, alcohol consumption, diabetes, hypertension, cardiovascular disease, neurological disease, and chronic kidney disease between the two groups. When we used osteoarthritis as the outcome, we found that the lumbar spine T score had a significant association with osteoarthritis, with a high T score associated with less osteoarthritis formation ($p = 0.024$, odds ratio (95% confidence interval) 0.06 (0-0.69)). **Conclusions:** Knee osteoarthritis was associated with lumbar spine bone density. This study provides the initial information required to develop clinical algorithms for the early identification of potential high-risk populations, as well as essential information for the development of policies for the detection and prevention of osteoarthritis in menopausal women.

Keywords: Factors, menopause, osteoarthritis, osteoporosis

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Background

Menopausal women have hormonal changes, such as a decrease in estradiol and an increase in serum follicle-stimulating hormone.[1-3] It is widely known that bone and muscle mass decline after menopause and that the risk of osteoporosis and sarcopenia increases in later life. Hormonal changes cause

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bone loss via decreased bone formation and increased bone turnover.[4,5] Hormonal changes after menopause have been reported to have an effect on the decline in muscle mass.[6,7]

Primary osteoarthritis (OA) can influence cartilage, bone, and regional soft tissue.[8] Menopausal women with knee osteoarthritis[9] typically have higher fat mass, lower lean body mass, higher body mass index (BMI), and higher bone mineral density (BMD). However, little is known about what influences osteoarthritis in menopausal women. This is important for primary care physicians. We, therefore, conducted the present study to determine factors that are associated with osteoarthritis in menopausal women.

Methods

Research methodology

This is a registry study of osteoporosis, sarcopenia, and osteoarthritis, which was conducted at CGMHK. The reporting of this study conforms to the STROBE statement.[10]

Inclusion criteria

1. Menopausal woman.
2. Documented clinical diagnosis of symptomatic OA affecting at least one knee for a minimum of 6 months before screening.
3. The study knee had OA as defined by the Kellgren and Lawrence (K-L) criteria.[11]
4. The patient could read and was willing to sign a written subject consent form.
5. The patient could cooperate with outpatient consultation.

Exclusion criteria

1. Those with rheumatoid arthritis or other autoimmune diseases.
2. Patients with an infection.
3. History of post-traumatic knee arthritis, or evidence of intra-articular bleeding identified during the study.
4. Subjects with clinical signs and symptoms of active knee infection at screening.
5. Subjects with a known malignancy.
6. Patients who refused to sign the informed consent form.

Radiography of the knee joint

Both knees were imaged in a weight-bearing position. All radiographs were read according to the K-L criteria,[11] and knee OA was defined as a K-L grade 2 or greater. The presence of osteophytes[12] in the medial and lateral tibiofemoral compartments of the knees was recorded. We only enrolled those patients who had osteophytes as part of their osteoarthritis diagnosis.

BMD dual-energy X-ray absorptiometry (DXA) and body composition evaluation

The bone mineral densities of the femoral neck, total hip, and lumbar spine, along with the appendicular muscle mass and total fat mass, were assessed via DXA analysis using dual-energy X-ray absorptiometry.[13]

General characteristics, covariates, and comorbidities

The general characteristics of the subjects were ascertained via a questionnaire to assess the presence of diseases, medications being taken, and lifestyle variables. Participants were asked to list their medications and diseases on a questionnaire which was completed at home, and research assistants then checked the questionnaires for completeness and accuracy in the presence of the participants. Biochemical parameters, including hemoglobin, urea, creatinine, calcium, phosphorus, and HbA1c were recorded.

Statistical analysis

Continuous variables were compared between groups using t-tests, while associations between categorical variables were assessed using the Chi-squared test. Logistic regression analyses were used to examine associations between the presence of osteoarthritis and BMD, muscle mass, and other parameters. A *P* value of less than 0.05 (two-tailed) or a 95% confidence interval (CI) not including the null point was regarded as indicating a statistically significant difference. All statistical analyses were performed using SPSS version 24.0 for Windows (Ying-Chou Chen, Chicago, IL, USA).

Results

A total of 139 patients were enrolled in the present study. The mean age of the patients was 73.86 ± 5.83 years in the osteoarthritis group and 74.53 ± 9.90 in the non-osteoarthritis group ($p = 0.663$). The mean BMI was 24.36 ± 3.64 kg/m^2 in the osteoarthritis group compared with 23.78 ± 3.61 in the non-osteoarthritis group ($p = 0.366$). The mean appendicular lean mass was 5.28 ± 0.79 kg/m^2 in the osteoarthritis group, compared with 5.25 ± 0.72 in the non-osteoarthritis group ($p = 0.817$). The lumbar spine T score was -2.06 ± 1.33 g/cm^2 in the osteoarthritis group and -1.25 ± 1.76 in the non-osteoarthritis group ($p = 0.006$). The femoral neck T score was -2.11 ± 1.26 in the osteoarthritis group, and -2.38 ± 1.03 in the non-osteoarthritis group ($p = 0.544$). The total hip T score was -1.12 ± 0.16 in the osteoarthritis group, and -1.25 ± 1.37 in the non-osteoarthritis group. There were no significant differences in smoking, alcohol consumption, diabetes, hypertension, cardiovascular disease, neurological disease, and chronic kidney disease between the two groups [Table 1]. When we used osteoarthritis as an outcome, we found that lumbar spine T score had a significant association with osteoarthritis, with a high T score associated with less osteoarthritis formation ($p = 0.024$, OR (95% CI) 0.06 (0-0.69)) [Table 2].

Discussion

To the best of our knowledge, this is the first study to report an association between lumbar spine T score with knee osteoarthritis

Table 1: Characteristics of the patients enrolled in the study

Variables	Osteoarthritis group (*n*=50)	No osteoarthritis group (*n*=89)	*P*
Age (years), mean±SD	73.86±5.83	74.53±9.90	0.663
Body mass index (kg/m^2), mean±SD	24.36±3.64	23.78±3.61	0.366
Smoking (%)	1 (2.0)	5 (5.6)	0.419
Alcohol consumption (%)	0 (0)	6 (6.7)	0.608
Diabetes mellitus (%)	9 (18)	25 (28.1)	0.221
Hypertension (%)	19 38.0)	36 (40.4)	0.857
Cardiovascular disease (%)	9 (18.0)	18 (20.2)	0.826
Neurological disease (%)	3 (6.0)	3 (3.4)	0.667
Chronic kidney disease (%)	3 (6.0)	6 (6.7)	0.586
Appen. Lean/Height^2 (kg/m^2) mean±SD	5.28±0.79	5.25±0.72	0.817
Lumbar spine T score, mean±SD	−2.06±1.33	−1.25±1.76	0.006
Femur neck T score, mean±SD	−2.11±1.26	−2.38±1.03	0.544
Total femur T score, mean±SD	−1.12±0.17	−1.25±1.37	0.64

SD=standard deviation

Table 2: Factors associated with osteoarthritis

Variables	Regression coefficient	SE	Wald	*P*	OR (95% CI)
Lumbar spine t score	-2.892	1.286	5.060	0.024	0.06 (0-0.69)
Age	-0.011	0.029	0.147	0.702	0.99 (0.94-1.05)
Body mass index	0.087	0.062	1.949	0.163	1.09 (0.97-1.23)
Smoking	-0.406	1.218	0.111	0.739	0.67 (0.06-7.25)
Alcohol consumption	-1.279	1.112	1.322	0.250	0.28 (0.03-2.46)
Diabetes	-0.318	0.491	0.418	0.518	0.73 (0.28-1.91)
Hypertension	-0.017	0.499	0.001	0.972	0.98 (0.37-2.61)
Cardiovascular disease	-0.015	0.577	0.001	0.979	0.99 (0.32-3.05)
Neurological disease	0.562	0.957	0.345	0.557	1.75 (0.27-11.45)
Chronic kidney disease	0.007	0.812	0.000	0.994	1.01 (0.21-4.94)

in menopausal women. Osteoporosis and osteoarthritis are two major bone and joint health problems among the elderly, which cause impairment of daily activity, leading to increased morbidity and mortality. It has been previously reported that age-related loss of bone density[14] and bone strength loss[15] were significantly higher in women compared with men.

Some studies have revealed that higher BMD is protective for OA progression.[16,17] It was reported that bone loss was independently associated with progressive OA compared with non-progressive osteoarthritis.[18] In another study, patients with hand OA had lower distal radius bone density.[19] So OA is inversely related to osteoporosis. A prospective study showed the same results and subjects with hip and knee OA had a loss of hip BMD over 2.6 years regardless of their symptoms.[20]

In rabbit models, it was shown that microstructure impairment by osteoporosis in the subchondral bone may aggravate osteoarthritis of the knee.[21,22] Some previous studies have focused on the bone turnover of both diseases and showed that the high rate of bone turnover in osteoporosis was related to the progression of osteoarthritis. A prospective study of 450 knee osteoarthritis patients reported that BMD was lower in patients with severe knee osteoarthritis, while biomarkers for bone turnover were higher in patients with worse osteoarthritis grading.[23]

Bone loss and remodeling are controlled by osteoprotegerin (OPG), and osteoclast differentiation factor (ODF). Osteoporosis patients had higher levels of OPG and a higher serum ODF/OPG ratio,[24] bone specimen,[25] and osteoblast[26,27] compared with those with osteoarthritis. Higher Wnt activity was also found in osteoarthritis patients compared with osteoporotic patients.[28] Another study showed that greater expression of Runx-2, osterix, and osteoclast was found in osteoarthritis patients compared with osteoporosis patients when undergoing hip arthroplasty.[29] In addition, lower levels of osteopontin were found in osteoporotic patients compared with those with osteoarthritis.[30] Higher levels of alkaline phosphatase were found in mesenchymal stem cells from the femurs of osteoarthritis patients compared with osteoporosis patients.[27] Osteoporosis patients had lower cell adhesion, attachment, and focal adhesion kinase signaling compared with osteoblasts from osteoarthritis patients.[31] Another study showed that osteoporosis patients had lower expression of osteogenesis and a lower capacity for differentiation and osteoblastic activity compared with osteoarthritic bone.[32] In a previous study, the risk of vertebral fractures was reported to be increased in osteoarthritis patients,[33] so it is considered that osteoarthritis is involved in the development of fractures due to osteoporosis.

In summary, the above literature indicates that osteoporosis is generally inversely related to osteoarthritis when studied cross-sectionally and systematically. So in the case of knee osteoarthritis, more aggressive treatment for osteoporosis is necessary, especially for those who require surgery, to enhance the success rate of the operation.

There were several limitations to the present study. The primary limitation was that the study comprised a relatively small number of participants. Therefore, the rate of lumbar osteoporosis and knee osteoarthritis in this menopausal group might be underestimated. A secondary limitation was related to the definition of knee osteoarthritis which was used. This study did not include the severity of osteoarthritis, which means we could not assess the effect of knee osteoarthritis severity on osteoporosis, and because our study only used radiological osteoarthritis grades, we could not predict the same results in symptomatic OA patients with knee pain. Third, the present study did not determine the cause-effect relationship between osteoarthritis and osteoporosis due to the cross-sectional nature of the database. A prospective, longitudinal study is needed to validate the results. Fourth, we could not assess the personal medication information, which can be associated with OA, OP, and other comorbidities. A lack of information about potential underlying medical conditions could have influenced the results.

In conclusion, the association between knee osteoarthritis and lumbar spine osteoporosis was clarified in menopausal women. This study can be used to develop clinical algorithms for the early identification of potential high-risk populations in menopausal women with osteoarthritis.

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Ethics approval

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, IRB No.: 201800897A3.

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Conflicts of interest

There are no conflicts of interest.

References

1. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, *et al.* Executive summary of the stages of reproductive aging workshop+10: Addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159-68.
2. Rannevik G, Carlstrom K, Jeppsson S, Bjerre B, Svanberg L. A prospective long-term study in women from pre-menopause to post-menopause: Changing profiles of gonadotrophins, oestrogens and androgens. Maturitas 1986;8:297-307.
3. Black DM, Rosen CJ. Postmenopausal osteoporosis. N Engl J Med 2016;374:2096-7.
4. Schiessl H, Frost HM, Jee WS. Estrogen and bone-muscle strength and mass relationships. Bone 1998;22:1-6.
5. Frost HM. On the estrogen-bone relationship and postmenopausal bone loss: A new model. J Bone Miner Res 1999;14:1473-7.
6. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, *et al.* Changes in body composition and weight during the menopause transition. JCI Insight 2019;4:e124865.
7. Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition: A prospective study in Chinese perimenopausal women. Int J Obes 2010;34:1265-74.
8. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005;365:965-73.
9. Board.Washington IoMFaN. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. DC: National Academy Press; 1998.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. PLoS Med 2007;4:e296.
11. Kellgren JH. Arthritis in populations. J Coll Gen Pract 1963;6:(suppl 3):2-7.
12. Brandt KD, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee osteoarthritis: Relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. Arthritis Rheum 1991;34:1381-6.
13. Celi M, Rao C, Scialdoni A, Tempesta V, Gasbarra E, Pistillo P, *et al.* Bone mineral density evaluation in osteoporosis: Why yes and why not? Aging Clin Exp Res 2013;25(Suppl 1):S47-49.
14. Breuil V, Trojani MC, Ez-Zoubir A. Oxytocin and bone: Review and perspectives. Int J Mol Sci 2021;22;8551.
15. Lang TF, Sigurdsson S, Karlsdottir G, Oskarsdottir D, Sigmarsdottir A, Chengshi J, *et al.* Age-related loss of proximal femoral strength in elderly men and women: The Age Gene/Environment Susceptibility Study--Reykjavik. Bone 2012;50:743-8.
16. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: The Chingford Study. Arthritis Rheum 2002;46:92-9.
17. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, *et al.* Osteoarthritis: New insights. Part 1: The disease and its risk factors. Ann Intern Med 2000;133:635-46.
18. Guler-Yuksel M, Bijsterbosch J, Allaart CF, Meulenbelt I, Kroon HM, Watt I, *et al.* Accelerated metacarpal bone mineral density loss is associated with radiographic progressive hand osteoarthritis. Ann Rheum Dis 2011;70:1625-30.
19. Kim SK, Park SH, Choe JY. Lower bone mineral density of forearm in postmenopausal patients with radiographic hand osteoarthritis. Rheumatol Int 2010;30:605-12.
20. Ding C, Cicuttini F, Boon C, Boon P, Srikanth V, Cooley H, *et al.* Knee and hip radiographic osteoarthritis predict total hip bone loss in older adults: A prospective study. J Bone Miner Res 2010;25:858-65.
21. Bellido M, Lugo L, Roman-Blas JA, Castañeda S, Caeiro JR, Dapia S, *et al.* Subchondral bone microstructural damage by increased remodelling aggravates experimental osteoarthritis preceded by osteoporosis. Arthritis Res Ther 2010;12:R152.
22. Zhang J, Chen S, Chen W, Huang Y, Lin R, Huang M, *et al.* Ultrastructural change of the subchondral bone increases the severity of cartilage damage in osteoporotic osteoarthritis of the knee in rabbits. Pathol Res Pract 2018;214:38-43.
23. Linde KN, Puhakka KB, Langdahl BL, Søballe K, Krog-Mikkelsen I, Madsen F, *et al.* Bone mineral density is lower in patients with severe knee osteoarthritis and attrition. Calcif Tissue Int 2017;101:593-601.
24. Jiang LS, Zhang ZM, Jiang SD, Chen WH, Dai LY. Differential bone metabolism between postmenopausal women with osteoarthritis and osteoporosis. J Bone Miner Res 2008;23:475-83.
25. Logar DB, Komadina R, Prezelj J, Ostanek B, Trost Z, Marc J. Expression of bone resorption genes in osteoarthritis and in osteoporosis. J Bone Miner Metab 2007;25:219-25.
26. Giner M, Rios MA, Montoya MA, Vazquez MA, Naji L, Perez-Cano R. RANKL/OPG in primary cultures of osteoblasts from post-menopausal women. Differences

between osteoporotic hip fractures and osteoarthritis. J Steroid Biochem Mol Biol 2009;113:46-51.

27. Zhang ZM, Jiang LS, Jiang SD, Dai LY. Osteogenic potential and responsiveness to leptin of mesenchymal stem cells between postmenopausal women with osteoarthritis and osteoporosis. J Orthop Res 2009;27:1067-73.
28. Velasco J, Zarrabeitia MT, Prieto JR, Perez-Castrillon JL, Perez-Aguilar MD, Perez-Nuñez MI, *et al.* Wnt pathway genes in osteoporosis and osteoarthritis: Differential expression and genetic association study. Osteoporos Int 2010;21:109-18.
29. Dragojevic J, Logar DB, Komadina R, Marc J. Osteoblastogenesis and adipogenesis are higher in osteoarthritic than in osteoporotic bone tissue. Arch Med Res 2011;42:392-7.
30. Tanaka S, Narusawa K, Onishi H, Miura M, Hijioka A, Kanazawa Y, *et al.* Lower osteocalcin and osteopontin contents of the femoral head in hip fracture patients than osteoarthritis patients. Osteoporos Int 2011;22:587-97.
31. Perinpanayagam H, Zaharias R, Stanford C, Brand R, Keller J, Schneider G. Early cell adhesion events differ between osteoporotic and non-osteoporotic osteoblasts. J Orthop Res 2001;19:993-1000.
32. Giner M, Montoya MJ, Vazquez MA, Miranda C, Perez-Cano R. Differences in osteogenic and apoptotic genes between osteoporotic and osteoarthritic patients. BMC Musculoskelet Disord 2013;14:41.
33. Bergink AP, van der Klift M, Hofman A, Verhaar JA, van Leeuwen JP, Uitterlinden AG, *et al.* Osteoarthritis of the knee is associated with vertebral and nonvertebral fractures in the elderly: The Rotterdam Study. Arthritis Rheum 2003;49:648-57.