doi: 10.2490/prm.20240022 Progress in Rehabilitation Medicine 2024; Vol. 9, 20240022

ORIGINAL ARTICLE

Effects of Locomotion Training on Bone Mineral Density in Patients with Rheumatoid Arthritis

Takeshi Mochizuki, MD, PhD [a] Koichiro Yano, MD, PhD [b] Katsunori Ikari, MD, PhD [b] and Ken Okazaki, MD, PhD [b]

Objectives: This study aimed to evaluate the effects of locomotion training on bone mineral density (BMD) and the factors associated with increased BMD in patients with rheumatoid arthritis (RA). **Methods:** We enrolled 85 patients with RA who underwent locomotion training for 6 months after receiving instructions from a physical therapist. We evaluated the BMD of the lumbar spine, total hip, and femoral neck 1 year before baseline (the start of locomotion training) and 1 year after baseline. **Results:** The change in BMD from 1 year before baseline (non-exercise period) and 1 year after baseline (exercise period) were 0.1 ± 3.1% and 1.6 ± 3.7% (P=0.007) for the lumbar spine, −0.2 ± 2.4% and 1.0 ± 2.4% (P=0.005) for the total hip, and −0.6 ± 3.9% and 1.8 ± 3.5% (P<0.001) for the femoral neck, respectively. The Health Assessment Questionnaire Disability Index score at baseline was associated with increased BMD at the femoral neck. No factor was associated with increased BMD in the lumbar spine or total hip. **Conclusions:** Locomotion training increased the BMD of the lumbar spine, total hip, and femoral neck during the exercise period compared with that during the non-exercise period. The current treatment for RA and osteoporosis accompanied by optional therapy with locomotion training might be effective in increasing BMD in patients with RA.

Key Words: bone mineral density; locomotion training; rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease with a significant concomitant risk of osteoporosis that may be exacerbated by inflammation, receptor activator of nuclear factor kappa beta ligand, use of glucocorticoids, immobility, and low body mass index.[1–4] The effectiveness of pharmacological treatments for osteoporosis in patients with RA has been reported.[5–9]

In previous studies, resistance training, walking, and muscle exercise were reported to have positive effects on bone mineral density (BMD).[10–14] Exercise has been recommended for postmenopausal women, patients receiving glucocorticoids, and older individuals.[15–17] In patients with RA, a 2-year exercise program (range of motion and stretching twice a week) resulted in maintenance of BMD of the lumbar spine and femoral neck at 5 years.[18] In another study of RA patients, a group that completed a 2-year program of high-intensity exercises with weight-bearing and impact-loading exercises showed a change in BMD of the total hip of −1.1%, whereas those receiving usual care showed a BMD change of −1.9%.[19]

The existing evidence for the effectiveness of exercise in maintaining BMD is mostly based on the general population, whereas information on the effectiveness of low-intensity exercise in patients with RA is lacking. This study retrospectively evaluated the effects of locomotion training, a low-intensity exercise, on BMD in patients with RA.

Received: February 1, 2024, Accepted: June 7, 2024, Published online: June 18, 2024
[a] Department of Orthopaedic Surgery, Kamagaya General Hospital, Kamagaya, Japan
[b] Department of Orthopaedic Surgery, Tokyo Women's Medical University, Tokyo, Japan
Correspondence: Takeshi Mochizuki, MD, PhD, 929-6 Hatsutomi, Kamagaya, Chiba 273-0121, Japan, E-mail: twmutamo@gmail.com

MATERIALS AND METHODS

Study Design

We enrolled 103 patients with RA who underwent locomotion training for 6 months in our previous study.[20] Overall, 85 patients who underwent evaluation of BMD of the lumbar spine, total hip, and femoral neck using dual-energy X-ray absorptiometry (Prodigy system; GE Healthcare, Madison, WI, USA) at the start of locomotion training (baseline), 1 year before baseline, and 1 year after baseline were included in this study. BMD of the lumbar spine was measured from L1 to L4. Of the 18 excluded patients, 15 were excluded because of a lack of BMD data, 1 was excluded because the patient switched to osteoporosis treatment during the 2-year study period, and 2 patients were excluded after switching to RA treatment following a phase change in accordance with the Japanese College of Rheumatology clinical practice guidelines.[21]

This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients. This study was approved by the Ethics Committee for Clinical Research of Kamagaya General Hospital (approval number: TGE01619-064).

Locomotion Training

Based on guidelines of the Japanese Orthopedic Association, the following exercises were performed at home for 6 months as locomotion training: single-leg standing with eyes open (1 min for each leg × three sets per day), squatting (five times × three sets per day), heel raises (ten times × three sets per day), and forward lunges (ten times × three sets per day).[22] To prevent falls, the participants performed the exercises while holding a solid support structure. Training records were self-reported by participants in a rehabilitation notebook and were monitored regularly.

Statistical Analysis

Comparison of percentage changes (Δ) in BMD of the lumbar spine, total hip, and femoral neck from 1 year before baseline (non-exercise period) and 1 year after baseline (exercise period) were assessed using the paired *t*-test. Increased BMD was defined as a greater increase in ΔBMD during the exercise period than during the non-exercise period. Factors associated with increased BMD were evaluated between patients with and without increased BMD using univariate and multivariate logistic regression analysis. Multivariate logistic regression analysis was performed using the variables identified in the univariate analysis with P<0.1. Statistical significance was set at P<0.05. All analyses were performed using the R Statistical Package, version 3.3.2 (http://www.r-project.org/).

Table 1. Demographic and clinical characteristics of patients at baseline

Variable	n=85
Age, years	68.5 (±11.6)
Sex, female	78 (91.8%)
Disease duration, years	13.8 (±9.6)
Body mass index, kg/m^2	22.7 (±3.3)
Anti-CCP Ab positive	64 (75.3%)
Current osteoporosis treatment	34 (40.0%)
Denosumab	18 (21.2%)
Bisphosphonate	12 (14.1%)
SERM	2 (2.4%)
Active vitamin D (alone)	2 (2.4%)
bDMARD or tsDMARD use	46 (54.1%)
Methotrexate use	58 (68.2%)
Glucocorticoid use	16 (18.8%)
CDAI	4.5 (±3.8)
HAQ-DI	0.2 (±0.4)
BMD T-score	
Lumbar spine	−0.6 (±1.4)
Total hip	−1.3 (±0.9)
Femoral neck	−1.8 (±1.0)

Data shown as mean ± standard deviation or number (percentage).

Anti-CCP Ab, anti-cyclic citrullinated peptide antibody; SERM, selective estrogen receptor modulator; bDMARD, biological disease-modifying antirheumatic drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index.

RESULTS

A total of 85 patients were enrolled in this study. The rate of patient compliance was 78.4% for a training adherence rate >80%. The demographic and clinical characteristics of the patients are summarized in **Table 1**. In patients receiving osteoporosis treatment, active vitamin D was used alone in 2 patients and in combination with other drugs in 20 patients.

The ΔBMD values for the non-exercise period and the exercise period were 0.1 ± 3.1% and 1.6 ± 3.7% (P=0.007) for the lumbar spine, −0.2 ± 2.4% and 1.0± 2.4% (P=0.005) for the total hip, and −0.6 ± 3.9% and 1.8 ± 3.5% (P<0.001) for the femoral neck, respectively (**Fig. 1**). The proportions of patients who showed increased BMD at the lumbar spine, total hip, and femoral neck were 55.3%, 60.0%, and 60.0%,

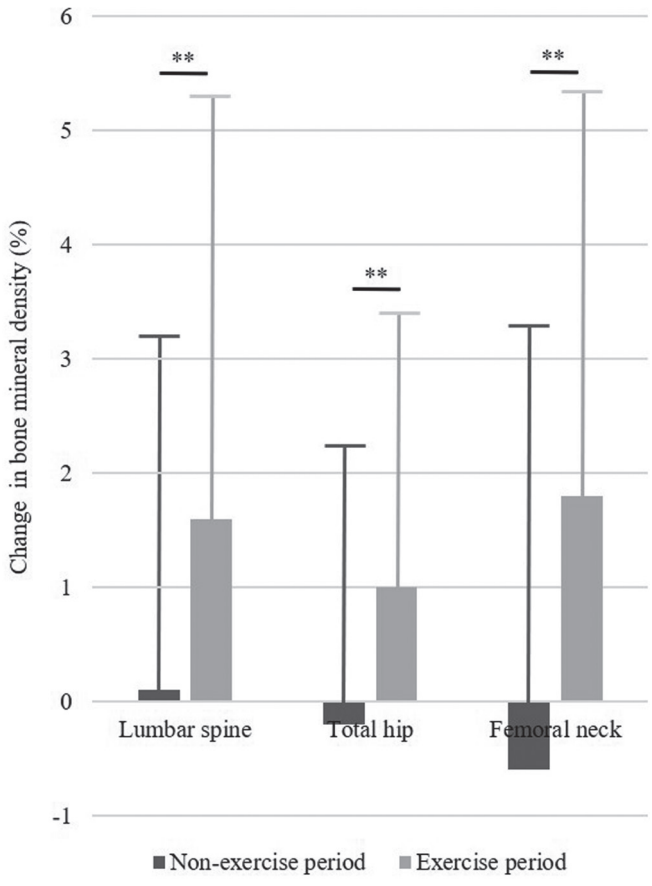

Fig. 1. Percentage changes in the bone mineral densities of the lumbar spine, total hip, and femoral neck for the non-exercise period (the year before baseline) and the exercise period (the year after baseline). Non-exercise period vs. exercise period: **P<0.01.

respectively. The factor most associated with increased BMD at the femoral neck was the Health Assessment Questionnaire Disability Index (HAQ-DI) score at baseline (odds ratio, 0.304; 95% confidence interval, 0.073–0.927) (**Table 2**). No factor was associated with increased BMD in the lumbar spine or total hip.

DISCUSSION

This study showed that locomotion training in patients with RA significantly increased the BMD of the lumbar spine, total hip, and femoral neck during the exercise period when compared with the trends of declining BMD data observed during the non-exercise period.[23,24] In patients with RA, the reductions in total hip BMD for those aged 40–49, 50–59, and 60–70 years were 3.7%, 6.0%, and 8.5%, respectively, whereas the reductions in the femoral neck BMD for those aged 50–59 and 60–70 years were 4.2% and 5.0%, respectively.[23] Our results showed that BMD at all sites did not decrease as much as that observed before locomotion training.

The effect of exercise on BMD is influenced by exercise intensity. In a study of patients with osteoporosis, the intervention group (high-intensity resistance exercise, maintaining intensity of 80%–85%, one-repetition maximum) showed significantly increased BMD in the lumbar spine (+2.9%) compared to that of the control group (−1.2%) and significantly increased BMD in the femoral neck (+0.3% vs. −1.9%).[17] In another study of healthy volunteers, the BMD of the femoral neck increased more in the intervention group (high-intensity exercise with aerobic threshold; +1.6%) than in the control group (+0.6%).[25] In studies on low-intensity exercise, walking more than 8000 steps per day for more than 4 days a week for 12 months was significantly associ-

Table 2. Factors associated with increased BMD for femoral neck

Variable	Increased BMD (+) (n=51)	Increased BMD (−) (n=34)	P value (univariate)	P value (multivariate)
Age, years	71 [62.5, 77.5]	70.5 (61.3, 74.8)	0.608	
Female	46 (90.2%)	32 (94.1)	0.697	
Body mass index, kg/m^2	21.9 [19.9, 23.9]	23.7 (22.1, 25.3)	0.041	0.074
Duration of RA, years	12 [7, 18.5]	12 (7, 17)	0.469	
Anti-CCP Ab (+)	38 (74.5%)	26 (76.4)	1.000	
Glucocorticoid use	10 (19.6%)	6 (17.6)	1.000	
Osteoporosis treatment	20 (39.2%)	14 (41.8)	1.000	
CDAI at baseline	2.8 [1.4, 6.5]	4.7 (1.8, 8.3)	0.190	
HAQ-DI at baseline	0 [0, 0.125]	0.125 (0, 0.5)	0.028	0.013

Data given as median [interquartile range] or number (percentage).

ated with an increased BMD in the lumbar spine relative to the control group (+1.7% vs. −1.9%).[14] A 6-week exercise program that included squats, front lunges, side lunges, calf raises, and toe raises improved pelvic BMD and knee extensor strength compared to the control group BMD, although the BMD of the spine was not increased in postmenopausal women.[26] In the present study, low-intensity exercise, such as locomotion training for over 6 months, may have contributed to increased BMD of the lumbar spine, total hip, and femoral neck.

In this study, the HAQ-DI score at baseline was associated with increased BMD of the femoral neck. Similarly, in previous reports, the HAQ-DI score was associated with the lumbar spine and trochanter in the hips of patients with early RA.[27] In patients with RA, BMD at the femoral neck but not at the lumbar spine was associated with quadriceps strength.[28] Locomotion training primarily involves lower extremity exercises. We believe that patients with low HAQ-DI scores had physical functions conducive to exercise, which led to increased BMD at the femoral neck.

This study has some limitations. First, the effects of osteoporosis and RA treatments 1 year before and 1 year after baseline were not fully elucidated. We believe that any effects of these altered treatments on the study results were minimal, because the same treatments for osteoporosis and RA were consistently maintained in the patients. Second, the period of locomotion training in this study was only 6 months, and the subsequent 6 months was not subject to any specific guidance on exercise continuity. Third, although the same patients were evaluated for BMD before and after locomotion training, a control group was not included. Despite these limitations, we believe that the results of this study are meaningful. In the future, a prospective study of patients with the same background of osteoporosis and RA treatments will be necessary to confirm the effects of locomotion training.

CONCLUSION

This study is the first to demonstrate that locomotion training increased the BMD of the lumbar spine, total hip, and femoral neck when compared with BMD data for the non-exercise period. The current treatment for RA and osteoporosis accompanied by optional locomotion training might be effective in increasing BMD in patients with RA who cannot perform high-intensity training.

ACKNOWLEDGMENTS

The authors thank the medical staff of the clinical research center in our institutions for their assistance.

CONFLICTS OF INTEREST

T. Mochizuki received honoraria for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Mochida, and Pfizer. K. Yano received honoraria for lectures from AbbVie, Astellas, Ayumi, Bristol-Meyers, Eisai, Hisamitsu, Mochida, and Takeda. K. Ikari received honoraria for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Eisai, Eli Lilly, Janssen, Takeda, Tanabe-Mitsubishi, and UCB. The remaining author declares no conflict of interest. The sponsors were not involved in the study design; collection, analysis, and interpretation of data; writing of the article; and/or the decision to submit the results for publication.

REFERENCES

1. Soós B, Szentpétery Á, Raterman HG, Lems WF, Bhattoa HP, Szekanecz Z: Effects of targeted therapies on bone in rheumatic and musculoskeletal diseases. Nat Rev Rheumatol 2022;18:249–257. https://doi.org/10.1038/s41584-022-00764-w, PMID:35273387
2. Tanaka S, Tanaka Y, Ishiguro N, Yamanaka H, Takeuchi T: RANKL: a therapeutic target for bone destruction in rheumatoid arthritis. Mod Rheumatol 2018;28:9–16. https://doi.org/10.1080/14397595.2017.1369491, PMID:28880683
3. Blavnsfeldt AB, de Thurah A, Thomsen MD, Tarp S, Langdahl B, Hauge EM: The effect of glucocorticoids on bone mineral density in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomized, controlled trials. Bone 2018;114:172–180. https://doi.org/10.1016/j.bone.2018.06.008, PMID:29913256
4. Arai K, Hanyu T, Sugitani H, Murai T, Fujisawa J, Nakazono K, Kondo N, Endo N: Risk factors for vertebral fracture in menopausal or postmenopausal Japanese women with rheumatoid arthritis: a cross-sectional and longitudinal study. J Bone Miner Metab 2006;24:118–124. https://doi.org/10.1007/s00774-005-0657-9, PMID:16502118

5. Takeuchi T, Tanaka Y, Ishiguro N, Yamanaka H, Yoneda T, Ohira T, Okubo N, Genant HK, van der Heijde D: Effect of denosumab on Japanese patients with rheumatoid arthritis: a dose–response study of AMG 162 (Denosumab) in patients with RheumatoId arthritis on methotrexate to Validate inhibitory effect on bone Erosion (DRIVE)—a 12-month, multicentre, randomised, double-blind, placebo-controlled, phase II clinical trial. Ann Rheum Dis 2016;75:983–990. https://doi.org/10.1136/annrheumdis-2015-208052, PMID:26585988
6. Mochizuki T, Yano K, Ikari K, Kawakami K, Hiroshima R, Koenuma N, Ishibashi M, Momohara S: Effects of denosumab treatment on bone mineral density and joint destruction in patients with rheumatoid arthritis. J Bone Miner Metab 2018;36:431–438. https://doi.org/10.1007/s00774-017-0848-1, PMID:28681148
7. Mochizuki T, Yano K, Ikari K, Hiroshima R, Nasu Y, Okazaki K: Three-year results of denosumab treatment for osteoporosis in women with rheumatoid arthritis and primary osteoporosis: a clinical observational study. Mod Rheumatol 2021;31:600–606. https://doi.org/10.1080/14397595.2020.1812793, PMID:32815449
8. Iwamoto N, Okamoto M, Tsuji S, Endo Y, Takatani A, Shimizu T, Umeda M, Fukui S, Sumiyoshi R, Igawa T, Koga T, Kawashiri S, Aramaki T, Ichinose K, Tamai M, Nakamura H, Origuchi T, Eguchi K, Ueki Y, Kawakami A: Denosumab is effective toward glucocorticoid-induced osteoporosis patients complicated with rheumatic diseases regardless of prior anti-osteoporotic drugs. J Bone Miner Metab 2019;37:554–562. https://doi.org/10.1007/s00774-018-0955-7, PMID:30187273
9. Mochizuki T, Yano K, Ikari K, Hiroshima R, Okazaki K: Comparison of romosozumab versus denosumab treatment on bone mineral density after 1 year in rheumatoid arthritis patients with severe osteoporosis: a randomized clinical pilot study. Mod Rheumatol 2023;33:490–495. https://doi.org/10.1093/mr/roac059, PMID:35689558
10. Kanis JA, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF): European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019;30:3–44. https://doi.org/10.1007/s00198-018-4704-5, PMID:30324412
11. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, Harris ST, Hurley DL, Kelly J, Lewiecki EM, Pessah-Pollack R, McClung M, Wimalawansa SJ, Watts NB: American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update. Endocr Pract 2020;26:1–46. https://doi.org/10.4158/GL-2020-0524SUPPL, PMID:32427503
12. Tai TW, Huang CF, Huang HK, Yang RS, Chen JF, Cheng TT, Chen FP, Chen CH, Chang YF, Hung WC, Han DS, Chan DC, Tsai CC, Chen IW, Chan WP, Chang HJ, Hwang JS, Wu CH: Clinical practice guidelines for the prevention and treatment of osteoporosis in Taiwan: 2022 update. J Formos Med Assoc 2023;122:S4–S13. https://doi.org/10.1016/j.jfma.2023.01.007, PMID:36781371
13. Bonaiuti D, Shea B, Iovine R, Negrini S, Robinson V, Kemper HC, Wells G, Tugwell P, Cranney A: Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev 2002;3:CD000333. https://doi.org/10.1002/14651858.CD000333, PMID:12137611
14. Yamazaki S, Ichimura S, Iwamoto J, Takeda T, Toyama Y: Effect of walking exercise on bone metabolism in postmenopausal women with osteopenia/osteoporosis. J Bone Miner Metab 2004;22:500–508. https://doi.org/10.1007/s00774-004-0514-2, PMID:15316873
15. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, Harbour RT, Caldwell LM, Creed G: Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Libr 2011;7:CD000333. https://doi.org/10.1002/14651858.CD000333.pub2, PMID:21735380
16. Kemmler W, Bebenek M, Kohl M, von Stengel S: Exercise and fractures in postmenopausal women. Final results of the controlled Erlangen Fitness and Osteoporosis Prevention Study (EFOPS). Osteoporos Int 2015;26:2491–2499. https://doi.org/10.1007/s00198-015-3165-3, PMID:25963237
17. Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR: High-intensity resistance and impact training improves bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis: the LIFTMOR randomized controlled trial. J Bone Miner Res 2018;33:211–220. https://doi.org/10.1002/jbmr.3284, PMID:28975661

18. Häkkinen A, Sokka T, Kautiainen H, Kotaniemi A, Hannonen P: Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a 5 year follow up. Ann Rheum Dis 2004;63:910–916. https://doi.org/10.1136/ard.2003.013003, PMID:15249317
19. de Jong Z, Munneke M, Lems WF, Zwinderman AH, Kroon HM, Pauwels EK, Jansen A, Ronday KH, Dijkmans BA, Breedveld FC, Vliet Vlieland TP, Hazes JM: Slowing of bone loss in patients with rheumatoid arthritis by long-term high-intensity exercise: results of a randomized, controlled trial. Arthritis Rheum 2004;50:1066–1076. https://doi.org/10.1002/art.20117, PMID:15077288
20. Mochizuki T, Yano K, Ikari K, Okazaki K: Effectiveness of locomotion training in patients with rheumatoid arthritis: a prospective clinical trial. J Phys Ther Sci 2023;35:810–816. https://doi.org/10.1589/jpts.35.810, PMID:38075516
21. Kawahito Y, Morinobu A, Kaneko Y, Kohno M, Hirata S, Kishimoto M, Seto Y, Sugihara T, Tanaka E, Ito H, Kojima T, Matsushita I, Nishida K, Mori M, Murashima A, Yamanaka H, Nakayama T, Kojima M, Harigai M: Drug treatment algorithm and recommendations from the 2020 update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis—secondary publication. Mod Rheumatol 2023;33:21–35. https://doi.org/10.1093/mr/roac017, PMID:35297492
22. Nakamura K, Ogata T: Locomotive syndrome: definition and management. Clin Rev Bone Miner Metab 2016;14:56–67. https://doi.org/10.1007/s12018-016-9208-2, PMID:27375370
23. Bejarano V, Hensor E, Green M, Haugeberg G, Brown AK, Buch MH, Emery P, Conaghan PG: Relationship between early bone mineral density changes and long-term function and radiographic progression in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:66–70. https://doi.org/10.1002/acr.20553, PMID:21770041
24. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK: Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County rheumatoid arthritis register. Arthritis Rheum 2000;43:522–530. https://doi.org/10.1002/1529-0131(200003)43:3<522::AID-ANR7>3.0.CO;2-Y, PMID:10728744
25. Heinonen A, Kannus P, Sievänen H, Oja P, Pasanen M, Rinne M, Uusi-Rasi K, Vuori I: Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. Lancet 1996;348:1343–1347. https://doi.org/10.1016/S0140-6736(96)04214-6, PMID:8918277
26. Hamaguchi K, Kurihara T, Fujimoto M, Iemitsu M, Sato K, Hamaoka T, Sanada K: The effects of low-repetition and light-load power training on bone mineral density in postmenopausal women with sarcopenia: a pilot study. BMC Geriatr 2017;17:102. https://doi.org/10.1186/s12877-017-0490-8, PMID:28464798
27. Gough A, Lilley J, Eyre S, Holder RL, Emery P: Generalised bone loss in patients with early rheumatoid arthritis. Lancet 1994;344:23–27. https://doi.org/10.1016/S0140-6736(94)91049-9, PMID:7912297
28. Madsen OR, Sørensen OH, Egsmose C: Bone quality and bone mass as assessed by quantitative ultrasound and dual energy x ray absorptiometry in women with rheumatoid arthritis: relationship with quadriceps strength. Ann Rheum Dis 2002;61:325–329. https://doi.org/10.1136/ard.61.4.325, PMID:11874835