

Bone Mineral Density (BMD) of Systemic Lupus Erythematosus (SLE) Patients and its Risk of Osteoporosis: A Literature Review

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Abstract

Systemic Lupus Erythematosus is a chronic autoimmune disease that affects multiple organs and has variations of clinical manifestations due to the involvement of multiple autoantibodies, immune complex formation and deposition, and immune processes. Previous studies suggested an increased risk of osteoporosis in systemic lupus erythematosus patients according to bone mineral density (BMD) values. This literature study aims to describe the definition of bone mineral density and systemic lupus erythematosus, the bone mineral density of systemic lupus erythematosus, and the risks of osteoporosis in systemic lupus erythematosus patients.

Keywords: SLE, BMD, Osteoporosis

1. Definition

1.1. Bone Mineral Density (BMD)

Bone has a natural composition that makes bones have unique mechanical properties, which mainly consist of an organic matrix (Type I Collagen) and a mineral matrix (hydroxyapatite crystal embedded in the collagen fibers). Judging from the effect of each material property, mineral components have a major influence on bone strength, while organic matrix has more influence on bone toughness and its plastic deformation. BMD is the mass of inorganic (mineral) matter per unit volume. BMD can be affected by many factors, such as age, dietary calcium, genetics, physical activity, sexual maturation, lifestyle, and hormonal status/menopause. The development of osteoporosis risks due to metabolic disorders or the physiological aging process leading to alterations in bone remodeling rates. This results in reduced bone strength and increased fragility and bone-fracture risk. Reduced bone strength can result in a decrease in the BMD values of the patient. Because of that, osteoporosis is often diagnosed by measurement of BMD, with the standard gold method used being dual-energy X-ray absorptiometry (DXA) scanning of the lumbar spine and hip [12,16].

1. 2. Systemic Lupus Erythematosus (SLE)

SLE is known to have the formation of pathogenic autoantibodies against nucleic acids and their binding proteins due to the self-intolerance of the body's components. This explains that each patient's symptoms might differ depending on what organs are attacked by the antibodies. And from a clinical perspective, SLE is a disease with unpredictable courses involving flares and remissions, where damage can be cumulative, affecting organ function and quality of life in patients [9,10].

The different manifestations in organs and laboratory results can be confusing because SLE has no inner pathogenic coherence but can appear non-concurrently. To assist the classification of SLE, criteria have been established, such as by The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), which jointly supported the development of a new SLE Classification. The 2019 EULAR/ACR new classification criteria for SLE include positive ANA at least once as the obligatory entry criterion. It is followed by additional weighted criteria grouped in 3 immunologic (SLE-specific antibodies, antiphospholipid antibodies, complement proteins) and seven clinical (constitutional, mucocutaneous, musculoskeletal, hematologic, neuropsychiatric, serosal, renal) domains and weighted from 2 to 10. And patients who accumulate ≥ 10 points are classified as SLE patients. And it was also found in the validation cohort that this new criterion had a sensitivity of 96.1% and a specificity of 93.4%, compared with 96.7% sensitivity and 83.7% specificity of the Systemic Lupus International Collaborating Clinics (SLICC) 2012 and 82.8% sensitivity and 93.4% specificity of the ACR 1997 criteria [2].

2. Bone Mineral Density on Systemic Lupus Erythematosus

A meta-analysis study stated that the prevalence of low BMD at any site in SLE patients was high percentage with 45% of total patients, not only in premenopausal patients, with a percentage of 40%, but also in postmenopausal patients, with a percentage of 43%. It also shows the prevalence of osteopenia in all patients at 38%, premenopausal at 42%, and postmenopausal at 25%. At the same time, the prevalence of osteoporosis was 13%, 9%, and 21%, respectively [16].

Another meta-analysis study also shows that SLE patients have significantly lower BMD levels than controls in the whole body, involving: the lumbar spine, femoral neck, and total hip. This supports that SLE patients have significant bone loss and may be at high risk of osteoporosis and fractures alongside other risks. Several studies suggest that the etiology of bone loss in SLE is multifactorial, including traditional risk factors of osteoporosis, hormonal factors, autoimmune inflammation, and corticosteroid-induced adverse impact, which may be the reason for the increased bone loss in patients with SLE. Aging causes alterations in cortical bone microstructure and higher bone porosity, and age corresponds negatively with BMD and bone strength. Fragility is the result of bone loss and degradation of bone structure. Assessment of osteon area and Haversian canal provided by an increase in osteon-remodeling rates with age indicates an increase in intracortical porosity, which may be used as an indicator for the diagnosis of osteoporosis and age-related risk of fracture. Furthermore, cortical BMD aging changes vary by skeletal site. The severity of BMD decline also depends on tissue mineralization, defined as the percentage of BM in the solid phase and the porosity above [8].

In general, an increased skew of the balance of bone remodeling toward bone resorption produces a decrease in BMD and bone strength in males and females. Peak bone mass will be reached at different ages depending on the skeletal site, with the earliest age signifying 14–18.5 years old for the hip in both sexes. Adult bone strength depends on skeletal development and growth in the first decades. Males tend to reach peak bone mass at an older age than females but with higher bone content and density at a later maturational stage. After attaining peak bone mass at the end of skeletal maturation, BMD degenerates. BMD values later in life represent the importance of skeletal development and changes in the rate of bone loss, with both factors being determinants of osteoporosis development in postmenopausal females [8].

Estrogen deficiency causes an increase in remodeling and consequent bone loss in this group, with low estrogen levels also reducing skeletal tissue formation in response to mechanical stimuli. At older ages, a higher incidence of osteoporosis is seen in females compared to males, regardless of the female's hormonal status, connecting the disorder not only to hormonal deficiency but also to lower female skeletal mass reaching puberty or essentially higher BMD loss with aging [8].

3. Risk of Osteoporosis on Systemic Lupus Erythematosus

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture, reflecting the integration of bone mineral density (BMD) and bone quality. The osteoporosis spectrum has displayed different rates of bone loss depending on the skeletal site and life stage. Furthermore, secondary osteoporosis does not occur of any underlying disease or medication. It is mostly seen in postmenopausal females, and males of advanced age are associated with a wide variety of underlying conditions, such as systemic lupus erythematosus (SLE) [7,8].

The musculoskeletal system is one of the most involved systems in SLE, and morbidity related to bone loss and associated fractures is very prevalent. Previous studies suggested possible bone loss and fracture risk in patients with SLE [3,14]. According to the World Health Organization (WHO) criteria, the diagnosis of osteoporosis is based on bone mineral density (BMD) assessment with 2.5 standard deviations (SD), or more below the young adult mean (a T-score < -2.5 SD). A T-score within -1.0 SD or above is the normal range, while a T-score between -1.0 and -2.5 SD is defined as low bone mass or osteopenia. The current gold standard method for assessing BMD is dual-energy X-ray absorptiometry (DXA) of the hip and spine. The T-score values for osteoporosis and osteopenia diagnosis are validated by WHO only when measured by DXA; hence another usage of BMD assessment is considered as screening [3,6,15].

A cohort study stated that several conventional risk variables, including age, postmenopausal status, low body mass index (BMI), glucocorticoid (GC) use, and chronic antiepileptic medicine, have been linked to osteoporosis [5]. Osteoclastic bone resorption and osteoblastic bone production are both decreased by systemic inflammation in SLE, which results in bone loss. IL-1, IL-6, IL-17, and TNF- α mainly drive the effect of a disrupted inflammatory status. These pro-inflammatory cytokines affect osteoblast and osteoclast differentiation

and function, resulting in alterations in bone modeling and remodeling. They alter it by promoting osteoclastogenesis to act on cells of the osteoclast lineage or, indirectly, by modulating expression in target cells of key molecules such as RANK-L.

RANK-L is a stimulatory factor that promotes the formation and activation of mature osteoclasts, which are the cells responsible for bone resorption. Osteoprotegerin (OPG), a soluble neutralizing receptor that blocks the effects of RANK-L, counteracts its effect. In addition to these effects on osteoclasts, inflammatory diseases are linked to decreased osteoblast function, most likely due to secondary inhibition of osteoblast differentiation and increased apoptosis [11,13]. Tumor necrosis factor (TNF) and oxidized low-density lipoprotein (LDL) levels are raised in the serum of individuals with the active illness. Oxidized lipids can stimulate T cells, which could lead to an increase in RANKL and TNF production. TNF and RANKL both promote osteoclast development and activity. Alternatively, by lowering osteoblast development, oxidized LDL may adversely affect bone production. Premenopausal women with untreated, recently diagnosed SLE had decreased serum levels of osteocalcin, a marker for bone production, decreased serum levels of osteocalcin, a marker for bone resorption, and increased crosslinks excretion in the urine were demonstrated in premenopausal women with recently diagnosed SLE [1,3].

GCs are widely used to treat SLE disease flare-ups and complications. GCs primarily induce trabecular bone and the cortical rim of the vertebral body. However, long-term use of GCs can harm the cortex of the long bones. GCs also have beneficial effects on bone by reducing the negative effects of systemic inflammation. Several studies have found a link between GC medication and low BMD or bone loss in SLE patients who take high glucocorticoids. They discovered that lumbar spine bone loss risks occur only in patients taking more than 7.5 mg of prednisone daily [3]. According to the literature, glucocorticoid use is linked to fractures, osteoporosis, and low BMD in SLE patients. Corticosteroids may inhibit the formation and function of osteoblasts, inhibit calcium absorption, increase osteoclasts, and affect GC-induced leucine zipper proteins, 11-hydroxysteroid dehydrogenase type 1, and other associated proteins that cause bone loss [16].

Metabolic factors are important in the association of SLE and low BMD or osteoporosis, especially regarding the Parathyroid Hormone (PTH) axis and vitamin D. In SLE patients, low BMD is seen in 15% of the population at the onset of the disease. It is associated with low BMD with high serum levels of PTH and low serum levels of calcium. Several factors that might negatively influence vitamin D status in SLE are photosensitivity, use of sunscreen, glucocorticoid (GC) medication, hydroxychloroquine (HCQ) medication, anti-vitamin D antibodies, etc. All SLE patient is educated to avoid sunlight and to use broad-spectrum sunscreens. These restrictions limit endogenous vitamin D production and cause a reduction of the circulating level of 25OH vitamin D. Furthermore, patients with nephritis may also have a deficit of 1-25 hydroxylation of vitamin D, developing secondary hyperparathyroidism with decreased intestinal calcium absorption [1,3].

4. Conclusions

It can be concluded from the literature that SLE patients have higher risks of developing osteoporosis by factors that affect the quality level of BMD in patients. However, a diagnosis of osteoporosis is needed using standard procedures such as DXA assessment or screening assessment such as QUS, QCT, and others, along with analysis in treating and managing SLE patients.

References

1. Adami, G. et al. (2019) 'Osteoporosis in rheumatic diseases,' *International Journal of Molecular Sciences*, 20(23). doi: 10.3390/ijms20235867.
2. Aringer, M. et al. (2019) '2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus,' *Annals of the Rheumatic Diseases*, 78(9), pp. 1151–1159. doi: 10.1136/annrheumdis-2018-214819.
3. Bultink, I. E. M. and Lems, W. F. (2016) 'Lupus and fractures', *Current Opinion in Rheumatology*, 28(4), pp. 426–432. doi: 10.1097/BOR.0000000000000290.
4. Bultink, I. E. M. (2012) 'Osteoporosis and fractures in systemic lupus erythematosus', *Arthritis Care and Research*, 64(1), pp. 2–8. doi: 10.1002/acr.20568.
5. Carli, L. et al. (2015) "Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus," *Lupus Science & Medicine*, 3(1), pp. 1–5. Available at: <https://doi.org/10.1136/lupus-2015-000098>.
6. Cosman, F., de Beur, S.J., LeBoff, M.S. et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int* 25, 2359–2381 (2014). <https://doi.org/10.1007/s00198-014-2794-2>
7. Indriyani, N. et al. (2017) 'Bone mineral density among systemic lupus erythematosus patients aged 5-18 years with glucocorticoid treatment in child and adolescent outpatient clinics, Cipto Mangunkusumo Hospital, Jakarta', *Journal of Physics: Conference Series*, 884(1). doi: 10.1088/1742-6596/884/1/012078.
8. Kranioti, E. F., Bonicelli, A. and García-Donas, J. G. (2019) 'Bone-mineral density: clinical significance, methods of quantification and forensic applications', *Research and Reports in Forensic Medical Science*, Volume 9, pp. 9–21. doi: 10.2147/RRFMS.S164933.
9. Putterman, C. et al. (2012) 'Systemic lupus erythematosus', *Clinical and Developmental Immunology*, 2012(May 2014). doi: 10.1155/2012/437282.
10. Rekvig, O.P. (2018) "Systemic lupus erythematosus: Definitions, contexts, conflicts, enigmas," *Frontiers in Immunology*, 9, pp. 1–16. Available at: <https://doi.org/10.3389/fimmu.2018.00387>.
11. Takayanagi, H. New developments in osteoimmunology. *Nat Rev Rheumatol* 8, 684–689 (2012). <https://doi.org/10.1038/nrrheum.2012.167>
12. Tinoco, H. A. (2017) 'Bone Mineral Density (BMD)', *Current Trends in Biomedical Engineering & Biosciences*, 2(1). doi: 10.19080/ctbeb.2017.02.555576.
13. von Scheven, E., Corbin, K.J., Stefano, S. et al. Glucocorticoid-Associated Osteoporosis in Chronic Inflammatory Diseases: Epidemiology, Mechanisms, Diagnosis, and Treatment. *Curr Osteoporos Rep* 12, 289–299 (2014). <https://doi.org/10.1007/s11914-014-0228-x>
14. Wang, X., Yan, S., Liu, C. et al. Fracture risk and bone mineral density levels in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Osteoporos Int* 27, 1413–1423 (2016). <https://doi.org/10.1007/s00198-015-3449-7>
15. Willson T, Nelson SD, Newbold J, Nelson RE, LaFleur J. The clinical epidemiology of male osteoporosis: a review of the recent literature. *Clinical Epidemiology*. 2015 Jan 9;7:65-76. doi: 10.2147/CLEP.S40966. PMID: 25657593; PMCID: PMC4295898.
16. Xia, J. et al. (2019) "Prevalence and risk factors of reduced bone mineral density in systemic lupus erythematosus patients: A meta-analysis," *BioMed Research International*, 2019, pp. 1–10. Available at: <https://doi.org/10.1155/2019/3731648>.