ABSTRACT

Objectives: This meta-analysis aims to investigate the possibility of bone mineral loss and fracture in sarcoidosis.

Materials and methods: A comprehensive search of the MEDLINE and Embase databases was performed from inception through August 2017. The inclusion criterion was observational studies evaluating the association between sarcoidosis and bone mineral density (BMD) or fracture. The pooled odds ratio (OR) of fracture, standardized mean difference (SMD) of volumetric BMD and areal BMD, and their 95% confidence interval (CI) were calculated using a random-effects meta-analysis to compare risk between sarcoidosis and controls. The between-study heterogeneity of effect-size was quantified using the Q statistic and I².

Results: Data were extracted from 10 studies involving a total of 6,448 sarcoidosis patients and 77,857 controls. The pooled result demonstrated no significant increased risk of fracture in sarcoidosis patients compared with controls (OR=1.68; 95% CI: 0.85-3.31, p value=0.14, I²=72%). There were no differences between the patients and controls in areal BMD (SMD=0.21 g/cm²; 95% CI:-0.12-0.54, p value=0.22, I²=0%) or volumetric BMD (SMD=0.04 mg/cm³; 95% CI:-0.51-0.58, p value=0.89, I²=83%).

Conclusion: Our study has not shown an increased risk of fracture or bone mineral loss in sarcoidosis. However, based on the currently available studies with heterogeneity in between, the conclusion for the osteoporosis screening and fracture risk assessment of patients with sarcoidosis cannot be drawn until more studies are available.

Keywords: Bone mineral density, fracture, meta-analysis, osteoporosis, sarcoidosis.

Bone Mineral Loss and Fracture in Sarcoidosis: A Systematic Review and Meta-Analysis

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Sarcoidosis is a systemic chronic inflammatory disorder that is characterized by non-caseating granulomas in different organs, such as heart, liver, eyes, muscle, nervous system, with a predilection for lung involvement. The prevalence of sarcoidosis has been reported to be estimated at 10-20 per 100,000 populations, but the incidence appears to be varying among geographical regions and specific races.1 African-Americans have a higher lifetime risk of sarcoidosis than Caucasian Americans (2.4% vs. 0.85%). Bone involvement has been described in about 13% of patients with sarcoidosis based on the current published case reports.2 Granulomatous infiltration of the bone can cause symptoms such as tenderness, swelling, stiffness, deformity, or erythema near the site of bone involvement or adjacent joints.2

Chronic systemic inflammatory diseases such as chronic obstructive pulmonary disease (COPD),3,4 rheumatoid arthritis (RA),5-7 ankylosing spondylitis,8,9 systemic lupus erythematosus,10,11 and inflammatory bowel disease12 have been known to cause secondary osteoporosis.
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independently of glucocorticoid, leading to increased risk of fractures. Several etiologies of bone mineral loss in inflammatory diseases have been reported, including immobilization, renal dysfunction, hormonal imbalance (low plasma androgen, hyperprolactinemia, and menopause), hypovitaminosis D, and utilization of immunomodulant/immunosuppressive drugs. The induction of inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-11, IL-15, IL-17, tumor necrosis factor-alpha (TNF-α), receptor activator of nuclear factor-κB ligand (RANKL), and macrophage colony-stimulating factor, has been reported to involve in the process of bone resorption. This process is initiated when monocytes differentiate into osteoclasts at the inflamed joint. Following the binding of RANKL to the RANK receptor on the osteoclasts and dendritic cells, it induces the signaling pathways that stimulate formation and activation of osteoclasts. Macrophage colony-stimulating factor plays a role in this process by activating the proliferation of osteoclasts. Furthermore, TNF-α can promote the formation of osteoclast lineage from monocyte precursors. Abundant interleukins (IL-1, IL-6, IL-7, IL-17) in the inflamed joint can also induce RANKL and upregulate osteoclastogenesis.

However, the reports on bone mineral loss or fracture in sarcoidosis have conflicting outcomes. Few studies have reported a high prevalence of fragility fractures and vertebral deformities in patients with sarcoidosis, but bone mineral density (BMD) in sarcoidosis has not been found to be reduced. It is essential to investigate the association between sarcoidosis and bone mineral loss or fracture because osteoporotic or fragility fracture reduces patients’ quality of life. Furthermore, sarcoidosis is primarily treated with glucocorticoids, which can further reduce the BMD. Thus, in this meta-analysis, we aimed to investigate the possibility of bone mineral loss and fracture in sarcoidosis.

**MATERIALS AND METHODS**

This systematic review and meta-analysis was conducted at Department of Internal Medicine, Bassett Medical Center between March 2017 and August 2017 and reported according to the Meta-analysis Of Observational Studies in Epidemiology statement and registered in international prospective register of systematic reviews (PROSPERO) (registration number: CRD 42017059491).

Three authors independently searched published studies indexed in MEDLINE and Embase from date of inception to August 2017. References of all selected studies were also examined. The following main search terms were used: sarcoidosis, osteoporosis, osteopenia, bone mineral density, bone mass, fragility fracture, osteoporotic fracture. The full search terms used were detailed in the Supplemental Material and Methods.

This review included all published observational studies including cross-sectional, prospective cohort, retrospective cohort and case-control studies that assessed the association of sarcoidosis, and decreased BMD or fracture. Reviews, case reports, and abstracts were excluded because the quality of studies could not be evaluated. Non-English publications were excluded because the quality of studies could not be assessed and the exclusion of non-English

Supplemental Material and Methods

**MEDLINE**

1. Exp Osteoporosis/or osteoporosis.mp. (78734)
2. Osteopenia.mp. (8765)
3. Bone density.mp. or exp Bone Density/ (63846)
4. Bone mass.mp. (17483)
5. Bone loss.mp. (31770)
6. BMD.mp. (26294)
7. Fragility fracture.mp. (1153)
8. Osteoporotic fracture.mp. or exp Osteoporotic Fractures/ (5623)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (141985)
10. Sarcoidosis.mp. or exp Sarcoidosis, Pulmonary/ or exp Sarcoidosis/(28992)
11. Sarcoid$.mp. (29828)
12. Besnier-Boeck.mp. (649)
13. Besnier-Boeck-Schaumann.mp. (537)
14. Lofgren syndrome.mp. (80)
15. 10 or 11 or 12 or 13 or 14 (29858)
16. 9 and 15 (120)

**EMBASE**

("sarcoidosis"/exp OR 'sarcoidosis') OR sarcoid$ AND ("osteoporosis"/exp OR osteoporosis) OR ("osteopenia"/exp OR 'osteopenia') OR ('bone density'/exp OR 'bone density') OR ('bone'/de AND 'mineral'/de AND 'density'/de) OR ('bone mass'/exp OR 'bone mass') OR ('bone'/de AND loss) OR ('osteolysis'/exp OR 'osteolysis') OR bmd OR ('fragility fracture'/exp OR 'fragility fracture') OR (osteoporotic AND 'fracture'/exp)
articles generally has limited effect on summary effect estimates. 23

We included studies that recruited participants from the general population or used data from medical records from healthcare facilities. Participants were adults with sarcoidosis or healthy individuals. The comparison was made between patients who were diagnosed with sarcoidosis by compatible clinical and radiographic manifestations in addition to histopathological evidence of non-caseating granuloma in various tissue specimens and participants who did not have sarcoidosis. The outcome of this study was a diagnosis of fracture or decreased BMD. The odds ratios (ORs), relative risks (RRs), hazard ratios (HRs) or the number of participants with the outcome of fracture were extracted. The diagnosis of fracture was reported as fragility fracture or osteoporotic fracture. Fragility fracture was defined as fracture of the vertebrae, proximal femur, distal forearm, or proximal humerus sites that occurred from a fall of standing height or less without major trauma. Osteoporotic fracture was defined as a fracture of the hip, radius/ulna, vertebrae, or humerus according to the World Health Organization’s definition. The outcomes of BMD were reported as volumetric BMD (vBMD) that were measured with quantitative computed tomography (QCT) or areal BMD (aBMD) that were measured with dual-energy X-ray absorptiometry. The normal values for QCT were determined by using a phantom.

All authors independently reviewed titles and abstracts of all citations that were identified. After abstracts were reviewed, data comparisons between the three investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus.

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. Data concerning study design, the source of information, participant characteristics, assessment of sarcoidosis, BMD and fracture were independently extracted. We contacted the authors of the original reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses.

A subjective assessment of methodological quality of observational studies was evaluated by all three authors using the Newcastle-Ottawa Scale, 24 which is a quality assessment tool for non-randomized studies. It uses a “star system” based on three major perspectives: the selection of the study groups (0-4 stars, or 0-5 stars for cross-sectional studies), the comparability of the groups by controlling for important and additional relevant factors (0-2 stars), and the ascertainment of outcome of interest or exposure (0-3 stars). A total score of 3 or less was considered poor, 4-6 was considered moderate, and 7-10 was deemed high quality. We excluded studies from our meta-analysis if they had poor quality. Discrepant opinions between authors were resolved by consensus.

Statistical analysis

We performed a meta-analysis of the included studies using Review Manager 5.3 software from The Cochrane Collaboration to generate forest plot and funnel plot and Comprehensive Meta-Analysis 3.3 software from Biostat, Inc. (Englewood, NJ, USA) to perform Egger’s regression test. We calculated pooled effect estimate of incidence or prevalence of fracture with 95% confidence interval (CI) comparing between sarcoidosis and control groups using a random-effects model. We used effect size (OR, HR, RR) from univariate or, if available, multivariate models with confounding factors (age, sex, or glucocorticoids use) adjusted in each study. The pooled standardized mean differences (SMD) of vBMD and aBMD with 95% CI comparing between sarcoidosis patients and controls were also calculated using a random-effects model. We excluded studies from the meta-analysis and only presented the result with narrative description (qualitative analysis) when there were not sufficient data available for calculating pooled effect size. The heterogeneity of effect estimates across these studies was quantified using the Q statistic and I² (p<0.10 was considered statistically significant). The Q statistic compared the observed between-study dispersion and expected dispersion of the effect size, and was expressed in p value for statistical significance. An I² is the ratio of true heterogeneity to total observed variation. An I² of 0 to 40% was considered to exclude heterogeneity, of 30 to 60% was considered to represent moderate heterogeneity, of 50 to 90% was considered to represent substantial heterogeneity, and of 75 to 100% was considered to represent...
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considerable heterogeneity. Publication bias was assessed using funnel plot and Egger’s regression test.

RESULTS

The initial search yielded 576 articles (Figure 1); 554 articles were excluded based on the title and abstract review. A total of 22 articles underwent full-length review. Twelve articles were excluded (eight articles had no placebo group; three articles did not report the outcome of interest, and one article did not study on the subject of interest). Data were extracted from 10 studies involving a total of 279 sarcoidosis patients and 382 controls in the BMD studies, and 6,169 sarcoidosis patients and 77,475 controls in the fracture studies for qualitative analysis. The included studies varied in study location, sample size, and source of data. One study was excluded from quantitative analysis because it only compared and reported the mean difference of vBMD of patients with values lower than the lower limit of the control group. Among nine eligible studies that were included in the meta-analysis, three studies reported fragility fracture or osteoporotic fracture; six studies reported vBMD or aBMD. Sarcoïdosis participants that were on glucocorticoids were excluded from two studies; BMD was measured before initiation of glucocorticoids in one study. Meanwhile, those studies that reported fracture as an outcome have stratified the risk of fracture based on average, duration or cumulative dose of glucocorticoids. The inclusion or exclusion of participants that were on treatment or prevention of bone loss with osteoporotic medications varied between studies. The characteristics of the 10 extracted studies included in this review were outlined in Table 1. The search methodology and selection process were detailed in the Figure 1.

The pooled result demonstrated no difference in fracture risk for hip (OR=1.45; 95% CI: 0.44-4.80, p=0.55, I²=79%) or vertebral fracture (OR=2.00; 95% CI: 0.90-4.44, p=0.09, I²=52%).

Figure 1. Flow of search methodology and selection process.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study year and location</th>
<th>Design</th>
<th>Diagnostic criteria</th>
<th>Disease duration (month)</th>
<th>Number Patient’s demographic</th>
<th>Patient’s demographic</th>
<th>Outcome</th>
<th>Quality assessment (Newcastle-Ottawa Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamada et al. 29</td>
<td>Kyoto, Japan</td>
<td>Cross-sectional</td>
<td>Histologically proven</td>
<td></td>
<td>76.7±65.1</td>
<td>33 42</td>
<td>46±12.7</td>
<td>N/A DEXA aBMD (L1-L4), Z score Selection=1 Comparability=2 Outcome=1</td>
</tr>
<tr>
<td>Rizzato et al. 31</td>
<td>Milan, Italy</td>
<td>Cross-sectional</td>
<td>Histologically proven</td>
<td></td>
<td>54.7±56.8</td>
<td>71 190</td>
<td>41.4±11.9</td>
<td>QCT vBMD (L1-L4), Z score Selection=1 Comparability=0 Outcome=1</td>
</tr>
<tr>
<td>Rizzato et al. 27</td>
<td>Milan, Italy</td>
<td>Cross-sectional</td>
<td>Histologically proven</td>
<td></td>
<td>52.3±537</td>
<td>32 84</td>
<td>42.8±12.9</td>
<td>QCT Difference of vBMD (L1-L4) between patient and control Selection=1 Comparability=0 Outcome=1</td>
</tr>
<tr>
<td>Rizzato et al. 30</td>
<td>Milan, Italy</td>
<td>Cross-sectional</td>
<td>Histologically proven</td>
<td></td>
<td>43.8±54</td>
<td>49 190</td>
<td>38.5±11.7</td>
<td>QCT vBMD (L1-L4), Z score Selection=2 Comparability=1 Outcome=1</td>
</tr>
<tr>
<td>Tervonen et al. 34</td>
<td>Kuopio, Finland</td>
<td>Cohort</td>
<td>Histologically proven</td>
<td></td>
<td>14.5±26.8</td>
<td>21 29</td>
<td>47.7±12.7</td>
<td>N/A 181Am γ-transmission Selection=2 Comparability=2 Outcome=1</td>
</tr>
<tr>
<td>Sipahi et al. 32</td>
<td>Pneumology Department, Cerrahpasa Medical Faculty of Istanbul University</td>
<td>Cross-sectional</td>
<td>Histologically proven</td>
<td></td>
<td>78.1±46.3</td>
<td>36 20</td>
<td>42±9.1</td>
<td>DEXA aBMD (L1-L4, femoral neck) Selection=2 Comparability=2 Outcome=2</td>
</tr>
<tr>
<td>Adler et al. 33</td>
<td>Veteran Affairs Medical Center, Richmond, Virginia</td>
<td>Prospective cohort study</td>
<td>Not reported</td>
<td></td>
<td>227.3±140</td>
<td>37 17</td>
<td>51.6±12.8</td>
<td>N/A DEXA aBMD (L1-L4, femoral neck) Selection=2 Comparability=2 Outcome=2</td>
</tr>
<tr>
<td>Oshagh et al. 28</td>
<td>Jan 1995 to Dec 2011, The Netherlands</td>
<td>Population-based case-control</td>
<td>Not reported</td>
<td></td>
<td>102 48,426</td>
<td>64.2±19.5 (of all population)</td>
<td>69 Not reported</td>
<td>N/A Osteoporotic fracture (hip, vertebral, radius, ulna) Selection=3 Comparability=2 Exposure=2</td>
</tr>
<tr>
<td>Ungprasert et al. 17</td>
<td>Jan 1996 to Dec 2013, Olmsted County, Minnesota</td>
<td>Population-based cohort</td>
<td>Not reported</td>
<td></td>
<td>345 345</td>
<td>Not reported</td>
<td>50 Not reported</td>
<td>N/A Frailty fracture of vertebral, proximal femur, distal forearm, the proximal humerus. Selection=3 Comparability=2 Outcome=3</td>
</tr>
<tr>
<td>Bours et al. 18</td>
<td>Jan 1987 to Sept 2012, United Kingdom</td>
<td>Retrospective cohort study</td>
<td>Not reported</td>
<td></td>
<td>5,722 28,304</td>
<td>48±13.4</td>
<td>51 953</td>
<td>N/A Osteoporotic (vertebral, hip, forearm, or humerus) and non-vertebral non-osteoporotic fracture Selection=3 Comparability=2 Outcome=3</td>
</tr>
</tbody>
</table>
The risk of any fracture in sarcoidosis patients was not greater than the control group (OR=1.68; 95% CI: 0.85-3.31, p=0.14, I²=72%) (Figure 2). There were no differences between the patients and controls in terms of aBMD (SMD=0.21 g/cm²; 95% CI: -0.12-0.54, p=0.22, I²=0%) (Figure 3) or vBMD (SMD=-0.07 mg/cm³; 95% CI: -0.54-0.39, p=0.75, I²=45%; female: SMD=0.13 mg/cm³; 95% CI: -1.00-1.26, p=0.82, I²=92%) among different sexes.

Sensitivity analysis, meta-regression, and publication bias were not performed because there were too few studies included in the analysis. Several confounders may have affected our study result including certain drugs or comorbidities. Most of the studies had excluded the common...
comorbid diseases which affect the bone mineral balance or calcium metabolism. Some of these studies also pre-specified the exclusion of patients on certain drugs particularly those using hormone replacement therapy, calcium, and vitamin D supplementation. For example, Hamada et al. excluded patients with primary parathyroid, thyroid diseases, or bone diseases. Their study also did not include patients aged more than 65 years to eliminate the effect of menopause on bone mineral. In spite of that, no significant difference in lumbar spine BMD between male and female; or between patient and control groups were identified.

While two studies by Rizzato et al. did not report patients’ comorbid diseases, exclusion of comorbidities, or the drugs that were used in patients with sarcoidosis, their other study reported that there were no diseases or conditions other than menopausal status in their patient group. Patients using hormone therapy, vitamin D, or other drugs known to affect calcium metabolism were also excluded. The specific drugs that affect calcium metabolism were not listed in this study. Rizzato et al. were only able to demonstrate osteoporosis in prednisone-treated patients with sarcoidosis but not in untreated patients. Menopausal patients with sarcoidosis were found to have lower Z-score than the premenopausal patients. In addition, the diseases that might affect the bone mineral balance were ruled out by clinical and laboratory tests in Tervonen et al. study. No patients in their study demonstrated clinical or radiographic evidence of hypertrophic pulmonary osteoarthropathy. The details of diseases or conditions were not elaborated in both studies. Even so, there was no significant difference in vBMD at the radius in Tervonen et al. study. Notably, Hamada et al., Rizzato et al., and Tervonen et al. measured their sarcoidosis patients’ BMDs before treatment with corticosteroids.

Furthermore, participants with renal failure, thyroid dysfunction, alcoholism, or using long-term anticoagulant, hormone replacement therapy, vitamin D and other drugs known to affect bone mineral metabolism were not included in Sipahi et al. study. None of the participants in Sipahi et al. study had fractures or secondary osteoporosis. The authors first classified patients based on their menopausal status, followed by sub-classification into prednisone-treated and untreated patients. The BMD values at lumbar spine were not significantly different among the subgroups for premenopausal participants either for untreated, treated, or control groups. Nonetheless, the BMD values at the femoral neck in treated premenopausal patients were significantly lower than untreated premenopausal patients and controls. For postmenopausal, the lumbar spine and femoral neck BMD in untreated and treated patients were lower than controls.
On the contrary, Adler et al., did not report the comorbid diseases or the exclusion criteria. Despite the inclusion of patients using calcium or vitamin D supplementations, patients with sarcoidosis had a lower BMD at lumbar spine but no significant difference compared with the COPD control group.

The remaining population based case-control or cohort studies were adjusted for the confounders. In the study of Oshagbemi et al., the ORs were adjusted for confounders such as age, sex, COPD, previous fracture, RA, inflammatory bowel disease, secondary osteoporosis, and the use of inhaled glucocorticoids, inhaled bronchodilators, antidepressants, anticonvulsants, antipsychotics, bisphosphonates, calcium supplement and hormone replacement therapy. The authors concluded that current use of glucocorticoids was associated with increased risk of fracture with no difference between patients with or without sarcoidosis. Thus sarcoidosis per se did not play a role in the fracture risk. In contrast, after adjustment for confounders such as smoking, congestive heart failure, asthma, COPD, and the use of glucocorticoids, calcium or vitamin D supplement, loop diuretics, benzodiazepines, antidepressants, proton-pump inhibitors, and anticonvulsants, patients with sarcoidosis were found to have an increased risk of vertebral fracture. Recent treatment with oral glucocorticoids further increased the risk of any fractures and osteoporotic fractures. These findings were supported by Ungprasert et al. as they also found an increased fragility fracture incidence among patients with sarcoidosis while the use of glucocorticoids did not seem to have an additive effect.

Regarding difference in biochemical parameters, serum 1,25-dihydroxyvitamin D level was either normal or there was no significant difference between patient and control groups. No significant difference in serum calcium between groups was reported in the study of Hamada et al. Also, the calcium levels were reported within the normal range in three other studies. Such findings also applied to the serum phosphate level indicated by Sipahi et al. and Adler et al. reported that the levels were within normal range; however, the control groups’ phosphate levels were not reported in these two studies. Lastly, there were only two studies that reported a normal range of serum alkaline phosphatase level with no comparison between control groups. The remaining studies did not publish or measure the levels of serum vitamin D, parathyroid hormone, calcium, phosphate, and alkaline phosphatase.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis exploring the association between sarcoidosis, bone mineral loss, and risk of fracture. As aforementioned, the studies of fracture in sarcoidosis are scarce and conflicting. In addition, the studies of bone mineral loss were also inconclusive. Ungprasert et al. found increased fragility fracture driven by significant risk of distal forearm fracture. Meanwhile, Bours et al. found an increased vertebral fracture, but the non-vertebral fracture and overall osteoporotic fracture risks were not significantly different than the control groups. The latest population-based record-linkage case-control study found that the risk of major osteoporotic fractures was comparable in current glucocorticoids users with or without sarcoidosis. The authors concluded that sarcoidosis per se does not cause fragility fracture and the osteoporotic fracture in sarcoidosis mainly was driven by the use of glucocorticoids. After cessation of glucocorticoids, the risk of fragility fracture in sarcoidosis diminished and was comparable with the control group who never used glucocorticoids and were without sarcoidosis. From the forest plot evaluating the risk of fracture, we failed to discover an increased risk of fracture caused by sarcoidosis. Subgroup analysis of fracture also did not detect an increased risk of fracture at the hip, femur, or vertebra. We were unable to pool the fracture risk at the forearm into the meta-analysis because of insufficient studies. Moreover, Ungprasert et al. showed no difference in the risk of humerus fracture in both patient and control groups. As opposed to our findings, there is one cross-sectional study that found an increased prevalence of fragility fractures despite a normal mean BMD in patients with sarcoidosis. However, we were unable to include this study because it did not have a control group.
Our study results on the risk of fracture are in line with the results of our study on aBMD and vBMD. Both aBMD and vBMD pooled analyses failed to reveal any association of sarcoidosis causing decreased BMD compared with general population. These findings also concur with other longitudinal studies\(^\text{16,19-21}\) that reported no bone density changes over time in patients with sarcoidosis. Noteworthily, Heijckmann et al.\(^\text{20}\) reported that patients with sarcoidosis had progressive vertebral deformities despite unchanged BMD. The authors found that the prevalence of vertebral deformities increased significantly from 20% to 32% in patients with sarcoidosis who were followed for 35-49 months.\(^\text{20}\) The vertebral deformities in this study were measured with morphometric X-ray absorptiometry. However, the number of these radiographic vertebral deformities that reflect the actual development of clinical vertebral fractures remains unknown, as Bours et al.\(^\text{18}\) have found that the total number of vertebral fractures in sarcoidosis was low in spite of the increased risk of clinical vertebral fractures. Nevertheless, most radiographic vertebral fractures are not accompanied by typical signs and symptoms of an acute vertebral fracture.\(^\text{19,20}\) Therefore, the actual prevalence of vertebral fracture might be underreported.

Nonetheless, most studies demonstrated that bone mineral loss was more frequent in sarcoidosis patients with prednisone use\(^\text{18,28,31,32,35}\) except one study\(^\text{19}\) comparing untreated, previous and current glucocorticoids users with sarcoidosis that has not found any difference in BMD at the femoral neck and trochanter. However, this study\(^\text{19}\) showed an increased bone turnover as shown by the Z-score of carboxy-terminal cross-linked telopeptide of type 1 collagen and procollagen type 1 amino-terminal propeptide. Based on our study findings and other studies, this may imply that sarcoidosis has different mechanisms to compensate the bone resorption from the inflammatory disease process\(^\text{19}\) or the inflammation cascade in patients with sarcoidosis may be different than the other inflammatory diseases. Further studies that include bone turnover markers would be helpful in determining the osteoporotic effect of sarcoidosis. Regardless, few studies have reported that a low dietary calcium intake, low creatinine clearance and higher 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D are associated with increased bone resorption and fracture risk in sarcoidosis.\(^\text{16,29}\)

We have put forth our best effort to exclude postmenopausal patients and patients on glucocorticoids in the BMD studies because these are the confounding factors. We used the premenopausal patients’ data as published in Sipahi et al.\(^\text{32}\) and Rizzato et al.\(^\text{30}\) Most of the studies’ populations were generally aged 40 to 50 years which reduced the risk of age-related osteoporosis confounding our results. Also, the studies on fracture were either matched or adjusted for age and sex. However, there are few limitations of our study. Most studies of aBMD and vBMD in patients with sarcoidosis were cross-sectional studies, thus unable to show the bone mineral changes over time. We were also unable to factor in the disease duration, glucocorticoids treatment dose and duration, menopausal status, and other drug use that may increase the risk of osteoporosis. The difference between methods used to identify patients with sarcoidosis and fracture may be the cause of heterogeneity among studies because some studies relied on the diagnostic code\(^\text{18,28}\) while other based on medical record review.\(^\text{17}\) Other causes of heterogeneity among studies may arise from the use of glucocorticoids and also a limited number of studies being published. We have attempted to search for disease stages, severity or organ involvement of sarcoidosis in these included studies; however, most of them did not report such baseline characteristics.

In conclusion, our study has not shown an increased risk of fracture or bone mineral loss in sarcoidosis. However, based on the currently available studies with heterogeneity in between, the conclusion for the osteoporosis screening and fracture risk assessment of patients with sarcoidosis cannot be drawn until more studies are available.

Declaration of conflicting interests

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