OSTEOPOROSIS IN RHEUMATIC DISEASES, WHAT'S NEW?

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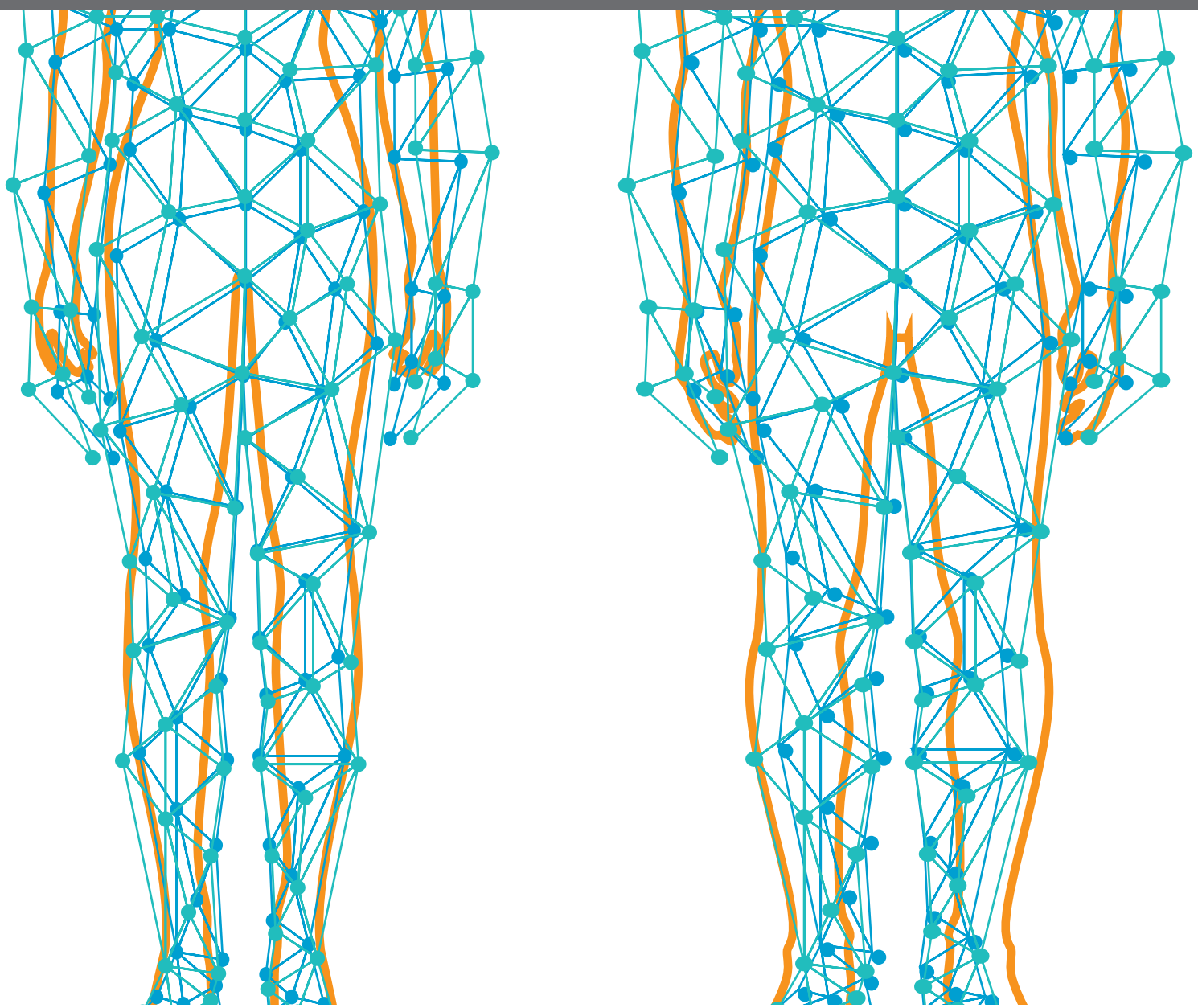

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OSTEOPOROSIS IN RHEUMATIC DISEASES, WHAT'S NEW?

Topic Editors:
Barbara Ruaro, University of Trieste, Italy
Serena Guiducci, University of Florence, Italy
José Antonio P. Da Silva, University of Coimbra, Portugal

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EDITORIAL
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Editorial: Osteoporosis in Rheumatic Diseases, What's New?

Barbara Ruaro[1], Serena Guiducci[2], José A. P. da Silva[3,4], Barbara Wade[5], Elisa Baratella[6†] and Marco Confalonieri[1†]*

[1] Pulmonology Department, University Hospital of Cattinara, University of Trieste, Trieste, Italy, [2] Division of Rheumatology, Department of Experimental and Clinical Medicine, University of Firenze, Florence, Italy, [3] Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, [4] Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [5] Azienda Ospedaliero Universitaria (AOU) City of Health and Science of Turin, Department of Science of Public Health and Pediatrics, University of Torino, Torino, Italy, [6] Department of Radiology, Department of Medicine, Surgery and Health Science, University of Trieste, Trieste, Italy

Keywords: osteoporosis, rheumatic diseases, connective tissue diseases, fragility fracture, bone mineral density (BMD), trabecular bone score (TBS), systemic sclerosis, rheumatoid arthritis

Editorial on the Research Topic

Osteoporosis in Rheumatic Diseases, What's New?

This Research Topic collection entitled *"Osteoporosis in Rheumatic Diseases, What's New?"*, compiled by authors from various countries, confirms that patients with rheumatic diseases are frequently also affected by osteoporosis (OP). All the articles included reported that OP is a major comorbidity in rheumatic patients due to factors like, chronic treatment, inflammation, immobility, low body mass index (BMI), and low vitamin D serum concentrations.

In the first article of the collection, the authors report on the effects vitamin D supplementation has on patients affected by both rheumatoid arthritis (RA) and OP. Interestingly, they observed that RA patients with OP on bisphosphonates and vitamin D supplementation had a higher BMD increase than those who did not receive the supplementation (Kwon et al.). They also emphasize that a vitamin D supplementation dose of ≥1,000 IU/day is more efficacious than one of 800 IU/day.

The second article underlines the role a surgeon's ability plays to evaluate all the parameters to improve the treatment of patients with advance knee OA (Molfetta et al.). The authors report that these patients have high risks of fragility fractures, e.g., vertebral and non-vertebral, e.g., the hip making it a must to obtain detailed information on bone mineral density (BMD). They also stress that more attention should be paid to identify and treat OP in elderly female patients with advanced knee OA with a total knee prosthesis (TKP). The third article focuses on some new imaging techniques, such as high-resolution peripheral quantitative computed tomography and trabecular bone score (TBS), for the evaluation of bone microarchitecture in patients with Axial Spondyloarthritis (axSpA) (Lim and Kang). Indeed, the authors report that BMD assessment by dual-energy X-ray absorptiometry, which is the primary diagnostic method for OP, may lead to an overestimation of bone density in axSpA as these patients often have abnormal calcification of spinal ligaments or syndesmophytes. This is in agreement with the fourth article where the authors argue that BMD may not provide adequate information on bone microarchitecture, and propose TBS be used as a diagnostic tool for the assessment of bone quality (Ruaro et al.). They demonstrate that systemic lupus erythematosus (SLE) patients have a higher frequency of trabecular bone loss and an increased risk of lower bone mass than healthy subjects. In the fifth article the authors discuss the utility of the Bone Strain Index (BSI), which includes local information on density distribution, bone geometry and loading (Ulivieri et al.). BSI differs from BMD and other variables of bone quality, including TBS, as they are all based on the quantification of bone mass and distribution averaged over the scanned region. In conclusion, the authors observe that BSI appears

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Edited and reviewed by:
Peter Mandl,
Medical University of Vienna, Austria

****Correspondence:***
Barbara Ruaro
barbara.ruaro@yahoo.it

† These authors share last authorship

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to be a powerful tool to assess bone strength and provides information on the physics of the skeleton resistance. In their narrative review, the authors of sixth manuscript, highlight that patients affected by rheumatic diseases run a high risk of low bone mass, evaluated by BMD, adding that TBS, which provides information on the bone microstructure, is also lower in these patients than in healthy subjects (Ruaro et al.). The authors of seventh article explore the relationship between different biologic mediators involved in the development of osteoporosis in RA patients (Llorente et al.). They underline that the RANK/RANKL/OPG and the Wnt/DKK-1/sclerostin pathways play a crucial role not only in the development of systemic and local OP, but also in bone erosions. Furthermore, different pro-inflammatory cytokines, i.e., TNF-α, IL-6, and IL-17 and autoantibodies, i.e., ACPA and anti-CarPA, play a relevant role in bone homeostasis regulation. They emphasize that biological therapies allow for the reversal of some of the negative effects RA has on bone and that they even seem to reduce the risk of osteoporotic fractures. The authors of the eighth article used dual X-ray absorptiometry (DXA) and the skeletal muscle mass index (RSMI) to make a prospective comparison of the long-term efficacy of bisphosphonates vs. denosumab, in a cohort of 98 elderly patients at 1 year from hip surgery (Pizzonia et al.). There was a slight, non-significant osteo-metabolic improvement in the alendronate group compared to the denosumab group and, interestingly, the denosumab group had a positive trend in the RSMI index.

In another review the researchers report that OP is a hallmark of inflammatory arthritidies and underline that, under these conditions, OP pathogenesis is, mainly driven by the predominant inflammation (Rotta et al.). This observation is an important feature in the evaluation of novel therapeutic agents for the treatment of inflammatory arthritidies. The pivotal role adequately controlling the inflammatory process plays was also confirmed in the tenth study where 128 patients with early rheumatoid arthritis (ERA) were enrolled (Bruno et al.). The authors observed that the presence of bone erosions is associated with systemic bone loss as from the earliest RA phases, suggesting that the inflammatory burden and autoimmune biology, that underpin RA, represent crucial enhancers of bone remodeling both at local and systemic levels.

The eleventh article carried out a bibliometric study summarizing the trends and developments in the field of osteoporosis in RA (Wu et al.). The study emphasizes that RA should be classified not only as a chronic disabling arthritis, but also as a condition leading to reduced bone mass. Indeed, they emphasize that multiple studies have demonstrated that RA patients frequently develop osteoporosis which may well lead to a reduced quality of life and an increase in healthcare costs.

In conclusion, this collection of papers stresses the importance of assessing osteoporosis in patients affected by rheumatic diseases by the use of a combination of standard methods, e.g., DXA and new techniques, e.g., the TBS score, with the aim of achieving an optimal management of this frequent and serious complication. Furthermore, numerous studies have emphasized the importance of vitamin D supplementation and the use of antiresorptive therapies, such as alendronate and denousumab, to enhance not only treatment regimens, but also the patients' quality of life. Last but not least, all the studies underline the pivotal role correctly treating rheumatic diseases plays in the prevention of secondary pathologies, such as osteoporosis.

AUTHOR CONTRIBUTIONS

BR, SG, and JS conducted the manuscript. EB and MC made the final amendments and approved the final version. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Effect of Vitamin D Supplementation on Bone Mineral Density in Rheumatoid Arthritis Patients With Osteoporosis

Oh Chan Kwon[1], Ji Seon Oh[2], Min-Chan Park[1] and Yong-Gil Kim[3]**

[1] Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea, [2] Department of Biomedical Informatics, Asan Medical Center, Seoul, South Korea, [3] Division of Rheumatology, Department of Medicine, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, South Korea

Objectives: To assess the effect of vitamin D supplementation on bone mineral density (BMD) in rheumatoid arthritis (RA) patients with osteoporosis and determine whether supplementation of more than 800 IU/day, which is the currently recommended dose, is beneficial.

Methods: RA patients with osteoporosis who received bisphosphonate were included. Patients were classified into four groups according to the dose of vitamin D supplementation (0, 400, 800, and ≥1,000 IU/day). Multivariable linear regression models were performed to evaluate the effect of each dose of vitamin D supplementation on 1-year% change of BMD.

Results: In total, 187 RA patients with osteoporosis were included. In the multivariate model adjusted for potential confounders, patients receiving vitamin D supplementation had a significantly higher increase in 1-year % change in lumbar spine BMD (400 IU/day: β = 2.51 [95% CI: 0.04–4.99], 800 IU/day: β = 2.90 [95% CI: 0.47–5.33], and ≥1,000 IU/day: β = 6.01 [95% CI: 3.71–8.32]) and femoral neck BMD (400 IU/day: β = 3.88 [95% CI: 1.83–5.94], 800 IU/day: β =4.30 [95% CI: 2.25–6.35], and ≥1,000 IU/day: β = 6.79 [95% CI: 4.87–8.71]) than those not receiving the supplementation. Notably, the ≥1,000-IU/day group had a significantly higher increase in 1-year % change in lumbar spine BMD (β = 3.11 [95% CI: 0.86–5.37]) and femoral neck BMD (β = 2.50 [95% CI: 0.63–4.36]) than the 800-IU/day group.

Conclusion: In RA patients with osteoporosis receiving bisphosphonates, vitamin D supplementation was associated with a higher increase in BMD. This effect was higher in the vitamin D supplementation dose of ≥1,000 IU/day than in 800 IU/day.

Keywords: rheumatoid arthritis, osteoporosis, vitamin D, supplementation, bone mineral density

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Edited by:
Barbara Ruaro,
Centro Cardinal Ferrari, Italy

Reviewed by:
Mario Salazar-Paramo,
University of Guadalajara, Mexico
Xavier Noguès,
Université de Bordeaux, France
José Antonio P. Da Silva,
University of Coimbra, Portugal

***Correspondence:**
Min-Chan Park
mcpark@yuhs.ac
Yong-Gil Kim
bestmd2000@amc.seoul.kr

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammatory arthritis (1). Since RA is a disease in which long-term glucocorticoid is commonly used (1), glucocorticoid-induced osteoporosis (GIOP) is an important comorbidity that needs to be considered when treating patients with RA. Indeed, population-based studies have reported a higher risk of osteoporosis in patients with RA (2, 3).

In the 2017 American College of Rheumatology guideline for the prevention and treatment of GIOP, a vitamin D intake of 600–800 IU/day has been recommended (4). Similarly, the Korean guideline for the prevention and treatment of GIOP also recommends a vitamin D intake of 800 IU/day (5). However, the recommended vitamin D intake of 600–800 IU/day is based on general population data, rather than those of patients with specific diseases, including RA, who require long-term glucocorticoid therapy (6). Due to the indirectness of the evidence, a vitamin D intake of 600–800 IU/day is only conditionally recommended in the GIOP guideline (4). Currently, data about the effect of vitamin D supplementation on bone mineral density (BMD) in RA patients with osteoporosis are limited, and the optimal dose of supplementation remains unclear.

Osteoporosis is characterized by low BMD and microarchitectural deterioration of the bone tissues, leading to an increased risk of fracture (7). Vitamin D affects the rate of bone turnover and the overall mineralization of the bone. Thus, vitamin D deficiency is associated with a higher bone turnover and incidence of fracture (8). Considering that vitamin D deficiency is highly prevalent in RA patients (9, 10), the required dose of vitamin D supplementation in RA patients with osteoporosis might be higher than the recommended intake of 600–800 IU/day (4), which is based on general population data.

This study aimed to assess the effect of vitamin D supplementation on BMD in RA patients with osteoporosis and to determine whether a dose higher than 800 IU/day is more effective in improving BMD in patients with RA.

PATIENTS AND METHODS

Study Population

Electronic medical records of RA patients who were newly diagnosed with osteoporosis and who started receiving bisphosphonates at two tertiary referral hospitals in Seoul, South Korea, between 2013 and 2017 were retrospectively reviewed. All patients met the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA (11). A diagnosis of osteoporosis was made based on the following BMD results: lumbar spine T-score ≤ -2.5 and/or femoral neck T-score ≤ -2.5. Patients who were taking medications other than bisphosphonates (selective estrogen receptor modulators, and teriparatide) for the treatment of osteoporosis, those with metabolic diseases, such as thyroid and parathyroid diseases, that can affect BMD, those with a history of previous fracture, and those who were current smokers were excluded.

This study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No: 3-2020-0043) and Asan Medical Center in Seoul, South Korea (IRB No: 2018-0090). Requirement of informed consent was waived because of the retrospective nature of the study.

BMD Assessment and Outcome Variables

BMDs of the lumbar spine (first to fourth vertebrae) and femoral neck were evaluated using dual-energy X-ray absorptiometry (GE Healthcare Lunar or Hologic system) (12). As per the insurance policy in our country, BMD was assessed annually (i.e., for insurance coverage, BMD data must be obtained every year). The same instrument was used for repeat BMD measurement in each patient. The BMD results of the Hologic system were converted to GE Healthcare Lunar BMD results using the conversion equation (13). Data about BMD results at the diagnosis of osteoporosis and after 1 year of treatment were collected for analysis. Outcome variables were 1-year % change in lumbar spine and femoral neck BMDs.

Vitamin D Supplementation

The average dietary intake of vitamin D is relatively low in South Korea (male: 160 IU/day, and female: 104 IU/day) (14), and as the majority of vitamin D intake comes from supplementation rather than diet, we focused on the dose of supplementation of vitamin D. Vitamin D supplements were in the form of calcium–vitamin D complex tablet or bisphosphonate–vitamin D complex tablet. Each tablet contained a specific amount of vitamin D [calcium–vitamin D complex for daily use: 400, 800, and 1,000 IU/tablet; bisphosphonate–vitamin D complex for weekly use: 5,600 IU/tablet [equivalent to 800 IU/day] (15); or bisphosphonate–vitamin D complex for monthly use: 24,000 IU/tablet [equivalent to 800 IU/day] (15)]. Thus, the vitamin D supplementation dose was used as a categorical variable rather than a continuous variable. The type of vitamin D supplement was chosen based on the treating physicians' preference. Patients were classified into four groups according to the dosage of vitamin D supplementation, which were as follows: 0, 400, 800, and $\geq$1,000 IU/day. As calcium supplementation was provided in the form of calcium–vitamin D complex tablet, the 0-IU/day group also did not receive any calcium supplementation, whereas the other three groups received 500–1,000 mg/day of calcium supplementation in the form of calcium–vitamin D complex tablet. The average dietary intake of calcium in South Korea is 542 mg/day (16). Therefore, the total calcium intake (total of diet and supplementation) of patients receiving vitamin D supplementation was $\sim$1,000–1,500 mg/day, which was in accordance with the recommended calcium intake of 1,000–1,200 mg/day (4).

Covariates

At the time of diagnosis of osteoporosis, the following data were collected: age, sex, body mass index (BMI), positivity to rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody, and disease activity score 28 with erythrocyte sedimentation rate (DAS28-ESR). Data about medications prescribed during the 1-year interval between the BMD tests, including cumulative dose of glucocorticoid, use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs), and type of bisphosphonate, were reviewed. For glucocorticoid use, the total glucocorticoid dose prior to the initial BMD test, and the current status (users or not) of glucocorticoid use at the initial BMD test were also reviewed.

Statistical Analysis

To compare the different groups, ANOVA was used for continuous variables and the chi-square test (when <20% of cells had expected count <5) or Fisher's exact test (when 20% or more cells had expected count <5) was used for categorical variables. Multivariable linear regression analyses were performed to assess the effect of vitamin D supplementation on 1-year % changes in BMD. For each category of vitamin D supplementation dosage, we estimated the mean difference (effect estimate [β] and 95% confidence interval [CI]) in 1-year % changes in BMD between patients with and without vitamin D supplementation. Potential confounders, such as age, sex, BMI, total glucocorticoid dose prior to the initial BMD test, cumulative glucocorticoid dose between BMD measurements, use of csDMARDs and bDMARDs, DAS28-ESR, and type of bisphosphonate, were adjusted in the multivariable models using enter method. The variation inflation factor (VIF) was assessed to exclude multicollinearity among covariates included in the multivariable analyses. VIFs of all covariates were less than 5, confirming the absence of multicollinearity. The normality of the residual was tested using a histogram and normal P–P plot of the regression standardized residual, and the homoscedasticity of the residual was assessed using the scatter plot: the residual followed a normal distribution and was homoscedastic. Further, to evaluate whether a vitamin D supplementation dose of >800 IU/day is more effective than that of 800 IU/day in terms of improving BMD, the mean difference in 1-year % change in BMD between the ≥1,000- and 800-IU/day groups was assessed. $P < 0.05$ was considered statistically significant. All analyses were conducted using the SPSS software (version 25.0; IBM Corporation, Armonk, NY, USA).

RESULTS

Comparison Among the Different Vitamin D Supplementation Dose Groups

A total of 286 patients with RA, who were newly diagnosed with osteoporosis, were identified. Thirty-two patients who received medication other than bisphosphonate (selective estrogen receptor modulators: 30 patients, and teriparatide: 2 patients) for the treatment of osteoporosis, 14 patients with thyroid disease, 2 patients with parathyroid disease, 12 patients with a history of previous fracture, and 39 patients who were current smoker were excluded. The remaining 187 RA patients with osteoporosis were included in the analysis. Sixty-one patients did not receive vitamin D supplementation (0-IU/day group), whereas 23, 73, and 30 patients received vitamin D supplementation at a dose of 400 IU/day (400-IU/day group), 800 IU/day (800-IU/day group), and ≥1,000 IU/day (≥1,000-IU/day group), respectively. In the ≥1,000-IU/day group, 26 (86.7%) patients received 1,000 IU/day, one (3.3%) patient received 1,200 IU/day, and three (10.0%) patients received 1,800 IU/day. Comparison results among the different groups are shown in **Table 1**. The four groups did not differ in terms of age ($p = 0.641$), sex distribution ($p = 0.570$), BMI ($p = 0.915$), positivity to RF ($p = 0.633$) and anti-CCP antibody ($p = 0.248$), total glucocorticoid dose prior to the initial BMD test ($p = 0.605$), proportion of current glucocorticoid users ($p = 0.109$), cumulative dose of glucocorticoid between BMD tests ($p = 0.246$), use of csDMARDs (methotrexate, $p = 0.416$; hydroxychloroquine, $p = 0.752$; sulfasalazine, $p = 0.731$; leflunomide, $p = 0.621$; and tacrolimus, $p = 0.946$) and bDMARDs (tumor necrosis factor inhibitor, $p = 0.134$; tocilizumab, $p = 0.610$; and abatacept, $p = 0.851$), and DAS28-ESR ($p = 0.846$). The type of bisphosphonate used (risedronate: $p < 0.001$, alendronate: $p < 0.001$, and ibandronate: $p = 0.001$) was different among the groups (**Table 1**).

According to the initial BMD, 94 (50.3%) patients had osteoporosis in the lumbar spine, 33 (17.6%) patients had osteoporosis in the femoral neck, and 60 (32.1%) patients had osteoporosis in both lumbar spine and femoral neck. The initial lumbar spine T-score ($p = 0.737$) and initial femoral neck T-score ($p = 0.252$) did not differ among the four groups. The mean values of 1-year % changes in the lumbar spine BMD and femoral neck BMD in the total study population were 3.92 and 1.19%, respectively. The 1-year % change of lumbar spine BMD ($p <0.001$) and femoral neck BMD ($p <0.001$) was significantly different among groups (**Table 1** and **Figure 1**).

Effect of Vitamin D Supplementation on 1-year % Changes in BMD

The results of linear regression analyses are shown in **Table 2**. The overall p value for the regression was $p <0.001$ for all univariable and multivariable analyses. The total amount of variance explained in the univariable and in the multivariable analyses was as follows: univariable (lumbar spine), 0.210; multivariable (lumbar spine), 0.298; univariable (femoral neck), 0.281; and multivariable (femoral neck), 0.370. In the multivariable analysis, the 1-year % change in lumbar spine BMD was significantly higher in the vitamin D supplementation groups (400 IU/day: β = 2.51 [95% CI 0.04–4.99], $p = 0.047$; 800 IU/day: β = 2.90 [95% CI 0.47–5.33], $p = 0.020$; and ≥1,000 IU/day: β = 6.01 [95% CI 3.71–8.32], $p <0.001$) than in the 0-IU/day group. Similarly, the supplementation of vitamin D, regardless of dose, was significantly associated with a higher 1-year % change in femoral neck BMD (400 IU/day: β = 3.88 [95% CI 1.83–5.94], $p <0.001$; 800 IU/day: β = 4.30 [95% CI 2.25–6.35], $p <0.001$; and ≥1,000 IU/day: β = 6.79 [95% CI 4.87–8.71], $p <0.001$) (**Table 2**). Coefficients and their significance levels of all variables included in the multivariable analysis are shown in **Supplementary Table 1**.

Comparison of 1-year % Changes in BMD Between the ≥1,000- and 800-IU/day Groups

In the multivariable linear regression analysis comparing the effects of ≥1,000 and 800 IU/day, a vitamin D supplementation of ≥1,000 IU/day was associated with a significantly higher 1-year % change in lumbar spine BMD (β = 3.11 [95% CI 0.86–5.37], $p = 0.007$) and femoral neck BMD (β = 2.50 [95% CI 0.63–4.36], $p = 0.009$) (**Table 3**).

TABLE 1 | Characteristics of patients ($n = 187$) according to the dose of vitamin D supplementation.

	0 IU/day ($n = 61$)	400 IU/day ($n = 23$)	800 IU/day ($n = 73$)	≥1,000 IU/day ($n = 30$)	*P*
Age (years), mean ± SD	65.7 ± 8.9	65.7 ± 9.3	64.0 ± 8.5	64.1 ± 8.7	0.641
Female, n (%)	58 (95.1)	22 (95.7)	65 (89.0)	27 (90.0)	0.570[F]
BMI (kg/m^2), mean ± SD	22.7 ± 3.2	23.0 ± 3.9	23.1 ± 3.1	22.9 ± 3.5	0.915
RF positive, *n* (%)	45 (73.8)	18 (78.3)	60 (82.2)	22 (73.3)	0.633[X]
Anti-CCP Ab positive, *n* (%)	45 (73.8)	19 (82.6)	62 (84.9)	21 (70.0)	0.248[X]
Total glucocorticoid dose prior to the initial BMD test (mg), median (IQR)	1612.5 (210.0–2033.8)	1435.0 (330.0–2570.0)	1035.0 (275.0–1922.5)	1762.5 (343.1–3490.0)	0.605
Current glucocorticoid users, *n* (%)	57 (93.4)	21 (91.3)	58 (79.5)	27 (90.0)	0.109
Glucocorticoid[a] (mg), mean ± SD	1295.2 ± 731.3	1218.1 ± 651.4	1022.2 ± 841.8	1172.3 ± 842.3	0.246
USE OF CSDMARDS, *N* (%)					
MTX	52 (85.2)	19 (82.6)	67 (91.8)	25 (83.3)	0.416[F]
HCQ	28 (45.9)	8 (34.8)	30 (41.1)	11 (36.7)	0.752[X]
SSZ	12 (19.7)	7 (30.4)	15 (20.5)	6 (20.0)	0.731[X]
LEF	9 (14.8)	5 (21.7)	9 (12.3)	3 (10.0)	0.621[F]
TAC	4 (6.6)	2 (8.7)	4 (5.5)	2 (6.7)	0.946[F]
USE OF BDMARDS, *N* (%)					
TNFi	1 (1.6)	0 (0.0)	6 (8.2)	3 (10.0)	0.134[F]
Tocilizumab	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.610[F]
Abatacept	2 (3.3)	0 (0.0)	1 (1.4)	0 (0.0)	0.851[F]
DAS28-ESR, mean ± SD	3.19 ± 1.04	3.11 ± 0.71	3.19 ± 0.93	3.03 ± 0.73	0.846
BISPHOSPHONATE, *N* (%)					
Risedronate	38 (62.3)	11 (47.8)	2 (2.7)	9 (30.0)	<0.001[X]
Alendronate	2 (3.3)	10 (43.5)	65 (89.0)	13 (43.3)	<0.001[X]
Ibandronate	21 (34.4)	2 (8.7)	6 (8.2)	8 (26.7)	0.001[X]
BASELINE BMD, MEAN ± SD					
Lumbar spine T-score	−2.93 ± 0.84	−2.72 ± 1.23	−2.85 ± 0.96	−2.99 ± 0.95	0.737
Femoral neck T-score	−2.41 ± 0.72	−2.35 ± 0.85	−2.17 ± 0.79	−2.43 ± 0.71	0.252
BMD AT 1 YEAR, MEAN ± SD					
Lumbar spine T-score	−2.85 ± 0.86	−2.46 ± 1.26	−2.52 ± 0.98	−2.50 ± 0.99	0.161
Femoral neck T-score	−2.44 ± 0.74	−2.28 ± 0.80	−2.11 ± 0.77	−2.29 ± 0.67	0.093
1-YEAR % CHANGE, MEAN ± SD					
Lumbar spine BMD	0.71 ± 5.29	3.89 ± 4.13	5.17 ± 4.93	7.42 ± 3.64	<0.001
Femoral neck BMD	−2.09 ± 4.74	1.82 ± 3.64	2.21 ± 3.00	4.78 ± 4.58	<0.001

[a] *Cumulative dose (mg of prednisolone or its equivalent) during the 1-year interval between BMD tests.*

[F] *P value calculated with Fisher's exact test.*

[X] *P value calculated with chi-square test.*

BMI, body mass index; RF, rheumatoid factor; anti-CCP Ab, anti-cyclic citrullinated peptide antibody; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine; LEF, leflunomide; TAC, tacrolimus; bDMARDs, biologic disease-modifying anti-rheumatic drugs; TNFi, tumor necrosis factor inhibitor; DAS28-ESR, disease activity score 28-erythrocyte sedimentation rate; BMD, bone mineral density.

DISCUSSION

In this retrospective study, we showed that in RA patients with osteoporosis who were receiving bisphosphonates, the supplementation of vitamin D was significantly associated with a higher increase in lumbar spine and femoral neck BMDs within 1 year. The mean differences in 1-year % changes in lumbar spine and femoral neck BMD were the highest in the ≥1,000-IU/day group. Notably, ≥1,000 IU/day of vitamin D supplementation was associated with a 3.11% (95% CI: 0.86–5.37%) and 2.50% (95% CI: 0.63–4.36%) higher increase in 1-year % changes in lumbar spine and femoral neck BMD, respectively, compared with 800 IU/day of vitamin D supplementation. This finding has an important clinical implication in that it indicates that a vitamin D supplementation dose higher than that recommended in the current GIOP guideline (4) might be beneficial in terms of improving BMD in RA patients with osteoporosis.

In previous studies evaluating the effect of vitamin D supplementation in non-osteoporotic participants, a 1-year % change in BMD was 1.0–2.5% higher in patients receiving vitamin D supplementation (400–800 IU/day) than in those

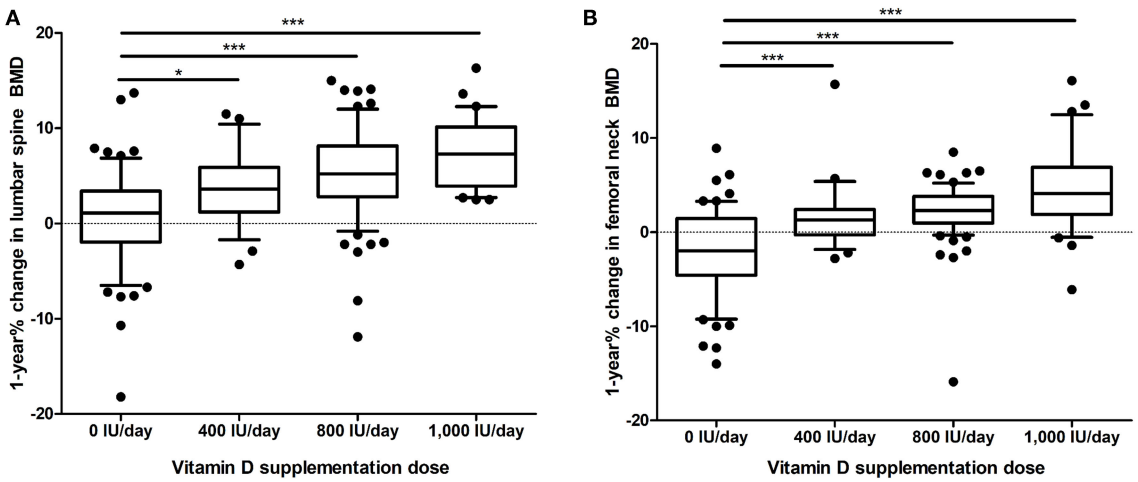

FIGURE 1 | One year % change in **(A),** lumbar spine BMD and **(B),** femoral neck BMD according to the dose of vitamin D supplementation. The whiskers represent the 10–90 percentile range, and the black dots represent values outside the 10–90 percentile range. $^{*}p < 0.05$, $^{***}p < 0.001$. BMD, bone mineral density.

TABLE 2 | Linear regression model estimates of the effect of vitamin D supplementation based on 1-year % changes in BMD.

	Univariable analysis		Multivariable analysis[a]	
	β (95% CI)	***P***	**β (95% CI)**	***P***
LUMBAR SPINE				
0 IU/day	0 (ref.)		0 (ref.)	
400 IU/day	3.18 (0.87–5.49)	0.007	2.51 (0.04–4.99)	0.047
800 IU/day	4.46 (2.82–6.10)	<0.001	2.90 (0.47–5.33)	0.020
≥1,000 IU/day	6.71 (4.61–8.82)	<0.001	6.01 (3.71–8.32)	<0.001
FEMORAL NECK				
0 IU/day	0 (ref.)		0 (ref.)	
400 IU/day	3.92 (1.99–5.84)	<0.001	3.88 (1.83–5.94)	<0.001
800 IU/day	4.30 (2.94–5.67)	<0.001	4.30 (2.25–6.35)	<0.001
≥1,000 IU/day	6.88 (5.12–8.63)	<0.001	6.79 (4.87–8.71)	<0.001

[a] *Multivariable model adjusted for age, sex, BMI, total glucocorticoid dose prior to the initial BMD test, cumulative glucocorticoid dose between BMD tests, use of csDMARDs and bDMARDs, DAS28-ESR, and type of bisphosphonate.*

TABLE 3 | Linear regression model estimates of the difference in 1-year % changes in BMD between the ≥1,000- and 800-IU/day groups.

	Univariable analysis		Multivariable analysis[a]	
	β (95% CI)	***P***	**β (95% CI)**	***P***
LUMBAR SPINE				
800 IU/day	0 (ref.)		0 (ref.)	
≥1,000 IU/day	2.25 (0.21–4.30)	0.031	3.11 (0.86–5.37)	0.007
FEMORAL NECK				
800 IU/day	0 (ref.)		0 (ref.)	
≥1,000 IU/day	2.57 (0.87–4.27)	0.003	2.50 (0.63–4.36)	0.009

[a] *Multivariable model adjusted for age, sex, BMI, total glucocorticoid dose prior to the initial BMD test, cumulative glucocorticoid dose between BMD tests, use of csDMARDs and bDMARDs, DAS28-ESR, and type of bisphosphonate.*

receiving placebo (17–19). The observed mean difference in 1-year % change in BMD between the ≥1000-IU/day group and the 0-IU/day group in our study was remarkably higher (6.01 and 6.79% in the lumbar spine and femoral neck BMD, respectively). Even in the comparison between the 400-IU/day group and the 0-IU/day group, the mean difference in 1-year % change in BMD was 2.51% and 3.88% in the lumbar spine and femoral neck BMD, respectively. The relatively higher mean difference in 1-year % change in BMD by vitamin D supplementation observed in our data is likely because we only included patients with osteoporosis, whereas the previous studies have included participants who did not present with osteoporosis and the effect of vitamin D supplementation was assessed for preventive measure in these studies (17–19). Moreover, patients not receiving vitamin D supplementation also did not receive calcium supplementation, which may also explain the higher magnitude of 1-year % change in BMD in our study.

In vitamin D deficiency, 1, 25-(OH)-vitamin D interacts with receptors in the osteoblasts, thereby leading to the increased formation of osteoclasts (20). The mature osteoclast then releases enzymes to break down the bone matrix, ultimately releasing calcium and other minerals into the circulation (21). Therefore, vitamin D supplementation is important in the treatment of osteoporosis (22). The higher increase in BMD observed in patients receiving a vitamin D supplementation dose higher than the dose (600–800 IU/day) recommended in the general osteoporosis patients might be attributable to the fact that patients with RA have a higher prevalence and more severe degree of vitamin D deficiency than the general population (9, 10, 23).

A previous study has shown that in trials in which a mean 25-(OH)-vitamin D level of 100 nmol/L was achieved, optimal prevention of osteoporotic fracture was observed (22). In studies in which baseline 25-(OH)-vitamin D levels were between 40 and 77 nmol/L, patients achieved a 25-(OH)-vitamin D level of 100

nmol/L with the supplementation of vitamin D at a dose of 700–800 IU/day (18, 24), whereas in studies in which the baseline levels were as low as 21–26 nmol/L, patients failed to achieve a 25-(OH)-vitamin D level of 100 nmol/L with the supplementation of vitamin D at a dose of 800 IU/day (19, 25). These findings support the notion that patients with vitamin D deficiency, such as those with RA, may benefit from a vitamin D supplementation dose higher than 800 IU/day to improve BMD. Moreover, considering that vitamin D deficiency is inversely associated with the disease activity of RA (9, 10), vitamin D supplementation at a higher dose might be beneficial in improving not only BMD but also the disease activity of RA. However, as vitamin D intoxication can result in the mobilization of skeletal calcium, leading to bone demineralization (26), increasing the dose of vitamin D supplementation indefinitely cannot be advocated. The suggested upper limit of vitamin D intake is 4,000 IU/day (6).

Treatment of RA may affect BMD in RA patients with osteoporosis (27–29). Use of glucocorticoid is associated with reduction in BMD (27), while use of tumor necrosis factor inhibitors is associated with increase in BMD in RA patients (28). Similarly, in our multivariable analysis, use of tumor necrosis factor inhibitor was associated with a higher increase of 1-year % change in lumbar spine BMD ($\beta = 2.89$ [95% CI: 0.93–4.85], $p = 0.004$), while the cumulative glucocorticoid dose between BMD tests was associated with a lower increase of 1-year % change in femoral neck BMD ($\beta = -0.001$ [95% CI: −0.002 to −0.001], $p = 0.001$) (**Supplementary Table 1**). In regard to csDMARDs, leflunomide may possibly be associated with an increase in lumbar spine BMD (29). In the present study, use of leflunomide had a positive effect on lumbar spine BMD ($\beta = 1.02$) as well, although it failed to reach statistical significance (95% CI: −1.01 to 3.04, $p = 0.324$) (**Supplementary Table 1**). We presume that this is because the outcome parameter was used as a continuous variable in the present study whereas in the previous study the outcome parameter was used as a categorical variable (29).

The present study had some limitations. First, this was a retrospective study, and data about the lifestyle habits of each patient, such as diet, alcohol intake, and exercise, were not available. The risk of confounding caused by these undetermined variables might exist. Further, due to the nonrandomized retrospective group allocation, possibility of selection bias cannot be excluded. Second, data about vitamin D levels were missing. Owing to the lack of these data, the proportion of patients with vitamin D deficiency at baseline was not identified and whether patients who are not deficient in vitamin D will also benefit from a higher dose of vitamin D supplementation was not evaluated. Third, although we found that ≥1,000 IU/day of vitamin D supplementation was associated with a higher increase in 1-year % change in BMD than 800 IU/day of supplementation, we were unable to determine the optimal dose of vitamin D supplementation because only a small fraction of patients received a dose of more than 1,000 IU/day. Further study investigating the optimal dose of supplementation of vitamin D, probably over 1,000 IU/day, is needed. Fourth, although we adjusted for the type of bisphosphonate in the multivariable analysis, bias which results from the higher use of risedronate in the 0-IU/day group and higher use of alendronate in the 400, 800, and ≥1,000-IU/day group cannot be fully adjusted.

In conclusion, we observed a significantly higher increase in lumbar spine and femoral neck BMD in 1 year in RA patients with osteoporosis receiving vitamin D supplementation compared with those who did not. The increase in BMD was the highest in patients who received a vitamin D supplementation dose of ≥1,000 IU/day. Our finding suggests that RA patients with osteoporosis who are receiving bisphosphonate may benefit more when a higher dose of vitamin D is supplemented than patients with osteoporosis in the general population.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (IRB No: 3-2020-0043) and Asan Medical Center in Seoul, South Korea (IRB No: 2018-0090). Requirement of informed consent was waived because of the retrospective nature of the study. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

M-CP and Y-GK conceived the study. OK, M-CP, and Y-GK designed the study. OK, JO, M-CP, and Y-GK participated in the acquisition of data, data analyses, and data interpretation. OK, M-CP, and Y-GK wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00443/full#supplementary-material

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Trabecular Bone Score and Bone Quality in Systemic Lupus Erythematosus Patients

Barbara Ruaro[1†], Andrea Casabella[2,3†], Sabrina Paolino[2,3], Elisa Alessandri[2], Massimo Patané[2], Emanuele Gotelli[2,4], Alberto Sulli[2,4] and Maurizio Cutolo[2]*

[1] Pulmonology Department, University Hospital of Trieste, Trieste, Italy, [2] Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine (Di.M.I.), IRCCS San Martino Polyclinic Hospital, University of Genova, Genoa, Italy, [3] Osteoporosis, Bone and Joint Disease Research Center, CROPO, Department of Internal Medicine Di.M.I., University of Genoa, Genoa, Italy, [4] Lupus Clinic, Department of Internal Medicine (Di.M.I.), IRCCS San Martino Polyclinic Hospital, University of Genova, Genoa, Italy

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Lai-Shan Tam, The Chinese University of Hong Kong, China

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***Correspondence:**
Barbara Ruaro
barbara.ruaro@yahoo.it

[†] These authors have contributed equally to this work and share first authorship

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Background: Systemic lupus erythematosus (SLE) patients run a higher risk of having low bone mass due to multifactorial events that include physical inactivity, persistent inflammation, low vitamin D levels, and glucocorticoid treatment. This study aimed at obtaining a comparison between bone involvement in SLE patients and healthy matched subjects (HS).

Methods: A total of 40 SLE females (average age 54.1 ± 16.3 years) and 40 age–gender matched HS (average age 54.2 ± 15.9 years) were enrolled after having obtained informed written consent. Bone mineral density (BMD, g/cm^2) of the lumbar spine (L1–L4) was analyzed by a dual-energy X-ray absorptiometry (DXA) scan (GE, Lunar Prodigy). The lumbar spine trabecular bone score (TBS) was derived for each spine DXA examination by the TBS index (TBS iNsight Medimaps).

Results: The lumbar spine TBS score was statistically significantly lower in SLE patients than in HS (0.797 ± 0.825 vs. 1.398 ± 0.207, $p < 0.001$, as was BMD ($p < 0.001$) in all areas examined.

Conclusions: SLE is associated with significant low bone mass as evidenced by DXA and TBS. This study emphasizes the importance of using DXA and TBS in the evaluation of the different aspects of bone architecture.

Keywords: osteoporosis, trabecular bone score (TBS), bone mineral density (BMD), autoimmune diseases (AD), bone loss

HIGHLIGHTS

- TBS is a diagnostic tool for the quantification of the bone quality in rheumatic diseases.
- Systemic lupus erythematosus (SLE) patients had a high trabecular bone loss.
- SLE patients have an increased risk of lower bone mass than healthy subjects.

INTRODUCTION

Systemic lupus erythematosus (SLE) is one of the most complex multisystemic autoimmune diseases as it encompasses a wide spectrum of clinical and serological manifestations (1, 2). Recent studies demonstrate a higher incidence of osteoporosis (OP) and fractures in SLE patients than in healthy subjects (HS) (3–5). There is a multifactorial etiology of bone loss in SLE, which includes systemic inflammation; serological, metabolic, and hormonal factors; and maybe also genetic factors and medication (5–8). Moreover, a high prevalence of morphometric vertebral fractures was observed in SLE patients, although 1/3 had normal bone density, in line with the multifactorial etiology of fractures in SLE (3–5).

The clinical consequences and economic burden of OP and fractures highlight the importance of a not only correct, but also early diagnosis of OP so the most suitable preventive therapies can be started.

Several studies demonstrate that patients with rheumatic inflammatory diseases have low vitamin D and an increased risk of low bone mass (3, 6–8). Currently, the clinical practice gold standard for OP diagnosis, including secondary causes, is a bone mineral density (BMD) analysis by dual-energy X- ray absorptiometry (DXA) (9–11).

It has recently been reported that the trabecular bone score (TBS), an index extracted by DXA that provides an indirect measurement of bone axial microarchitecture, provides vital information on bone quality in several rheumatic diseases (6, 7, 12).

The aims of this study were to assess bone involvement in SLE and to compare the results with matched HS using TBS and DXA.

TABLE 1 | Clinical findings in patients with systemic lupus erythematosus (SLE) and healthy subject (HS), prednisolone (PRED, average 5 mg/day), hydroxychloroquine (HCQ, average 150 mg/day), mycophenolate (MMF, average 1,500 mg/day), azathioprine (AZA, average 50 mg/day), proton pump inhibitors (PPI), Not Applicable (NA).

	SLE#40	HS#40	*p* value
	Median (IQR)	Median (IQR)	
Age (years)	55 (12)	54 (11)	$p > 0.05$
Age of menopause (years)	49 (6)	50 (5)	$p > 0.05$
Gender (Female/Male)	40/0	40/0	NA
BMI (kg/m^2)	22 (2)	23 (3)	$p > 0.05$
Disease duration (years)	6 (5)	NA	NA
Autoantibodies (dsDNA/negative)	34/6	0/40	NA
SLEDAI	5 (2)	NA	NA
Smoking status, current (number)	3/40	4/40	$p > 0.05$
25(OH)D (ng/ml)	15 (4)	28 (2)	$p < 0.001$
ALP bone (UI)	7 (2)	17 (3)	p<0.001
Treatments (PRED/MMF/HCQ/AZA/PPI)	21/8/20/6/2	0/0/0/0/2	NA

METHODS

Study Population

A total of 40 female patients affected by SLE (2012 criteria) (13) (average age 54.1 ± 16.3 SD years, average disease duration 5.2 ± 4.9 years) and 40 age–gender matched HS (average age 54.2 ± 15.9 years) were enrolled after obtaining written informed consent during routine clinical assessment in our rheumatology department from January 2015 to November 2017. All SLE and HS were in the postmenopausal period (see **Table 1**).

A complete medical history was collected and a clinical examination performed for all subjects enrolled. Demographic data, such as age, gender, height, weight, and body mass index (BMI) were also recorded (see **Table 1**).

All patients were not affected by secondary causes of OP, such as metabolic or endocrinological disease or drug-induced OP.

The inclusion criteria were an SLE diagnosis and having been on a stable drug regimen for at least 4 months prior to study entry.

The exclusion criteria were being on a drug regimen that could potentially influence the final data, such as vitamin D and/or bisphosphonate, and a glucocorticoid dosage of more than 7.5 mg/day in the 4 months prior to study entry.

Any concomitant treatment in SLE patients and in HS are reported in **Table 1**.

The patients' history included information as to vertebral and nonvertebral fractures assessed by lateral spinal radiographs of the thoracic and lumbar spine and other districts whenever possible.

Bone Mineral Density

The BMD of the lumbar spine (L1–L4) and left hip (femoral neck; Ward's triangle; trochanter; total hip) was obtained by a DXA scan (Lunar Prodigy, GE Lunar, Madison, WI, USA) in both groups. The weight, height, age, and gender of each subject were used to estimate the BMD, expressed as a T-score (expressed as g/cm^2 and standard deviation scores) and compared to the HS BMD values. This number shows the amount of bone present compared to a young adult of the same gender with peak bone mass (9–11). A score above−1 is considered normal in BMD T-scores obtained at the femur and lumbar spine, a score between−1 and−2.5 is classified as osteopenia (low bone mass), and a score below−2.5 is classified as OP.

We also calculated the Z-score. This number reflects the amount of bone present compared to others in the same age group of the same size and gender. If this score is unusually high or low, further medical tests may be advisable (9–11).

Trabecular Bone Score

The lumbar spine TBS, a texture analysis parameter correlated to the bone micro-architecture parameters (9, 12), was derived for each spine DXA examination by the TBS index (TBS iNsight Medimaps). The lumbar spine L1–L4 TBS was calculated on each spine DXA examination with the operator blinded to clinical parameters and outcomes (6, 7, 12).

A normal range for TBS values in postmenopausal women has been proposed: a TBS of ≥1.350 is considered normal; a TBS between 1.200 and 1.350 is considered consistent with partially degraded microarchitecture, and a TBS of ≤1.200 defines degraded microarchitecture (9, 12).

Bone Parameters

After obtaining written informed consent, a complete blood chemistry evaluation of bone metabolism was made (alkaline phosphatase, parathormone, 25 OH vitamin D, calcium, and phosphorus) (6, 7) for all subjects enrolled.

Statistical Analysis

Statistical analyses were performed by Graph Pad PRISM version 5.02. Nonparametric tests were used for the statistical analysis. The Mann–Whitney *U*-test was performed to compare unpaired groups of variables and the Kruskal–Wallis test to compare continuous variables with nominal variables with more than two levels. The Spearman rank correlation test was used to search for any relationships between variables along with linear regression tests. Any *p*-values lower than 0.05 were considered statistically significant. The results are reported as mean along with standard deviation (SD) and median and interquartile range (IQR).

RESULTS

The lumbar spine TBS score was significantly lower in SLE patients than in HS (0.797 ± 0.825 vs. 1.398 ± 0.207, $p < 0.001$), and BMD was significantly lower in all areas (the lumbar spine, femoral neck, Ward's triangle, trochanter, and hip) than in the HS group ($p < 0.001$ for all areas) (See **Table 2**). There was a 39% and 16% prevalence of osteopenia and OP in SLE patients, respectively. Most SLE patients (60%) had a significantly lower bone loss than the HS group ($p < 0.001$). A total of 30% of the SLE patients had a history of high-dose oral glucocorticoids in the 2 years before the study (> 10 mg/day), and this was associated with the preservation of BMD in the lumbar spine but not in the spinal trabecular bone as observed in the TBS analysis.

A total of 24 SLE patients (40%) had a previous vertebral fracture, and all the patients with previous vertebral fractures had a low bone mass, 29 patients (42%) had osteoporosis, and 32 (54%) osteopenia.

Noteworthy is the fact that the TBS values in the SLE group had a positive correlation with the BMD values measured at the level of the spine ($p = 0.04$), femoral neck, and the whole femur ($p < 0.01$, respectively).

TABLE 2 | Trabecular bone score (TBS) and bone mineral density (BMD) values in systemic lupus erythematosus (SLE) patients and controls (CNT).

	SLE, $n = 40$ median (IQR)	HS, $n = 40$ median (IQR)	*p* value
TBS	0.803 (0.729)	1.344 (0.236)	$p < 0.001$
Lumbar spine (L1-L4) BMD (g/cm^2)	0.536 (0.392)	1.478 (0.831)	$p < 0.001$
Femoral neck BMD (g/cm^2)	0.841 (0.352)	0.957 (0.313)	$p = 0.02$
Ward's triangle BMD (g/cm^2)	0.569 (0.210)	0.736 (0.245)	$p < 0.05$
Trochanter BMD (g/cm^2)	0.712 (0.206)	0.895 (0.216)	$p = 0.05$
Total hip BMD (g/cm^2)	0.628 (0.572)	1.251 (0.314)	$p = 0.01$

SLE patients had statistically significantly lower serum levels, i.e., 25 (OH) D, than did the HS (17.1 ± 2.3 ng/ml vs. 27.8 ± 1.4 ng/ml, $p < 0.001$).

A total of 70% of the SLE patients had a 25 (OH) D insufficiency (<30 ng/ml) as did 10% of the HS.

SLE patients with previous fractures had statistically significantly lower vitamin D values than those without vertebral fractures (7.4 ± 6.6 ng/ml vs. 15.2 ± 7.6 ng/ml; $p < 0.0001$). Bone alkaline phosphatase (ALP bone) level was lower in the SLE patients than in the HS (7.5 ± 2.1U/l vs. 18.5 ± 4.5 U/l; $p < 0.001$). No statistically significant differences were observed between SLE and HS groups for serum calcium, phosphorus, or PTH.

In addition, no differences regarding the most important risk factors for OP, such as smoking condition, alcohol consumption, age of menopause, and familiarity with hip fractures, were observed between SLE patients and the healthy subjects.

There was no correlation between the TBS values and the BMD measured at the spine, femoral neck, and level of the whole femur or between the vitamin D, PTH, calcium, and phosphorus values in SLE patients and HS. Although there was a positive correlation between the TBS values and the bone alkaline phosphatase values in the SLE patients ($p = 0.01$), no statistically significant correlation was observed between the TBS values and SLE disease duration in years or the SLEDAI value.

DISCUSSION

To the best of our knowledge, this is the first study to assess bone involvement in SLE and to compare the results with matched HS using TBS and DXA.

This study confirms that SLE is associated with significant trabecular bone loss. This study emphasizes the pivotal role TBS plays as an innovative and safe diagnostic tool for the quantification of bone quality in chronic and systemic inflammatory rheumatic diseases, such as SLE.

Osteoporosis is the most serious bone metabolic disorder and is characterized by a reduction of bone mass and micro-architectural deterioration associated with an increased risk for fragility fractures (1–3). As it frequently involves patients with rheumatic diseases, the high morbidity and mortality of fractured subjects and the increased socioeconomic costs suggest it can be considered a major health problem. Therefore, there is a need for either a precocious identification of subjects with fragile "bones" or the institution of specific diagnostic–therapeutic strategies. Enhanced knowledge of bone pathophysiology coupled with progress in pharmaceutical development has provided the opportunity to make early identification of subjects at high risk of fragility fractures and to start preventive therapy (13, 14).

This study also confirms that patients with SLE, a complex systemic autoimmune connective tissue disease, have an increased risk of bone loss (osteopenia and OP) and fractures (15, 16). The increased risk of bone loss associated with SLE is multifactorial and caused by a lack of motor activity, disturbance of hormonal balance, increased inflammatory cytokines, kidney impairment, nutritional disorders, vitamin D deficiency, and medications such as corticosteroids (17–20). In particular, long-term use of corticosteroids may induce OP in patients with SLE by influencing their bone turnover, increasing bone resorption, and decreasing bone formation, preventing the formation of collagen and osteocalcin as well as reducing bone matrix mineralization (17–20). In addition, there are many cytokines involved in the pathogenesis of OP. Recently, several studies underline the important role in the osteoporotic process of IL-33 (21–23). These studies indicate that IL-33 may play a role in bone remodeling, likely influencing osteoblast and osteoclast function. Furthermore, IL-33 is an inducer of Th2 immune responses and presents a pivotal role in the development of many autoimmune diseases, such as SLE (21–23).

The data of our study also confirm that SLE patients have an increased risk of 25 (OH) D insufficiency as frequently reported in rheumatic diseases (24, 25). The effect of vitamin D on improving the BMD in SLE patients is yet unclear. However, vitamin D regulates several genes involved in innate and adaptive immunity, so it can possibly play a role in SLE through its immunomodulatory effects, which include downregulating Th1 immune responses, modulating the differentiation of dendritic cells, reducing the proliferation of activated B-cells, upregulating regulatory T-cells, and preserving innate immune responses (24, 25). Further, vitamin D has also been found to hinder the production of interferon alpha, which is known to play a key role in the etiology and pathogenesis of SLE (24, 25). Recent studies have shown that long-term supplementation with different doses of vitamin D (400–1200 IU) and calcium (1–1.5 g) can have a better effect on the BMD of postmenopausal osteoporotic women (25–27). A recent study indicates that supplementation with higher doses of vitamin D (1400 IU cholecalciferol per day) and calcium carbonate (1,250 mg per day) for 6 months improves bone mineral density and decreases the rates of osteopenia and OP in corticosteroid-treated patients. Probably, 1.25 (OH)-D can activate osteoblast and bone formation as well as decrease bone resorption through inactivation of osteoclasts (25–27). Furthermore, the authors underline that high calcium supplementation may improve the bone matrix and, consequently, prevent its destruction (25–27).

Confirming the pivotal role TBS plays in the assessment of bone microarchitecture further, two recent reviews reports a high prevalence of morphometric vertebral fractures although there is normal bone density in 1/3 SLE patients (9, 14–16).

Our present study has some limitations, including (a) a small number of participants, which limits the statistical investigations (e.g., multivariate analysis assessing the possible effect of confounding factors); (b) single-center recruitment; and (c) enrollment of SLE patients with quiescent disease (to reduce the use of treatment that could have created a bias), which could explain the lack of correlation between the TBS values and disease duration or the disease activity index (SLEDAI) in SLE patients.

In conclusion, this study demonstrates that SLE patients run a higher risk of low bone mass and that it is important to evaluate the different aspects of bone architecture with DXA and TBS and bone parameters, such as vitamin D, as soon as possible.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of San Martino Polyclinic Hospital, Genoa, Italy, and this study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BR, AC, and MC: substantial contributions to the conception and design of the work, the acquisition, analysis and interpretation of data, drafting the work and revising it critically for important intellectual content, and final approval of the version to be published. SP, EA, MP, EG, and AS: substantial contributions to the analysis, interpretation of data, final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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REVIEW
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Osteoporosis in Rheumatoid Arthritis: Dangerous Liaisons

Irene Llorente[1], *Noelia García-Castañeda*[1], *Cristina Valero*[1], *Isidoro González-Álvaro*[1*†] *and Santos Castañeda*[1,2*†]

[1] Rheumatology Division, Hospital Universitario de La Princesa, IIS-IP, Madrid, Spain, [2] Cátedra UAM-Roche, EPID-Future, Department of Medicine, Universidad Autónoma de Madrid (UAM), Madrid, Spain

Osteoporosis has been classically considered a comorbidity of rheumatoid arthritis (RA). However, recent advances in the pathogenesis of osteoporosis in RA have shown a close interplay between cells of the immune system and those involved in bone remodeling, introducing new actors into the classic route in which osteoclast activation is related to the RANK/RANKL/OPG pathway. In fact, the inflammatory state in early stages of RA, mediated by interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF)-α has the ability to activate and differentiate osteoclasts not only through their relationship with RANKL, but also through the Wnt/DKK1/sclerostin pathway, leading to bone loss. The role of synovial fibroblasts and activated T lymphocytes in the expression of the RANKL system and its connection to bone destruction is also depicted. In addition, autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies are other pathogenic mechanisms for the development of bone erosions and systemic osteoporosis in RA, even before the onset of arthritis. The aim of this review is to unravel the relationship between different factors involved in the development of osteoporosis in RA patients, both the classic factors and the most novel, based on the relationship of autoantibodies with bone remodeling. Furthermore, we propose that bone mineral density measured by different techniques may be helpful as a biomarker of severity in early arthritis patients.

Keywords: rheumatoid arthritis, bone erosions, inflammation, osteoimmunology, osteoporosis, RANKL/RANK/OPG, Wnt signaling

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***Correspondence:**
Isidoro González-Álvaro
isidoro.ga@ser.es
Santos Castañeda
scastas@gmail.com

† These authors have contributed equally to this work

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that primarily affects diarthrodial joints and is associated with disability, the presence of multiple comorbidities and decreased life expectancy (1). A recent cross-sectional epidemiological study estimates that the prevalence of RA in Spain is 1.07% [95% confidence interval (CI): 0.70–1.44] (2), similar to that described in western countries (1).

Osteoporosis (OP) is a frequent systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in bone fragility and susceptibility to fracture. Fragility fracture is defined as a spontaneous fracture that results from minimal or no identifiable trauma and represents a sign of OP (3).

The prevalence of OP in the general population ranges from 9 to 38% for women and 1 to 8% for men depending on the countries (3). In the European Union, it was estimated that 22 million women and 5.5 million men had osteoporosis in 2010 (4). A study calculated that the prevalence of global OP at the lumbar spine or femoral neck in Spanish female population was 12.7% according

to densitometric criteria (5). More specifically, in women older than 50 years, prevalence was 22.8% at lumbar spine and 9.1% at femoral neck (5).

On the other hand, the prevalence of OP in RA is around 30% (up to 50% in post-menopausal women), which might be a two-fold increase over the general population (6, 7). Furthermore, RA patients can experience fractures with higher bone mineral density (BMD) compared to patients without RA (8). In a meta-analysis, the incidence of fragility fractures in RA and general population were 33.00 and 15.31 per 1,000 person-years, respectively (9). The spine is often the most commonly affected site and the incidence of vertebral fractures in RA might be up to 5 times the rate of healthy controls (9, 10). Interestingly, the prevalence of osteopenia and osteoporosis in a large cohort of patients with RA using Vertebral Fracture Assessment (VFA) technique is around 40–60%, while the prevalence of vertebral fractures through VFA images in the same cohort was 13% (11). Paradoxically, in the Princesa Early Arthritis Register Longitudinal (PEARL) study, we observed that cortical bone in mid-forearm seemed to be more susceptible to bone loss than trabecular bone in ultra-distal forearm when disease activity was not adequately controlled (**Figure 1**).

OSTEOPOROSIS RISK FACTORS IN RA

OP and RA share some common risk factors such as female gender (female: male ratio in RA: 3–4:1) and smoking. Other general OP risk factors such as age, low body mass index (BMI), menopause, diabetes or thyroid disorders (6, 13–15) are equally applicable to patients with RA and to the general population.

Other risk factors that can account for OP in RA include systemic inflammation associated with disease activity, local effect of immune cells leading to bone erosions, glucocorticoid (GC) therapy and impairment of physical activity (14). Therefore, OP and fractures are more frequent in patients with high disease activity (according to DAS28), presence of periarticular bone erosions and cumulative structural damage, RA disease duration $\geq$ 10 years, high HAQ score or high titers of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) positivity (6, 9, 10, 14–16). In one study, vertebral fracture risk in RA patients was related to longer disease duration, dose and duration of GC treatment, higher HAQ, Sharp score (cumulative structural damage), ACPA and older age (10). Indeed, ACPA positivity is independently associated with severe trabecular bone loss (13). Furthermore, previous studies have described that the risk of fracture in the next 10 years measured by FRAX is increased in ACPA positive patients (17). By contrast, recent publications show that patients achieving early RA remission have a similar OP risk profile than the general population (15).

Regarding therapeutic agents for RA, GC therapy deserves a special mention. Indeed, GCs suppress osteoblast bone formation, which is associated with a rapid suppression of procollagen type 1 N-terminal pro-peptide (PINP, a biomarker of bone formation), leading to an early reduction in trabecular bone (18). Interestingly, GCs also suppress osteoclast activity, certainly increased in active arthritis patients, which might have a protective effect in some cases (19). In fact, some studies show that GC use in RA could even be beneficial, with a low impact on BMD due to their anti-inflammatory and suppressive effect on arthritis activity (13, 14, 16, 20). Therefore, low doses of GCs could provide protection from inflammatory bone loss during polyarthritis flares and might counteract their unfavorable effects on bone resorption leading to neutral or even positive net skeletal balance (20, 21). The cumulative GC dose (long-term or high dose) as well as the continuous vs. alternative GC dosage strategy are correlated with an increased risk of fracture or a reduced BMD in juxta-articular bone, spine and femoral neck (10, 14, 22, 23). In addition, GCs induce muscle wasting which secondarily increases the risk of falls and fractures (20). However, a daily dose below 5 mg may have a relatively small impact on BMD in RA patients (23).

Besides, the effect of GC therapy is controversial due to limitations in the studies such as concomitant use of anti-resorptive treatment, indication bias of GCs in patients with high disease activity or chronic use of GCs in patients with low disease activity.

Other pharmacological agents involved in fracture risk are opioids, some anti-depressants such as selective serotonin reuptake inhibitors, anti-psychotics, benzodiazepines and proton pump inhibitors (24). The risk related with opioids, higher for vertebral fractures than for non-vertebral fractures, and selective serotonin reuptake inhibitors might be mainly associated with falls (22).

BONE HOMEOSTASIS AND BONE REMODELING AND THE IMMUNE SYSTEM

In the past, the bone seemed to be a static structure, but nowadays is considered a dynamic tissue in constant activity, being the entire skeleton renewed around every 10 years. The dynamic process of bone formation and resorption is known as bone remodeling. This process has a complex regulation, determined by mechanical, molecular and cellular factors. Indeed, osteoclasts, osteoblasts and osteocytes are the main cellular actors involved in bone remodeling. Different signaling pathways of these and other cells of the immune system regulate their function and bone remodeling (25–29) (**Figure 2**). Indeed, the bone and the

Abbreviations: ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; Anti-CarPA, anti-carbamylated protein antibodies; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CTX-I, carboxy-terminal telopeptide of type 1 collagen; CXCL8, C-X-C motif chemokine ligand 8; DAS28, disease activity score counted over 28 joints; DDK-1, Dickkopf-1 protein; DMARD(s), disease modifying anti-rheumatic drug(s); DXA, dual X-ray densitometry; DXR, dual X-ray radiogrammetry; EULAR, European league against Rheumatism; FRAX, fracture risk assessment tool; GC(s), glucocorticoid(s); HAQ, health assessment questionnaire; hTNF-tg, human tumor necrosis factor transgenic; Ig, immunoglobulins; IL, interleukin; IFN-ϒ, interferon gamma; M-CSF, macrophage colony-stimulating factor; OP, osteoporosis; OPG, osteoprotegerin; PEARL, Princesa early arthritis register longitudinal; PINP, procollagen type 1 N-terminal propeptide; RA, rheumatoid arthritis; RANK/RANK-L, receptor activator of nuclear factor (NF)-kB (RANK) and its ligand; RF, rheumatoid factor; TNF-α, tumor necrosis factor; TNFi, TNF-α inhibitors; Th, T helper lymphocytes; Treg, regulatory T cells; uNTx, cross-linked N-telopeptide of type I collagen; Wnt, drosophila segment polarity gene *wingless* and *integrated* or *int-1* of the vertebrate homolog.

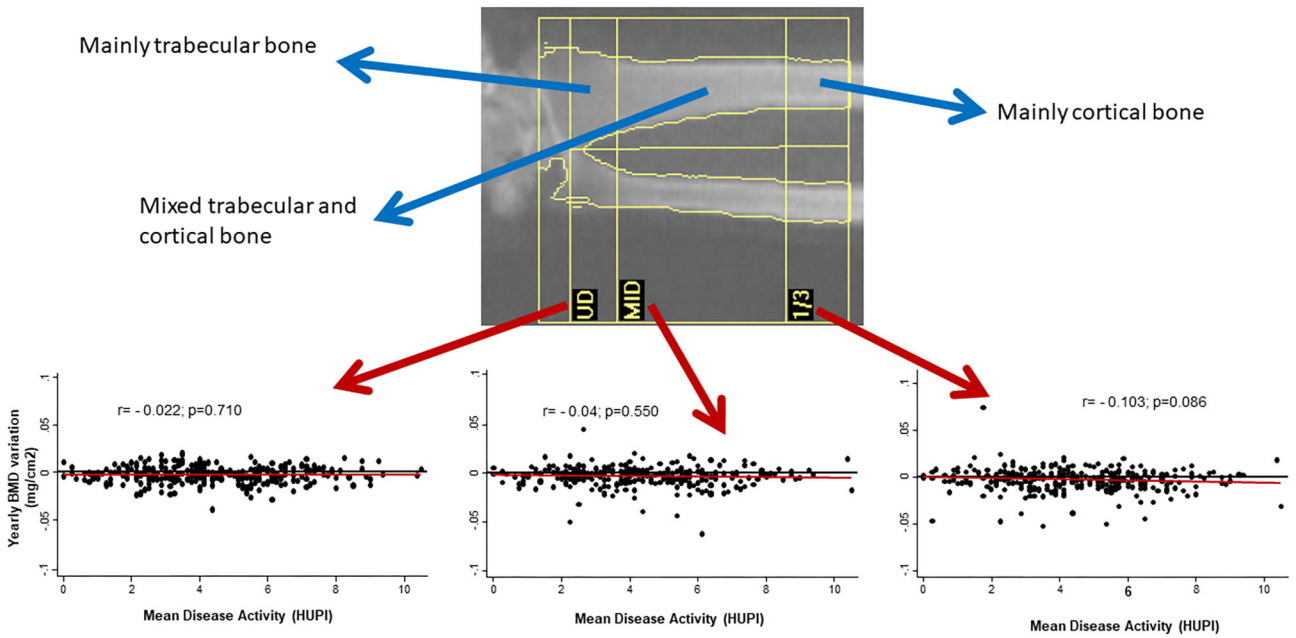

FIGURE 1 | Yearly variation of BMD in mid-radius, but no in other regions of forearm, correlates with cumulative disease activity (assessed by HUPI) after 2 years of follow-up in early arthritis patients. BMD, bone mineral density; UD, ultradistal radius; MID, middle distal radius; 1/3, third distal radius; HUPI, Hospital Universitario de la Princesa index [composite rheumatoid arthritis disease activity index, ref: (12)]; *r*, Pearson's correlation coefficient.

immune system maintain a close relationship both anatomical - since the bone houses the bone marrow- and functional through different molecular and cellular signaling pathways and a myriad of cytokines (25, 26, 28, 29). Accordingly, osteoimmunology is a discipline that attempts to address all these interrelations (30) and has undergone a great development in recent years.

RA is the prototype of osteoimmunologic disease where bone loss is one of the most characteristic findings. In RA, there are three kind of bone loss: local, juxta-articular and systemic, causing periarticular osteopenia, bone erosions and generalized osteopenia and/or osteoporosis far from inflamed joints, respectively (25–27). The misbalance in bone remodeling that occurs in RA causes an increase in bone resorption that leads to a reduction of bone mass and a decrease in bone formation that inhibits bone repair. Different cells, cytokines and signaling pathways are involved in both processes and could be potential therapeutic targets to prevent radiographic progression and osteopenia/osteoporosis associated with RA.

Increased Bone Resorption in RA

Osteoclasts are the main cell population responsible for bone loss in RA patients. These multinucleated large cells are involved in bone resorption through degradation of the bone matrix by acidic and catalytic enzymes, leading to bone erosions in RA (31). They originate from hematopoietic stem cells of the macrophage/monocyte lineage. For their differentiation they require the intervention of the macrophage colony-stimulating factor (M-CSF) (32). In addition, numerous molecules and signaling pathways are involved in the processes of osteoclast differentiation and activation. Among them, the receptor activator of nuclear factor (NF)-kB (RANK) and its ligand (RANKL) are the most important (**Figure 2**). They are proteins belonging to the TNF superfamily. RANKL is expressed, both soluble and membrane-bound forms, in different bone cells (osteoblasts and osteoclasts) and also in different cell subsets of the immune system (25, 28, 29). By contrast, RANK is mainly expressed in osteoclasts. Osteoprotegerin (OPG) is another protein of the TNF superfamily, which has a regulatory role in bone remodeling (33), working as a RANKL decoy receptor, blocking its effect through its interaction and therefore inhibiting osteoclastogenesis. In fact, RANKL was initially known as the OPG-ligand (34). Therefore, the RANK/RANKL/OPG axis is an essential pathway in the regulation of bone remodeling.

Synovial tissue in RA is the main source of RANKL (35), being synovial fibroblasts and activated T cells the main cells involved in its production (36). Danks et al. found that fibroblasts are the main source of RANKL in synovium, and therefore one of the main responsible for osteoclastogenesis rather than T cells. In fact, in an animal experimental model, the absence of RANKL expression in fibroblasts of mice with collagen-induced arthritis appears to have a protective effect on the appearance of bone erosions. This is not the case for RANKL deficiency in T cells. Therefore, the production of RANKL by fibroblasts could be a possible therapeutic target for the prevention of erosions in RA (37). In addition to RANKL expression, fibroblasts induce osteoclastogenesis through decreasing OPG (38).

T cells also play a crucial role in bone metabolism in RA. As shown in **Figure 2**, there are different phenotypes of T cells (Th1, Th2, Th17, and Treg), showing patterns of expression of different molecules and of release of distinct cytokines that play different

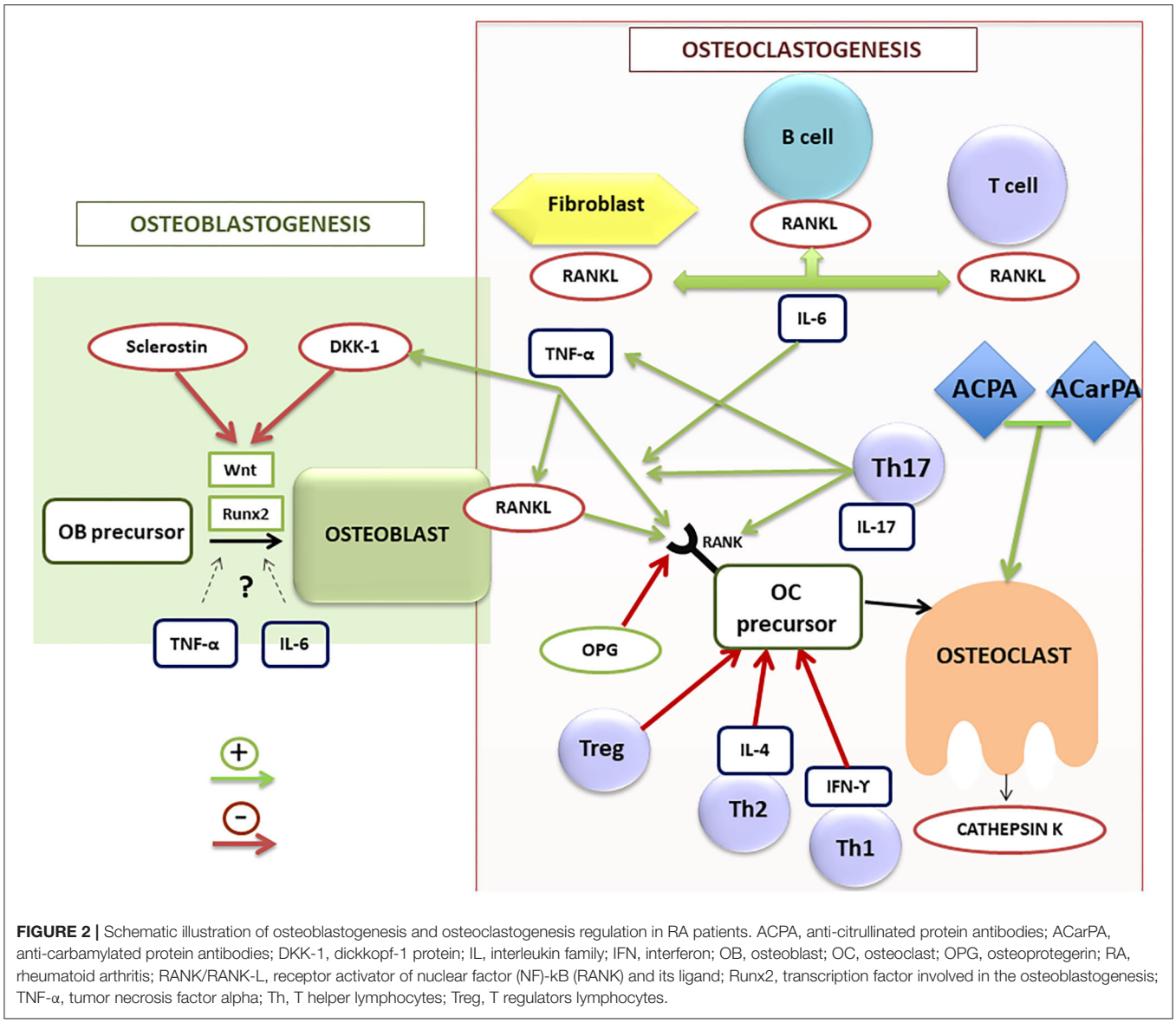

FIGURE 2 | Schematic illustration of osteoblastogenesis and osteoclastogenesis regulation in RA patients. ACPA, anti-citrullinated protein antibodies; ACarPA, anti-carbamylated protein antibodies; DKK-1, dickkopf-1 protein; IL, interleukin family; IFN, interferon; OB, osteoblast; OC, osteoclast; OPG, osteoprotegerin; RA, rheumatoid arthritis; RANK/RANK-L, receptor activator of nuclear factor (NF)-kB (RANK) and its ligand; Runx2, transcription factor involved in the osteoblastogenesis; TNF-α, tumor necrosis factor alpha; Th, T helper lymphocytes; Treg, T regulators lymphocytes.

roles in the regulation of bone remodeling. The first two subsets play a negative regulatory role on osteoclastogenesis, secreting inhibitory cytokines such as interferon gamma (IFN-γ) and IL-4 (39). Regulatory T cells (Treg) also work as negative regulators of osteoclastogenesis, being responsible for regulating tolerance and self-reactivity, while Th17 cells are critical stimulators of osteoclastogenesis in RA. Treg cells appear to have an anti-inflammatory action in animal models of TNF-induced arthritis, inhibiting osteoclast differentiation and promoting osteoblast activity (40).

By contrast, Th17 cells have been described as a subtype of Th cells inducing osteoclastogenesis by various mechanisms (41). These cells produce RANKL and IL-17, a cytokine that in turn stimulates RANKL production by fibroblasts and osteoblasts. Furthermore, they stimulate the production of M-CSF and RANKL by osteoblasts and stromal cells, produce TNF-α and increase RANK expression in osteoclast precursors (42). However, although an important role of IL-17, both proinflammatory and osteoclastogenic (43), has been described in RA, treatment with IL-17 inhibitory drugs has not demonstrated clear efficacy in RA patients (44). Therefore, further studies in RA patients are necessary to better define the real role of this cytokine and the profile of patients who could benefit from this targeted therapy. Thus, the balance between Tregs and Th17 cells is crucial for the pathogenesis and the onset of low bone mass and erosions in RA (39, 42).

Finally, B cells, in addition to being antibody-producing cells, also appear to play a role in bone resorption in RA, since they are able to produce RANKL under stimulation. In RA, activated B cells of synovial fluid and peripheral blood have been found to secrete high RANKL levels, thus participating in osteoclastogenesis and bone resorption (45).

In addition to cell subsets, numerous cytokines involved in the pathogenesis of RA have been described, among which TNF-α and IL-6 stand out, because they not only play a role in inflammation, but also seem to have a direct effect on bone remodeling in RA (25–27). In fact, they are two of the main therapeutic targets of the novel RA therapies. **Table 1** shows the main cytokines involved in bone destruction and formation in patients with inflammatory diseases.

TNF-α has a net osteoclastogenic effect. It stimulates bone resorption by promoting osteoclast differentiation, increasing RANKL expression in T and B lymphocytes and osteoclasts, as well as promoting RANK expression in osteoclast precursors (46). TNF-α also contributes to inhibition of bone formation through stimulation of Dickkopf-1 (DDK-1) production (**Figure 2**). *In vitro* and *in vivo* studies have described a controversial role of TNF-α in osteoblastogenesis, describing both inhibitory (47) and potential promoter effects (48), depending on the stage of the osteoblast differentiation. Accordingly, therapy with TNF-α inhibitors (TNFi) has proven effective not only on inflammation in RA, but also on bone balance, both at the level of systemic bone mass and prevention of radiographic progression (49).

IL-6 is another key cytokine in the pathogenesis of RA (50). In addition to its clear role on inflammation, a direct effect on general and local bone loss has been described in RA (51). IL-6 promotes bone resorption by enhancing the expression of RANKL by osteoblasts, fibroblasts and T cells (52) and is involved in the differentiation of Th17 cells (53). However, IL-6 has a controversial role on bone formation, since both pro-osteoclastogenic (54) and inhibitory (55) roles have been found in *in vitro* studies, depending on the stage of osteoblast precursors. Indeed, therapy with IL-6 inhibitors is effective in controlling inflammation and the radiological progression of RA (56).

Since RANK/RANKL/OPG pathway is crucial in osteoclastogenesis, inhibition of RANKL is a possible therapeutic target to prevent erosions and bone mass loss in RA. In a T cell-dependent animal model of arthritis, blocking RANKL by OPG prevents bone destruction, but not inflammation (57). Furthermore, in a phase II trial to assess the efficacy of denosumab, a RANKL inhibitor human antibody, on several bone parameters in patients with RA, they found that the association of denosumab with methotrexate and other therapies for controlling RA reduces bone erosions, increases BMD and decreases biomarkers of bone resorption, so it could be a potential treatment for erosive RA (58). However, as denosumab has neither an effect on inflammation nor over joint space narrowing, it has not been approved for RA treatment.

Another interesting molecule involved in bone resorption is cathepsin K, a lysosomal cysteine protease expressed predominantly in osteoclasts (59). It is overexpressed in synovial tissue, fibroblasts and serum in RA patients (60). In an animal model of arthritis using human TNF-transgenic mice (hTNF-tg), cathepsin K deficiency inhibits osteoclast activation, preventing joint erosion and presenting a regulatory role on the immune system. Therefore, inhibition of cathepsin K could be a potential adjuvant therapeutic target against bone destruction associated with an inflammatory response (61) if safety issues are finally elucidated.

TABLE 1 | Main mediators involved in bone remodeling.

Pro-bone resorption factors	Main effects in bone
TNF-α	Osteoclast activation. Osteoblast inhibition
IL-6	Osteoclast activation. Osteoblast inhibition
IL-1	Osteoclastogenesis stimulation
IL-8	Osteoclastogenesis stimulation
IL-11	Osteoclastogenesis stimulation
RANKL	Osteoclast activation
IL-17	Osteoclast activation
IL-23	Osteoclast activation
Cathepsin K	Osteoclast activation
M-CSF	Osteoclastogenesis stimulation
Anti-bone resorption factors	
IFN-ϒ	Osteoclast inhibition
IL-2	Osteoclast inhibition
IL-4	Osteoclast inhibition
OPG	Osteoclast inhibition
Anti-bone formation factors	
DKK-1	Osteoblast inhibition
Sclerostin	Osteoblast inhibition
TNF-α	Osteoblast inhibition (dual effect)
IL-6	Osteoblast inhibition (dual effect)

DKK-1, Dickkopf-1; IFN, interferon; IL, interleukin family; M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor (NF)-kB ligand; TNF, tumor necrosis factor.

Reduced Bone Formation in RA

In the process of bone formation by osteoblasts, cells of mesenchymal origin, different molecules and cell signaling pathways contribute in different ways. One of the most important signaling routes is the Wnt pathway. The name Wnt results from a fusion of the name of the Drosophila segment polarity gene *wingless* and the name of the vertebrate homolog, *integrated* or *int-1*. Wnt signaling pathways are a group of signal transduction pathways which begin with proteins that transduce signals into the cell through cell surface receptors, activating the transcription of genetic factors that regulate osteoblast maturation and therefore bone formation, among other important functions in embryogenesis and organogenesis. There are also different endogenous inhibitors of this pathway, among which DKK-1 and sclerostin are the most important and best known (62). In RA, there is an increase in the expression of these inhibitory factors of the Wnt pathway and therefore a reduction in bone formation. Consequently, this pathway could be involved in the repair of bone erosions in RA (63) (**Table 1**).

Similarly, an increase in DKK-1 has been reported in patients with RA in inflamed synovium and serum. DKK-1 elevation is associated with an increased risk of erosions in RA patients (64). Its levels seem to depend on the pro-inflammatory state, while inhibiting TNF-α reduces them. Blocking DKK-1 by monoclonal antibodies reduces the occurrence of bone erosions regardless of the inflammatory state in arthritis animal models (65). Therefore,

DKK-1 plays an important role in the development of erosions in a pro-inflammatory environment such as RA, and could be a therapeutic target for reducing such erosions.

Sclerostin is another inhibitor of the Wnt pathway, mainly secreted by osteocytes. Blocking sclerostin by a monoclonal antibody in human tumor necrosis factor transgenic (hTNFtg) mice model of arthritis reduces loss of systemic bone mass, periarticular bone destruction and cartilage damage, without any effect on inflammation. The combination of sclerostin and TNF-α inhibition produces normalization of systemic bone mass, inhibits and repairs bone erosions and cartilage damage, thus protecting from structural joint damage (66). However, other studies in animal models of arthritis have not found that sclerostin inhibition decreases or repairs bone erosions or reduces bone loss (67). Therefore, further studies are needed to clarify the role of sclerostin inhibition in RA patients.

ROLE OF AUTOANTIBODIES IN OSTEOPOROSIS ASSOCIATED TO RA

RA is a systemic inflammatory disease in which the development of different autoantibodies is an early pathogenic event that is associated with structural joint damage, the appearance of erosions and juxta-articular osteopenia (68, 69). The most frequent autoantibodies associated with RA are RF and ACPA. RF is directed against the Fc region of IgG and it mainly appears as an IgM isoform. Although RF is present in a high percentage of RA patients, it is not very specific, since it can appear in other autoimmune diseases and even in healthy population, especially in elderly people. On the contrary, ACPA are more specific of RA and very rare in general population, having demonstrated evidence of their prognostic role on radiological progression and the appearance of erosions. At present, it is well-established that ACPA can be detected in human sera during the pre-RA stage, even 10 years before the onset of symptoms (70).

RA-Related Autoantibodies as Drivers of Bone Resorption

As already mentioned, the mechanisms by which systemic osteoporosis appears in RA are complex including sustained inflammation, GC use, decrease of physical activity and as a consequence of some disease modifying anti-rheumatic drugs (DMARDs). At present, there is enough evidence to support that autoantibodies play also a role in the pathogenesis of bone loss, either systemic or local, in RA. Different animal models have demonstrated that ACPA can induce osteoclasts differentiation and activation even before arthritis onset (71, 72). During osteoclasts differentiation, the myeloid precursors express citrullinated vimentin in their membrane that can be the target for their specific ACPA. These kind of ACPA attach to Fc-gamma receptor which induces the production of CXCL8 promoting the proliferation and maturation of osteoclasts (71, 72). The presence of immune complexes of ACPA and their targets can also induce this process (73, 74).

Furthermore, Kleyer et al. have demonstrated a decrease in systemic cortical bone mass in a limited population of healthy ACPA-positive subjects without arthritis (75). In this regard, our group has described in patients of an early arthritis cohort with a median symptom duration about 5 months that the ACPA positive subjects showed a significantly lower systemic bone mass at hip and lumbar spine, but not at periarticular level in metacarpophalangeal joints. This effect was independent of the effect of classical risk factors for low bone mass, such as female gender, menopause or BMI (76, 77). Similar data have been described by Bugatti et al. in an untreated early arthritis cohort (78).

In both cohorts, patients had a very short disease duration, with low/no treatment exposure of either GCs or DMARDs, suggesting that ACPA probably have an initial role in the mechanism of BMD loss in these patients. On the other hand, the perpetuation of inflammation and the use of osteoporosis-inducing drugs may collaborate in peripheral BMD loss.

Although the strongest evidence on the role of antibodies as diagnostic and prognostic biomarkers in RA is for ACPA, included as a highly weighted item in the ACR/EULAR criteria for RA classification (79), this role has also been identified for other autoantibodies that recognize post-translational modification of proteins. Among them, anti-carbamylated proteins antibodies (anti-CarPA) have the strongest evidence regarding their role in the pathogenesis of RA compared to anti-acetylated proteins or other modifications. Interestingly, many of these modifications (citrullination, acetylation or carbamylation) include vimentin, pointing to this protein as an important target in RA pathogenesis. Anti-CarPA have shown a clear overlap with ACPA, but some studies have identified them as an independent prognostic biomarker, especially regarding the appearance of erosions (80).

The role of anti-CarPA in BMD has also been studied in early arthritis cohorts. Regueiro et al. described that high titers of anti-CarPA were associated with lower systemic BMD, either at lumbar spine or hip, in these patients, but not at local level in metacarpophalageal joints, and this association was independent of ACPA titers (81).

As mentioned above, the sustained presence of inflammatory cytokines in RA plays an important role in regulating osteoclast activation. But there is also evidence of the importance of autoantibodies and immune complexes for the production of these inflammatory cytokines by macrophages, showing in an indirect way how these immune complexes contribute to bone mass loss through regulation of osteoclasts.

All together, these data suggest that ACPA probably have an initial role in systemic osteoporosis in the earliest moments of the disease, and lead to local BMD loss in later stages through the perpetuation of inflammation and the progressive increase in their titers.

BONE MINERAL DENSITY AS POSSIBLE SEVERITY MARKER IN RA

Currently, the diagnostic and therapeutic strategies aim at the early detection and treatment of the disease (82). Indeed, in the PEARL study the implementation of early DMARD treatment in

tight control and treat to target strategies have led to prevention of erosive disease and arrest of radiological progression (83), both due to a better control of the disease and a reduced use of long-term osteopenizing drugs. Furthermore, the decrease of autoantibody titers has probably also contributed to a lower loss of both systemic and local BMD. Therefore, it is important to have prognostic biomarkers that help us better understand disease evolution and detect and treat these patients early and correctly to avoid long-term comorbidities.

The association of RA-related autoantibodies with worse BMD suggests that measurement of bone mass could help to predict prognosis of patients with early arthritis. Regarding this topic, there is evidence that measurement of BMD by dual X-ray radiogrammetry (DXR) at metacarpal diaphysis in the non-dominant hand of RA patients is associated with disease progression, appearance of bone erosions and even, in some studies, with increased mortality (84, 85). In addition, DXR is a very sensitive procedure to detect loss of BMD in the hand, which in long-standing RA has been associated with high titers of autoantibodies, mainly ACPA, radiographic progression and the appearance of erosions (86).

However, DXR is a poorly accessible and expensive technique. On the contrary, conventional dual X-ray densitometry (DXA) is the gold standard for assessing BMD in OP, and is also a simple and more accessible technique all over the world. Of note, our group has recently proved that measurement of BMD at metacarpal diaphysis with conventional DXA is reproducible and closely correlates with DXR measurements (87, 88).

SOMETHING IS CHANGING IN OSTEOPOROSIS ASSOCIATED WITH RA

Interestingly, a decrease in the prevalence of OP and fractures has been described in the last 10 years, likely due to improved therapeutic options that have allowed rheumatologists to lead more RA patients to remission (15).

Most of the information comes from TNFi, which have been associated with a reduced number of fractures and improvement of BMD in both vertebral and non-vertebral anatomical locations (22, 89, 90). Regarding bone turnover markers, the results of the studies were quite consistent, often showing an increase in bone formation markers along with a decrease in bone resorption ones (89–92). Less often, they showed either a decrease in bone resorption with stabilization of bone formation (93, 94), or stabilization of bone resorption and increased formation (95, 96). A recent paper showed, in patients with early RA treated with TNFi (certolizumab pegol), that bone turnover markers and Wnt/B-catenin pathway inhibitors may change quickly after starting therapy, with a decrease in carboxy -terminal telopeptide of type 1 collagen (CTX-I), an increase in PINP and the decrease in DKK-1 and sclerostin, already evident from the first week of therapy (92).

Other biological agents such as tocilizumab, rituximab, and abatacept have shown a significant decrease in bone resorption markers and RANKL expression, which provides evidence of a beneficial effect on bone remodeling process slowing down bone loss (15). In a study, a 2-year treatment with tocilizumab showed improvement in BMD and significantly decreased levels of β-CTX in ACPA positive patients (97). Another study disclosed the efficacy of abatacept for increasing BMD at the femoral neck without differences in urinary levels of cross-linked N-telopeptide of type I collagen (uNTx) and bone-specific alkaline phosphatase (98).

Finally, most information about DMARDs reflects a non-deleterious effect on BMD, especially with methotrexate (99), although in another study, leflunomide was the only DMARD associated with significant increase in lumbar spine BMD without differences in femoral neck (100).

All together, this evidence suggests that the relationship between RA disease activity, systemic inflammation and OP is mediated by pro-inflammatory cytokines (mainly M-CSF, IL-17, TNF-α, IL-1, and IL-6) that regulate osteoclastogenesis and are important stimulators of RANKL synthesis. During the inflammatory process, their production exceeds the synthesis of their physiologic inhibitors and decoy receptor OPG. Therefore, the imbalance between osteoblast and osteoclast activity is directly responsible for bone loss and local erosions in RA (15, 16). Nevertheless, this imbalance can also occur at systemic level. This fact posits that BMD loss in RA may be an early predictor of erosive disease (16), as suggested by a study in which BMD loss at the metacarpal site was the main independent predictor of subsequent articular radiographic progression (14).

CONCLUSIONS

OP is a common complication of RA patients, mainly due to shared demographic characteristics as well as common pathogenic pathways to both entities. The mechanisms involved in the pathogenesis of RA-associated OP are complex. It is evident that the RANK/RANKL/OPG and the Wnt/DKK-1/sclerostin pathways play a crucial role in the development of systemic and local OP as well as bone erosions. Furthermore, different pro-inflammatory cytokines involved in RA pathogenesis such as TNF-α, IL-6 and IL-17, among others, have a relevant role in the regulation of bone homeostasis. Despite these mechanisms are complex and controversial, targeting these molecules clearly provides a drastic arrest of radiographic progression as well as an improvement of disability and quality of life of RA patients. Recently, some studies suggest that this strategy also reduces OP and fractures, further improving the clinical outcome of these patients, especially in long-term disease.

Regarding the role of autoantibodies, both ACPA and anti-CarPA have shown a pathogenic role affecting bone homeostasis through their involvement in the development of systemic OP and bone erosions. These autoantibodies also allow classifying different phenotypes of RA patients regarding evolution and prognosis. Some doubts that need to be clarified still remain, such as the duality of some inflammatory molecules and their involvement in bone homeostasis in RA. There are also unmet needs like clinical studies that correlate these findings and identify prognostic factors capable of helping

in decision-making and in the monitoring and treatment of these patients.

Finally, we must be optimistic as biological therapies developed in recent years make it possible to reverse part of the negative effects of RA on bone and even seem to reduce the risk of osteoporotic fractures.

AUTHOR CONTRIBUTIONS

All the authors have contributed to the design, interpretation of data, writing, and supervision of the final version of this manuscript.

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MINI REVIEW
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What Role Does Trabecular Bone Score Play in Chronic Inflammatory Rheumatic Diseases?

Barbara Ruaro[1†], Andrea Casabella[2,3†], Luigi Molfetta[4], Francesco Salton[1], Paola Confalonieri[1], Marco Confalonieri[1], Elisa Baratella[5], Antonio De Tanti[6] and Cosimo Bruni[7]*

[1] SC Pneumologia, ASUGI, Trieste, Italy, [2] Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, San Martino Polyclinic Hospital, University of Genoa, Genoa, Italy, [3] Department of Internal Medicine Di.M.I, Osteoporosis, Bone and Joint Disease Research Center, CROPO, University of Genoa, Genoa, Italy, [4] Department of Integrated Surgical and Diagnostic Sciences, School of Medical and Pharmaceutical Sciences, University of Genoa, Genoa, Italy, [5] Department of Radiology, Department of Medicine, Surgery and Health Science, University of Trieste, Trieste, Italy, [6] Cardinal Ferrari Centre, S. Stefano Rheabilitation, Fontanellato, Italy, [7] Division of Rheumatology, Department of Experimental and Clinical Medicine, University of Firenze, Florence, Italy

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Lai-Shan Tam,
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Bruno Vidal,
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João Eurico Fonseca,
University of Lisbon, Portugal

****Correspondence:***
Barbara Ruaro
barbara.ruaro@yahoo.it

†These authors have contributed equally to this work and share first authorship

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Patients suffering from rheumatic inflammatory diseases, e.g., systemic sclerosis, rheumatoid arthritis, and ankylosing spondylitis, are at risk of low bone mass. Dual-energy X-ray Absorptiometry (DXA) is the traditional radiological measurement technique for bone mineral density (BMD). The recently developed trabecular bone score (TBS) enhances the skeletal information provided by standard BMD. It re-analyzes the spatial dynamics of pixel intensity changes in lumbar spine DXA images, defining a quantitative index, characterizing trabecular bone microarchitecture. It has been demonstrated that low TBS values are associated with an increased incidence of fractures in patients with rheumatic diseases. These methods used together for bone damage evaluation can be of value to identify individuals who will potentially fracture. The main scientific literature on the clinical aspects of osteoporosis, including the use of TBS in evaluating this pathology, are herein reported aimed at shedding light on the role trabecular bone score plays in chronic inflammatory rheumatic diseases.

Keywords: osteoporosis, rheumatic diseases, Trabecular Bone Score (TBS), Bone Mineral Density (BMD), osteopaenia

HIGHLIGHTS

- Patients affected by rheumatic diseases are prone to an increased risk of low bone mass.
- The trabecular bone score provides information on the bone microstructure of patients with rheumatic diseases.
- Patients with rheumatic diseases have lower TBS values than healthy subjects.

INTRODUCTION

The trabecular bone score (TBS) a grayscale measurement of texture which is derived from the evaluation of the experimental variogram obtained from the Dual-energy X-ray Absorptiometry (DXA) images, is a relatively new tool to evaluate bone microarchitecture (1). TBS is an indirect measurement of bone axial microarchitecture, providing information on bone quality,

e.g., trabecular quantity, trabecular separation, connectivity density, and Parfitt parameters (1–3). Previous reports proposed a normal TBS value for post-menopausal women of 1.350 or more; conversely, scores between 1.200 and 1.350 were attributed to a partially degraded microarchitecture and a TBS below 1.200,a degraded microarchitecture (3–5). These cut-off points were established by analogy with the three bone mineral density (BMD) categories, i.e., normal bone mass, osteopenia and osteoporosis (OP) (3–5). More recently, Anderson et al. developed reference ranges for TBS suitable for use in a clinical setting in an Australian male cohort: scores equal to, or lower than, 1.003 were considered for the determination of degraded microarchitecture (6). The authors also demonstrated a linear life-time decrease in TBS amongst the males, (whereas the decrease in women is better modeled with a cubic function) (6). The strength of TBS lies in its ability to provide more information on the potential risk of vertebral fractures than the DXA and BMD. Indeed, its use as an adjuvant to the standard DXA exam was approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (4, 7, 8). Despite this, to date, there are no guidelines on how to apply it to standard practice, even if the World Health Organization (WHO) established operational definitions of osteoporosis (OP) and osteopenia in postmenopausal Caucasian women (4, 5, 7, 8). These were based on BMD values and aimed at guiding researchers and clinicians in the classification of degrees of bone loss, as early as 1994. Several studies reported that patients with chronic rheumatic inflammatory diseases have a higher OP and osteopenia risk, based on BMD (5, 7, 8). However, several limitations in BMD sensitivity have been reported, such as its low power in determining bone quality (5, 7, 8), an important factor when assessing bone fragility. Indeed, it has recently been demonstrated that bone microarchitecture plays a pivotal role in bone strength. Evidence to date indicates that the TBS bone texture index is able to add further skeletal information to that obtained by the standard BMD (6, 9–11). Several studies confirmed that TBS can discriminate patients with altered bone microstructure and have proposed its use as a clinical-radiological tool in OP diagnosis in patients with chronic inflammatory rheumatic diseases, such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) (12–18).

TBS AND SYSTEMIC SCLEROSIS

SSc is a connective tissue disease characterized by early microvascular impairment, skin, and internal organ fibrosis (19–26). Several studies have also recently demonstrated an increased risk of OP in SSc patients, correlated with multiple factors, i.e., low vitamin D levels (1, 5, 13, 15, 27). Other studies have reported lower BMD and TBS values in SSc patients compared to healthy matched controls (1, 2, 5, 13). Ruaro et al. reported that SSc patients with a "Late" nailfold capillaroscopy pattern had lower TBS values than patients with an "Active" or "Early" pattern ("Late" vs. "Active" and "Early" pattern, $p < 0.001$) (5, 13); whilst no statistically significant difference in BMD values was observed when comparing the three different capillaroscopy patterns (5, 13). The negative correlation between the reduced bone microarchitecture, evaluated by TBS, and the progression of microvascular damage studied by nailfold videocapillaroscopy (NVC), suggested that the microvascular damage in SSc patients is also correlated to bone impairment and other systemic complications (5, 13, 22, 26). Furthermore, these studies confirmed that SSc patients have a higher OP and osteopenia risk associated with the BMD obtained by DXA (1, 2, 5, 13, 15). Various articles report that TBS is an index of bone texture which is able to enhance the skeletal information obtained by the standard BMD, also in SSc patients (2, 5, 13). Indeed, several reports demonstrated that bone microarchitecture plays a pivotal role in bone strength and that TBS can be a clinical tool for OP diagnosis in scleroderma patients (1, 2, 5, 13).

Bone damage may have multi-factorial underlying causes: disability, age, longstanding diseases, low Body Mass Index (BMI), chronic systemic inflammation, low vitamin D levels, and some treatment regimes (1, 2, 5, 13, 27). Numerous authors demonstrated the presence of lower serum 25-hydroxy-vitamin D (25(OH)D) levels in SSc patients than in healthy subjects (HS) (5, 13, 27). Two recent studies have reported that the 25(OH)D level is significantly lower in the "Late" than in the "Active" or "Early" capillaroscopy pattern patients ($p = 0.002$), probably attributable to a reduced vitamin D intestinal absorption (5, 13, 27). The same studies demonstrated that a positive 25(OH)D value correlated with TBS but not with BMD, as also observed by Koumakis et al. (2). Ruaro et al. reported that there were statistically significant lower bone alkaline phosphatase (bone ALP) levels in SSc patients than in HS and that the "Late" pattern patients had lower ALP levels than those with an "Active" or "Early" one, probably due to a reduced turnover and neo-bone formation (5, 13, 27). Furthermore, there was a positive correlation between the TBS and the bone ALP values ($p < 0.0001$) and a negative correlation with the onset of Raynaud's phenomenon in the SSc patients ($p < 0.01$). Conversely, there was no statistically significant correlation between the TBS values and calcium or phosphorus blood levels (5, 13).

In conclusion, all these studies demonstrated that SSc patients run a high risk of having low bone mass and support the importance of evaluating the different aspects of bone architecture with DXA, TBS, and bone parameters, such as vitamin D circulating levels, as part of the periodical clinical assessment (1, 2, 5, 13, 27).

TBS AND SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease, characterized by a wide spectrum of clinical and serological manifestations (14, 28–30). Recent studies have demonstrated a higher incidence of OP and bone fractures in SLE patients compared to HS (14, 30–36). The bone loss observed in SLE has a multi-factorial etiology, including: systemic inflammation, kidney impairment, nutritional disorders, serological, metabolic, and hormonal factors and

maybe also genetic factors and drugs, such as glucocorticoids (GC) (14, 30–40). Moreover, a high prevalence of morphometric vertebral fractures has been observed in SLE patients, despite the fact that 1/3 of them had normal bone density, in line with the hypothesized multi-factorial etiology of fractures in SLE (14, 30–40). Indeed, long-term use of corticosteroids may induce OP in SLE patients by influencing bone turnover (increasing bone resorption and decreasing bone formation), preventing the formation of collagen and osteocalcin, as well as reducing the bone matrix mineralization (14, 30–40). Moreover, numerous cytokines are involved in OP pathogenesis, due to their influence on osteoblast and osteoclast function, i.e., IL-33 (35, 37–39). Vitamin D deficiency may also be a predisposing factor for bone loss in SLE (14, 35, 37–39). Several studies have demonstrated that SLE patients have an increased risk of low bone mass, assessed by DXA and TBS (14, 30–40).

Lai et al. and Ruaro et al. emphasized the important role TBS plays as an innovative and safe diagnostic tool for the quantification of bone quality in chronic and systemic inflammatory rheumatic diseases, such as those observed in SLE. In fact, both studies confirmed that SLE patients have a higher risk of bone loss (osteopenia and OP) and fractures than do HS (34, 40).

Lai et al. analyzed 147 SLE patients and observed that TBS had a higher diagnostic accuracy for vertebral fractures than densitometric measurements (area in the ROC curve for TBS, L spine and left femur BMD: 0.811 vs. 0.737 and 0.605, respectively), supporting the assessment of bone microarchitecture by TBS as an enhancer of the information provided by BMD and showing that TBS identified degraded microarchitecture mainly associated with vertebral fractures in SLE patients (34).

Ruaro et al. were the first to evaluate bone involvement in SLE and compare the results with matched HS, using TBS and DXA (40). They observed that the lumbar spine TBS score was significantly lower in SLE patients than in HS ($p < 0.001$) and that BMD was significantly lower in all areas (the lumbar spine, femoral neck, Ward's triangle, trochanter, and hip) than in HS ($p < 0.001$, for all areas) (40). Furthermore, this study showed that SLE patients had an increased prevalence of 25(OH) vitamin D insufficiency ($p < 0.001$) than HS, as frequently reported in rheumatic diseases (36, 40). Interestingly, SLE patients with previous fractures had statistically significantly lower vitamin D values than those without ($p < 0.0001$) (36, 40).

Another recent study has indicated that supplementation with high vitamin D doses (1.400 IU cholecalciferol per day) and calcium carbonate (1.250 mg per day) for 6 months improved bone mineral density and decreased the osteopenia and OP rates in corticosteroid-treated patients. Most likely, vitamin D can activate osteoblast and bone formation, as well as decrease bone resorption, through the inactivation of osteoclasts (37–39).

Therefore, we consider the early identification of OP and osteopenia is a must in a SLE subjects with "fragile bones," as is the set-up of specific diagnostic-therapeutical strategies. Enhanced knowledge of bone pathophysiology, coupled to progress in pharmaceutical development, has provided the opportunity to make early identification of subjects at high risk of fragility fractures and to start preventive therapy for fractures.

TBS AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease which affects the joints, with progressive and destructive consequences and may also have extra-articular manifestations (41, 42).

These manifestations could be related to the localization of the rheumatoid process in other tissues, i.e., serosa (pericardium, pleura), skin (rheumatoid nodules) or medical therapy complications, such as OP (41, 42).

Some studies reported that the frequency of OP in women with RA ranged from 30 to 50%, depending on the areas assessed by the DXA, this datum was also confirmed in males (43); osteopenia had a prevalence of about 80% (43). Several factors may lead to adverse effects on bone mass and to an increased risk of fracture in RA patients, i.e., reduced sun exposure leading to low serum 25(OH) vitamin D levels, reduced physical activity, proximal muscle atrophy due to a sedentary lifestyle, prolonged use of GC and disease-induced bone mass reduction. Indeed, RA patients tend to develop early OP and are prone to fragility fractures (2, 9, 12, 43–45).

Several studies have demonstrated decreased BMD values using DXA but only a few studies have made use of TBS in RA patients. Breban et al. proposed evaluating the diagnostic TBS as a complement to the BMD on DXA or as an independent risk factor for vertebral fractures (VF) in populations on GC or anti-TNF therapy (43). TBS values were lower in patients on GC compared to those who were not ($p = 0.0001$). Furthermore, TBS was significantly lower in VF patients compared to those without fractures ($p = 0.0001$) and it had a better discrimination value to predict VF in RA patients than the lumbar spine BMD alone (43, 45).

TBS was assessed in patients with RA and AS and compared with healthy subjects (HS) in a case-control study by Toussirot et al. (44). Moreover, they made a prospective examination of the changes in the BMD values of lumbar spine and hip, along with the TBS values whilst on anti-TNF drugs. The study enrolled 30 RA and 30 AS patients not on GC and a comparative HS group of 50 subjects. TBS values from L2 to L4 were measured and the BMD and T-Score were evaluated at the hip in RA patients. They observed that both values were significantly lower in the RA subjects than in the HS ($p = 0.005$). Interestingly, the subgroup of 20 patients on anti-TNF (8 RA and 12 AS patients) monitored for 2 years during the perspective phase of the study, showed a significant increase in the lumbar spine BMD values (+6.3 and + 2.4%, respectively, for RA and AS). However, TBS significantly decreased in RA patients, whilst it remained stable in AS patients, which may be explained by the different influences these drugs have on the bone. The final analysis of the study showed that TBS in RA patients on anti-TNF allows for a greater discrimination of the population at lumbar spine fracture risk, increasing the percentage of the population to be treated with anti-osteoporotic therapies compared to the data provided by DXA alone (44).

Koumakis et al. and Ruaro et al. compared RA, SSc, and HS using TBS and DXA in conjunction (2, 5). Koumakis et al. observed no significant difference in the average lumbar spine TBS values between RA and SSc patients; similarly, BMD at the lumbar spine, femoral neck, and total hip did not differ among the three groups. The fracture prevalence was similar in the RA and SSc groups (29.2 vs. 33.3%, respectively, $p = 0.682$). The TBS values did not differ between RA and HS ($p = 0.128$), despite lower cumulative and daily GC dose ($p < 0.0001$). Furthermore, no association between GC and TBS was observed in the RA group (2). Ruaro et al. selected 98 RA patients on a daily GC dose of <5 mg/day and 60 HS. They observed that 78/98 of the RA group (80%) had bone loss at DXA and BMD. BMD was significantly lower in RA patients than in the control group ($p < 0.001$) (5). Similarly, lumbar spine TBS was significantly lower in RA patients than in HS ($p < 0.001$). Furthermore, their study confirmed that 25(OH)-D serum levels were statistically significantly lower in RA patients than in HS ($p < 0.001$) (5).

Similar results were confirmed by Casabella et al., who evaluated 108 females affected by RA and 60 HS. They performed DXA and TBS at the level of the lumbar spine (L1-L4) and evaluated the serum 25(OH) vitamin D concentrations, for all patients. The lumbar spine TBS score was significantly lower in RA sufferers compared to HS ($p < 0.001$). Moreover, subjects with RA had lower 25(OH) vitamin D concentrations than HS ($p < 0.04$) (45).

TBS AND ANKYLOSING SPONDYLITIS

AS is a chronic inflammatory form of arthritis involving the axial skeleton (46, 47), affecting the spinal vertebrae and sacroiliac joints, causing debilitating pain and loss of mobility. It has been proposed that the sites of attachment of the ligaments or tendons to the bone, known as entheses, are the major target of the inflammatory, traumatic, and degenerative pathological changes occurring in AS (46–48). Enthesitis is believed to play a primary role in the ligament calcification process, which leads to pain. It can cause reduced flexibility of the spine and eventually complete loss of spinal mobility, destruction as well as ankylosis (fusion) of the spine and sacroiliac joints.

New bone formation, which includes the development of syndesmophytes and ankylosis of the spine, is almost pathognomonic for AS (47–51).

The altered new bone formation in the vertebral cortical area and the impairment of trabecular bone at the level of the vertebral body increase the risk of both OP and VF. Furthermore, these bone alterations and ligament ossification modify the BMD data and falsely increase lumbar spine BMD values (41, 47, 51).

Since AS mainly affects young men and BMD gives falsely increased values, there is often a delay in prevention and/or treatment of OP in this condition. Therefore, appropriate bone assessment to determine bone strength, microstructure and any ossifications is a must to start correct treatment in routine practice (17, 18, 47–51).

Toussirot et al. assessed TBS in 30 patients with RA and AS compared the data to those of 50 HS, also including 20 patients who had been on anti-TNF drugs for 2 years (44). The lumbar spine BMD did not differ between AS and HS patients, whilst there was a decrease in the hip T-score in AS patients ($p = 0.02$) (44). Several studies reported a 25% OP prevalence in AS patients and from 10 to 43% radiographic vertebral fractures (17, 18, 47–51).

Ivanova et al. evaluated the relationship between physical function, disease activity, spine mobility, and bone parameters, TBS and BMD, in AS patients (50). The study concluded that lumbar BMD can be affected by osteoproliferation and that, despite this, AS patients have a lower TBS score than HS. Moreover, more evident alterations are also reported in bone microarchitecture in older patients, without significant differences between genders. There was an inverse correlation between the mobility scores and the three bone parameters (TBS, BMD, and T-score femoral), showing a relationship between the state of skeletal health and vertebral functional deterioration (50).

Recently, Richards et al. reported the first analysis of TBS for fracture prediction as an incident event in AS: TBS was shown to independently predict major osteoporotic and clinical spine fractures in AS, whatever the FRAX score (48). Similar predictive power was confirmed by Nam et al., who studied 215 AS patients (75.8% males) and reported that TBS could predict the risk of major osteoporotic fractures. They also stated that TBS is not influenced by spinal osteo-proliferation in AS patients, even in those with advanced spinal changes (49, 51).

These data could overcome the bias derived from previous reports with falsely elevated DXA values at the level of the lumbar spine in AS (49–51). This finding is most likely due to the fact that DXA measures only the quantity and not the *quality* of the bone, therefore confirming its limitations for fracture prediction in this patient group.

TBS AND OTHER RHEUMATIC DISEASES

Recent studies reported that TBS could also be useful in other rheumatic diseases, such as osteoarthritis (OA) and polymyalgia rheumatica (PMR) (52–54). Kolta et al. enrolled 1,254 menopausal women and evaluated 727 of them for 6-years. Patients with lumbar OA had a higher BMD than those without lumbar OA at the lumbar spine, but not at the hip. Conversely, spine TBS did not differ between patients with or without lumbar OA ($p = 0.70$). Interestingly, there was a negative correlation between spine TBS and BMD at all sites and age ($p < 0.0001$) (52). In conclusion, numerous studies have shown that whilst BMD values can be overestimated in patients with OA, TBS evaluations do not seem to be affected by OA changes in the lumbar spine. Furthermore, as TBS is mildly impacted by OA, it could be a better predictor of fracture than spine BMD (52, 53).

Several studies reported that TBS could also be a supplementary tool to discriminate osteoporotic fractures in postmenopausal patients with PMR (54). Kim et al. compared BMD, TBS and the frequency of VF in patients with PMR, RA, or HS. The researchers demonstrated that in PMR patients had a significantly higher VF frequency than RA and HS patients ($p = 0.017$). The average TBS in PMR patients was significantly lower

TABLE 1 | Milestones in the study of bone microarchitecture analyzed by trabecular bone score (TBS) in rheumatic diseases.

Authors	Study type	Rheumatologic population	Control population	Summary of results
Kounakis et al. (2)	CS	138 RA, W	227 mHC	TBS did not differ between controls and RA patients, despite lower cumulative, and daily glucocorticoid (GC) dose. No association between GC and TBS was found in RA
Choi et al. (9)	CS	279 RA, pW	NA	The TBS was negatively correlated with the cumulative dose of glucocorticoids (GCs), but not with the disease activity score for 28 joints (DAS28) or erythrocyte sedimentation rate
Casabella et al. (12)	P	55 RA, W	55 mHC	Most of RA patients (80%) had lower BMD than control group Lumbar spine TBS was found significantly lower in RA patients compared with mHC Positive correlation between the TBS and relative skeletal mass index (RSMI) in RA patients
Ruaro et al. (13)	P	60 RA, W	60 mHC	The BMD values and the T-score measured on the vertebral column, the femoral neck, and the whole femur were significantly lower in RA patients than those in the control group Lumbar spine TBS was found significantly lower in RA patients compared with mHC
Kim et al. (16)	P	100 RA, W aged ≥50	NA	Twenty-six patients were revealed to have moderate to severe vertebral fractures There was a modest negative correlation between fracture risk assessment score (FRAX) and TBS. There was no correlation between FRAX and L-spine BMD
Breban et al. (43)	P	185 RA, W	NA	T-scores were significantly lower in patients with VFs than in patients without VFs, the largest difference being observed at femoral neck. TBS was significantly lower in patients with VFs vs. without VFs
Toussirot et al. (44)	CC, P	30 RA, W	50 mHC	RA patients had lower BMD, lower T score, and lower TBS at the hip compared to mHC Under anti-TNFa, in patients with RA, TBS score decreased
Casabella et al. (45)	P	108 RA, W	60 mHC	78 RA patients (80%) presented a bone loss that was significantly lower when compared with mHC. Lumbar spine TBS score was significantly lower in RA patients compared with mHC
Ruaro et al. (5)	P	84 SSc, pW	60 mHC	TBS and BMD were significantly lower in SSc patients than in mHC TBS values were found to be lower in SSc with a "Late" nailfold videocapillaroscopy (NVC) pattern, compared with the "Active" or "Early" patterns
Ruaro et al. (13)	P	60 SSc pW	60 mHC	The SSc patients showed higher Dkk-1 serum levels than mHC SSc patients, showing the "Late" NVC pattern had statistically higher Dkk-1 serum levels than patients with either the "Active" or "Early" patterns Only in the "Late" NVC pattern group of SSc patients was there a significant negative correlation between Dkk-1 and TBS values
Ruaro et al. (40)	P	40 SLE, W	40 mHC	The lumbar spine TBS score was statistically significantly lower in SLE patients than in mHC
Casabella et al. (14)	P	70 SLE, W	65 mHC	Lumbar spine TBS score and BMD value were found significantly lower in SLE patients compared with CNT
Caparbo et al. (18)	P	73 AS, M	52 mHC	No difference was observed in lumbar spine BMD in AS patients and CNT, but total hip BMD and TBS were lower in AS patients
Nam et al. (49)	P	215 AS, 75.8% M	NA	TBS, hip BMD, and L-spine lateral BMD showed comparably high areas under the curve for predicting FRAX-major osteoporotic fractures. TBS negatively correlated with modified Stoke AS Spine Score (mSASSS) in both male and female patients
Toussirot et al. (44)	P	30 AS, 27 M	50 mHC	Hip T score in patients with AS was also decreased Lumbar spine (LS) BMD did not differ between patients and mHC, whileTBS was lower in AS compared to HC LS and hip BMD increased after 24 months under anti-TNFa, with significant changes at the spine in patients with AS, TBS progressively increased
Ivanova et al. (50)	P	50 AS, 27 M, 23 W	NA	Lumbar spine BMD can be erroneously influenced by osteoproliferation, unlike the TBS and TBS T-score. The limitations in spinal mobility predicted abnormal results for these two TBS parameters
Wildberger et al. (51)	P	51 AS, M	NA	axSpA men with and without syndesmophytes have lower results compared to the normal population regarding hip BMD, spine TBS, and spine BMD except for men with syndesmophytes who have a normal BMD spine T-score

(Continued)

TABLE 1 | Continued

Authors	Study type	Rheumatologic population	Control population	Summary of results
Boussonalim et al. (17)	P	95 axSpA	NA	Lumbar BMD was positively correlated with TBS, while disease duration, disease activity score and serum PTH levels were negatively correlated with TBS More than half of the patients with a BMD level above −2.5 T-score had a low TBS value
Kolta et al. (52)	P	1,254 patients (including patients with OA), pW		Patients with lumbar osteoarthritis had an BMD higher than those without lumbar osteoarthritis at the lumbar spine, but not at the hip. In contrast, spine TBS was not different between patients with and without lumbar osteoarthritis
Kim et al. (54)	CS, P	53 PMR pW	106 mHC	The mean TBS of patients with PMR was significantly lower than those in CNT TBS could be a supplementary tool for discriminating osteoporotic fractures in postmenopausal patients with PMR

AS, ankylosing spondylitis; axSpA, axial spondylarthritis; BMD, bone mass density; CC, case-control study; CS, cross-sectional study; GC, glucocorticoids; LS, lumbar spine; M, male patients; mHC, age- and gender-matched healthy controls; NA, not applicable; OA, osteoarthritis; P, prospective study; pW, postmenopausal women; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TBS, trabecular bone score; VF, vertebral fractures; W, women.

than that of RA and HS patients ($p < 0.001$). Their multivariate analysis demonstrated that a lower TBS is associated with VF in PMR patients ($p = 0.043$). In conclusion, TBS is a promising technique, even if further studies should be carried out to clarify the role this technique plays in other specific rheumatic disorders (see **Table 1**).

CONCLUSIONS

Various imaging techniques able to provide direct information on trabecular bone microarchitecture are currently available, such as magnetic resonance and computed tomography. However, their use in clinical practice is hampered by the fact that they are expensive, not always readily available and can examine only the peripheral bone area (18).

There is increasing evidence that TBS values are associated with the incidence of fractures in rheumatic diseases. TBS provides data on trabecular bone microarchitecture, as it is an index of bone texture and enhances the information obtained by the standard BMD. DXA and TBS, used together for bone damage evaluation, can be of value to identify individuals with potentially increased risk on bone fractures and, therefore, guide treatment decisions, particularly in patients with complicated diseases such as rheumatic inflammatory disorders (1, 5, 13, 50, 54, 55).

In conclusion, current evidence supports the use of an integrated assessment plan with TBS and BMD in conjunction, offering advantages in clinical practice over the use of BMD alone when facing the assessment of bone status, also in rheumatic diseases (1, 5, 50, 54–57). Moreover, future research agenda should aim at further studies investigating into the role of TBS as an outcome measure in the evaluation of anti-osteoporotic treatment efficacy.

AUTHOR CONTRIBUTIONS

BR, AC, and CB: made substantial contributions to the conception and design of the work, the acquisition, analysis, and interpretation of data, drafting the work and revising it critically for important intellectual content, and the final approval of the version to be published. LM, FS, PC, MC, and AD: made substantial contributions to the analysis and interpretation of data and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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REVIEW
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Osteoporosis in Inflammatory Arthritides: New Perspective on Pathogenesis and Treatment

Denise Rotta, Angelo Fassio, Maurizio Rossini, Alessandro Giollo, Ombretta Viapiana, Giovanni Orsolini, Eugenia Bertoldo, Davide Gatti and Giovanni Adami*

Rheumatology Unit, University of Verona, Verona, Italy

Osteoporosis is a skeletal disorder characterized by impaired bone strength and increased risk of fragility fracture and is among the most relevant comorbidities of rheumatic diseases. The purpose of the present review is to discuss the pathogenesis of local and systemic bone involvement in inflammatory arthritides, especially Rheumatoid Arthritis, Psoriatic Arthritis, and Spondyloarthritides, as well as the effect of anti-rheumatic treatments and anti-osteoporotic medication on bone health and fracture incidence, including recent data on novel therapeutic perspective.

Keywords: osteoporosis, rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, fractures, bone mineral density

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Barbara Ruaro,
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University of Lisbon, Portugal

****Correspondence:***
Denise Rotta
denise.rotta.dr@gmail.com

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INTRODUCTION

Inflammatory arthritides are frequently associated to systemic skeletal complications, such as osteoporosis and fragility fractures. Herein, we presented a review of the available literature on osteoporosis in inflammatory arthritides, with a special focus on Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Spondyloarthritides (SpA). We also concentrated on the effects of anti-osteoporotic medications on the skeletal involvement in such diseases and on the effects of anti-rheumatic treatments on bone heath and fracture incidence.

RHEUMATOID ARTHRITIS

Pathogenesis of Osteoporosis in Rheumatoid Arthritis

RA is a chronic systemic disease characterized by pain and joint inflammation with a prominent involvement of the small joints of the hands and feet, leading to joint deformity and functional loss (1).

Due to the presence of a variable grade of systemic inflammation, many comorbidities can accompany the joint involvement, such as extra-articular manifestations and osteoporosis (2–4).

Osteoporosis (OP) is a relevant comorbidity of RA and is caused by the concurrence of several factors such as systemic inflammation, cytokine secretion and circulating autoantibodies. Moreover, the frequent and chronic use of glucocorticoids in RA can also exacerbate the development of OP. Despite adequate strategies in OP primary prevention, such as vitamin D and calcium repletion, most patients will develop OP during their disease history (5).

There are several mechanisms involved in the pathogenesis of OP in RA patients, which is characterized by two main features: local and systemic bone loss (5).

Local bone loss, also called periarticular osteopenia, is characterized by both an impairment of trabecular and cortical bone. Indeed, RA patients have an increased cortical porosity with lower

volumetric bone mineral density (vBMD) (6, 7). The cortical thinning has been demonstrated to affect the entire surface of the bone but it is particularly pronounced at the insertion of the synovia, a susceptibility that drives the genesis of bone erosions in RA (5, 8).

Periarticular bone loss, generally preempted by the presence of bone marrow edema (5), appears during an early stage of the disease and is independently associated with the development of bone erosions (9).

The pathogenesis of local bone loss is multifactorial, and many mechanisms contribute to it, such as proinflammatory cytokine secretion (es. IL-6 and TNF) (6, 7), T-cell derived receptor activator of nuclear factor kappa B ligand (RANKL) hyperexpression (10, 11) and a hypothesized direct effect of autoantibodies against citrullinated proteins (ACPA) (7, 12, 13). It was demonstrated that RA patients develop ACPA years before the clinical onset of the arthritis and frequently local bone loss is already present during the preclinical phase of the disease (14, 15). Moreover, the presence of local bone loss at the metacarpal site, detected with High Resolution peripheral Quantitative Computed Tomography (HRpQCT), was observed in RA patients with ACPA positivity, but not in ACPA-negative subjects or in other seronegative inflammatory arthritides such as psoriatic arthritis (PsA) (16). Indeed, ACPA positivity in PsA patients was associated with an erosive form of the disease, strengthening the theory of a direct role played by these antibodies in causing periarticular bone loss (17). This effect might be potentially mediated by a direct stimulation of autoantibodies and osteoclasts FcγR, enhancing osteoclasts maturation (18). In addition macrophages, stimulated by autoantibodies, release inflammatory cytokines which might be able to enhance osteoclast differentiation and function (18).

Osteopenia affects both trabecular and cortical bone, but cortical sites, such as femoral neck and distal radius, seem to be maximally involved (19). Several mechanisms contribute to the detrimental effect on bone homeostasis, overlapping their pathogenetic role on local bone loss.

Inflammatory cytokines such as TNF, IL-6, IL-1, and immune cell-derived RANKL stimulate osteoclastogenesis, while decreasing osteoblastogenesis (20). Moreover, higher levels of circulating senescent CD4+ CD28- T cells were found in RA patients with lower BMD. This subpopulation is known to present a major expression of RANKL compared to CD28+ T cells and to induce osteoclastogenesis in a more efficient way (11).

Furthermore, a subset of patients with RA develops functional antibodies to osteoprotegerin (OPG) and the presence of these antibodies has been associated to higher disease activity and increased bone resorption (21).

Metabolic factors have a central role as well. Dickkopf-related protein 1 (Dkk-1), a Wnt signaling inhibitor, is involved in bone remodeling and OP development (22) and greater serum levels of this inhibitor of bone formation were detected in RA patients compared to healthy controls (23, 24).

As previously discussed, ACPA positivity is an independent risk factor for local bone loss in RA patients, but their action seems to be detrimental also for systemic bone loss. Indeed, a correlation between the low BMD and ACPA serum titer has been demonstrated recently (25).

Systemic and local bone loss are strictly linked and the presence of systemic bone loss, found in almost 60% of early RA patients, is a strong predictor of radiographic joint damage (26). Moreover, a possible association between low systemic BMD and atlantoaxial subluxation occurrence was suggested in subjects affected by RA (27). This evidence suggests that OP could increase susceptibility to bone erosions in RA patients (28, 29).

Chronic treatment with glucocorticoids represents an independent risk factor for the premature onset of OP in RA patients, even if there is still some controversy regarding the safe dosage for bone health. Indeed low-dose and short-term treatment with glucocorticoids in patients with active RA may have a favorable effect by reducing bone resorption driven by systemic inflammation, as seen in many studies and meta-analyses that showed non-significative BMD changes in low-dose glucocorticoid users affected by active RA (30–33). Nevertheless, glucocorticoids have a well-documented detrimental effect on bone homeostasis (34–36) and other studies showed that even low-doses or intra-articular glucocorticoids may have a relevant role in increasing the risk of fracture in RA patients (37, 38).

Not surprisingly, post-menopause is a supplemental risk factor for OP in RA women (39).

Epidemiology of OP in RA

As previously discussed, RA patients have lower BMD levels at lumbar spine and femoral sites than healthy subjects and this difference can be detected also in an early phase of the disease.

The prevalence of osteoporosis and osteopenia is estimated to be doubled in RA patients as compared to healthy controls (40, 41) with a prevalence ranging from 30 to 50% (40, 42, 43). The risk of developing OP in RA is correlated with the duration and the severity of the disease (19, 44) and even RA pre-menopausal women or men are exposed to a greater risk of osteoporosis in comparison with age- and sex-matched healthy controls (45, 46). A prospective longitudinal study on 379 patients identified some biomarkers predictive of BMD change in patients with RA (47). It was found that the annual BMD change at the lumbar spine had a significant association with glucocorticoids use, bisphosphonate or vitamin D use, and homocysteine. On the other hand, BMD changes at the femur were associated with DAS28, C-reactive protein (CRP), and ACPA titer (47). These results further highlight that there is a strict association between cortical bone health (femoral site) and disease activity while trabecular bone is more affected by classical risk factors (i.e., vitamin D assumption, glucocorticoid use).

Albeit OP is a major problem in the management of RA patients, the percentage of patients receiving calcium and vitamin D supplementation is about 45% and only 5.4% are treated with bisphosphonates (48).

RA Therapy and OP

Several studies investigated the effect of conventional disease modifying anti-rheumatic drugs (cDMARDs) on bone turnover markers in RA patients (49). Overall, the body of evidence orients toward a decrease in osteoclastic activity induced by cDMARDs,

leading to a positive effect on bone mineral density. However, it is not clear if such positive effect corresponds to a fracture risk reduction (50).

Again, controversial results have been found regarding the effect of biological DMARDs (bDMARDs) on BMD and bone markers changes, possibly in relation to the presence of confounding factors such as vitamin D deficiency or corticosteroid therapy (51–56). However, treatment with biologics seemed to be associated with a decrease in bone loss (52).

The first molecules to be studied among bDMARDs were TNF inhibitors, which were associated with a significant, although small, reduction of the vertebral fracture risk in RA patients (57).

A recently published study investigated the effect of TNF inhibitors on BMD and bone biomarkers in patients with RA and ankylosing spondylitis (AS) (58). It was demonstrated that 12 months treatment with anti-TNF drugs prevented further generalized bone loss at both lumbar spine and femoral neck. Moreover, it was found an inverse correlation of baseline C reactive protein (CRP) levels with BMD values, both at baseline measurement and after 12 months treatment, suggesting that baseline high-grade inflammation was associated with lower BMD (58).

IL-6 blocking agents showed an efficacy in reducing systemic bone resorption. As highlighted in a substudy of the OPTION trial, a decrease in bone degradation markers was found in patients treated with tocilizumab, an anti-IL6 agent, plus methotrexate (MTX) as compared to MTX plus placebo (59). In addition, the RADIATE study confirmed such finding in anti-TNF refractory patients (60). Moreover, IL-6 blocking agents were successful in reducing RA localized bone loss, as discussed in a study performed by Axmann et al. (61). Indeed, they found that IL-6 blockade reduced bone erosion in TNF-α transgenic murine models through a direct effect on osteoclast activity which was independent from the anti-inflammatory action (61). Other studies on human subjects further confirmed the positive effect of tocilizumab on bone erosions (62) and systemic bone loss, especially in ACPA positive patients (52, 63).

In 2012 the first Janus Kinases (JAK) Inhibitor was approved for the treatment of RA. The data on the efficacy of these small molecules in reducing systemic bone loss are scarce. A small pilot study showed that tofacitinib, possibly by halting inflammation, can regulate the secretion of serum RANKL and OPG, with a favorable effect on the RANKL/OPG ratio. The interesting speculation of the authors was that tofacitinib could regulate synovial hyperexpression of RANKL via the inhibition of the secretion of IL-17 and IL-6. These effects on RANKL promoted an increase in the osteocalcin levels from 6.9 ± 4.3 ng/mL at the baseline to 8.8 ± 6.1 after 12 weeks of treatment with a concomitant reduction in NTx serum levels (64).

OP Treatment in RA

Bisphosphonates (BPs) are widely used in post-menopausal OP treatment, because of their attested efficacy in fracture prevention with an acceptable safety profile (65, 66). The majority of data on fracture risk reduction in RA patients of these medications are available only from indirect evidence coming from glucocorticoid induced osteoporosis (GIOP) clinical trials (67). In a 2006 placebo-controlled RCT RA patients on glucocorticoids were randomized to receive placebo or daily doses of alendronate (68). A significant difference was found between the two groups in BMD increase at lumbar spine and femoral site (major in the alendronate group), although without any relevant difference in fracture reduction (68). However, the RCT was not powered to detect any fracture difference.

A recent study explored the effect of zoledronic acid on secondary osteoporosis in 66 RA patients (69). Patients were randomized into three groups: combination-therapy (zoledronic acid and methotrexate), zoledronic acid monotherapy and methotrexate monotherapy and followed over a 12 months period. A significant improvement in lumbar spine and hip BMD within the combination-therapy group was demonstrated.

Another recent study (RISOTTO study) investigated efficacy of sodium Risedronate for glucocorticoid-induced osteoporosis in patients with RA finding a significant increase in lumbar BMD in the Risedronate group compared to the placebo one after 6-month treatment, with no significant difference in femoral neck and total hip BMD (70).

Denosumab is a human monoclonal antibody against RANKL (51, 71).

A recent study showed that denosumab was superior in improving spine and hip BMD to risedronate in GIOP patients, 40% of them affected by RA (72). The 24 months extension of this study, further confirmed the superiority of denosumab over risedronate, albeit no significant differences were found in fracture incidence (73). However, as opposite to the FREEDOM study, which was performed on >7,000 patients followed for 3 years, this GIOP study didn't have an adequate statistical power to detect fracture differences between denosumab and risedronate (an active comparator) (71).

A clinical observational study, recently published, showed the results of denosumab therapy over a 3-years period within two groups of female patients, the former with RA, the latter with primary OP (74). The ΔBMD for the total hip, femoral neck and lumbar spine as well as ΔP1NP did not differ significantly between the two groups at any time points (1, 2, and 3 years assessment), hence, denosumab treatment for osteoporosis had a similar efficacy over 3 years among women with RA and OP.

Another randomized, placebo-controlled study investigated the effects of Denosumab combined with Methotrexate on bone erosion progression in Japanese patients with RA (75, 76). Denosumab significantly inhibited radiographic progression of the disease.

In a recently published study these data have been confirmed (77). This study, named DESIRABLE study, proved the efficacy of denosumab in reducing erosions when added to csDMARD therapy in RA patients. Since there was no improvement in disease activity level, it is reasonable presuming that denosumab action is driven only by a direct effect on bone metabolism rather than an additional indirect way on immune system cells (2). Moreover, denosumab prevented bone erosion but it did not prevent joint space narrowing (77–79), showing its effect in impairing bone destruction but not cartilage destruction. In

addition, no differences in infection rate were found between the two groups (77).

Also combined with biological DMARDs (bDMARDs) denosumab was attested to be more efficient in reducing radiographic progression rather than bDMARDs alone (80, 81).

Moreover, switching from bisphosphonates to denosumab significantly reduced radiographic joint destruction compared to continuing bisphosphonates (82). In the same cohort, switching from bisphosphonates to teriparatide was associated with a worse outcome on bone erosions. This result was somehow expected given the detrimental effect of teriparatide on cortical bone health (83).

Romosozumab is a humanized monoclonal antibody that binding to sclerostin neutralizes its blocking effect on Wnt signaling bone formation pathway (84). So romosozumab increases bone formation and, differently from classical osteoanabolic agents, suppresses bone resorption. The role of romosozumab in RA patients or GIOP patients is still unclear. In particular, caution should be taken regarding sclerostin inhibition in RA patients. Indeed, sclerostin inhibition was shown to induce an exaggerated inflammatory response in an arthritis mouse model by promoting TNF secretion (85).

New suggestions for future treatment perspectives have been debated in a very recent review by Gambari et al. which explored the mechanisms regulating monocytes/macrophages fusion and multinucleation (M-FM), a key process to generate mature multinucleated cells such as giant cells (GCs) and osteoclasts (OCs), depending on environment features (86). As discussed in the article, targeting M-FM process in OP therapy might be an interesting alternative to decrease OCs function while preserving osteoblasts (OBs)-OCs communication. In this field, different molecules have been found, like miRNA, that can specifically inhibit M-FM and could be a challenging area to be explored. But targeting the process of monocyte-macrophage differentiation could have interesting implications also for RA therapy strategies. In fact, activated macrophages has an established role in feeding the inflammatory milieu at the synovium site in RA, leading to bone remodeling and erosions; indeed drugs targeting inflammatory cytokines such as TNF, IL-1, and IL-6 have a significative impact on osteoclastogenesis and prevent generalized and local bone loss. A new intriguing opportunity might be to modulate the activation status of macrophages by targeting macrophage fusion and multinucleation, instead of inflammatory cytokines, as a way for preventing an excessive OCs and GCs formation and inflammatory activation (86). In this perspective F-MF inhibition, a mechanism already listed for OP, might be helpful also for preventing bone loss in RA. However, albeit good promises as therapeutic strategy for OP and RA bone loss, clinical trials are mandatory to validate the efficacy, safety and potential superiority of multinucleation inhibitors to current drugs.

PSORIATIC ARTHRITIS AND SPONDYLOARTHRITIS

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease commonly associated with psoriasis (PsO), that can be characterized by heterogeneous manifestations, including peripheral arthritis, axial involvement, enthesitis, and dactylitis (87). PsA has an estimated prevalence in the general population of 0.05–0.25%, with little discrepancy depending on the country examined (87, 88). Many comorbidities are associated with PsO/PsA such as increased cardiovascular risk, diabetes, osteoporosis, metabolic syndrome, ophthalmic disease, depression, and anxiety (89).

Epidemiology of OP in PsA and the Other Spondyloarthritides

Several observational studies have investigated the association between psoriasis or psoriatic arthritis and low BMD values or osteoporosis, with conflicting results.

A cross-sectional study performed on a large population sample with PsO or PsA found that these conditions were significantly associated with osteopenia, osteoporosis, and fragility fractures (90). Moreover, a 2013 population-based analysis showed a significant association between osteoporosis and previous diagnosis of psoriasis in both sexes (91).

On the contrary, a Norwegian study based on hospital-derived fractures data found no association between psoriasis and forearm/hip fracture risk or between psoriasis and osteoporosis (92). Moreover, no differences were found in lumbar spine BMD between Spanish patients with or without PsA (93) and similar findings were underlined during another study conducted in Norway (94).

In 2020, Xia et al. explored the correlation between psoriasis, psoriatic arthritis and osteoporosis considering potential confounding factors that could justify the aforementioned controversial results (95). Conditional regression analyses were performed, and three models were examined: model 0, which included age, height, weight, smoking, and drinking status, model 1, which included all the factors comprised in model 0 plus regular physical activity and model 2, which included all the factors of model 1 plus concomitant medications. In their analyses no estimated bone mineral density (eBMD) difference was highlighted between patients with psoriasis (without arthritis) and healthy controls, therefore psoriasis alone was not correlated to osteopenia and osteoporosis.

More interestingly, it was found that PsA was significantly associated with low eBMD levels even after adjustment for confounding factors in model 0 (age, sex, height, weight, smoking, and drinking status), but this significance became less strong when physical activity was included. Moreover, the association between PsA and low eBMD levels disappeared when conditioning on treatment with methotrexate or ciclosporin (model 2) (95). Therefore, PsA was associated with low eBMD and higher risk of osteopenia, but it seems that this association was somehow mediated by the medical treatment (such as methotrexate or ciclosporin). Furthermore, using a systematic Mendelian Randomization (MR) in order to explore the relationship between PsO/PsA and osteoporosis no causal effects for these factors on BMD score and viceversa were found, reinforcing the idea that the increased risk might be mediated by the treatment and not by the disease itself (95).

However, it's to be noted that all these data refer to quantitative ultrasound (QUS) estimated BMD at heel site, which has high specificity but whose sensitivity to predict BMD as defined by dual-energy x-ray absorptiometry (DEXA) can be significantly variable depending on QUS parameters.

A recently published study compared the incidence of fragility fractures in patients with PsA matched with controls by age and sex (96) and no differences were found in the overall fracture incidence rate. This result was true even for vertebral fractures, that were apparently more frequent in PsA patients compared to controls, but this difference did not reach the statistical significance (96).

Beyond PsA, data on the other Spondyloarthritides (SpA) with axial involvement (axSpA), such as Ankylosing Spondylitis (AS), are heterogeneous (51). Moreover, in patients with axSpA the proper evaluation of vertebral deformities and BMD levels is frequently altered by the presence of syndesmophytes and periosteal bone proliferation (97).

Nevertheless, several data confirm that axSpA patients have lower BMD levels as compared to healthy controls even in the early stage of the disease, independently from spine mobility and exercise (98, 99). The mechanism involved in this process is, at least in part, related to the prevalent inflammation, which can contribute to local bone loss especially in those sites interested by Bone Marrow Edema (BME)/osteitis (100, 101). In fact, inflammation leads to trabecular bone loss, which is associated with the presence of lesions defined as BME/osteitis on MRI that quintuplicate the risk of finding low spine BMD. Hence, the presence of inflammation signs on MRI represents the main risk factor associated with low BMD in axSpA.

Interestingly, the lumbar spine seemed to be more susceptible to bone loss in patient with non-radiographic axSpA (nr-axSpA) as compared to the femur (102).

In addition, the estimated prevalence of osteopenia and osteoporosis within 10 years from the onset of AS is about 51–54% and 13–16%, respectively (99).

Results from a primary care-based nested case-control study showed that AS patients had a higher risk of clinical vertebral fractures without an increased risk of non-vertebral fractures, further highlighting that AS is a risk factor for fractures, but limited to the axial skeleton (103).

In order to find more effective methods to predict the risk of fragility fractures in AS patients, a recent study investigated the usefulness of the trabecular bone score (TBS) in assessing bone strength in patients with AS compared with DEXA (104). TBS showed promising results in improving the ability to detect patients at high risk of fractures, especially in patients with normal or osteopenic BMD levels at standard DEXA (104).

Another recent study investigated the effect of vertebral ankylosis on scanographic bone attenuation coefficient (SBAC), measured from L1 to L5, in AS patients (105). It was found that patients with at least one bony bridge had lower SBAC values, while there was a correlation between the presence of full ankylosis and the probability of presenting SBAC $\leq$145 HU (fracture threshold), suggesting an impact of ankylosed vertebrae on trabecular bone deterioration.

Bone Remodeling in PsA and the Other Spondyloarthritides

In contrast to RA, PsA, and the other SpA, such as AS, are characterized by the simultaneous occurrence of both bone resorption and bone formation signs, the latter of which has not been observed in patients with RA (106).

While most of the mechanisms leading to bone erosions are well-understood and overlap those in RA (107), part of the mechanisms of bone formation in SpA remain unknown. Pro-inflammatory cytokines (such as TNF-α and IL-17) and signaling pathway (including Wnt pathway) have been shown to be involved (108). IL-17, the prevailing inflammatory cytokine in many patients with SpA (109), has been shown to promote both OC bone resorption and OB bone formation (109), while TNFα has a greater effect on promoting bone erosion and suppressing OBs function. Entheses, are poorly populated by OCs and when reached by the IL-17 inflammatory stimulus, bone formation may be induced in a way that can overcome bone resorption (109).

Nevertheless, despite several data, many features of this process remain still incompletely clarified.

IL-23 is another distinctive cytokine that is abundantly present in the affected tissues of PsA patients. IL-23 is generally overexpressed in PsA, leading to an upregulation of IL-22 and consequently to osteoblast-related genes induction, which eventually results in osteoblast expansion and enthesophytes formation (110). Moreover, a recent study exploring Wnt pathway regulators found significantly lower levels of Dkk-1 in patients with PsA rather than RA or healthy controls, suggesting another possible explanation for the different bone phenotype between RA (erosive) and PsA (erosive-proliferative) (111). Furthermore, possibly in relation to a negative feedback response, a rapid increase in Dkk-1 after 6 months of secukinumab, an anti-IL17 antibody, was recently observed (112). This finding might well-explain the promising results that IL-17 blockade had achieved in halting the syndesmophytes progression in AS. Indeed, in this setting, the raise of Dkk-1 might be even beneficial by stopping the bone proliferation induced by the Wnt pathway.

Moreover, a dysregulation in RANK-RANKL pathway had been reported in patients with AS. Increased expression of intracellular RANKL levels in CD4+ and CD8+ T cells and a significantly lower expression of membrane-bound RANKL were found in AS patients (113).

A 2016 study explored the association of Dkk-1 levels with low BMD and vertebral fracture prevalence among patients with AS (114). AS patients had lower levels of Dkk-1 compared to healthy controls; however Dkk-1 serum levels inversely correlated with lumbar spine Z-score BMD and higher serum levels of Dkk-1 were associated with a higher prevalence of 1 or more vertebral fractures. So serum Dkk-1 titer, even though lower in AS patients, than in healthy controls, appears to be associated with an increased risk of severe osteoporosis (114).

Furthermore, a correlation between Dkk-1 and PTH was observed, with higher levels of PTH and lower levels of Dkk-1 measured in AS patients rather than healthy controls (115). Then dividing the patients in two equal groups according to disease duration, the association between PTH and Dkk-1

remained only in the group with longer disease duration, where Dkk-1 levels were also correlated with higher CTX and lower BMD (Z-score ≤ -1) (115).

In addition anti-OPG antibodies has been isolated in a cohort of SpA patients and a correlation with low BMD and fractures was found (116).

In summary, multiple players are involved in bone remodeling of PSA/SpA, with a combination of systemic effects mainly driven by inflammatory cytokines and metabolic factors.

SpA Therapy and OP

Non-steroidal anti-inflammatory drugs (NSAIDs) play a pivotal role in the treatment of SpA, especially in those with an axial involvement (axSpA), in whom NSAIDs represent the first line treatment (117). However, despite their wide use, few data have been collected about their possible effects on bone (51). A case-control study found a decreased risk of any clinical fracture in patients with AS treated with NSAIDs (103). Moreover, data from a large population-based public health database supported the protective role of NSAIDs on clinical fracture risk in SpA patients, highlighting a higher fracture risk in those not assuming chronic NSAIDs (118).

TNF inhibitors use was associated with an increase in lumbar spine and total hip BMD and maintenance of femoral neck BMD for up to 2 years in patients with AS (119). Another study investigated the effects of 4-years course with anti-TNFs in patients with long-term AS and albeit no differences were found in the incidence of fragility fractures the authors found an improvement in BMD levels during 4 years period (120).

Moreover, a single-center study explored the effect of the TNF-blocker infliximab vs. i.v. neridronate (a potent amino-bisphosphonate) on bone turnover and disease activity after 3–6 months treatment in AS patients (121). As regards bone metabolism, no significant BMD variations were observed at 6 months in the infliximab group, while a significant BMD increase at LS site, was found in the bisphosphonate arm ($p<0.05$ vs baseline and vs infliximab) (121). In addition i.v. neridronate was as effective as infliximab in controlling the leading symptoms (as assessed by BASDAI or BASFI) of AS even without, as expected, any changes in systemic inflammation parameter (CRP and ESR), suggesting that, at least in part, the symptoms of AS are related to bone metabolic factors.

In fact, as known (122), bisphosphonates reduce bone resorption, which is elevated mainly in the early stages of AS. Furthermore, through the coupling of osteoclast and osteoblast activity, this mechanisms leads to later inhibition also of bone formation and causes an increase in serum sclerostin, which is low in AS and negatively correlated to the development of syndesmophytes (123, 124).

As concerning PsA, a recent study compared the effects of methotrexate (MTX) with bDMARDs on bone structure and biomechanical properties (125). It was found that bDMARD-treated patients had higher bone mass and better bone strength than patients receiving MTX or no DMARDs (despite longer disease duration in bDMARDs-treated group) (125).

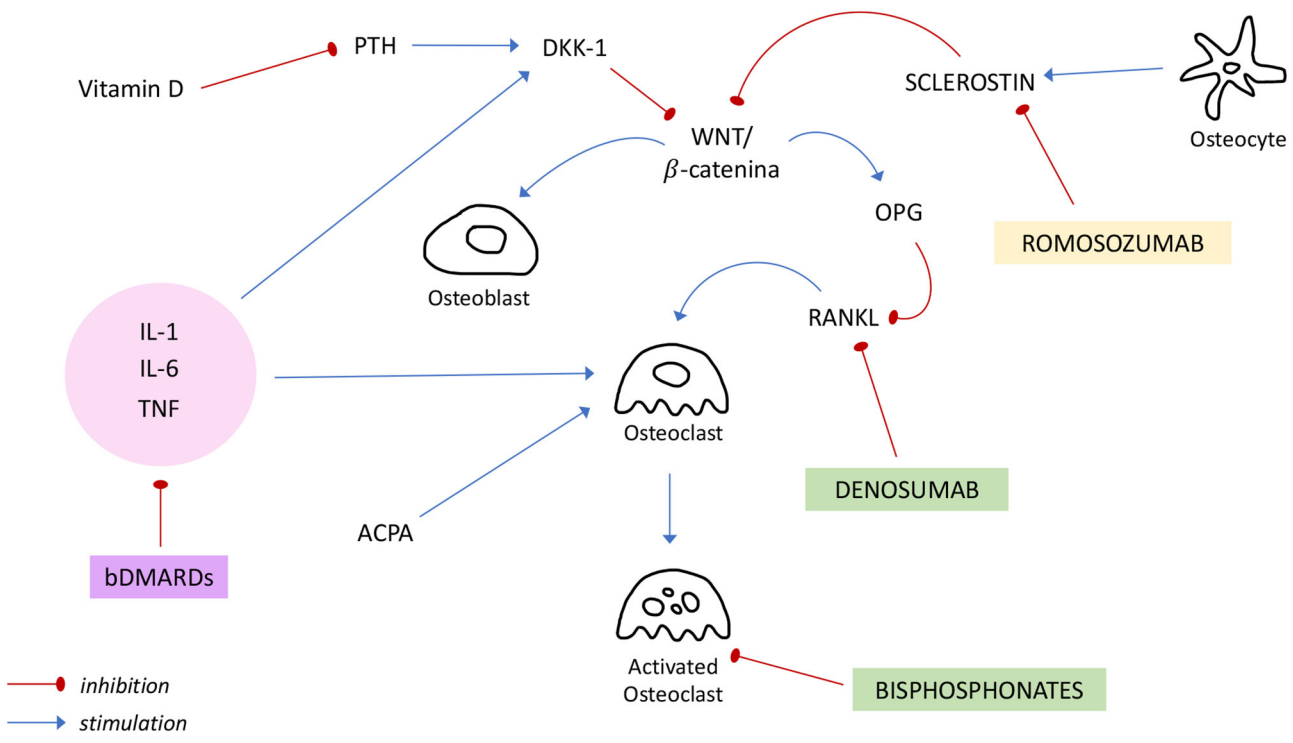

FIGURE 1 | Regulation of bone metabolism and mechanisms of action of bDMARDs and anti-osteoporotic drugs. *ACPA*, anti-citrullinated protein antibody; *bDMARDs*, biologic Disease Modifying Anti Rheumatic Drugs; *DKK-1*, Dickkopf-1; *IL*, interleukin; *OPG*, osteoprotegerin; *PTH*, Parathormon; *RANKL*, receptor activator of NF-κB ligand; *TNF*, tumor necrosis factor.

JAK-inhibitors had been recently approved for the treatment of SpA. While a reduction in articular bone erosion in RA and PsA patients has been shown during treatment with tofacitinib, still no data on BMD or osteoporosis has been published (110).

CONCLUSIONS

OP is a hallmark of inflammatory arthritides. Its pathogenesis is manly driven by the predominant inflammation, notwithstanding that, other metabolic factors are increasingly believed to play a crucial role in the development of OP and fragility fractures in such diseases. Novel therapeutic agents have been approved for the treatment of inflammatory arthritides and their role in preventing or even treating osteoporosis is becoming clearer.

In the figure above (**Figure 1**) the principal targets of bDMARDs and anti-osteoporotic drugs previously discussed are summarized.

Nevertheless, albeit clinicians can benefit from new treatment discovery, further research is needed to expand our knowledge about the interaction between bone metabolism and inflammation, in order to find shared mechanisms to target and expand the therapeutic armamentarium available in the clinical practice either to prevent or to treat the bone loss in arthritides.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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A Contemporary View of the Diagnosis of Osteoporosis in Patients With Axial Spondyloarthritis

Mie Jin Lim[1] *and Kwi Young Kang*[2,3]*

[1] Division of Rheumatology, Department of Internal Medicine, College of Medicine, Inha University, Incheon, South Korea, [2] Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [3] Division of Rheumatology, Department of Internal Medicine, College of Medicine, Incheon Saint Mary's Hospital, The Catholic University of Korea, Incheon, South Korea

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily affects the axial joints. Altered bone metabolism associated with chronic inflammation leads to both new bone formation in the spine and increased bone loss. It is known that patients with axSpA have a high prevalence of osteoporosis and fractures. However, there is no consensus on which imaging modality is the most appropriate for diagnosing osteoporosis in axSpA. Bone mineral density measurement using dual-energy X-ray absorptiometry is the primary diagnostic method for osteoporosis, but it has notable limitations in patients with axSpA. This method may lead to the overestimation of bone density in patients with axSpA because they often exhibit abnormal calcification of spinal ligaments or syndesmophytes. Therefore, the method may not provide adequate information about bone microarchitecture. These limitations result in the underdiagnosis of osteoporosis. Recently, new imaging techniques, such as high-resolution peripheral quantitative computed tomography, and trabecular bone score have been introduced for the evaluation of osteoporosis risk in patients with axSpA. In this review, we summarize the current knowledge regarding imaging techniques for diagnosing osteoporosis in patients with axSpA.

Keywords: osteoporosis, axial spondyloarthritis, dual energy absorptiometry, trabecular bone score (TBS), quantitative computed tomography (QCT)

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***Correspondence:**
Kwi Young Kang
kykang@catholic.ac.kr

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INTRODUCTION

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture caused by minimal or low trauma. Bone strength was considered mainly dependent on bone density and quality (e.g., microarchitecture) (1). A deterioration in trabecular microarchitecture with a loss of connectivity between the trabeculae and cortical thinning is a typical trait of osteoporosis (2). Osteoporosis is a recognized entity in many inflammatory diseases. An increasing body of evidence indicates that current approaches for diagnosing osteoporosis are insufficient, and new methods are required to account for the different characteristics of chronic inflammatory arthritis.

Axial spondyloarthritis (axSpA) is one of the most common types of inflammatory arthritis and is known to be accompanied by a high prevalence of osteoporosis. AxSpA predominantly affects the axial skeleton, such as the sacroiliac joints and vertebrae. The term *axial spondyloarthritis* covers both patients with visible structural damage in the sacroiliac joints or spine, as seen on radiographs

and categorized as ankylosing spondylitis (AS) or radiographic axSpA, and patients without such structural damage, categorized as non-radiographic axSpA (nr-axSpA) (3).

Bone disease in patients with axSpA is a complex phenomenon involving both bone loss and new bone formation, which impact the clinical features of the disease (4). Bone loss can occur locally, as erosions in the sacroiliac joints and vertebrae, or systemically, leading to an increased risk of osteoporosis and fracture (5). Patients with axSpA have a higher prevalence of both osteopenia and osteoporosis than age- and sex-matched controls (6). In axSpA, osteoporosis has multifactorial origins and can occur because of limited spinal mobility, increased proinflammatory cytokine levels, physical inactivity, or malabsorption (if inflammatory bowel disease is present) (5). Fragility fractures are a common outcome of osteoporosis. The high prevalence of osteoporosis in patients with axSpA leads to a higher risk of fracture (7). Therefore, it is important to assess the risk of osteoporosis in the early stages of axSpA and provide appropriate management.

Timely screening performed with dual-energy X-ray absorptiometry (DXA) is essential. Low bone mineral density (BMD) is a well-known feature of axSpA. The hallmarks of axSpA are sacroiliitis and spinal damage due to both bony erosion and abnormal bone formation. This can lead to the development of syndesmophytes, perivertebral bone formation, ankylosis of zygapophyseal joints, and pathological new bone formation in the ligamentous apparatus. This extensive osteoproliferation can make traditional DXA assessment of the spine in the anterior–posterior (AP) view, particularly in cases of structurally advanced disease, difficult to perform (4). This gives an illusion of a reassuringly normal BMD, even in cases in which osteoporosis may be present. Although not many axSpA patients show low BMD, bone structure and the quality of microarchitecture might be degraded in these patients (8). As patients with axSpA might still have poor bone health and fractures despite having a normal BMD, osteoporosis could be underestimated in such patients. There have been inconsistent reports on the association between low BMD and fractures in AS (9, 10). In axSpA patients with syndesmophytes, DXA of the hip or lateral spine can be performed (11). However, in such cases, DXA cannot assess bone quality. Increased fracture risk in axSpA patients is likely to be multifactorial, resulting from traditional osteoporosis risk factors and additional disease-related factors such as systemic inflammation, which affect not only BMD but also bone quality (12, 13). Therefore, including bone quality assessment when performing BMD measurements will enable a more accurate assessment of the risk of osteoporosis.

Recently, several new techniques to measure bone density or quality have been proposed to enhance fracture risk assessment in routine clinical practice. Some examples are trabecular bone score (TBS) and high-resolution peripheral quantitative computed tomography (HR-pQCT). TBS is a novel tool of estimating bone microarchitecture at the lumbar spine using DXA imaging. It is considered a non-invasive method for the assessment of trabecular microarchitecture (14). TBS has an additional advantage in that it is not affected by new bone formation, such as spinal osteophytes, which may lead to the overestimation of BMD in patients with lumbar spine osteoarthritis (15), as caused by syndesmophytes in patients with axSpA. HR-pQCT analyzes the trabecular and cortical compartments separately at the tibia and radius (16). It allows the measurement of large portions of distal bones with limited irradiation. HR-pQCT measures microarchitecture parameters, as well as volumetric density (16, 17).

Here, we review the appropriate methods for diagnosing osteoporosis in axSpA, focusing on recent studies on imaging methods used to assess bone impairment.

BONE MINERAL DENSITY ASSESSMENT USING DUAL-ENERGY X-RAY ABSORPTIOMETRY

DXA for BMD measurement is a standardized diagnostic tool for osteoporosis screening in patients with axSpA. Low bone mass, including osteopenia or osteoporosis according to the World Health Organization guidelines based on *T* scores (18), is frequently found in patients with axSpA (**Table 1**). Low bone mass is a well-known risk factor for vertebral fractures (20). There is a substantial increase in the risk of thoracolumbar compression fractures in patients with AS (32–34). Even AS patients with mild disease are at a higher risk of fractures than controls [odds ratio (OR), 5.92] (35). The risk of clinical spine fractures peaks in the first 2.5 years of AS, warranting early detection and treatment of low bone mass in these patients (34).

Lumbar spine DXA in the AP view includes both the vertebral body and posterior part of the vertebra, mainly consisting of dense cortical bone (36). Patients with nr-axSpA showed lower AP lumbar BMD values and *T* and *Z* scores than age- and sex-matched controls (37). A high frequency of vertebral fractures in patients with early spondyloarthritis (SpA) was associated with low BMD of the lumbar spine (38). A longitudinal study on early AS suggested that spine and hip BMD decrease in patients, especially during the active inflammatory stage (21, 39–41). Thirty-four early AS patients without ankylosis were followed up for 19 months; the follow-up lumbar spine and femoral neck BMD were reduced by 5% and 3%, respectively, in patients with active AS (42). However, patients with advanced AS frequently develop syndesmophyte and ligament ossification, resulting in false increases in AP lumbar BMD (25, 40, 43–47). When 168 patients with AS were followed up for 5 years, AP lumbar spine BMD increased, although femoral neck and radius BMD decreased (30). Thus, AP lumbar spine BMD is sensitive to bone loss in the early stages of the disease but not in the advanced stage. Therefore, alternative imaging techniques and parameters, including lateral spine or proximal femur BMD or QCT, are required for accurate diagnosis.

Lateral lumbar spine DXA evaluates the trabecular-rich vertebral body (36), making the technique less prone to the effects of new bone formation at the cortex. Lateral lumbar spine DXA is more sensitive than its AP counterpart in detecting low BMD in patients with AS (26, 46, 48, 49). An increase in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), the tool used to assess the presence of changes related to

TABLE 1 | Prevalence of low bone mineral density measured by DXA in patients with axSpA.

References	Number (male/female)	Mean age (years)	Mean disease duration (years)	Prevalence of low BMD at AP lumbar spine	Prevalence of low BMD at the lateral lumbar spine	Prevalence of low BMD at the femoral neck	Prevalence of low BMD at the radius
Kim HR et al. (19)	60 (51/9)	32.1	5.5	56%	NA	74%	NA
Wang et al. (20)	504 (417/87)	29.1	7.7	3% (OP only)	NA	9% (OP only)	1% (OP only)
Karberg et al. (21)	103 (66/37)	40.1	9.3	45%	NA	76%	NA
Malochet-Guinam et al. (22)	89 (52/37)	44.4	10.2	328% 39% (in 28 females)	32.1% (in 28 females)	43%	NA
Toussirot et al. (23)	71 (49/22)	39.1	10.6	47%	NA	27%	NA
Kaya et al. (24)	55 (42/13)	35.8	11.05	56%	NA	55%	NA
Muntean et al. (25)	44 (44/0)	41	13.3	48%	NA	60%	NA
Klingberg E et al. (26)	204 (87/117)	50	15	21% 25% (in females)	33% (in females)	29% 24% (in females)	26% 21% (in females)
Meirelles et al. (27)	30 (27/3)	37	17	50%	NA	86%	NA
Korczowska et al. (28)	66 (66/0)	51.6	17.4	NA	NA	56%	68%
Speden et al. (29)	66 (0/66)	43.4	21.1	26%	NA	58%	NA
Deminger et al. (30)	168 (92/76)	55	24	10% (OP only)	NA	7% (OP only)	8% (OP only)
Magrey M. et al. (31)	100 (74/26)	46.1	83% of patients had >5 years	62% (≥50 years of age)	NA	41% (in patients ≥50 years of age)	NA

BMD, bone mineral density; AxSpA, axial spondyloarthritis; DXA, dual-energy X-ray absorptiometry; AP, anterior–posterior; NA, not available; OP, osteoporosis.

chronic AS, has been significantly correlated with a decrease in lateral lumbar spine BMD but not with AP lumbar spine BMD (26). Lateral spine BMD values were also significantly lower in AS patients belonging to a fracture group (46). Although the International Society for Clinical Densitometry guidelines currently do not recommend lateral lumbar spine DXA for the diagnosis of osteoporosis, they suggest that the technique be used to monitor the condition (50). Hence, lateral lumbar spine DXA could serve as a screening tool in late-stage AS patients with syndesmophytes (21).

Femoral neck BMD is sensitive to systemic bone loss in patients with axSpA. BMD at the femoral neck is reduced in patients with AS (40), and low bone mass, including osteopenia and osteoporosis, is significantly more common at the femoral neck than at the AP lumbar spine (19, 21, 22, 24, 25, 27–29, 31, 39, 43, 46). Prospective studies have shown that the BMD at the femoral neck decreased with the disease duration in patients with AS (24, 30, 31); such a decrease at a 2-year follow-up has been related to systemic inflammation, as demonstrated by elevated erythrocyte sedimentation rates (ESRs) (41). An increase in the mSASSS has been shown to be negatively correlated with femoral neck BMD ($r = -0.324$) and total hip BMD ($r = -0.201$) (26), suggesting that femoral neck BMD is less affected by new bone formation in AS. Low femoral neck BMD is also correlated with an increased risk of vertebral fracture (42, 51, 52), and AS patients with fractures display low femoral neck BMD (13, 46). In contrast to previous results in patients with axSpA, BMD and T and Z scores at the proximal femur in patients with nr-axSpA were similar to those in matched controls (37). Therefore, the best site to assess bone loss by DXA may be the femoral neck in patients with axSpA but not in patients with nr-axSpA.

Demineralization of the axial skeleton occurs in the early stages of AS, and as the disease progresses, the cortical bone of the peripheral skeleton also demineralizes (43). BMD at the radius in patients with AS tends to decrease during a 5-year follow-up (39), and patients with advanced AS (mean disease duration = 20.3 years) show depressed carpal BMD as compared to age-matched controls (53). Thus, for advanced stages of the disease, DXA of the wrist could prove a useful diagnostic tool.

TRABECULAR BONE SCORE

TBS is a new method used to evaluate bone microarchitecture. It is a textural index that evaluates pixel gray-level variations in two-dimensional (2D) projection images of lumbar spine DXA scans, providing an indirect index of the trabecular microarchitecture of the lumbar spine (14). TBS obtained via a reanalysis of DXA scans is correlated with three-dimensional (3D) microarchitecture

TABLE 2 | Prevalence of low trabecular bone score in patients with axSpA.

References	Classification criteria	Number of patients (male/female)	Mean Age (years)	Mean disease duration (years)	Mean TBS	Prevalence of low TBS*
Caparbo et al. (59)	AS	73 (73/0)	42	16	1.31	56%*
Kim et al. (62)	AS	54 (38/16)	40	8	1.37	41%#
Kang et al. (63)	AS	100 (100/0)	34	6	1.38	22%*
Wildberger et al. (58)	AxSpA	51 (51/0)	52	NA	1.26	NA
Hamoud et al. (60)	nr-AxSpA	60 (29/31)	35	NA	1.27	NA
Kang et al. (61)	AxSpA	248 (193/55)	39	10	1.38	22%*
Boussoualim et al. (64)	AxSpA; 65 pSpA; 4 Mixed; 26	95 (50/45)	41.1	8.4	1.34	46%#

TBS, trabecular bone score; AxSpA, axial spondyloarthritis; pSpA, peripheral spondyloarthritis; nr-AxSpA, nonradiographic axial spondyloarthritis; NA, not available.
**Low TBS was defined as a score <1.31, #low TBS was defined as a score <1.35.*

variables measured by QCT and HR-pQCT (54). Therefore, it may provide additional information on bone quality that cannot be captured by BMD measurement. The higher the TBS, the stronger the bone microarchitecture, which in turn leads to more resistance to fractures. A recent meta-analysis divided TBS into three groups based on fracture risk (55): normal, TBS $\geq$ 1.31; partially degraded, 1.31 > TBS > 1.23; degraded, TBS $\leq$1.23. TBS can predict osteoporotic fractures in postmenopausal women independent of the areal BMD of the hip or spine (56). Moreover, it is associated with hip fracture and major osteoporotic fracture risk in men older than 50 years (57). TBS has an advantage in evaluating osteoporosis in that it is not affected by spinal syndesmophytes, which may contribute to the overestimation of BMD in patients with axSpA (58).

Recently, several studies on TBS in patients with axSpA have been reported. Patients with axSpA had lower TBS than age- and sex-matched controls (59–61). However, the reported prevalence of low TBS varied widely, ranging from 22 to 56% (58–64) (**Table 2**). This variation may be associated with a difference in the applied patient-recruitment criteria [the Association of SpondyloArthritis International Society classification criteria for axSpA (65) or the New York classification criteria for AS (66)] and disease severity in the study patients.

TBS is not only associated with disease activity in patients with axSpA, as measured by inflammatory markers such as ESR and C-reactive protein and the Ankylosing Spondylitis Disease Activity Score (63, 64, 67), but is also negatively correlated with inflammation in patients with AS, as presented on lumbar spine magnetic resonance imaging (68). Additionally, we have reported a longitudinal association between disease activity measures and trabecular bone loss for 4 years in patients with axSpA (69). These findings mean that TBS might be a useful method for assessing osteoporosis risk related to inflammation in patients with axSpA.

A few studies on the association between TBS and the risk of fracture in axSpA have been reported (59, 63, 67, 70). Caparbo et al. studied 73 male AS patients and found an association between low TBS values and the prevalence of vertebral fractures. AS patients with low TBS (<1.310) tended to show higher frequencies of vertebral fracture (36.7 vs. 16.3%, $P = 0.058$) when compared with those with high TBS ($\geq$1.310) (59). In a cross-sectional study of 255 patients with axSpA, we found that low TBS was associated with prevalent vertebral fracture, whereas lumbar spine BMD was not and that TBS showed better discriminatory values for prevalent vertebral fracture than total hip BMD (67). In addition, Richards et al. reported that baseline TBS independently predicted major osteoporotic and clinical vertebral fractures in 188 patients with AS, independent of Fracture Risk Assessment Tool scores (70). This finding suggests that TBS could be used as a useful method for incident fracture prediction.

Taken together, TBS derived from DXA images can be directly compared with BMD because both measure the same lumbar spine region. Not only does DXA enable fast and low-cost imaging, but it is also available in most clinical practice settings. Therefore, adding TBS assessment to BMD measurement can provide information about bone quality to detect bone impairment in patients with axSpA. TBS assessment is expected to be able to predict future fractures, as it can indirectly assess axSpA-induced changes in bone microstructure, beyond and independently of BMD.

QUANTITATIVE COMPUTED TOMOGRAPHY

Central QCT provides volumetric BMD (mg/cm^3), as well as macrogeometry parameters at the level of the hip and spine (16, 71, 72). The bone geometry measurements from QCT are 3D parameters, whereas DXA-derived evaluations are extrapolated from 2D parameters (73). Several studies have performed hip

or spinal QCT on patients with AS and assessed the results. Hip QCT was performed in 60 patients with AS and 57 healthy controls. Patients with AS had clinically lower areal BMD in the cortical bones and total bones of the proximal femur than healthy controls (74). In another study, 37 patients with AS were followed up for 10 years, and both DXA and QCT were performed at baseline and during the follow-up period (75). Spine QCT showed a statistically significant decrease in bone density, whereas spinal DXA showed an increasing trend in bone density. Correlation analyses performed between lumbar QCT and lumbar DXA found that the QCT trabecular volumetric BMD (vBMD) had the strongest correlation with DXA vBMD ($r_S = 0.636$; $P < 0.001$), followed by lateral lumbar spine BMD ($r_S = 0.537$; $P < 0.001$) and AP lumbar spine BMD ($r_S = 0.380$; $P = 0.002$) (75). QCT cortical vBMD was correlated with lateral DXA BMD ($r_S = 0.595$; $P < 0.001$), AP DXA BMD ($r_S = 0.541$; $P = 0.002$), and DXA vBMD ($r_S = 0.431$; $P < 0.001$) (16). Thus, QCT is more effective than lumbar spine DXA in revealing reduced BMD of the lumbar spine (76), although it has drawbacks of higher radiation doses and greater costs than DXA (16).

Single-energy QCT (SEQCT) offers the advantage of 3D evaluation of bone structure; Lange et al. reported a comparison of DXA and SEQCT in patients with AS (77). Patients were divided into four groups according to the degree of spine involvement. Both DXA and cortical bone measurement by SEQCT showed a decrease in bone density as spine involvement progressed and a sudden increase in bone density at the ankylosing stage. In contrast, trabecular analysis by SEQCT showed a gradual reduction in bone density as the disease progressed to the ankylosing stage (77). This study reflected two opposite trends of AS at the ankylosing stage: central trabecular bone loss and peripheral new bone formation of the spine, both characteristic features of AS. The disadvantage of SEQCT is that it significantly underestimates trabecular vBMD (depending on the actual vBMD, by up to 30%) when compared with dual-energy QCT (DEQCT), as the latter corrects for the effects of bone marrow fat (78). Although DEQCT has higher radiation exposure and variability than SEQCT, current scanners protect from radiation exposure and reduce variability to an acceptable range (78). Karberg et al. reported a satisfactory correlation between DEQCT at the spine and DXA at the femoral neck (21). Overall, low bone density was significantly more common at the DXA the femoral neck, followed by DEQCT and DXA at the lumbar spine. When patients were divided according to disease duration osteoporosis in patients with early AS (disease duration <5 years) was detected by DXA at the lumbar spine and femoral neck in 15% and 11% of patients, respectively, and no patients were found to be have osteoporosis on DEQCT (21). In contrast, the proportion of osteoporotic patients with long-standing AS (disease duration >10 years) assessed by DXA at the lumbar spine and femoral neck was 4 and 29%, respectively. Moreover, 18% of the patients with long-standing AS (disease duration >10 years) were found to have osteoporosis by DEQCT (21). The likelihood of finding syndesmophytes increased as the disease progressed. In patients with syndesmophytes, the frequency of low bone density was higher as measured by DXA at the femoral neck or DEQCT than by lumbar spine DXA (21). Therefore, osteoporosis was more frequently detected in patients with syndesmophytes and long disease duration, when measured by DXA at the femoral neck and DEQCT.

HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

HR-pQCT has been gaining attention as an alternative modality by which to assess BMD. It is distinguished from QCT by the creation of a high-resolution image, allowing for examination of the bone trabecular and cortical microstructure, an essential correlate of bone strength. This technology calculates BMD, cortical BMD, and trabecular BMD simultaneously while exposing the patient to a far lower dose of radiation than in typical computed tomography (CT) (79, 80). HR-pQCT measures the trabecular and cortical compartments separately at the tibia and radius, allowing measurement of large portions of distal bones with good spatial resolution and minimal irradiation (16, 17). HR-pQCT measures microarchitecture parameters such as trabecular thickness, number and distribution, and cortical porosity of the tibia and radius, thus resembling a virtual bone biopsy of the peripheral bone (16, 79, 81, 82). It was previously argued that osteoporosis in patients with axSpA primarily affects the axial skeleton (23, 83). HR-pQCT helps reveal poor microarchitecture of the trabecular and cortical bones in the peripheral skeleton of patients with AS. Klingberg et al. performed HR-pQCT, QCT, and DXA of the lumbar spine in 69 male patients with AS and healthy controls and successfully compared these three bone-analyzing techniques (13). HR-pQCT of the radius and tibia showed lower vBMDs both in the cortical bone of the radius and in the trabecular bone of the tibia in patients with AS than in controls (13). Low lumbar trabecular vBMD measured by QCT significantly correlated with poor bone microarchitecture indices measured by HR-pQCT, such as thinner trabecula, lower trabecular number, thinner cortex, lower cortical volumetric BMD, and increased cortical porosity (13). AS patients with a vertebral fracture had substantially lower cortical lumbar vBMD as measured by QCT and lower BMDs as measured by DXA at the hip, AP, and lateral lumbar projection than age-matched AS controls without fractures (13). HR-pQCT also displayed significantly lower trabecular and cortical vBMDs in the radius and lower trabecular thickness, cortical thickness, and cross-sectional area in both the radius and tibia in AS patients with fractures than in the age-matched AS controls without fractures (13). Increases in mSASSS correlated significantly with decreases in trabecular vBMD in the lumbar spine by QCT ($r_s = -0.620$, $P < 0.001$), increases in cortical porosity ($r_s = 0.352$, $P = 0.004$ in the radius; $r_s = 0.363$, $P = 0.002$ in the tibia), and decreases in trabecular thickness ($r_s = -0.528$, $P < 0.001$ in the radius; $r_s = -0.488$, $P < 0.001$ in the tibia) and vBMD of the trabecular and cortical bone ($r_s = -0.4$, $P = 0.001$ in the radius; $r_s = -0.475$, $P < 0.001$ in the tibia) as measured by HR-pQCT (13). With the existence of syndesmophyte as the binary outcome, decreasing lumbar trabecular vBMD [$B = -0.058$; $P < 0.001$; OR = 0.943; 95% confidence interval (CI),

0.917–0.970] and increasing lumbar cortical vBMD ($B = 0.019$; $P = 0.016$; OR, 1.019; 95% CI, 1.004–1.035) were independently associated with syndesmophyte formation (13). In another study by Neumann et al., HR-pQCT showed pronounced bone loss in the cortical area, cortical thickness, and cortical BMD in patients with nr-axSpA as compared to controls. However, trabecular vBMD did not differ between patients and controls (81). Patients with short disease duration (<2 years) also showed a significant reduction in cortical thickness and cortical area when compared with controls, and the decrease in cortical thickness was more prominent in long-term patients (disease duration >2 years). Therefore, bone loss in the cortical bone probably develops in the early stages of SpA. HR-pQCT aids in the identification of many structural and compartmental changes in bone tissue in patients with axSpA.

FINITE ELEMENT ANALYSIS IN PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY

Finite element analysis (FEA) is an approach that has been established as useful in describing bone quality. FEA is a standard method for bone fragility determination both *in vivo* and *in vitro*. Finite element–based simulation models integrate both bone quantity and quality. FEA can assess bone fragility directly from the bone mass distribution, material behavior of the bone extracellular matrix, and classic mechanics principles (84). High-quality CT, including QCT and HR-pQCT, allows finite element modeling. Finite element models for bones may be divided into two groups: micro-finite element (μFE) models, in which the trabecular and cortical bone morphology is modeled in detail (85, 86), and homogenized, continuum-level (hFE) models, in which one element covers a wider bone area, which is considered as homogeneous material (87, 88). Although both models have unique strengths and weaknesses, μFE models are highly accurate, and they are considered to be the gold standard for bone models (84). μFE models, which are usually based on HR-pQCT of the proximal tibia and distal radius, lay out the trabecular and cortical bone morphology in detail (79), whereas hFE models, based on QCT images, do not achieve the same levels of detail (84). Several studies have assessed bone fragility in patients with AS using FEA of HR-pQCT data (8, 59). Patients with AS exhibited lower values for bone strength parameters of the distal tibia (59) and distal radius (8) than healthy controls. Besides assessing bone quality in patients with AS, FEA also provides a biomechanical model that enables creation of a 3D model of the AS kyphotic spine (89) and simulation of the effects of surgical implants on AS-related spinal fractures (90). These findings show that FEA could be used to evaluate bone fragility in patients with axSpA.

CONCLUSION

We reviewed current literature regarding imaging techniques for diagnosing osteoporosis in patients with axSpA, including more recent modalities for assessing bone quality. An increasing body of evidence shows that the inclusion of bone quality assessment by using other modalities (e.g., TBS or QCT) in traditional evaluation of BMD is essential for osteoporosis risk assessment in patients with axSpA. Future studies should focus on whether these specific imaging techniques for optimizing the diagnosis and management of osteoporosis can decrease the incidence of new fractures in patients with axSpA.

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REVIEW
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Beyond Bone Mineral Density: A New Dual X-Ray Absorptiometry Index of Bone Strength to Predict Fragility Fractures, the Bone Strain Index

Fabio Massimo Ulivieri[1*†] *and Luca Rinaudo*[2]

[1] Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Unità Operativa (UO) Medicina Nucleare, Milan, Italy, [2] Technologic Srl, Turin, Italy

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***Correspondence:**
Fabio Massimo Ulivieri
ulivieri@gmail.com
orcid.org/0000-0003-1357-3425

†Present address:
Fabio Massimo Ulivieri,
Centro per la Diagnosi e la Terapia dell'Osteoporosi, Casa di Cura La Madonnina, Milan, Italy

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For a proper assessment of osteoporotic fragility fracture prediction, all aspects regarding bone mineral density, bone texture, geometry and information about strength are necessary, particularly in endocrinological and rheumatological diseases, where bone quality impairment is relevant. Data regarding bone quantity (density) and, partially, bone quality (structure and geometry) are obtained by the gold standard method of dual X-ray absorptiometry (DXA). Data about bone strength are not yet readily available. To evaluate bone resistance to strain, a new DXA-derived index based on the Finite Element Analysis (FEA) of a greyscale of density distribution measured on spine and femoral scan, namely Bone Strain Index (BSI), has recently been developed. Bone Strain Index includes local information on density distribution, bone geometry and loadings and it differs from bone mineral density (BMD) and other variables of bone quality like trabecular bone score (TBS), which are all based on the quantification of bone mass and distribution averaged over the scanned region. This state of the art review illustrates the methodology of BSI calculation, the findings of its in reproducibility and the preliminary data about its capability to predict fragility fracture and to monitor the follow up of the pharmacological treatment for osteoporosis.

Keywords: DXA (dual x-ray absorptiometry), TBS (trabecular bone score), BSI (bone strain index), BMD (bone mineral density), osteoporosis, HSA (hip structural analysis)

INTRODUCTION

Rheumatological diseases are chronic inflammatory illnesses characterised by local and systemic multifactorial bone loss (1). Systemic inflammation, with the secretion of pro-inflammatory cytokines, and steroid drugs, frequently prescribed for the therapy, play a crucial role in the local and systemic pathogenesis of bone loss and its common manifestations, like reduced bone mass, osteopenia and osteoporosis (2, 3).

This classification of bone derangement is based on the commonly used diagnostic dual X-ray absorptiometry (DXA) method to assess bone quantity (bone mineral density, BMD), bone quality (trabecular bone score, TBS) and bone geometry (hip structural analysis, HSA) (4–6). Osteoporosis is present when BMD, expressed in standard deviation from a healthy young population, is ≤ -2.5 for postmenopausal women and for over 50 years old men, while osteopenia is defined as a T-score ≤ -1.0. For the other ages of men and premenopausal females, BMD is expressed as a standard deviation from age- and sex-matched population with the cutoff set at ≤ -2.0 (7).

Even though DXA devices are the most widespread, other methods can be used to investigate bone status. QCT (8) and Quantitative UltraSound (QUS) (9) have been applied for several years in osteoporosis management, and more recently a radiofrequency echographic technique based on the analysis of raw ultrasound signals has been proposed (10–12).

Bone involvement is a well-known implication in Rheumatoid Arthritis (RA), where systemic bone loss is one of the most common comorbidities, that starts early in disease development, even before the clinical onset of this rheumatological disease (1).

The skeletal sites affected are mainly those with cortical bone, like femoral neck and distal radius and those with prevalent trabecular bone, like lumbar spine (2, 13), with significant lower BMD values related to disease duration and regardless of treatment (14). A reduction in BMD also characterizes periarticular local bone loss in RA (15, 16), and this manifestation seems to be associated with the development of aggressive systemic disease (17). Glucocorticoids (GC) are often prescribed at a higher dose in the treatment of RA and its detrimental effect on the bone with increased risk of fragility fracture has long been documented in the literature (3). Dual X-ray absorptiometry is widely used also in rheumatological diseases to assess BMD (18), but the occurrence of fragility fractures in GC patients at higher than expected BMD, with a risk factor substantially independent of BMD, arises the question if other bone factors than density have to be assessed for a better comprehension of bone failure (19). Trabecular bone score, an indirect DXA index of bone texture, appears to be a valid index of bone quality that may explain fracture events at a higher BMD in patients receiving GC (3, 20). However, TBS, as a lumbar spine textural index, does not provide all the necessary information to evaluate the resistance of bone to compressive, torsional e flexural loads. Hip geometry is another constructive data that could be of help in understanding bone failure. Hip structural analysis derived from a DXA femoral scan provides useful parameters to assess bone resistance to flexural and torsional loads, like those acting on the femoral neck (21). Despite its premises and promises to data, there is no clear evidence that HSA is useful in RA bone assessment.

The bone quality assessment has also been considered in other rheumatological diseases, like Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SS), Ankylosing Spondylitis (AS), in order to improve fracture risk assessment. Degraded bone texture measured by TBS appears to be associated with a prevalent vertebral fracture in SLE (22). Patients with SLE also show a derangement in bone geometry, with correlation between major/hip fractures, SLE duration, steroid use and neck buckling ratio (BR), index of neck stability under axial loads, in a long follow up cohort of patients (23). Trabecular bone score has been investigated in SS with a finding of a correlation with a condition of more altered microvascular damage (24, 25). In AS patients, lower TBS is associated with vertebral fractures (26) and the severity of disease in young male (27).

Bone mineral density, TBS and HSA are undoubtedly useful, particularly BMD, to assess bone status in rheumatological disease, but from a constructive point of view, they provide incomplete information about bone resistance to load, whereas strength relating data are missing. A new DXA-derived index based on the Finite Element Analysis (FEA) on a greyscale of density distribution measured on spine and femoral scan, namely Bone Strain Index (BSI), has recently been developed. Bone Strain Index includes local information on density distribution, bone geometry and loadings and it differs from BMD and also from other variables of bone quality like TBS, which are based on the quantification of bone mass and its distribution, averaged over the scanned region. Bone Strain Index appears to be a new frontier in the bone assessment that could provide useful information to a better comprehension of bone quality derangement in rheumatological diseases. This state of art review illustrates the methodology of BSI calculation, the findings of its in reproducibility and the preliminary data about its capability to predict fragility fracture and to monitor the follow up of the pharmacological treatment for osteoporosis. The text was structured in a chapter titled "Beyond Bone Mineral Density" with three sub-chapter: the first titled "Background" with the overview of the mathematic and the physic underlying the BMD derived indexes; the second titled TBS with the description of the TBS index; the third titled "Hip geometry" with the explanation of the hip structural analysis; the fourth titles "BSI" with the description of the new DXA index and the scientific evidence published in the literature. The Authors have consulted PubMed and Scopus. The literature considered for BSI was restricted to the *in vitro* and *in vivo* clinical studies. Search terms were: bone strain index, strength index of bone and their acronyms.

Beyond Bone Mineral Density

Background

Bone is assimilable from the constructive point of view to a complex object, built with a particular design of its structure and geometry, in order to meet the mechanical and metabolic requirements that characterise its natural function. The mechanical function is primarily that of the resistance of the skeleton to loads, both compressive, torsional and flexural.

When a structure is loaded, stresses and strains are generated inside the object. The distribution of these stresses, their magnitudes and their orientations throughout the structure, depend not only on the loading configuration, but also on the geometry of the structure and of the material properties. The object is preserved until these stresses and strains remain below a certain level of solicitation named yield point, above which permanent damage starts to occur, until final fracture. Thus, despite the widespread belief in non-engineering environments, bone resistance is governed by several mechanical parameters that relate to bone density, bone geometry, internal trabecular structure and cortical thickness. Investigation and definition of

Abbreviations: DXA, dual X-ray absorptiometry; BMC, bone mineral content; BMD, bone mineral density; BSI, bone strain index; TBS, trabecular bone score; FEA, finite element analysis; FEM/s, finite element model/s; HAS, hip structure analysis; NN, narrow neck; IT, inter trochanter; FS, femur shaft; CSA, cross section area; CSMI, cross section moment of inertia; Z, section modulus; BR, buckling ratio; RA, rheumatoid arthritis; GC, glucocorticoid; SLE, systemic lupus erythematosus; SS, systemic sclerosis; AS, ankylosing spondylitis; HU, hounsfield unit; CT, computed tomography; BMI, body mass index.

these parameters are typically based on medical images, and particular attention is required to understand the appropriate mechanical meaning. Depending on the technology used to acquire the image, the quantification of these features can rely on 3D data, in case of computed tomography (CT) usage, or 2D data as traditional radiography (X-ray) and dual-energy X-ray absorptiometry (DXA).

In CT derived images, local bone material properties are typically defined by converting voxel values in Hounsfield unit (HU), to bone mineral density values (BMD) ($\rho = a \times HU + b$). Geometrical aspects of the bone, like the shape and the cortical thickness, can be accurately measured in the whole bone volume. Furthermore, models based on 3D images can directly describe the architectural design for proper evaluation of trabecular structure quality.

On the other hand, the amount of data and measures acquired in 3D, leads to high level of complexity in the analysis, that require thorough mechanical knowledge and a more in-depth evaluation in the clinical process. Several methods have been proposed in order to take into account the different aspects involved in the resistance evaluation of an object (28–30).

Classic (Euler–Bernoulli) beam theory provides a calculation method to assess the level of solicitation of a beam and has been extensively applied for stress estimation in long bones (28, 31, 32). Although methodologically straightforward, it requires the objects to be approximated as beams, sometimes resulting in an oversimplification of the real situation, especially for complex irregular bones.

Another method used in engineering is a mathematical approach called Finite Element Model (FEM) (33). The FEM concept is based on the idea that a complex problem can be divided into simpler and smaller elements that easily can be handled to find the solution. In particular, the Finite Element Model applied to structural simulation requires the definition of the object by a simple shape element mesh, the definition of the material properties and the definition of boundary conditions (constraints and forces acting on a system). As a result, stress and strain distribution inside the considered object can be evaluated for proper fracture risk assessment.

Finite Element Model has been applied for many years in the design and manufacturing processes, and still today represents the standard reference for many engineering applications. In the medical field, it was introduced first to orthopedic biomechanics in 1972 (34). Since then, it has been applied with increasing frequency, and it is still used today. In recent years several implementations of models based on CT images have been proposed (35–37).

Most of the studies were successful in showing that FEA strength predictions outperform areal BMD as a predictor for fracture for their respective datasets (8). Although the use of Finite Element Method represents a simplification of reality, the "computational cost" associated with 3D models is still too high and, to date, cannot be included in the routine clinical evaluation.

Furthermore, QCT-based finite elements models demonstrated to be extremely sensitive to the different acquisition protocols and model definitions. The positioning of the patient, the slice thickness, the field of view (FOV) and reconstruction kernel (an algorithm that filters the acquired images before reconstruction in CT acquisition), inter-scanner variation, and manual definition of boundary conditions are just some of the several parameters that could lead to errors that may vary from 4% to up to 20% (38, 39). Further aspects that limit the spreading of CT based FEM in the clinical practice for fracture risk evaluation purposes are the low availability of high-resolution CT, and major invasiveness of the examination compared to DXA (40).

2D Models are a further simplification of the reality that in the last decade has been investigated with different assumptions (41–44). Even though they all rely on DXA images or simulated DXA images, differences in the implementation and design aspects may influence results and comparisons.

Luo et al. first introduced three fracture risk indices expressed as ratios of internal forces caused by impact forces occurring in sideway fall to bone ultimate cross-section strength at the femoral neck, intertrochanteric region, and subtrochanteric region (41, 45). The proposed finite element modeling procedure was validated against six representative clinical cases, where initial and follow-up DXA images have been taken to monitor the longitudinal variation of areal BMD. It was found from the clinical validation that variations in the proposed fracture risk indices have the same trends as those indicated by the conventional areal BMD and T-score.

In the same year, Den Buijs and Dragomir-Daescu validated a two-dimensional finite element method against experimental measurements with stress test and high-speed video recording (42). In this study, femur images were derived from the projection of quantitative computed tomography scans of human cadaveric femurs, and simulated FEM results were compared with the femoral stiffness and fracture load measured. Furthermore, digital image correlation analysis was used to calculate the strain distribution from the high-speed video recordings.

Later in 2013, Naylor et al. conducted a study to investigate whether bone strength derived from FEM analysis was associated with hip fracture risk in a longitudinal study. It was found that the DXA-based FE model was able to discriminate incident hip fracture cases from controls independently from FN BMD, prior fracture, VFA, and FRAX (44).

The association of estimated strength with incident hip fracture was partially confirmed in a subsequent case-cohort study by Yang et al. finding a correlation significantly better than Total Hip BMD and FRAX, but not significantly better than FN BMD (46). In this study for each DXA image was generated a stress ratio map (von Mises stress divided by the apparent yield stress), and the estimated femoral strength was calculated by scaling the peak impact force by the minimum stress ratio in the area with the highest stress.

Although several models have been developed in the last years, and although they all agree with underlying good prediction performance vs. Bone mineral density, there is still no consensus regarding which model best can describe the mechanical behaviour of bone. Significant differences can be found in material properties assignment, loading configurations and failure criteria.

In 2016 Dall'Ara et al. conducted a study to validate DXA-based finite element models to predict femoral strength in two loading configurations [one-legged standing configuration and side fall onto the greater trochanter (47)]. In both configurations, the DXA-based FE model provided a good agreement with the experimental data and demonstrated to predict femoral strength.

In a following *in vivo* validation study, Luo et al. found that automated FE model and femoral BMD could be applied to discriminate the fracture cases from the controls with considerably improved accuracy (48).

Recently, Yang et al. and Leslie et al., proposed femoral neck (FN), intertrochanter (IT), and subtrochanteric (ST) Fracture Risk Indices (FRIs) (45, 48), based on a plane stress model and the sideways fall assumption. In this case, bone failure was determined by the ratio between von Mises stress and bone yield stress over the defined ROI (e.g., femoral neck, intertrochanter, and subtrochanteric). Even though the coefficients of variation founded for the femoral neck, intertrochanter, and subtrochanteric FRIs were 5.5, 5.8, and 8.4%, respectively, the indexes were able to further stratify risk independently from BMD and FRAX, suggesting that they could improve potentially hip fracture risk assessment.

Although many FEMs have been developed for this purpose, most of them are not routinely used in the clinic. The main reason is that the computer programs that implement FEMs have not been completely automated, and heavy training should be required before clinicians can effectively use them.

Moreover, a standard tool should be available to investigate the mechanical behaviour of both femoral and lumbar anatomic site, usually scanned with DXA examination. Despite the availability of a certain number of studies investigating FEMs performance on the femur, only a few are dedicated to models of the lumbar spine.

A single two dimensional FEM of the first to fourth lumbar vertebra was first proposed by MacNeil et al. (43). In that model, bone tissue stiffness was assigned based on the BMD of the individual vertebrae, and adjusted for patient's age. Vertebral width was not measured from the image, but assumed to be constant for L1–L4 based on the height of L1 multiplied by 1.25, and middle vertebral width was assumed to be 95% of superior and inferior vertebral width.

Axial compression boundary conditions were applied with a force proportional to body mass.

The FEM ROC curve of the overall strain demonstrated better performance compared to BMD.

Another study by Lu et al. demonstrated that the simulated DXA-based 2D FE model has a better capability for predicting the vertebral failure than densitometric measurements. Since there is currently no consensus on which failure criterion should be used for bone tissues, four different failure criteria were considered in this study: the principal stress, the principal strain, the von Mises stress and the equivalent strain. Yield stresses, Young's modulus, tensile and compressive yield strains were derived using empirical linear equations (49). One of the major outcomes of this study was that the failure loads predicted by the DXA-based 2D FE models using different failure criteria are strongly correlated with each other, demonstrating that adoption of different failure criteria has a minimal influence on the results of the 2D FEMs (50).

Another recent approach considers using bi-planar dual-energy (BP2E) X-rays absorptiometry to build vertebral FEM using sagittal and frontal plane radiographs from QCT scans (51). Compressive tests were conducted using uniform load application onto the upper surface of the specimen. Experimental vertebral strength was defined as the ultimate load achieved and axial stiffness was calculated as the slope of the linear region of the force-displacement curve. The results of this study suggest that FEMs are better experimental vertebral strength predictors than areal BMD measured with DXA.

In conclusion, although different assumptions may be used, any new FEM that use specific parameters for bone material properties, specific boundary conditions or failure criteria should be verified. The assumptions used to build the model may reflect reality in different degrees, and thus it is important to validate each model to determine its capability to predict a known outcome (52).

In the last years, a new parameter based on FEM and named BSI has been introduced (53). The Authors demonstrated a good correlation between yield strain index (calculated by using the load causing the yield in each sample) and experimental yield measured on porcine vertebra samples. As the average strain index calculated in the cited paper is closer to ultimate strength ($R^2_{adj} = 0.65$), the algorithm has then been adapted to human vertebrae, assuming a specific thickness of the model-dependent from the average width of the vertebra, from the material properties derived according to experimental Morgan equations (54), and from patient-specific loading configuration based on Han et al. study (55).

In the next sections of this work, we will investigate the basic concepts of DXA images and some of the derived indexes most used in clinical practice that demonstrated to add useful information to BMD. Dual X-ray absorptiometry is the gold standard method in clinical practice to assess and to monitor bone status, due to its high accuracy, widespread of bone densitometry, low cost and low radiation exposure (56). The measured BMD is an areal BMD (g/cm^2) and therefore differs in technical terms from the physical definition of density of an object (g/cm^3), and thus also from the volumetric BMD measured by CT.

Being DXA a projective X-ray device, the BMD measured in a district is a function of bone mineralisation (and therefore of volumetric BMD), and the amount of bone encountered in the X-ray direction, which in turn is related to the thickness (32).

As described in **Figure 1**, areal BMD can be represented by the sum of the mineral content in the X-ray direction. Bone mineral density is used in clinical routine to classify the patient in different risk classes depending on an epidemiological criterion of distribution of BMD in healthy subjects and patients affected by fragility fracture (57). Bone mineral density is also used to evaluate patient's response the pharmacological treatment prescribed to reduce fracture risk. However, assessment of BMD does not entirely explain fracture risk, since many patient fractures still occur in a population with normal or slightly reduced bone mass (58). Many other building factors of the

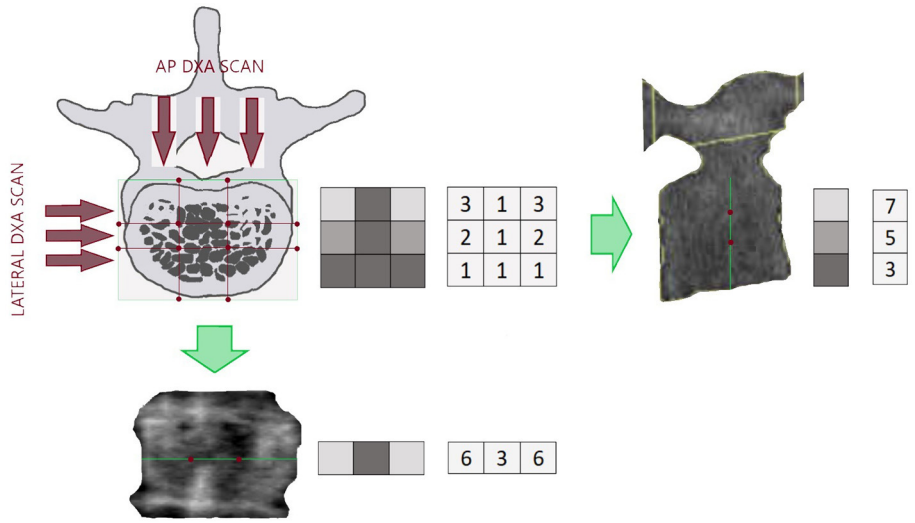

FIGURE 1 | Example of a section of a lumbar vertebra with the relating lateral DXA scan (right) and the Antero Posterior (AP) DXA scan (bottom). The green lines on the DXA images represent the projection of the lumbar section in the X-ray direction. Red points are reference points that separate areas with different density. On the right side of each picture there is a representation of BMD distribution in the investigated section and the resulting lines, being the lines the projection of the lumbar section. Density distribution is shown in a grayscale form and numerical form, to better understand how high density (light gray colored squared) and porosity (dark gray colored squared) affect the resulting images.

skeleton have to be considered to explain bone strength (59) and to improve our ability to predict structural failure. Bone mineral density provides a valuable measure of the quantity of material used in the construction, but the architecture and external loads should equally be investigated to understand if the construction is appropriately designed.

Trabecular Bone Score

The TBS is a densitometric index that can be provided automatically analysing a lumbar DXA scan. Trabecular bone score evaluates bone mineral variations in lumbar DXA images in order to describe the internal structure of the bone.

Trabecular bone score calculation is based on the fact that DXA image areas with soft gray variations are typical of a dense trabecular structure. Conversely, big dark areas are characteristic of low connectivity, low trabecular number and wide space between trabeculae (60).

Referring to **Figure 1** and keeping the same calculation method provided by Hans et al. (60) as an example, we can resume BMD and TBS different calculation as follows:

The DXA BMD resulting from the projection of the investigated lumbar section is given by summing in column (x-ray direction) the corresponding volumetric BMD

$$3 + 2 + 1 = 6$$
$$1 + 1 + 1 = 3$$
$$3 + 2 + 1 = 6$$

The BMD contribution of that line to areal BMD provided by DXA is $6 + 3 + 6 = 15$ and does not depend on bone distribution inside the section.

Conversely, TBS calculation of that line is $(3–6)^2 + (6–3)^2 = 18$, and as explained in detail by Hans et al. (60), it does depend on the distribution of bone inside the section. In this example, it demonstrates how TBS value depends on the variation of density in the three different areas in the DXA line.

Of course, being TBS based on DXA image, it is able to explain porosity and density variation in the frontal plane, but it is not able to catch porosity and density variations in the sagittal plane, that for example should be visible from a lateral DXA scan (**Figure 1**).

The calculation of TBS is based on the same mathematical matrix DXA source used for BMD measurement, but it represents a different feature of bone status and is able to discriminate between patients with similar BMD, but different trabecular microarchitecture.

Trabecular bone score can discriminate fractured patients and can predict fracture, partially independently from BMD (61). More recently, the literature demonstrates that TBS is also useful in the follow-up of the pharmacological treatment of osteoporosis (62). Trabecular bone score usage has also been investigated in rheumatoid arthritis (63) showing its ability to detect patients with vertebral fractures in osteopenic population.

Recently, TBS behaviour has been investigated on DXA knee images to examine the bone quality at the distal femur and proximal tibia regions in patients with Spinal Cord Injury (64). Even though the software has been designed for the lumbar spine, in this study the L1, L2, L3, and L4 areas have been used to identify the diaphysis, the metaphysis and the epiphysis regions. The results indicate significant differences in TBS between groups only at femoral regions, despite large reductions in BMD at both distal femur and proximal tibia.

Another recent study that evaluates TBS performance on the distal femur and proximal tibia regions has been performed on patients that underwent Total Knee Arthroplasty (65). A TBS texture Research Investigational Platform (TRIP) that allows assessment of many skeletal sites has been used on DICOM images, observing lower values in the surgical leg, consistent with the bone loss that follows TKA (65).

Further research will be necessary to determine if TBS measurement at the knee, or other regions, may complement and strengthen fracture risk assessment.

Hip Geometry

Despite the predominant role that material properties, and thus BMD, had in fracture risk assessment, geometry and size are fundamental parameters that rule the mechanical resistance of the bone (66). In the last years, HSA programme has been proposed to provide a structural description of the proximal femur, and further improvement of fracture prediction (32). This method uses a proximal femur DXA image to extract information about cross-sectional geometry in three different regions of interest: the narrowest portion of the femur neck: narrow neck (NN), the inter-trochanteric region (IT) and the femoral shaft region (FS). For each location, the distribution of the bone mass is computed, and femoral mechanical properties are derived from femur geometry (**Figure 2**).

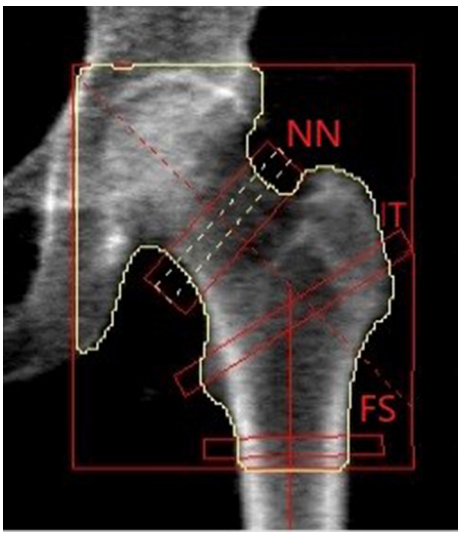

FIGURE 2 | Hip image from a Hologic DXA scanner showing positions of thin analysis regions across the femur at the neck (NN region), intertrochanteric (IT), and shaft (FS).

Hip structural analysis parameters are Cross-Sectional Area (CSA), indicative of the bone surface area in the cross-section; Cross-Sectional Moment of Inertia (CSMI), that describes how the bone mass is distributed around the femoral axis; Section modulus (Z), that indicates the maximum bending stress.

Under compression condition, forces parallel to the long axis are uniformly distributed over the surface of the cross-section (CSA). Conversely, considering bending loads, the resistance of bone varies at the square of the distance from the neutral axis. Thus, bone near the outer surface contributes to bone strength much more than bone near the femoral axis.

Considering that the femoral internal stresses and strains generated by external forces are mainly due to compression and bending (67), the higher are CSA and CSMI, the better is bone resistance, respectively, to axial compression and bending.

Another critical parameter provided by HSA is the ratio of the outer radius to the cortical thickness, named buckling ratio (BR). In engineering, buckling indicates a sudden collapse of an object subjected to an axial load, before the axial compression stress reaches the stress limit. If the ratio exceeds a factor of about 10, the cross-section begins to lose strength through susceptibility to local instability (32).

Studies showed that HSA results are important in predicting the occurrence of hip fracture (68, 69). However, the usage in clinical practice is still limited by the problematic interpretation of the several structural parameters associated with measured BMD and lack of evidence in clinical practice regarding fracture prediction (5).

Also International Society for Clinical Densitometry (ISCD) guidelines recommends that at this stage HSA parameters should not be used to assess hip fracture risk (70). Conversely, it has been reported in this official positions that Hip Axis Length could be clinically useful, being significantly associated with a fracture in various populations.

Another geometric parameter that can be automatically obtained by DXA images is the Neck shaft angle, but it is not yet clear if it can be used in clinical practice as a fracture risk parameter independent from BMD (70).

A New Index of Bone Strength: The Bone Strain Index

Over the past few years, FEM based on DXA images had particular prominence (30, 46). Considerable effort has been directed toward a variety of patient-specific structural engineering and FEMs of the proximal femur to estimate femoral strength and to assess hip fracture risk. However, just a few studies deal with the lumbar anatomic site. Recently, a new bone FEM structural DXA parameter named BSI, has been proposed in order to improve fracture risk prediction and take into account all the features involved in bone strength (53). Bone Strain Index calculation can be obtained in <10 s ($=10$ second) directly from images generated by DXA device (71). The automatic FEA uses a constant strain triangular mesh following the contour of the bone segmented by DXA dedicated software. The derived image is analysed building a separate model for each vertebra with the load applied to the upper plate and the constraints to the lower plate, according to the model described by Colombo et al. (53).

The thickness of the plane stress model is calculated from the average width of the vertebra, and material properties are assigned to each element according to the experimental formula provided by Morgan et al. at the lumbar site (54). The force acting on the upper plate is derived from simulated forces in standing position and for patient-specific weight and height (55).

Regarding the femoral region, BSI is calculated on the hypothesis of a sideway fall condition with constraints placed on

the head and on the lower part of the shaft, and a force applied to the greater trochanteric area, according to Terzini et al. (72).

The thickness of the model is derived from the width of the central area of the neck region accordingly to previous studies (44, 46). Even for this anatomical site, the relations used to calculate the stiffness of each element of the model have been derived from the experimental equations in Morgan et al. study (54).

In both cases (lumbar and femoral), BSI represents the average equivalent strain inside the bone, with the assumption that a higher strain level (high BSI) indicates a more significant risk condition. Differently from the calculations provided in previous FEA studies regarding femoral region (44, 46, 72), the calculated BSI is not related to a specific strain/strength limit, according to the last studies focused on the lumbar region (73). No strain limit has been considered in the calculation of both parameters since specific strain distributions and limits should be found for different kind of populations depending on sex, age and pathology (52, 74, 75). Furthermore, yield point and stress-strain limits, in case of bone, are dependent on the material and on mineral composition (49, 76).

Being BSI a strain, this parameter is unitless because it refers to the variation of the size related to the original size ($\varepsilon = dl/l_o$, where dl is the change of length and l_o is the initial length), and thus normally is expressed in percentage.

For easy reading, the average strain in the lumbar area has been expressed in percentage and multiplied by 100, whereas femur bone strain values must be intended as the percentage multiplied by 10. This order of size difference is expected because, accordingly to the models adopted so far, lumbar simulation is conducted in stand-up condition, whereas femur simulation is conducted in sideways fall, with higher forces acting on the bone.

The information provided by DXA through BMD, TBS and BSI describes the same situation from a different point of view. To understand what each tool provides to the clinician, one has to consider a parallelism with two horizontal structures that must support the weight of two different persons.

As shown in **Figure 3**, BMD describes the material (e.g., wood or concrete), whereas TBS is an independent parameter that illustrates the different inner structure of the two beams. In both cases, detailed geometry information and load definition are missing. To access a complete view of the situation, we should take into account all the above variables to evaluate the proper mechanical behavior and the risk of failure.

Bone Strain Index calculation is obtained using a constant strain triangular mesh following the contour of the bone segmented by DXA software. Bone Strain Index model relies on a triangular mesh built around the bone segmented in DXA software. Each triangle of the model has an Elastic Modulus depending on the BMD of the object, according to Morgan et al. equations (54).

The force acting on the object is precisely calculated and based on each patient's height and weight. Furthermore, the distribution of the strain is represented on the object showing the location of the most stressed region. If BMD can be defined as a bone quantity value and the TBS as a bone quality value, BSI should be described as a bone strength value, being its nature related to the capability to withstand an applied load.

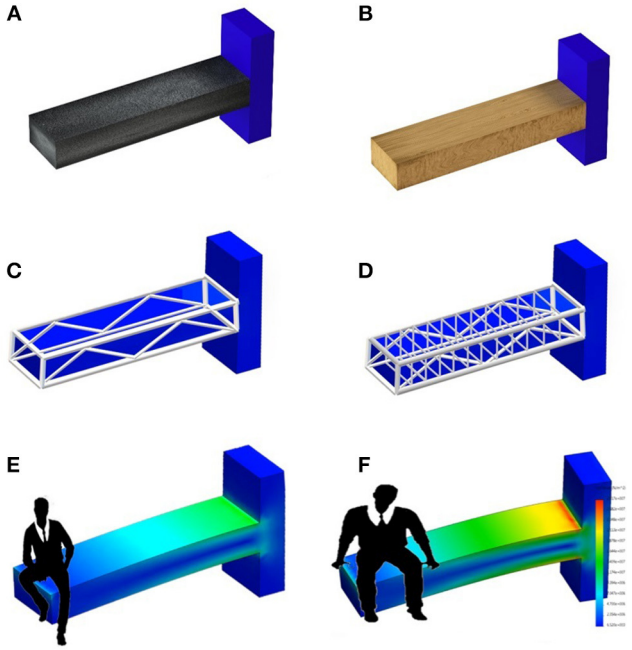

FIGURE 3 | Example of the information level provided by BMD, TBS and BSI related to a man sitting on a beam. **(A,B)** Show the difference in materials (e.g., concrete and wood) that can be assessed by BMD DXA measurement. **(C,D)** Relate to internal structure design showing a difference between a dense and a sparse structure, and using the same concept of TBS. **(E,F)** Show the stress-strain status of a bar made up of a specific material and with a specific structure, with two different people sitting on the top. The information provided by **(E,F)** is the same provided by BSI.

Figure 4 shows a comparison between DXA image, TBS image and BSI image with a superimposed triangular mesh. Trabecular bone score image shows in red the areas with low TBS values and in green the areas with high TBS values, where TBS value is based on the variations of gray level related to the trabecular structure, as previously explained.

Bone Strain Index image, conversely, represents the strain distribution inside the object with a colour scale that goes from blue/green (low strain) to yellow (mid strain level) and red (high strain), as shown in **Figure 5**.

Since trabecular distribution in the femur region is asymmetric and more complicated, no TBS-like evaluation has yet been developed for femoral trabecular structure. Conversely, BSI evaluation for femoral region follows the same criteria used for the lumbar region, except for material properties and boundary conditions.

An example of BSI calculation of right and left femur is presented in **Figure 5** without the superimposed mesh.

Recent clinical studies have investigated the usefulness of BSI to identify the osteoporotic patient's subgroup particularly prone to fragility fractures (77) and to predict further fragility fractures (73, 78) (**Table 1**). Ulivieri et al., using artificial neural network

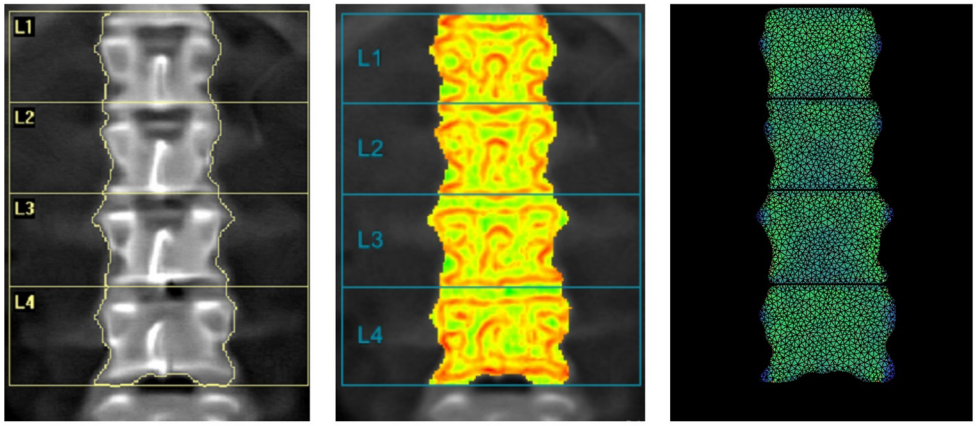

FIGURE 4 | Example of images provided by DXA: BMD L1L4 = 0.868 g/cm^2 (left); TBS L1-L4 = 1.361 (center) and BSI L1L4 = 1.57 (right).

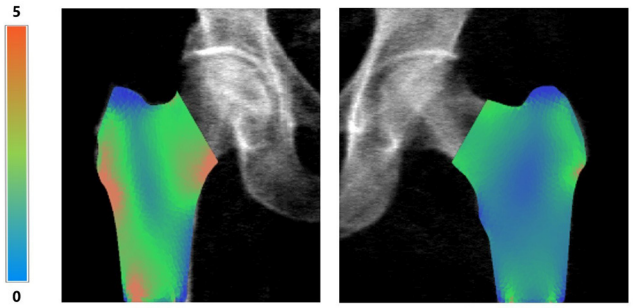

FIGURE 5 | Examples of right femur BSI analysis (on the left, BMD total value = 0.55 g/cm^2, Femur BSI = 2.09) and of left femur BSI analysis (on the right, BMD total value = 0.82 g/cm^2, Femur BSI = 1.29) of two different patients. The heat map related to the strain distribution shows a major strain concentration on the red area. The head of the femur is not represented because the colored regions represent the same regions identified by DXA analysis (neck, intertrochanteric and trochanteric).

analysis (ANNs), investigated 125 consecutive postmenopausal women assessing bone quantity and quality DXA parameters, biochemical markers of bone turnover and clinical data. A low fracture risk seemed to be related to a low carboxy-terminal cross-linking telopeptide of type I collagen level, whereas a positive Romberg test, together with compromised bone strength DXA parameters (high lumbar BSI), appears to be strictly connected with fragility fractures, indicating in this way the path that leads to fragility fracture in a postmenopausal population (77). More recently, Messina et al. have demonstrated in a multicentric validation study, that lumbar BSI is an independent predictor of a subsequent fragility re-fracture (78). The Authors investigated 234 consecutive fractured patients with primary osteoporosis who performed a spine X-ray for the calculation of Spine Deformity Index (SDI) and DXA densitometry for BMD, TBS and lumbar BSI measurement at the basal time and in the follow up at each clinical check. A subsequent fracture has been considered as one unit increase of SDI. For each unit increase of the investigated indexes, the univariate hazard ratio of re-fracture, 95% CI, p-value and proportionality test p-value are: for age 1.040; 1.017–1.064; 0.0007; 0.2529, respectively, and for lumbar BSI 1.372; 1.038–1.813; 0.0261; 0.5179, respectively. Lumbar BSI remained in the final multivariate model as a statistically independent predictor of a subsequent re-fracture (1.332; 1.013–1.752; 0.0399) together with age (1.039; 1.016–1.064; 0.0009. Multivariate model proportionality test p-value was 0.4604.

Lumbar BSI also recently demonstrated its ability to characterise young patients affected by secondary osteoporosis (77, 79) (**Table 1**). As regard patients affected by mastocytosis the Authors found a relation between lumbar BSI and severity of bone deteriorating involved in 96 consecutive patients (46 women and 50 men) affected by cutaneous (CM) or systemic (SM) mastocytosis. Tryptase was inversely correlated with lumbar BMD ($r = -0.232$; $p = 0.022$) and TBS ($r = -0.280$; $p = 0.005$), and directly with lumbar BSI ($r = 0.276$; $p = 0.006$). Lumbar BSI remained statistically significant ($p = 0.006$; adjusted $R^2 = 0.101$) in the multivariate regression model with Tryptase as dependent variable, being lumbar BMD and TBS not statistically significant. Tryptase increased about 22 units for each unit increase of lumbar BSI. Moreover, lumbar BSI was statistically lower in women than in men, suggesting that men have a worse lumbar bone resistance to compressive loads, according to the more severe bone involvement of mastocytosis in the male sex (79) (**Table 1**).

Another aspect that contributed to DXA conventionally established as the gold standard method for the diagnosis of reduced bone mass and its follow up is the higher reproducibility and precision (80). International Society for Clinical Densitometry states that precision is defined as the ratio between standard deviation and mean (CoV). Per cent least significant change (LSC%) is calculated as 2.77 × CoV, and reproducibility is calculated as the complement to 100% of LSC% (7). Usually, BMD reproducibility is known to be very good and typically represents the standard of reference for other

TABLE 1 | Bone Strain Index reproducibility and clinical studies.

Topic	Author	Year	Patients no.	Main findings
In vivo reproducibility	Messina et al.	2020	30	BSI *in vivo* reproducibility of Total Femur (CoV = 3.89%, reproducibility = 89.22%) was better compared to that of Femur Neck (CoV = 4.17%, reproducibility = 88.46%).
Prediction of vertebral re-fracture (multicentric retrospective study)	Messina et al.	2020	234	BSI hazard ratio (95% CI) of incident re-fracture for each unit increase was 1.372 (1.038–1.813), *p*-value = 0.0261, proportionality test *p*-value: 0.5179.
Bone geometry and structural indexes in Mastocytosis (retrospective study)	Ulivieri et al.	2020	96	Tryptase showed a statistically inverse correlation with Lumbar Spine BMD ($r = -0.2326$; $p = 0.0226$) and with TBS ($r = -0.2801$; $p = 0.0057$) and a direct correlation with Lumbar BSI ($r = 0.2759$; $p = 0.0065$). In the multivariate regression model only the Lumbar BSI remained statistically significant in systemic Mastocytosis ($p = 0.0064$) and non-systemic Mastocytosis ($p = 0.0338$).
Prediction of vertebral re-fracture (multicentric retrospective study)	Ulivieri et al.	2020	143	The hazard ratio of re-fracture for each unit increase of BSI, BMD and TBS were, respectively, 1.201, 0.231, and 0.034. BSI resulted in being the nearest to the statistical significance to predict a re-fracture, with greater values associated with higher re-fracture risk.
DXA parameters response to Teriparatide (retrospective study)	Messina et al.	2020	40	In the entire population, the ameliorations after therapy regarded BSI (-13.9%), TBS (5.08%), BMD (8.36%). Significant HSA variations were shown only at the femoral shaft, but of very small entity [FS_BMD (0.23%), FS_CSA (−0.98%), FS_SEC_MOD (−2.33%) and FS_BR (1.62%)].
In vivo reproducibility	Messina et al.	2020	150	BSI best reproducibility value was observed in the group with BMI between 25 and 30 kg/m^2 (CoV 1.97%, reproducibility 94.5%), while the worst was in the group with BMI > 30 kg/m^2 (CoV 3.96%, reproducibility 89.0%). BSI reproducibility progressively worsened from lower BMI to higher BMI, but the amount of this reduction was never statistically significant.
In vitro reproducibility and soft tissue thickness influence	Messina et al.	2019	Phantom based study	The highest value of BSI reproducibility was 98.3% (1-cm soft tissue thickness, HD-mode), whereas the lowest one was 96.1% (6 cm soft tissue thickness, HD-mode). Variations between scans with superimposed 0–6 cm thickness of soft tissue were between 0.76% and 1.46% for BMD, and between 1.03% and 1.57% for BSI.
DXA derived parameters in haemophilic patients (retrospective study)	Ulivieri et al.	2018	70	A reduced bone mass was present at the femoral neck in 55.7%, at total femur in 18.6%and at the lumbar spine in 54.3% of patients. Lumbar spine BMD, TBS and lumbar BSI did not correlate with HJHS (Hemophilia Joint Health Score). HSA bone geometric parameters correlated negatively with HJHS.
Clinical observational retrospective study	Ulivieri et al.	2018	125	A low fracture risk seems to be related to a low carboxy-terminal cross-linking telopeptide of type I collagen level. In contrast, a positive Romberg test, together with compromised BSI, appears to be strictly connected with fragility fractures characterizing the pathway leading to fracture in postmenopausal women.

DXA-based measurements. This has been recently confirmed by Messina et al. BMD reproducibility ranging around 99% in all the densitometric scan modalities, while the reproducibility of BSI is lower than that of BMD being the CoV found between 0.6 and 1.4% and the LSC about three times higher than that of BMD (81, 82).

An overview of BMD and BSI *in vitro* and *in vivo* precision is reported in **Table 1**. For what concerns *in vivo* results, a comparison between different BMI groups and different waist circumference is reported in Messina et al. study, where almost the same difference between BMD and BSI reproducibility has been found on the previous phantom study (83). Worse reproducibility compared to BMD has been already investigated in other bone quality parameters (84, 85), suggesting that BMD measurement still represents the best choice for detecting small bone variation in the disease's follow up. Despite this, not necessarily BMD small variations result in significant changes in bone structure and bone strength, as indicated by the TBS and BSI LSC. Thus, these investigation tools maintain unaltered their ability to describe bone quality and bone strength status but require a longer period to observe significant variations.

Moreover, reproducibility of all DXA parameters (BMD, TBS and BSI) slightly worsen in obese patients and in those with the greater waist circumference. This behaviour can be commonly justified by the soft tissue superimposed to the bone, that affects the x-ray image generating noise and reducing image quality and accuracy (86).

A recent clinical study validated the BSI ability to monitor the effect of anabolic treatment for osteoporosis (87). Forty osteoporotic patients with fractures were studied before and after 2 years of daily subcutaneous 20 mcg of teriparatide and BMD, HSA, TBS, and BSI were measured. Both classical statistical approach and ANNs were used for the analysis that demonstrated a significant amelioration after therapy regarded BSI (−13.9%), TBS (5.08%), BMD (8.36%). Dividing patients into responders (BMD increase >10%) and non-responders, the first presented TBS and BSI ameliorations (11.87% and −25.46%, respectively, while non-responders presented an amelioration of BSI only (−6.57%). This finding suggests that an increase in bone strength may explain the known reduction in fracture risk not merely justified by BMD increase.

The limitation of all the reported clinical studies is the utilized samples size, if compared to the magnitude of the cases involved in BMD and TBS studies. However, it must be considered that BSI is a recently proposed index and the validation studies on large case series, of thousands of patients, require a long time, and they are still in progress.

The Frontiers of DXA in Rheumatology

Rheumatological diseases present bone involvement characterise not only by bone quantity but also by bone quality impairment. Osteoporosis secondary to rheumatological diseases is a multifactorial local and systemic pathology aggravated by the intake of glucocorticoids which represents one the more significant factor interfering with bone resistance to load and fatigue. The amount of bone, its spatial distribution, its geometry and its strength determine skeletal resistance to load and fatigue and a complete clinical assessment of fracture risk needs to identify and measure all these characteristics. Trabecular bone score, nowadays, is a widely studied bone textural index, able to discriminate fractured patients and to predict fracture both in primary and in secondary osteoporosis where bone architecture is damaged. Hip structural analysis needs further evidence of its ability in bone geometry assessment and fracture risk prediction.

Bone strength is the last field where knowledge is necessary to understand all the physical implications of bone resistance to loads and fatigue in order to provide the medical clinician with all what is necessary to manage better patients affected by rheumatological diseases. BSI appears to be a powerful index of the strength of the bone that will provide informations on the physics of the skeleton resistance to the loads that are still lacking.

AUTHOR CONTRIBUTIONS

FU and LR have conceptualized and written the manuscript. Both authors contributed to the article and approved the submitted version.

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REVIEW
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The Patellar Resurfacing in Total Knee Prosthesis: Indications for Bone Stock and Patellar Morphology

Luigi Molfetta[1], *Andrea Casabella*[1]* *and Augusto Palermo*[2]

[1] DISC Department, Research Centre of Osteoporosis and Osteoarticular Disease, School of Medical and Pharmaceutical Sciences, University of Genoa, Genoa, Italy, [2] Unit of Orthopaedic Surgery, IRCCS Istituto Auxologico Italiano, Capitanio Hospital, Milan, Italy

The patellar resurfacing is still a controversial and unresolved problem. The choice to use the patellar resurfacing in the total knee prosthesis (TKP) is decided by the surgeon's experience; he analyzes the thickness, the shape, consumption of the surface and he chooses the use of patellar resurfacing or to limit itself to cheiloplasty, denervation, or often to the release of the lateral wing ligament. He also assesses the metabolic state of the bone linked to Osteoporosis and the potential fragility of the joint and kneecap in particular. Bone loss after total knee arthroplasty (TKP) may lead to periprosthetic fractures that are associated with significant costs (morbidity, economic, etc.) and pose a challenge to operative fixation. The literature doesn't express a definitive judgment on the two options, since the results can be overlapped on average. Each option has advantages and disadvantages to be considered in the overall balance of the patellar operation. In reality, however, this technical choice requires more consolidated decision-making criteria so as to minimize the incidence of post-surgical femoral-patellar pain syndrome, the second cause of failure, which frequently leads to revision of the implant. The balance between experience and evidence can be a compromise in the choice of surgery. The experience documented in the literature must identify the parameters capable of constructing an algorithm aimed not only at the secondary resurfacing rate, but at the overall clinical evaluation. This has implications also for the rehabilitation of these patients after surgery.

Keywords: knee, prosthesis, patellar resurfacing, anterior pain, revision, osteoporosis

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Barbara Ruaro,
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Roberta Bruno,
University of Genoa, Italy

***Correspondence:**
Andrea Casabella
andrea.casabella@unige.it

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INTRODUCTION

The management of the patella in total knee prosthesis (TKP) remains controversial. Some surgeons prefer the Patellar Resurfacing (PR) to counter the increase in revisions or other interventions and reduce the incidence of anterior knee pain such as in prosthesis without patellar resurfacing (NR). Other surgeons don't use the prosthesis to avoid complications such as fractures, tendon damage and secondary instability (1). In this procedural dichotomy we summarize the problem of the patella in the TKP. Since the 1980s, with the optimization of the design of the PTGs, the problem of the patella prosthesis has been posed, correlated with the incidence of postoperative anterior pain, which is not only patellar but multifactorial.

The average rates of PR vary in the various international cases; Fraser et al. have documented that in the period 2004–2014 the percentage of PR ranged from 4% (Norway) to 82% (United States), with Sweden between 15 and 2%, and Australia between % and 59% and with a global percentage value of 38% of PR in all registers outside the United States in 2010 (2).

Therefore, it is not a simple surgical option; it is based on the indication, on the technique, on the foreseeable outcome and today on the possible legal medical judgment.

The femoral-patellar pain in the TKP frequently leads to revision of the implant with the secondary patella operation, in variable percentage, up to 20%; it represents by implication the second cause of failure of the TKP (3, 4). Numerous randomized and controlled trials with a final end-point related to the clinical picture or to the prosthetic revision document this concept. Burnett et al. (5) in a randomized trial show the statistically significant equivalence between the two NR and PR groups about ROM, the clinical score, global and patella femoral pain and patient satisfaction; on the contrary, the revision rate (12%) in NR vs. (9%) R is higher. The same conclusions are reached by Ikejiani et al. (6) who in a retrospective study show that PR does not seem to influence clinical outcomes ROM, pain and postoperative complications. A dynamic-kinematic study conducted on NR and PR plants Pollo et al. (7) exclude statistically significant differences in groups about the biomechanics of walking, climbing stairs and getting up from the chair.

The surgeon doesn't use prosthesis of patella when it appears in good condition with not serious chondropathy, with good frontal alignment, of not excessive thickness, of good size, in right height, in young, not obese patient. Currently over 20 million people in the world have knee or hip joint arthroplasties, and unfortunately, there is a rise in periprosthetic fractures. The majority of these cases are fragility fractures which are difficult to manage surgically and are associated with high costs, prolonged length of stay, and poorer outcomes. Approximately one quarter of patients with osteoarthritis awaiting lower extremity arthroplasty have concomitant osteoporosis. Major risk factors for fracture are older age, female gender, and presence of osteoporosis which are common in those undergoing total knee arthroplasty (TKP). A potential strategy to reduce periprosthetic fracture risk is to identify suboptimal bone status and provide appropriate treatment if indicated. A frequently overlooked factor is the joint osteometabolic state and patella in particular. The flogosis present in the gonarthritis, especially in the most advanced states, characterizes not only the condropatia femoro-rotulea, it lacks the suffering of the subcondral bone that at RM is highlighted as Bone Marrow Lesion. In our experience, postoperative fragility fractures after TKA occur almost exclusively on the ipsilateral side. The etiology of these fractures is likely multifactorial (e.g., altered gait mechanics increasing ipsilateral falls); however, these events may be related to post-surgical weight-bearing changes through an implant leading to decreased ipsilateral BMD. Previous studies with small sample sizes have reported a decrease in ipsilateral distal femur BMD ranging from 1 to 44% (8, 9). However, there are no large studies that report results from multiple patient populations, surgeons, and implant designs. The verification of the good kneecap tracking and the absence of distal inpingment of the patella comfort the surgeon in the choice of non-prosthesis (10). Are these clinical elements sufficient to justify the choice of NR, or should we refer only to the percentage fear of secondary patellar resurfacing?

PATELLAR RESURFACING VS. NOT RESURFACING

The patellar resurfacing requires a preliminary evaluation of the functional anatomy of the knee in the prosthesis. In the clinical examination, femoral-patellar arthrosis has a different clinical profile for each patient for anterior pain intensity: pain-starter, difficulty in descending the stairs, hypo or immobility of the patella, size of the same compared to the lateral counter, etc. Preoperative pain, obesity or the degree of intraoperative chondromalacia have absolutely no predictive value of the possible anterior pain syndrome or a possible high need for secondary implant revision as pointed out by Barrach et al. (11) and by Marcacci et al. (12). From the clinical point of view, the presence of an evident painful anterior component of the degenerated knee (primitive or secondary) is a factor which generally suggests for PR. Radiographic examination of the patella in lateral and axial vision at 30° allows a more detailed morphological evaluation of thickness, height or osteophytosis. About the thickness of the patella, in cadaver studies, have shown as 5 mm thick plus 30% increase in contact stresses in knee flexion (13). The thicker patella limits the recovery of postoperative flexion and obliges the forced mobilizations for rigidity while the lateral osteophytosis influences the frontal kinematics of the quadricipital apparatus.

The CT better highlights the morphology of the patella and its relationships with the femur (14), just as the SPECT / CT method has been demonstrated in the study by Slevin et al. an ideal imaging modality for the evaluation of patellar-femoral disorders before and after TKP (15).

The thickness of the patella is the main element for the choice; 26 mm for men and 23 mm for women are the thicknesses, calibrated intraoperatively, of reference beyond which the surgeon must pose the problem, under which he can neglect it. According to Roessler et al. before the primary TKP, the inclination, the width and the thickness must be measured for the possible risk of post-surgical resurfacing (16). The thickness then correlates with the holding of the patella abutment resected for a possible secondary fracture. The thickness of the patella, although optimized, may not be sufficient if the femoral component is oversized and therefore thwarts the good technical gesture on the patella. Hsu et al. (17) confirm the need to reproduce the same pre-operative thickness in the PR; the decrease in thickness reduces the pressure, but increases the risk of fracture; an increase in thickness increases the low-bending quadricipital lever arm, but reduces the Range of Motion (ROM), as the compression forces increase 70 and 95° (18).

The position of the patella evaluated in the lateral radiograph according to various criteria, the main one of which the Insall-Salvati (19) correlates with the kinematics of the prosthesis

itself; a low patella can create a distal impingement with component wear and a severe risk of separation. The correct femoral-patellar ratios provide that the patellar prosthesis should be placed on the resection area mainly in the upper middle and the more lateralized femoral component placed in external rotation, so as to ensure a more physiological patellar tracking. Therefore, it is necessary to avoid the flexion of the component, its anterior projection, the intrarotation or the medialization, negative factors for the kinematics and for the survival of the patellar component. Intrarotation is a negative factor of particular importance, well documented by Berger (20); the degree of rotation always greater, from 1 to 4°, 3 to 8°, or >8°, involves, respectively, a painful condition, the subluxation or the luxation with mobilization of the liner. The patellar prosthesis is therefore also influenced by the height of the articular line; a "high" rhyme due to excessive femoral resection creates greater ligament pararotulea tension and therefore pain; more important is a "low" patella for excessive tibial resection because it induces an impingement with the polyethylene insert. Figgie et al. establish the minimum limit of the joint interline in 8 mm which does not cause undesirable effects (21).

The deformation of the patella evaluated intraoperatively constitutes a further element of choice. The prosthesis becomes necessary when the shape of the patella is concave or flat; in this case the patellar tracking becomes impossible or in any case already predisposed to subluxation.

The degree of chondropathy according to Rodriguez-Merchan et al. obliges the patellar resurfacing; in grade IV, the revision rate of prosthesis in the study was 10 times greater (11.6%) than in the group with lower grade chondropathy (0.6%) (22). The same conclusion was reached by Schroeder-Boersch et al. (23) in a randomized 2-years study; the prosthesis in advanced patellar arthritis guarantees better functional results. The diagnosis of rheumatoid arthritis (RA), due to the peculiar condition of osteoporosis and of anatomical and pathological damage, makes the decision more problematic. Kawabubo et al. (24) analyzing the radiographic changes of the patella in the TKP of patients with RA, considers the mandatory resurfacing. On the contrary, the retrospective study by Seo et al. (25) shows instead that there is no correlation between the degree of articular defect and the patellar resurfacing in terms of clinical and radiological outcomes. Certainly the surgical gesture toward the anterior femoral patellar compartment is complex and also concerns the soft parts. Hwang et al. (26) have stated that the positive role of soft tissue balancing and prosthetic design can orientate toward a kneecap -plasty, even in the knees with severe f kneecap - femoral arthrosis. The patellar denervation with electrocautery was studied in a meta-analysis by Li T. et al. for the purpose of evaluating the reduction of postoperative pain in the anterior knee (Anterior knee pain = AKP). In the five randomized controlled trials (RCTs) with 572 patients and 657 knees, perirotuleal denervation was associated with improved pain and postoperative articular function, whereas complications did not differ significantly between the two groups (27). Denervation therefore supports the choices on resurfacing but is not a clear alternative to prosthetics.

The prosthetic design concerns the geometry and the shape of the components, especially of the femoral shield, in relation to the depth and width of the femoral throat and to the symmetry or not of the patellar pattern. Rader et al. have shown how the matel-backed of the patella component can affect the failure rate equal to 8.4% from 12 to 24 months, up to 33.3% after 6 years, with a 10-years projection of 50% of failure (28). Braakmann et al. analyzed the patella in poly, metal-backed and non-resurf and concluded that no difference exists in the three groups about ROM, stability, movement deficit, pain, alignment, walking distance and use of walking aids (29). Studies on total knee arthroplasty with LCS bearing have shown the importance of soft tissues, in particular ligaments, in the decision for patellar resurfacing or not (30).

PATELLAR RESURFACING AND COMPLICATIONS

The patellar resurfacing in PKT is inspired today, above all, by the surgeon's experience. Post-surgical anterior pain according to Burnet shows no statistically significant differences in PR and NR patients (5). Calvisi et al. in a study conducted on 5 meta-analyzes, a systematic review and six randomized trials, conclude that non-resurfacing leads to a higher incidence of pain, less surgical satisfaction, even if at the same recovery of the ROM (31). Breeman et al. in the largest randomized controlled trial of PR reported to date, the functional outcome, the rate of new intervention and the cost of total health care 5 years after total knee arthroplasty weren't significantly affected by the addition of resurfacing patellar to the surgical procedure (32). Functional results and subjective satisfaction are equivalent in the two strategies; however Barrack et al. they show how the possibility of secondary prosthesis due to post-prosthetic pain (11) increases in the NR patella. However, Bonnin et al. emphasizes that in the prosthetic patella but with insufficient or asymmetric bone resection, the revision percentage nevertheless reaches 5%; in this case the prosthesis is less complex and difficult than the revision of a patellar prosthetis (33). The surgeon who prosthesis the patella knows that he has to face his complications. The mobilization of the patellar prosthesis is generated by numerous causes: the metal back stimulates it up to 15% compared to polyethylene (4%), while the considerable thickness of the prosthetic patella increases the contact and cutting forces and therefore stimulates the separation (5). It should also be considered the metabolic state of the bone, as a pathogenic moment of cleavage for poor bone-prosthesis or bone-cement-prosthesis integration. Nonetheless, orthopedic surgeons, particularly those caring for patients with advanced knee OA, have shown relatively little interest in the management of osteoporosis. This may be due to the traditionally held belief that patients with advanced knee OA are less likely to develop osteoporosis. Several previous studies have reported the existence of an inverse relationship between osteoporosis and OA, particularly in the hip and knee Furthermore, a higher body mass index has been reported to increase the risks of the development and progression of OA of the knee but to decrease the risk of osteoporosis. Clements et al. (34) report the revision

rate of 3.1% in NR and 5% in PR for 5 years. With reference to the anterior pain, the revision rate was 17% in NR and 1% in PR. Burnett et al. refer to differences between NR and PR that are not significant for ROM and patient satisfaction; for the anterior pain the difference between NR and PR was 12 and 3%, respectively; finally, the revision rate between NR and PR was 12 and 9%, respectively (35). The fracture of the patella, the most fearful complication, can occur intraoperatively or postoperatively with a stimulated frequency around 3%; it recognizes numerous pathogenic factors, such as the thickness of the patella due to excess of resection, osteoporosis, the technical gesture, revision, maltracking, denervation, and oateometabolic suffering related to the presence of district bone edema or the condition of general and joint osteoporosis. A considerable proportion of elderly female patients with advanced knee OA undergoing TKA also have osteoporosis. These anecdotal observations seemingly contradict the previously held inverse relationship between knee OA and osteoporosis. However, this inverse relationship had been demonstrated by the studies using community-based populations with various stages of OA and it is still unclear whether this relationship would also be found in patients with advanced knee OA undergoing TKA. If our observation is the case, more functional deterioration in the knee OA patients might be related to lower bone mineral density (BMD). However, little information is currently available regarding this speculation (36).

DISCUSSION

The analysis in Literature of the problem offers substantially overlapping results in the various systematic reviews, Cochrane or randomized studies. Both the PR and NR options can be used. Thus, post-prosthesis anterior pain and secondary resurfacing risk are the dominant elements of systematic analysis of knee prostheses. Each meta-analysis oscillates between the disadvantages of NR compared to the incidence of surgical revision and the disadvantages of PR over complications of kneecap prosthetics. There were no significant differences between PR and NR about the incidence of anterior knee pain; a higher rate of reoperations was observed in the NR group. The model of total knee replacement does not influence the incidence of secondary resurfacing; Pavlou et al. analyzed 18 randomized controlled trials of level I with a total sample size of 7,075 knees (3463 PR and 3612 NR), in order to reoperation rate, to anterior pain and to functional scores as outcome measures. The increased incidence of re-operations in the NR group should be considered simply as an additional surgical option for the treatment of anterior knee pain after TKP, thus artificially increasing the rate of re-interventions in the NR group (37). Longo et al. in the PR group they showed significantly higher postoperative pain with higher incidence of revision of the NR group (6.9 vs. 1%), concluding that primary resurfacing is the most effective option (38). Despite the same conclusions, Kai Chen et al. referring to a meta-analysis of 1,725 randomized trials, they consider the risk difference related to reoperation should be evaluated (39); Fu et al. (40) found that 76% of patients with postoperative anterior pain benefit from secondary resurfacing vs. a negative 24%. Post-prosthetic anterior pain is certainly a less parametric clinical parameter than the percentage statistic incidence of revisions. Fu et al. (40), He et al. (41), and Li et al. (42) they found no difference between the groups (PR and NR) in terms of anterior knee pain, but only in terms of increased risk of revision; Lindstrand et al. (43) documented the same incidence of revisions between the two groups. A prospective study by Patil et al. (44) related to three groups (PR, NR, and patelloflex) documented an improvement in the KSS scores and the patient satisfaction index, as well as a systematic review of 20 randomized controlled trials, whereby the reoperation rate of the patellar resurfacing group was lower than the non-resident group in the 1–2 year, follow-up; the differences disappeared and the incidences over 2 years equalized (45).

In conclusion, all the numerous papers analyzed state that studies designed with large samples and long-term follow-up are necessary, for a strong and definitive final recommendation about the kneecap resurfacing in the TKP. It is believed to share the conclusions of Grassi et al. (46): PR benefit is limited and it can reduce risks of secondary resurfacing. On a practical level, the results between PR and NR are comparable, as also supported by Pavlou et al. (37) who state that neither the PR nor the prosthetic design affect the clinical outcomes of TKP. Therefore, there is no clear superiority of R over NR (43). In a study of over 15,000 patients, the reasons for NR were the condition of the cartilage almost normal (56%), the young age (8%), the thin of patella (13%) and the choice of surgeons (23%) (47).

The increased risk of secondary resurfacing should be interpreted with caution due to the methodological limitations of the meta-analyzes concerning the search criteria, the heterogeneity and the intrinsic bias of an easier indication to reoperation when the kneecap was not prosthetic. Hans-Peter et al. (48) express the same judgment of caution about secondary resurfacing, considered a treatment option available to resolve post-prosthesis pain, even for non-homogeneous outcomes of secondary resurfacing itself; the Authors believe that there is currently no evidence-based recommendation for the use of secondary kneecap resurfacing; it would be desirable according to van Jonbergen et al. (48) a uniformly validated scoring system to analyze retro kneecap degeneration for secondary resurfacing purposes. Finally, the authors point out that the cause of anterior knee pain after TKP is not always related to the patella, but to other causes such as the insufficient posterior cruciate ligament, the intrarotiated femoral and/or tibial component, the tendinosis, etc. Therefore, secondary resurfacing is a still controversial procedure with uncertain results and burdened by complications (infections and alterations of wound healing, patellar instability and patellar fracture). This systematic review supports only a weak recommendation for secondary patellar resurfacing if patient satisfaction and clinically important improvement of functional outcomes are the desired endpoints.

Koh et al. (49) underline that the alleged improvement of secondary PR produces a satisfactory result in two out of five operated patients, who were oblivious to the advantages of the second surgical treatment, implemented to eliminate the anterior pain (50).

In conclusion, protected by evidence based medicine that considers both surgical options (PR and NR) both the multifactorial pain in NR or the need for secondary R cannot be considered to be a weak choice or a malpractice error. The role of the surgeon's experience emerges and of his ability to evaluate all the parameters in a clinical reasoning that analyzes as many factors as possible to prosthetize or not the patella, in the absence of clear and definitive recommendations of the Literature. In addition to secondary effect of TKP, number of previous studies in community-based populations have presented evidence of an inverse relationship between osteoporosis and OA. However, little information is available on whether patients with advance knee OA would be far less likely to develop osteoporosis by the inverse relationship. As the patients with advanced knee OA have elevated risks of incident vertebral and non-vertebral (including hip) fractures, precise information on the nature of BMD in this patient group would be valuable to those involved in patient care and to those interested in social health care burden imposed by advanced knee OA.; and so advanced knee OA *per se* does not have a marked protective effect against osteoporosis demostring that that more attention should be paid to identification and treatment of osteoporosis in elderly female patients with advanced knee OA undergoing TKP.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Systemic Bone Density at Disease Onset Is Associated With Joint Erosion Progression in Early Naive to Treatment Rheumatoid Arthritis: A Prospective 12-Month Follow-Up Open-Label Study

Dario Bruno[1], *Anna Laura Fedele*[2], *Barbara Tolusso*[2], *Angelina Barini*[3], *Luca Petricca*[2], *Clara Di Mario*[1], *Antonella Barini*[3], *Luisa Mirone*[1,2], *Gianfranco Ferraccioli*[1], *Stefano Alivernini*[1,2] *and Elisa Gremese*[1,2]*

[1] Division of Rheumatology, Università Cattolica del Sacro Cuore, Rome, Italy, [2] Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [3] Istituto di Biochimica e Biochimica Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

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***Correspondence:**
Elisa Gremese
elisa.gremese@unicatt.it

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Objectives: Osteoporosis and bone erosions are hallmarks of rheumatoid arthritis (RA) since disease onset is underpinned by the inflammatory burden. In this observational study, we aimed to dissect the putative RA-related parameters and bone-derived biomarkers associated with systemic and focal bone loss at disease onset and with their progression.

Methods: One-hundred twenty-eight patients with early rheumatoid arthritis (ERA) were recruited at disease onset. At study entry, demographic, clinical, and immunological parameters were recorded. Each ERA patient underwent plain X-rays of the hands and feet at study entry and after 12 months to assess the presence of erosions. After enrollment, each patient was treated according to the recommendations for RA management and followed up based on a treat-to-target (T2T) strategy. At baseline, blood samples for soluble biomarkers were collected from each patient, and plasma levels of osteoprotegerin (OPG), receptor activator of nuclear factor κB ligand (RANKL), Dickkopf-1 (DKK1), and interleukin 6 (IL-6) were assessed by enzyme-linked immunosorbent assay (ELISA). Seventy-one ERA patients underwent bone mineral density (BMD) measurement at the left femoral neck and second to fourth lumbar spine vertebrae (L2–L4) by dual-energy X-ray absorptiometry (DXA).

Results: Among the whole cohort, 34 (26.6%) ERA patients with bone erosions at study entry had a higher disease activity ($p = 0.02$) and IL-6 plasma levels ($p = 0.03$) than non-erosive ones. Moreover, at DXA, 33 (46.5%) ERA patients had osteopenia, and 16 (22.5%) had osteoporosis; patients with baseline bone erosions were more likely osteopenic/osteoporotic than non-erosive ones ($p = 0.03$), regardless of OPG, RANKL, and DKK1 plasma levels. Obese ERA patients were less likely osteopenic/osteoporotic than normal weight ones ($p = 0.002$), whereas anti-citrullinated protein antibodies

(ACPA) positive ERA patients were more likely osteopenic/osteoporotic than ACPA negative ones ($p = 0.034$). At logistic regression analysis, baseline Disease Activity Score measured on 44 joints (DAS44) [OR: 2.46 (1.11–5.44)] and osteopenic/osteoporosis status [OR: 7.13 (1.27–39.94)] arose as independent factors of erosiveness. Baseline osteopenic/osteoporotic status and ACPA positivity were associated with bone damage progression during the follow-up.

Conclusions: Bone erosions presence is associated with systemic bone loss since the earliest phases of RA, suggesting that the inflammatory burden and autoimmune biology, underpinning RA, represent crucial enhancers of bone remodeling either locally as at systemic level.

Keywords: rheumatoid arthritis, osteoporosis, osteopenia, disease activity, biomarkers

INTRODUCTION

Patients with rheumatoid arthritis (RA) present more bone loss than age- and sex-matched healthy controls (HC), regardless of treatment regimens (1). Traditionally, osteoporosis has been described as one of the common comorbidities linked to RA, with a prevalence of 10–50% depending on the studied population (2). Although bone loss may manifest in RA as juxta-articular loss and systemic bone loss (3), the most important feature is the focal bone loss as periarticular erosions, which are characterized by distinct differences in the pathogenesis. Given that in RA, a tight link exists between the inflammatory milieu and the bone remodeling process, a higher rate of bone loss should result as directly related to disease duration and disease activity. In early RA, where disease duration is limited, studying bone loss and bone erosions should give insights into the different mechanisms leading to the bone damage.

Therefore, RA is an excellent model to gain insights into the pivotal role of the immune system within the bone remodeling process involving multiple mechanisms. While bone surface erosions are due to the aberrant action of activated osteoclasts at sites of synovitis (4), the mechanisms guiding the juxta-articular and systemic bone loss and the decreases in bone mineral density (BMD) are less intuitive.

Osteoprotegerin (OPG), receptor activator of nuclear factor κB (RANK), and its ligand receptor activator of nuclear factor κB ligand (RANKL) play a central role (1, 5), involving members of the tumor necrosis factor (TNF) superfamily and its receptor and regulating the fine balance of bone resorption (6).

RANKL leads to the differentiation and activation of osteoclast precursors, by binding to surface RANK and determining the activation of nuclear factor κB and the transcription of osteoclastogenetic genes, with subsequent induction of preosteoclast differentiation, increased osteoclast activity, and prolonged their lifetime. Moreover, OPG is the soluble decoy receptor of RANKL, reducing osteoclastogenesis and bone resorption (1, 4, 6). In addition, the Wnt/β-catenin system is pivotal for bone mass regulation (7). In this pathway, the binding of Wnt-protein ligand to the surface Frizzled receptor induces an intracellular signaling cascade involving low-density lipoprotein receptor-related protein 5/6 (LRP-5/6), disheveled, and glycogen synthase kinase 3 that finally drives to β-catenin translocation into the nucleus leading to the upregulation of osteoblastic differentiation and survival gene transcription. Moreover, Dickkopf-1 (DKK1) acts as an endogenous antagonist of the Wnt pathway by interfering with LRP-5/6 phosphorylation (7).

Several studies have shown that osteoclasts activity and RANKL expression are risen at sites of RA synovitis (4, 8) and OPG acts as a bone loss protective factor in RANKL knockout mice despite active joint inflammation (6). Concerning DKK1, its plasma and synovial tissue levels are significantly increased in RA patients compared with HC, correlating with disease activity, supporting the putative critical role of DKK1 in bone erosions development in RA (7, 9).

Among the multiple factors promoting bone remodeling in RA, autoantibodies, as anti-citrullinated protein antibodies (ACPA) as well as anti-carbamylated peptide (anti-CarP) antibodies, have been associated with the development and progression of bone erosions and juxta-articular bone resorption as well as a decreased BMD (10–15). Therefore, systemic activators of bone remodeling and local osteoclastogenesis, in combination, lead to bone damage.

Besides autoantibodies, there have been advances made in understanding how inflammatory RA cytokines, such as TNF, IL-6, and interleukin 1 (IL-1), promote osteoclasts activation and inhibit osteoblasts function, interfacing with the complex system of bone turnover (1). Specifically, IL-6 acts as a bone resorbing cytokine by stimulating both osteoclasts precursor maturation and osteoblasts lineage expression of RANKL, in order to enhance osteoclastogenesis (16). Moreover, data from the ESPOIR cohort indicated that baseline IL-6 plasma levels were associated with structural damage over 3 years of follow-up, independently from disease activity and serological status (17).

Based on these issues, the aims of the present study were (i) to dissect the putative disease-related parameters (clinical and autoimmune) and bone-derived biomarkers associated with systemic and focal bone loss in terms of BMD and erosions at disease onset and (ii) to test their possible association with the progression of RA-related bone damage.

MATERIALS AND METHODS

Patient Enrollment

In this single-center study, 128 patients, fulfilling the 2010 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for RA (18), were consecutively recruited between 2011 and 2019. Each RA patient had symptoms duration <12 months at study entry, and patients with disease duration <3 months were defined as "very early RA" (VERA) (19). At study entry, demographic, clinical, and immunological parameters were recorded, and each enrolled RA patient was naive to conventional disease-modifying antirheumatic drugs (cDMARDs) or biological DMARDs (bDMARDs). At enrollment, low dose steroid treatment (prednisone equivalent ≤5 mg/day) was allowed. After enrollment, each RA patient was treated according to the current recommendations for RA management (20), and at each study visit, the ACR/EULAR core data set [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen joint count (SJC), tender joint count (TJC), physician and patient global assessment, pain, and Health Assessment Questionnaire (HAQ)] was recorded. Moreover, each enrolled RA patient was followed up based on a treat-to-target (T2T) strategy, with clinical assessment every 3 months recording the clinical improvement and remission based on the Disease Activity Score measured on 44 joints (DAS44) values (21, 22) and ACR/EULAR criteria, respectively (23). Twenty age- and sex-matched healthy subjects were included as the comparison group. The study protocol was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore. All subjects provided signed informed consent.

Detection of Autoantibodies

At study entry, immunoglobulin A (IgA)- and immunoglobulin M (IgM)-rheumatoid factor (RF) (Orgentec Diagnostika, Bounty, UK) and ACPA (Menarini, Italy) were assessed using the enzyme-linked immunosorbent assay (ELISA) or chemiluminescent methods, respectively. The cut-off levels were 20 U/mL for IgM-RF and IgA-RF and 5 U/mL for ACPA. Seronegative RA patients were defined as those negative for ACPA, IgM-RF, and IgA-RF; all the other subjects were described as seropositive.

Assessment of Inflammatory and Bone Remodeling-Related Serum Biomarkers

At study entry, each enrolled RA patient underwent peripheral blood drawing after overnight fasting, and plasma was stored at −80°C until analysis. Bone turnover markers as OPG (sensitivity: 0.14 pmol/L; Biomedica, Austria), RANKL (sensitivity: 0.02 pmol/L; Biomedica, Austria), and DKK1 (sensitivity: 0.38 pmol/L; Biomedica, Austria) plasma levels and interleukin 6 (IL-6, sensitivity: 0.7 pg/ml, Bio-Techne, UK) plasma levels were detected by ELISA.

Bone Damage Assessment

Each enrolled patient underwent plain X-rays of the hands and feet at study entry and after 12 months of follow-up. The presence of erosions was assessed, with an anterior and posterior view, using the van der Heijde modified Total Sharp Score (mTSS) (24) and the Larsen scores, respectively (25), by one experienced rheumatologist unaware of the patients' clinical and laboratory status. Erosive patients were defined by the presence of erosions. Moreover, the appearance of one new erosion (as a worsening of erosion score) was recorded at 12 months of follow-up, respectively.

BMD Measurements

At study entry, seventy-one ERA patients underwent BMD measurement at the left femoral neck and second to fourth lumbar spine vertebrae (L2–L4) by dual-energy X-ray absorptiometry (DXA), using Lunar Prodigy equipment. A daily quality check of the DXA machine was done. A densitometric diagnosis of osteoporosis was based on BMD measurement according to the World Health Organization (WHO), and detected BMD was compared with the mean BMD of sex-matched young normal adults. In particular, considering the standard deviation (SD) from the mean peak bone mass (T score), osteoporosis status was defined as <-2.5 SD in at least one site, and osteopenia (low BMD) as a T score between −1.0 and −2.5 SD, whereas normal BMD was defined as a T score between +2.5 and −1 SD, respectively (26).

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS, Chicago, IL, USA) and Prism software (GraphPad, San Diego, CA, USA). Categorical and quantitative variables were described as frequency, percentage, and mean ± SD. Data on demographic and clinical features were compared between patients by the non-parametric Mann–Whitney U test or X^2 test, as appropriate. Spearman's rank correlation test was used for correlation in all analyses. We performed a logistic regression model to determine the influence of the dependent variable "presence of bone erosions at disease onset" by the independent variables that reached the value of $p < 0.10$ at the univariate analysis. The values are expressed as odds ratio (OR) and 95% confidential interval (95% CI), respectively. A $p < 0.05$ was considered statistically significant.

RESULTS

Baseline Bone Damage in ERA Patients Is Related to Disease Burden and Systemic Bone Loss Regardless of Bone-Derived Biomarkers

Demographic, clinical, and radiological characteristics of the enrolled ERA cohort at study entry are summarized in **Table 1**. Among the enrolled ERA cohort, 115 (89.8%) patients were women who did not differ based on age (53.03 ± 14.54 years) compared with men ERA patients (57.38 ± 16.34 years, $p = 0.24$).

Each ERA patient underwent plain radiographs of the hands and feet at study entry to evaluate bone erosions. Among the whole cohort, 34 (26.6%) ERA patients showed bone erosions. In particular, as shown in **Figures 1A,B**, erosive ERA patients had more likely a higher disease activity and inflammatory status as underlined by a significantly higher IL-6 plasma levels (24.53 ±

TABLE 1 | Demographic and clinical characteristics of ERA patients at diagnosis, according to erosiveness.

Variable	ERA patients (*N* = 128)	Erosive (*N* = 34) (26.6%)	Non-erosive (*N* = 94) (73.4%)	*P*
Age (years)	53.4 ± 14.7	55.38 ± 14.4	52.79 ± 14.9	0.30
Gender, female (%)	115 (89.8)	29 (85.3)	86 (91.5)	0.31
Symptom duration (months)	5.62 ± 3.50	5.62 ± 3.43	5.62 ± 3.55	0.84
VERA (%)	45 (35.2)	10 (29.4)	35 (37.2)	0.41
Smokers (%)	38 (29.9)	9 (26.5)	29 (30.9)	0.60
Obese (BMI ≥ 30 kg/m^2) (%)	16 (12.5)	4 (11.8)	12 (12.8)	0.88
Seropositive (%)	92 (71.9)	23 (67.6)	69 (73.4)	0.52
ACPA positive (%)	82 (64.1)	21 (61.8)	61 (64.9)	0.75
IgM-RF positive (%)	67 (52.3)	19 (55.9)	48 (51.1)	0.63
IgA-RF positive (%)	41 (32.0)	14 (41.2)	27 (28.7)	0.18
ESR (mm/1st h)	37.64 ± 23.82	38.59 ± 27.89	37.30 ± 22.32	0.74
CRP (mg/L)	16.44 ± 25.93	22.16 ± 38.02	14.33 ± 19.57	0.57
IL-6 (pg/mL)	20.74 ± 40.53	24.53 ± 32.01	19.52 ± 42.99	**0.03**
SJC44	8.73 ± 6.45	10.94 ± 7.06	7.94 ± 6.05	**0.03**
TJC44	12.94 ± 8.07	13.44 ± 7.73	12.76 ± 8.22	0.52
DAS44	3.53 ± 0.99	3.82 ± 1.15	3.43 ± 0.92	**0.02**
CDAI	26.67 ± 12.51	28.93 ± 13.98	25.84 ± 11.91	0.19
SDAI	28.32 ± 13.61	31.15 ± 15.15	27.27 ± 12.92	0.14
HAQ	1.09 ± 0.71	1.23 ± 0.82	1.04 ± 0.66	0.24

Data are shown as mean ± SD or n (%). VERA, very early rheumatoid arthritis; BMI, body mass index; ACPA, anti-citrullinated protein antibodies; IgM, immunoglobulin M; IgA, immunoglobulin A; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; SJC44, 44 swollen joint count; TJC44, 44 tender joint count; DAS44, Disease Activity Score measured on 44 joints; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; HAQ, Health Assessment Questionnaire. Bold values indicate p < 0.05.

32.01 pg/ml) and DAS44 (3.82 ± 1.15) than non-erosive ERA patients (IL-6: 19.52 ± 42.99 pg/ml, $p = 0.03$ and DAS44: 3.43 ± 0.92, $p = 0.02$, respectively), regardless of ACPA positivity.

Among the whole ERA cohort, 71 patients underwent lumbar spine and femur DXA to investigate the rate of systemic bone loss (**Supplementary Table 1**). At study entry, 33 (46.5%) ERA patients had osteopenia, and 16 (22.5%) had osteoporosis, respectively. As shown in **Figure 1C**, ERA patients with baseline bone erosions were more likely osteopenic/osteoporotic at DXA (86.4%) than ERA patients without bone erosions (61.2%, $p = 0.03$).

In particular, at baseline, erosive ERA patients had a lower lumbar spine T score (−1.61 ± 0.94) than non-erosive ERA patients (−0.61 ± 1.60, $p = 0.004$) (**Figure 1D**). Lumbar T score at study entry inversely correlated with Sharp ($R = -0.38$, $p = 0.003$) and Larsen ($R = -0.37$, $p = 0.003$) scores (**Figures 1E,F**). Nevertheless, no significant association was detected between erosiveness and BMD measurement at the femoral neck in the same cohort. Interestingly, at study entry, obese ERA patients were less likely osteopenic/osteoporotic (36.4%) than normal weight ERA (84.4%, $p = 0.002$). Conversely, ACPA^{pos} ERA patients were more likely osteopenic/osteoporotic (77.7%) than ACPA^{neg} ERA patients (53.8%, $p = 0.03$) before any pharmacologic treatment (**Figure 1G**), whereas no significant association was found between IgA/IgM-RF positivity and baseline BMD in our ERA cohort (data not shown).

Considering the symptoms duration, patients with VERA did not differ in terms of baseline disease activity, IL-6 plasma levels, BMD measurement, or erosiveness rate compared with no VERA ones (data not shown).

Finally, at logistic regression model, baseline DAS44 [OR: 2.46 (1.11–5.44)] and osteopenic/osteoporosis status [OR: 7.13 (1.27–39.94)] arose as independent factors of erosiveness, whereas baseline IL-6 plasma levels were not independently associated with bone erosions presence in ERA.

Bone-Derived Biomarkers Are Related to Clinical and Immunological Features in ERA Patients at Disease Onset

Since bone remodeling is an active process involving multiple soluble factors as DKK1, OPG, and RANKL, we investigated their expression in the peripheral blood of our ERA cohort in relation to the clinical and immunological features of the disease (including IL-6 plasma levels) as well as erosiveness.

As shown in **Figure 2A**, ERA patients showed significantly higher plasma levels of IL-6 (21.04 ± 40.80 pg/ml) and OPG (4.31 ± 2.25 pmol/L) and lower plasma levels of DKK1 (37.02 ± 32.86 pmol/L) than HC (IL-6: 2.51 ± 1.63 pg/ml, $p = 0.0006$; OPG: 2.65 ± 2.11 pmol/L, $p = 0.0002$; DKK1: 55.48 ± 32.70 pmol/L, $p = 0.0048$), whereas RANKL plasma levels were comparable.

Moreover, women had significantly higher DKK1 plasma levels (37.99 ± 33.63 pmol/L) than men ERA (28.39 ± 45.04 pmol/L), whereas no differences were found for OPG and RANKL plasma levels (**Supplementary Figure 1**). However,

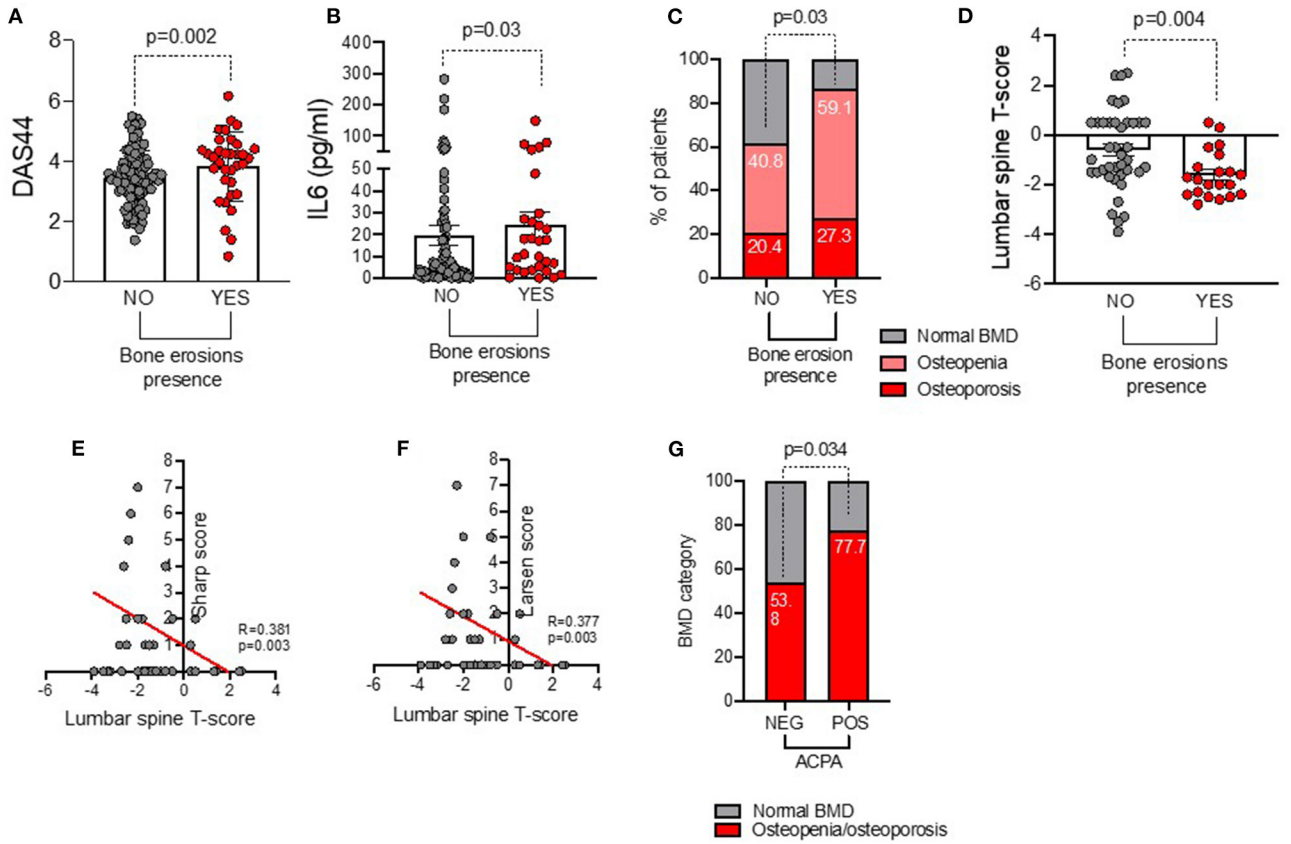

FIGURE 1 | (A–G) Associations between baseline bone damage in ERA patients with disease burden and systemic bone loss. **(A)** DAS44 value in ERA patients stratified based on the presence of baseline bone erosions at plain radiographs of the hands and feet, Mann–Whitney U test. **(B)** IL-6 plasma levels in ERA patients stratified based on the presence of baseline bone erosions at plain radiographs of the hands and feet, Mann–Whitney U test. **(C)** Rate of systemic bone loss at baseline lumbar spine and femur DEXA in ERA patients ($n = 71$) stratified based on the presence of baseline bone erosions at plain radiographs of the hands and feet, X^2 test. **(D)** Lumbar spine T score value in ERA patients stratified based on the presence of baseline bone erosions at plain radiographs of the hands and feet, Mann–Whitney U test. Correlation between lumbar spine T score value and Sharp **(E)** and Larsen **(F)** scores, Spearman rank correlation test. **(G)** Rate of osteopenia/osteoporosis in ERA patients at baseline stratified based on ACPA positivity, X^2 test. A $p < 0.05$ was considered statistically significant. DAS44, Disease Activity Score measured on 44 joints; IL-6, interleukin-6; BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry.

stratifying ERA patients based on sex and age categories, women older than 50 years old showed significantly higher DKK1 (38.06 ± 35.79 pmol/L) plasma levels than men ERA older than 50 years old (10.86 ± 12.86 pmol/L, $p = 0.003$) and higher RANKL plasma levels (0.55 ± 1.14 pmol/L) than men ERA younger than 50 years old (0.06 ± 0.04 pmol/L, $p = 0.05$), respectively (**Figure 2B**). Conversely, regardless of sex, ERA patients older than 50 years old showed significantly higher OPG plasma levels (4.78 ± 2.05 pmol/L) than ERA patients younger than 50 years old (3.63 ± 1.79 pmol/L), mainly in men (**Figure 2B**). In line with these findings, among the bone-derived biomarkers, only OPG plasma levels directly correlated with age at diagnosis in ERA patients ($R = 0.366$, $p < 0.0001$) (**Figure 2D**). Moreover, stratifying ERA patients based on the autoimmune profile, autoantibody positivity *per se* at study entry was not related to OPG, RANKL, and DKK1 plasma levels (**Figure 2C**). However, considering the individual autoantibody positivities, OPG plasma levels were significantly increased in IgA-RF^{neg} (4.62 ± 2.49 pmol/L) and IgM-RF^{neg} (4.82 ± 2.51 pmol/L) ERA patients compared with seropositive ones (IgA-RF^{pos}: 3.66 ± 1.44 pmol/L, $p = 0.05$ and IgM-RF^{pos}: 3.85 ± 1.88; $p = 0.02$, respectively) (**Figure 2C**). ACPA positivity was not related to OPG, RANKL, or DKK1 plasma levels in ERA patients at study entry. Furthermore, DKK1 plasma levels directly correlated with disease activity parameters in ERA patients at disease diagnosis [DAS44: $R = 0.224$, $p = 0.01$ and Clinical Disease Activity Index (CDAI): $R = 0.185$, $p = 0.04$, respectively], whereas no correlations were found for OPG or RANKL plasma levels (**Figure 2D**). At enrollment, ERA patients under treatment with low-dose of steroid did not differ in terms of OPG, DKK1, or RANKL plasma levels compared with free of steroid treatment ERA patients (data not shown). Finally, in our cohort of ERA patients, we did not observe any significant difference in terms of OPG, RANKL, and DKK1 plasma levels based on the erosive status at disease onset (**Supplementary Figure 2**) and symptoms duration.

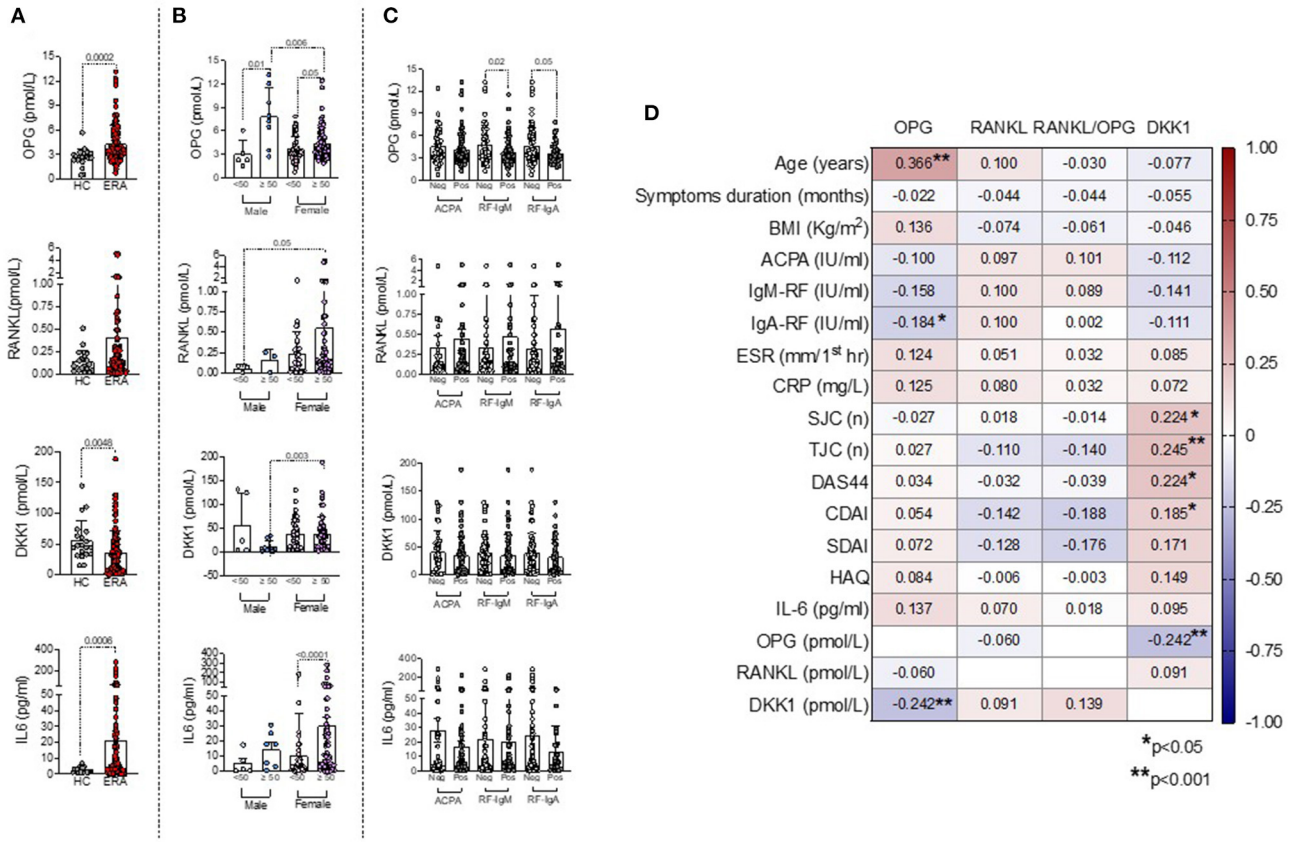

FIGURE 2 | (A–D) Associations between bone-derived biomarkers with clinical and immunological features in ERA patients at disease onset. **(A)** OPG, RANKL, DKK1, and IL-6 plasma levels at baseline in ERA patients and HC, Mann–Whitney U test. **(B)** OPG, RANKL, DKK1, and IL-6 plasma levels at baseline in ERA patients stratified based on sex and age categories, Mann–Whitney U test. **(C)** OPG, RANKL, DKK1, and IL-6 plasma levels at baseline in ERA patients stratified based on individual ACPA, IgA/IgM-RF positivity, Mann–Whitney U test. **(D)** Heatmap showing the correlations between bone-derived biomarkers and RA features, Spearman rank correlation test. A $p < 0.05$ was considered statistically significant. ERA, early rheumatoid arthritis; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa beta; DKK1, Dickkopf-1; ACPA, anti-citrullinated protein antibodies; IgA/IgM-RF, immunoglobulin A or immunoglobulin M isotypes rheumatoid factor; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SJC, swollen joint count; TJC, tender joint count; DAS44, Disease Activity Score measured on 44 joints; CDAI, Clinical Disease Activity Index; SDAI, Simple Disease Activity Index; HAQ, Health Assessment Questionnaire; IL-6, interleukin-6.

Baseline Variables Associated With Bone Damage Progression in ERA Patients During Tight Control Scheme

To assess the bone damage progression, 114 (89.1%) ERA patients underwent plain radiographs of the hands and feet at 12 months of follow-up within a T2T therapeutic approach. Particularly, 9 (7.9%) ERA patients experienced new onset or worsening of bone erosions. Of note in this time-frame, 25 (21.9%) ERA patients had begun a bDMARD. As shown in **Figure 3**, baseline BMD category was associated with bone damage progression in ERA patients since ERA patients experiencing new development or worsening of bone damage across the 12 months of follow-up were more likely osteopenic/osteoporotic (100%) than ERA patients not experiencing bone damage (57.5%, $p = 0.0015$). Moreover, neither disease activity and symptoms duration at baseline nor the rate of treatment response in terms of remission achievement was significantly different in ERA patients experiencing bone damage worsening compared with ERA patients without any sign of bone damage. Nevertheless, considering the autoimmune profile, 100% of ERA patients who experienced new bone erosions or their worsening within 12 months of follow-up were $ACPA^{pos}$, whereas no significant differences of bone damage across 12 months of follow-up were found considering IgA- or IgM-RF positivity. Finally, considering the bone-derived biomarkers, ERA patients experiencing bone damage progression did not differ in terms of OPG, DKK1, and RANKL plasma levels compared with ERA patients not experiencing any bone damage progression (data not shown).

DISCUSSION

In this cohort of early RA, we provide evidence that systemic bone loss is a common finding in ERA, is linked to disease activity and ACPA positivity, and is an independent factor of bone damage at disease onset.

It is well-known that osteoporosis is one of the most common comorbidities in RA leading to an increased fracture risk (2, 3).

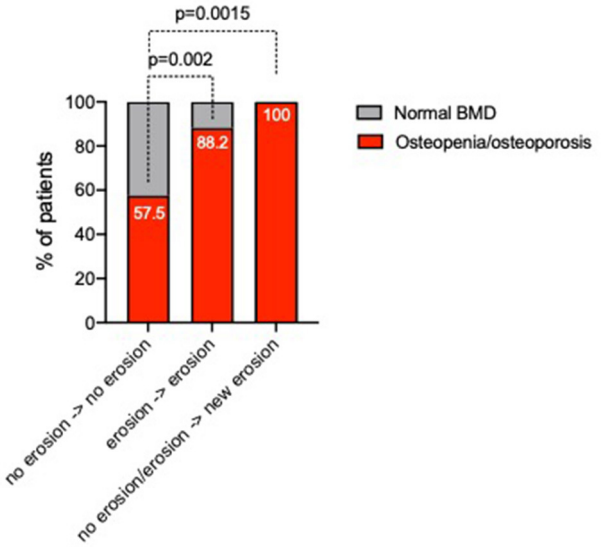

FIGURE 3 | Rate of changes of bone damage across 12 months of follow-up in ERA patients stratified based on baseline BMD category. ERA patients were stratified as follows: no erosion at baseline and no bone damage progression, stable bone damage despite baseline erosion presence, and new development or worsening of bone erosions, respectively. A $p < 0.05$ was considered statistically significant. BMD, bone mineral density; ERA, early rheumatoid arthritis.

Nevertheless, despite in long standing RA, osteoporosis may be considered as a natural consequence of disease burden, sustained glucocorticoid exposure, and decreased mobility due to functional joint impairment. In ERA patients, the pathogenetic process promoting focal and systemic bone remodeling and damage might be more complex. In this contest, it is reasonable to assume that bone damage occurring in ERA patients mainly results from inflammatory cytokines' detrimental action, able to stimulate both systemic and local osteoclasts activation (1). Among them, TNF and IL-6 play a crucial role in the regulation of osteoclasts differentiation inducing the expression of RANKL on osteoblasts membrane (27–30); in addition, IL-6 may act indirectly on bone homeostasis, enhancing and mediating bone resorption-inducing effects exerted by TNFα and IL-1 (1).

In our study, we enrolled consecutive ERA patients at disease onset without previous exposure to conventional or biological DMARDs in whom plasma levels of bone-derived biomarkers were assessed, finding that women older than 50 years old have higher DKK1 plasma levels than men older than 50 years old and higher RANKL plasma levels than men younger than 50 years old. Moreover, we found that in ERA patients, OPG plasma levels directly correlated with age at disease onset regardless of sex, as was previously demonstrated in healthy subjects (31) as well as in systemic diseases characterized by bone loss (32). This might reflect a compensatory self-defense mechanism against age-related osteoporosis. In addition, DKK1 plasma levels were found to mirror disease activity at ERA onset (i.e., DAS44 and CDAI), supporting the ESPOIR cohort previous data (7), despite no clear correlation emerged between DKK1 plasma levels at ERA onset and erosiveness or systemic bone loss.

Furthermore, considering the serological status, we found that OPG plasma levels were more likely increased in IgA/IgM-RF^{neg} than in seropositive ERA at baseline, thus supporting the well-known lower tendency to erosiveness of seronegative RA (33).

Concerning bone damage, 34 (26.6%) ERA patients had RA-related bone erosions at baseline plain radiographs, associated with a higher disease activity and inflammatory disease burden than non-erosive ERA patients. In particular, in our ERA cohort, erosive patients showed significantly higher IL-6 plasma levels and DAS44 than non-erosive patients, underlying the tight link between disease activity and bone loss (34).

Despite a direct correlation between bone-derived biomarkers, as DKK1, and bone erosions progression in ERA patients at disease onset (7), no data were available on the systemic bone loss equilibrium in such cohort. Therefore, in our study, ERA patients underwent lumbar spine and femur DXA to investigate the rate of BMD loss and its link with focal bone damage and clinical or immunological features of the disease. Interestingly, we observed that, at baseline, erosive ERA patients had a significantly lower lumbar spine T score than non-erosive ERA patients and baseline lumbar T score was inversely correlated with Sharp and Larsen radiological scores, whereas no significant associations were found with BMD measurement at the femoral neck. These findings are in line with the ones previously reported by Hafez and colleagues (35) and are probably related to the increased presence of the trabecular bone at lumbar spine level (compared with the hip), which might be more sensitive to the inflammatory cytokine RA milieu, due to its increased metabolism (35). Interestingly, we found that erosive ERA patients were more likely osteoporotic than non-erosive ERA patients, despite no significant differences in terms of OPG, RANKL, and DKK1 plasma levels.

Among putative environmental and immunological disease-related factors that may influence BMD measurement in RA patients, we considered the body mass index (BMI) that might underestimate osteopenia/osteoporosis prevalence (36). As previously observed in the normal population (36), stratifying ERA patients based on their BMI, obesity was related to less incidence of osteopenia/osteoporosis at disease onset as suggested by the significantly higher plasma levels of IL-1 receptor antagonist in obese naive to treatment RA patients, which might antagonize the potent osteoclastogenic effects of IL-1β (37). Moreover, at baseline, ACPA^{pos} ERA patients, naive to any pharmacological treatment, had more likely osteopenia/osteoporosis of the lumbar spine and femur than ACPA^{neg} ERA patients, as previously demonstrated (38).

Nevertheless, little is known about the possible prognostic biomarkers of bone damage progression to be used at the first medical assessment within ERA patients management (34, 38). In our study, we investigated disease-related biomarkers possibly enabling the identification of ERA patients at higher risk of bone damage progression. In particular, after adopting a T2T approach, nearly 8% of patients had progression of focal bone damage, in terms of new erosions development or their worsening. Among baseline variables associated with

bone damage progression, ERA patients experiencing new development or worsening of bone damage across 12 months of follow-up were more likely ACPA^{pos} than ERA patients without bone damage worsening or development (38). Therefore, we fully confirm that ACPA positivity is the most important prognostic risk factor for baseline systemic bone loss and future erosions despite a T2T strategy in ERA patients (38).

CONCLUSION

In summary, our study confirms that focal bone damage (bone erosions) is associated with systemic bone loss (osteopenia/osteoporosis) since the earliest phases of RA, suggesting that the inflammatory burden and the autoimmune biology, underpinning RA, represent crucial enhancers of bone remodeling either at the local as at the systemic level. Thus, early RA is a pathognomonic model to define the molecular mechanisms of systemic and local bone damage progression.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Università Cattolica del Sacro Cuore. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DB, AF, and EG: conceived the study. DB, AF, BT, AngB, LP, CD, AntB, LM, GF, and SA: collected the clinical data. DB, AF, BT, AngB, CD, and AntB: performed the experiments. DB, BT, SA, and EG: performed the statistical analysis. DB, AF, BT, AngB, LP, CD, AntB, LM, GF, SA, and EG: drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.613889/full#supplementary-material

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BRIEF RESEARCH REPORT
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Osteosarcopenia in Very Old Age Adults After Hip Fracture: A Real-World Therapeutic Standpoint

Monica Pizzonia[1†], Andrea Casabella[1,2†], Marta Natali[1,2†], Lorena Petrocchi[1,2], Luca Carmisciano[3], Alessio Nencioni[1,2], Luigi Molfetta[4], Chiara Giannotti[1,2], Gerolamo Bianchi[5], Andrea Giusti[5], Federico Santolini[1] and Fiammetta Monacelli[1,2*]*

[1] Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Policlinico San Martino, Genoa, Italy, [2] DIMI, Department of Internal Medicine and Medical Specialties, Section of Geriatrics, University of Genoa, Genoa, Italy, [3] DISSAL, Department of Health Science, University of Genoa, Genoa, Italy, [4] DISC, Department of Integrated Surgical and Diagnostic Sciences, University of Genoa, Genoa, Italy, [5] Rheumatology Unit, Department of Musculoskeletal Sciences, Local Health Trust 3, La Colletta Hospital, Genoa, Italy

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Edited by:
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***Correspondence:**
Federico Santolini
federico.santolini@hsanmartino.it
Fiammetta Monacelli
fiammetta.monacelli@unige.it

[†]These authors have contributed equally to this work

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Loss of bone and muscle mass and strength (i. e., osteosarcopenia) is a highly prevalent clinical condition in older adults, associated with an increased risk of fragility fractures and unfavorable clinical outcomes. Although sarcopenia is a potential risk factor for osteoporosis and subsequent fracture, and the management of this hazardous duet is the key to preventing osteoporotic fracture, evidence pertaining to the treatment of sarcopenia for the purpose of preventing fragile fractures remains insufficient. Given this scenario we aimed at prospectively compare the long-term effectiveness of bisphosphonates vs. denosumab, on bone and muscle, in a cohort of old age hip fractured patients by virtue of a timely osteo-metabolic and sarcopenic assessment. Ninety-eight patients consecutively enrolled at the IRCCS Hospital San martino, Genoa, Italy, received at baseline comprehensive geriatric assessment and Bone Densitometry (DXA) with the quantitative and quantitative bone analysis and evaluation of relative skeletal muscle index (RSMI) and longitudinally after 1 year form hip surgery. The results showed a slightly and non-significant osteo-metabolic improvement in the Alendronate group compared to the Denosumab group, and a positive trend of RSMI measurements in the Denosumab group. Although preliminary in nature, this is the first report to longitudinally analyze osteosarcopenia in a real-world cohort of very old age patients after hip fracture and moved a step forward in the understanding of the best osteo-metabolic therapy for long- term treatment, exploring as well the potential dual role of denousumab as antiresorptive and muscle strength specific drug for osteosarcopenia in this vulnerable population.

Keywords: longitudinal assessment, muscle strength, denosumab, osteosarcopenia, hip fractured very old age patients

INTRODUCTION

It is growingly acknowledged that the increase of fracture risk with aging reflects a multifactorial basis, including bone mineral density (BMD) loss, poorer bone quality with insufficient bone strength, and overarching the diagnosis of osteoporosis. In line with that, it is generally accepted that osteoporosis (1, 2) is a major clinical problem in older adults that can have a significant

impact on the day life activities, and similarly, substantial long-term morbidity is associated with hip fractures. Namely, the disability, mortality, and cost of hip and vertebral fractures, the most burdening osteoporosis-related complications, are substantial in the rapidly growing aging population so that prevention and treatment of osteoporosis is a major public health concern (3).

However, from a clinical standpoint, it is increasingly recognized that the simultaneous presence of bone and muscle weakness dramatically contributes to higher fracture risk in older adults, and this is especially true in presence of clinical frailty, that is, a very common geriatric syndrome characterized by diminished homeostasis and increased susceptibility to environmental stressors with increased unfavorable clinical outcomes.

The term *sarcopenia*, describes an "age-associated loss of skeletal muscle mass and functions which are strength and performance as well" (4). Doubtlessly, it is a widespread clinical condition of the old age, that is tightly associated with key relevant clinical complications, such as functional decline, physical disability, mobility limitations, increased risk of falls, and poorer quality of life (5). Sarcopenia has been reported to affect more than 40% of older adults ≥70 years of age, ∼50 million people worldwide. This number is estimated to increase to 500 million people in the year 2050 (6, 7), and although it is frequently appreciated by clinicians, it is rarely formally diagnosed.

As reported by the milestone paper of Brinkley et al., the time has come to emphasize the key relevance of this duality, suggesting that the definition of sarco-osteoporosis is proposed to facilitate the early identification and appropriate clinical management of those old-age patients at higher fracture risk (1).

Some evidence showed that sarcopenia is associated with decreased bone density, and common risk factors such as vitamin D deficiency, malnutrition, and disuse have been reported to lead simultaneously to loss of bone and bone strength with decreased muscle mass and a higher predisposition to falls (8–10), suggesting that bone fractures, including both hip and vertebral fractures, are caused by a combination of osteoporosis and sarcopenia. Additionally, osteosarcopenia has been related to the development of dysmotility syndromes that are a key relevant complication for old-age patients, accelerating disability and frailty trajectories (11, 12).

Notwithstanding that, there has been a delay in the understanding of the pathophysiology of muscular regeneration and sarcopenia in the aged environment (13) that could be responsible, at least partially, for the limited awareness pertaining the cooccurrence of sarcopenia in patients with osteoporotic (OP) fractures in old-aged populations (12–16). As a result, a fragmentation in the timely diagnosis and in the appropriateness of treatments has been observed, especially in multimorbid, frail old-age patients. Although sarcopenia is a potential risk factor for osteoporosis and subsequent fracture, and the management of this *hazardous duet* is the key to preventing OP fracture, evidence pertaining to the treatment of sarcopenia for the purpose of preventing fragile fractures remains insufficient (17–22).

Whereas, several drugs are approved for the treatment of osteoporosis, so far, no therapy has been demonstrated to exert sufficiently positive effects on muscle to be approved for the treatment of sarcopenia. It is well-known that a monoclonal antibody targeting RANKL, denosumab, was observed to reduce fracture risk, and it is now widely used to treat osteoporosis (23). RANKL is also expressed in skeletal muscle and activation of the NF-κB pathway mainly inhibits myogenic differentiation, which leads to skeletal muscle dysfunction and loss (24). In line with that, limited *in vivo* evidence underscored that a neutralizing antibody against receptor activator of the NF-kB ligand (RANKL), denosumab, improved muscle strength and insulin sensitivity, restoring bone strength. In addition, OP women, taking denosumab for more than 3 years, ameliorated their appendicular lean mass and hand-grip strength compared with no treatment, whereas the use of bisphosphonate did not (25). These observations led to hypothesize that RANKL inhibitors could exert a positive influence on muscle mass and strength, particularly in conditions of osteoporosis and/or sarcopenia.

Given this scenario, the aim of the study was to prospectively compare the long-term effectiveness of bisphosphonates vs. denosumab, on bone and muscle, in a cohort of old-age hip fractured patients by virtue of a timely osteo-metabolic and sarcopenic assessment.

SUBJECTS AND METHODS

We performed an observational prospective study, including 125 consecutive old-age patients with hip fracture admitted at the U.O. Emergency Orthopedics and Traumatology of the IRCSS Policlinico San Martino hospital Genoa, Italy, with geriatric co-management, between April and November 2018. The protocol was approved by the Local Ethical Committee and met guidelines of the local governmental agency. Patients or their proxies provided written informed consent prior to study inclusion. Qualified patients were ≥65 years old and had sustained hip fractures due to low-energy trauma (fragility fractures), requiring immediate hospitalization. They were excluded if informed consent was lacking, surgery was prohibited by surgical or clinical instability, high-energy trauma was involved, or fractures were pathologic or periprosthetic in nature. Twenty-seven patients met exclusion criteria for clinical instability ($n = 14$) and pathological fractures ($n = 13$) leaving a total of 98 patients for study (**Figure 1**).

All patients received in-hospital comprehensive geriatric assessment (CGA), including the Barthel index (26), to assess functional status; activities of daily living (ADL) to assess functional status (27); instrumental activities of daily living (IADL) to assess instrumental activities of daily living (28); cumulative illness rating scale (CIRS) to assess multimorbidity (29); mini nutritional assessment (MNA-SF) (30); and short portable mental status questionnaire (SPMSQ) to assess cognitive status (31, 32).

The diagnosis of sarco-osteoporosis was formulated in the presence of the combination of Dual Energy X-ray Absorptiometry (DEXA) values for poor BMD, the clinical presence of hip fracture, and the cut-off values for poor relative skeletal muscle index (RSMI) as above described. The inclusion of hand-grip strength with cut off was also included for the diagnosis of sarcopenia (4).

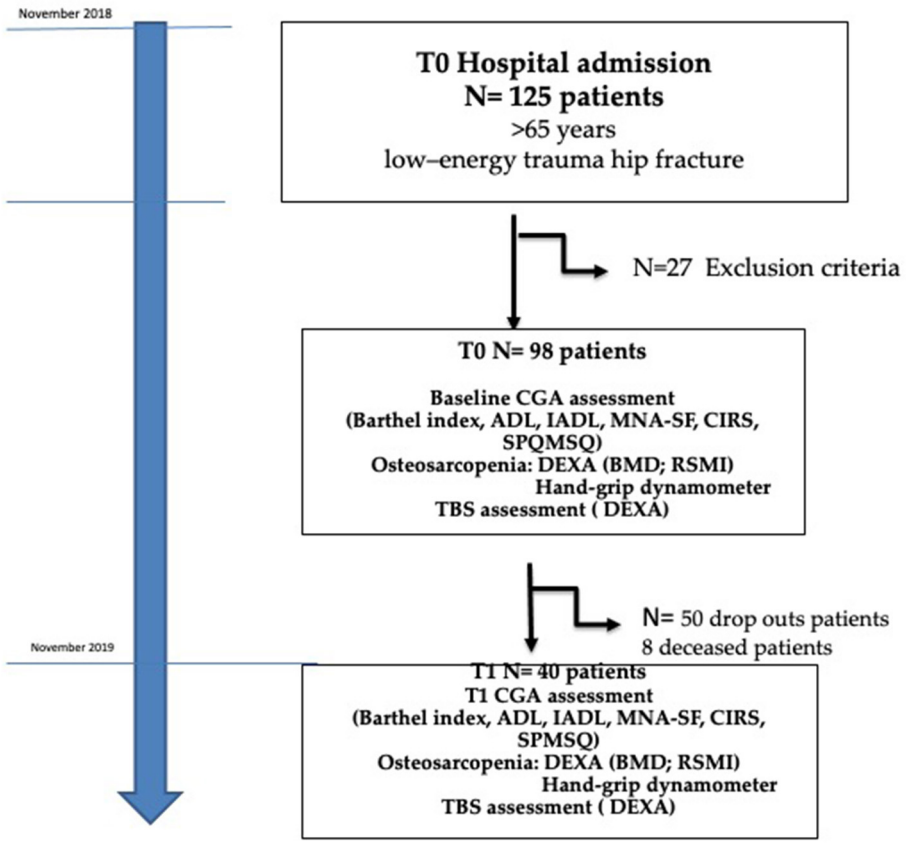

FIGURE 1 | Patients' flowchart assignment.

Bone densitometry (DXA Lunar Prodigy Scan Advance Ge Medical) with the quantitative analysis of the BMD analysis was performed to assess osteoporosis. Namely, the expressed in g/cm^2 at the lumbar spine (L1–L4) and femoral neck along with the whole body and seven different anatomic areas (head, upper limbs, lower limbs, trunk, spine, ribs, pelvis). Subjects were classified as osteopenic (T-score $= -1.0$ to -2.4 DS) or OP (T-score < -2.5 DS) according to the T-score.

The bone qualitative assessment was also investigated with the trabecular bone score (TBS) analysis [iNsight (Medimaps group/GE Healthcare Needham, MA, USA, software version 2.1.0.0)]. The TBS is an index of bone quality derived from dual-energy (33). The lumbar spine L1–L4 TBS (unit-less) was calculated on each spine DXA examination. A normal range for TBS values in postmenopausal women has been proposed as follows: a TBS of $\geq$1.350 is considered normal; a TBS between 1.200 and 1.350 is considered consistent with partially degraded microarchitecture, and a TBS of $\leq$1.200 defines degraded microarchitecture (34).

A dedicated software analyzed, by non-invasive techniques, the whole-body composition and the different body composition of three major areas (arms, legs, and trunk) describing total body mass (TM) (gr), total lean mass (LM) (gr), total fat mass (FM) (gr) and bone mineral content (BMC) (gr) for each area. The RSMI was calculated using Baumgartner's equation and, according to the European Working Group on Sarcopenia in Older People criteria (4), we classified patients by having or not sarcopenia; RSMI was derived from the ratio between appendicular skeletal lean mass and height squared and sarcopenia is defined with values (< 5.5 kg/m^2 in women and < 7.26 kg/m^2 in men). The limited radiogenic emission required for the study of body composition has allowed the use of this method without invasiveness indices. The limited radiogenic emission required for the study of body composition has allowed the use of this method without invasiveness indices.

All patients performed Hand-Grip assessment to screen for sarcopenia (Camry; EH101 Units: Kg/libbers; Maximum capacity 90 Kg; Power 2X 1.5 V AAA batteries; Tolerance $\pm$ 0.5 Kg dynamometer) and lower cut-off values for sarcopenia were defined, respectively, as handgrip measurement <27 kg for males and <16 kg for females (35).

Patients were assigned to alendronate and/or denosumab anti-OP regimens, according to patient's clinical characteristics and based on the AIFA 79 prescription note (36). Namely, 26 patients were assigned to bisphosphonate treatment with alendronate 70 mg once a week, and 15 patients were assigned to denosumab treatment 60 mg 1 fl *via* subcutaneous injection one

TABLE 1 | Clinical characteristics of the study population along with mean DEXA osteo-metabolic parameters.

	Overall, *N* = 40	Alendronate, *N* = 25	Denosumab, *N* = 15	*p*
Age, Mean (SD)	82.1 (5.8)	81.4 (6.3)	83.3 (4.8)	0.315
Female, *N* (%)	35 (87.5)	22 (88.0)	13 (86.7)	0.999
Hip fracture type	16 (40.0)	12 (48.0)	4 (26.7)	0.317
BMI, Median (IQR)	22.7 (20.5, 25.6)	23.4 (20.6, 27.9)	21.0 (19.4, 23.6)	0.069
Hand Grip, Median (IQR)				
Females	15.70 (10.85, 17.75)	15.75 (11.10, 17.47)	15.00 (10.00, 17.80)	0.785
Males	22.50 (22.10, 24.30)	22.50 (19.70, 24.70)	23.20 (22.65, 23.75)	0.999
Barthel, Median (IQR)	90 (75, 100)	90 (70, 95)	95 (85, 100)	0.143
ADL, Median (IQR)	6 (5, 6)	6 (6, 6)	6 (5, 6)	0.247
IADL, Median (IQR)	7.0 (3.8, 8.0)	7.0 (5.0, 8.0)	7.0 (1.5, 8.0)	0.597
MNA-SF, Median (IQR)	12 (9, 13)	12 (10, 13)	12 (9, 12.5)	0.357
CIRS comorbidity, Median (IQR)	4.0 (2.8, 5.2)	4.0 (2.0, 5.0)	4.0 (3.5, 5.5)	0.977
CIRS severity, Median (IQR)	1.8 (1.6, 2.1)	1.8 (1.5, 2.1)	1.9 (1.7, 2.1)	0.769
N. of drugs, Median (IQR)	5.0 (3.0, 7.0)	5.0 (2.0, 7.0)	5.0 (4.5, 8.0)	0.338
<5	15 (37.5)	11 (44.0)	4 (26.7)	0.367
5–7	16 (40.0)	10 (40.0)	6 (40.0)	
8 or more	9 (22.5)	4 (16.0)	5 (33.3)	
SPMSQ Median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	2.0 (0.0, 3.0)	0.954
VIT.D 25-OH (ng/ml), Median (IQR)	15.60 (7.53, 25.45)	15.40 (6.20, 22.00)	21.40 (9.45, 26.60)	0.295
PTH (ng/L) Median (IQR)	33.50 (25.00, 50.50)	33.00 (25.00, 48.00)	35.00 (26.50, 51.50)	0.557
FN-BMD, Median (IQR)	0.65 (0.62, 0.73)	0.66 (0.63, 0.72)	0.63 (0.59, 0.73)	0.395
TH-BMD, Median (IQR)	0.72 (0.65, 0.77)	0.72 (0.65, 0.77)	0.72 (0.63, 0.78)	0.893
LS-BMD, Median (IQR)	0.96 (0.87, 1.07)	0.97 (0.88, 1.14)	0.91 (0.82, 1.03)	0.235
TBS, Median (IQR)	1.09 (0.96, 1.18)	1.07 (0.92, 1.13)	1.15 (1.06, 1.23)	0.050
RSMI kg/m^2, Median (IQR)	5.90 (5.12, 6.86)	6.22 (5.18, 7.02)	5.76 (5.08, 6.60)	0.299

BMI, body mass index; FN, Femoral neck; LS, Lumbar spine; TH, Total hip; ADL, activities of daily living; IADL, instrumental activities of daily living; CIRS, cumulative illness rating scale; MNA-SF, Mini nutritional assessment; SPMQS, short portable mental status questionnaire; PHT, parathormone; BMD, Bone marrow density; TBS, Trabecular bone score; RSMI, Relative skeletal muscle index.

every 6 months, respectively, due to the presence of renal failure (clearance < 30 ml/min) (70%) for the presence of esophagitis (5%) and the inability to comply with alendronate administration regimen (25%).

Data were collected at baseline (T0) and prospectively after 1 year (T1) from hip surgery at the orthogeriatric outpatient's office of the same hospital. This was an intention to treat analysis irrespective of patient's compliance and adherence to the prescribed drug regimens.

STATISTICAL ANALYSIS

Continuous variables were described as mean and standard deviation (SD) or median and inter-quartile range (IQR) and compared, respectively, with *t*-test or Mann-Whitney test. Categorical variables were expressed as number and proportion of patients and compared using the Chi-squared test.

The improvement of osteosarcopenic parameters was defined as any positive value of the difference between the last (after 1 year) and the first assessment. Unavailable measurements at the follow-up time were considered as not improved.

P-value < 0.05 was considered statistically significant. *P*-value < 0.005 was considered statistically significant. R-software version 4.0.2 (37) was used for all statistical analyses.

RESULTS

Baseline Clinical and Osteo-Metabolic Characteristics

Patients' clinical characteristics along with mean DEXA osteosarcopenic parameters, including median BMD scores, TBS scores, and RSMI scores are summarized in **Table 1**. Mean patients' ages were 82.1 years (SD = 5.8, range 67–94), and women were 87.5%. Baseline characteristics were comparable between treatment groups (**Table 1**), except for a lower BMI that was observed in the denosumab group compared to the alendronate group (median difference = −2.4, Mann-Whitney $p = 0.069$) and a slightly higher baseline TBS value in the denosumab group compared to the alendronate group (median difference = +0.08, Mann-Whitney $p = 0.050$).

The Longitudinal Patients' Osteosarcopenic Assessment After 1-Year From Hospital Dischage

Forty patients out of the 98 patients enrolled at baseline underwent longitudinal assessment (T1) after 1-year from hospital discharge and were included in the final analysis. Namely, eight patients deceased, and 50 patients discontinued the follow-up for higher istituzionalization rate, accounting for the higher dropout rate at follow-up.

TABLE 2 | Proportion of patients with osteo-metabolic and sarcopenic improvement at T1 assessment, on the basis of the assigned treatment groups.

Parameter	Overall, *N* = 40	Alendronate, *N* =25	Denosumab, *N* =15	*p*
FN-BMD, *N* (%)	23 (57.5)	16 (64.0)	7 (46.7)	0.457
TH-BMD, *N* (%)	25 (62.5)	17 (68.0)	8 (53.3)	0.555
LS-BMD, *N* (%)	29 (72.5)	21 (84.0)	8 (53.3)	0.082
TBS, *N* (%)	15 (37.5)	12 (48.0)	3 (20.0)	0.152
RSMI, *N* (%)	18 (45.0)	10 (40.0)	8 (53.3)	0.622
Hand grip, *N* (%)	18 (45.0)	12 (48.0)	6 (40.0)	0.870

FN, Femoral neck; LS, Lumbar spine; TH, Total hip; BMD, Bone marrow density; TBS, Trabecular bone score; RSMI, Relative skeletal muscle index.

The number of treatment responders for each osteosarcopenic parameters is reported in **Table 2**. At T1 assessment, we observed a slightly and non-significant BMD improvement in the alendronate group compared to the denosumab group, in all measured BMD districts (FN: 64.0 vs. 46.7%; TH: 68.0 vs. 53.3%; LS: 84.0 vs. 53.3%). Similarly, a slight and non-significant higher proportion of patients in the alendronate group showed a mild improvement of bone quality (TBS scores) compared to the denosumab group (48.0 vs. 20%), respectively. Moreover, a positive trend of RSMI measurements was observed in the denosumab group compared to the alendronate group (53.3 vs. 40%) (**Figure 2**).

Similarly, **Figure 2** illustrates the overmentioned longitudinal osteosarcopenic improvements on the basis of the patient's treatment group.

In addition, hand-grip longitudinal (T0-T1) measurements were reported in overall 31 female patients and, namely, a mean difference was reported in 19 patients treated with alendronate (19/22) [mean difference To-T1: +0.85 (SD = 4.8) Kg] and in 12/13 females treated with denosumab [mean difference T0-T1: +0.97 (SD = 6.0) Kg], respectively, indicating a positive HG grip trend over time (**Figure 3**). The missing number of hand-grip measurements were considered as non-responders.

Namely, in males, hand-grip longitudinal measurements(T0-T1) were reported for three patients treated with alendronate (2/3) (+2.3 Kg and +10 Kg from T0) and in one sole patient treated with denosumab (1/2) (−13.3 Kg from T0).

DISCUSSION

The present findings are preliminary and showed a relatively early trend of OP improvement in both BMD and bone microarchitecture (i.e., TBS) in the alendronate group as compared with denosumab, in a 1-year longitudinal observation.

However, a trend of improvement in sarcopenia (RSMI) was observed in the denosumab group as compared with the alendronate group, and similarly, although the high number of missing data and the prevalent female sex may be a selection bias, the hand-grip measurements showed a positive longitudinal trend in both assignment group.

To the best of our knowledge, although speculative in nature, this is the first report to longitudinally analyze osteosarcopenia in a real-world cohort of very old age patients after hip fracture.

Sparse clinical evidence exists for the impact of osteoporosis treatments in the given old age range, and no clinical trials have exclusively looked at people aged 80 years and more as the primary target.

On one hand, bisphosphonates have been the therapeutic mainstay for decades, and current guidance suggests and initial treatment course for 3–5 years for their early anti-resorptive effect pursuing a net bone density improvement. However, further treatment period might be considered on an individual basis to minimize the risks associated with more prolonged treatment, especially in frail and older populations (38).

On the other hand, it is known that bone histomorphometry findings for denosumab over years 2/3, year 5, and year 10 of treatment are consistent with the mechanism of action of denosumab, which potently inhibits bone resorption and remodeling and increases bone mass and strength over time (39). Namely, denosumab contributes to gains in BMD and may also contribute to reductions in fracture risk by increasing bone matrix strength and stiffness. On the basis of these findings, our limited longitudinal observation (1-year) may count for the unchanged bone density in the denosumab group.

Additionally, persistence of anti-resorptive drugs, including both denousmab and bisphosphonate, is a key factor for the successful management of osteoporosis and fragility fractures, especially in old, multimorbid patients receiving multiple drugs regimens. In the light of the current evidence, a high persistence of denosumab was observed in old-age women with fragility fractures, suggesting the need for further longitudinal analysis on the main determinants of persistence of both anti-resorptive drugs over time in such a comorbid and highly vulnerable population (40, 41).

So far, there is a paucity of data on the role of anti-resorptive drugs on bone microarchitecture in very old individuals, and the present findings seem to support a timely role for alendronate on bone quality compared to denosumab. In contrast with that, denosumab was previously observed to improve TBS independent on BMD in postmenopausal women with osteoporosis (42). However, it is to underscore that TBS assessment at baseline was slightly statistically unbalanced for the regression of the mean effect, creating an overestimation of the 1-year alendronate effect on TBS. Thus, a further statistical adjustment based on a longer clinical trajectories and different time points for osteometabolic assessment is warranted to strengthen this preliminary and partially reliable evidence.

Moreover, in humans, scant data are available on the beneficials effects of denosumab on skeletal muscle function (43), and this is especially true in frail older adults after a highly impacting environmental event, such as hip fracture. In particular, in a proof-of-concept trial, denosumab was reported to improve muscle mass and strength and hand grip in postmenopausal women with osteoporosis for an average duration of 3 years, compared to no treatment. The changes in appendicular lean mass and hand-grip strength were also strongly correlated with changes in lumbar spine BMD.

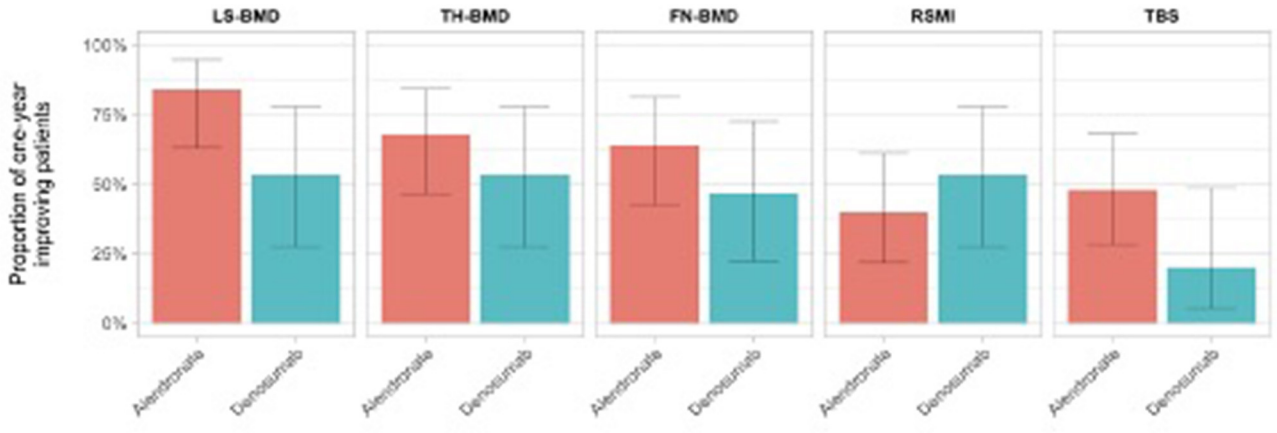

FIGURE 2 | Proportion of patients with osteosarcopenic improvement at T1 assessment on the basis of the assigned treatment group.

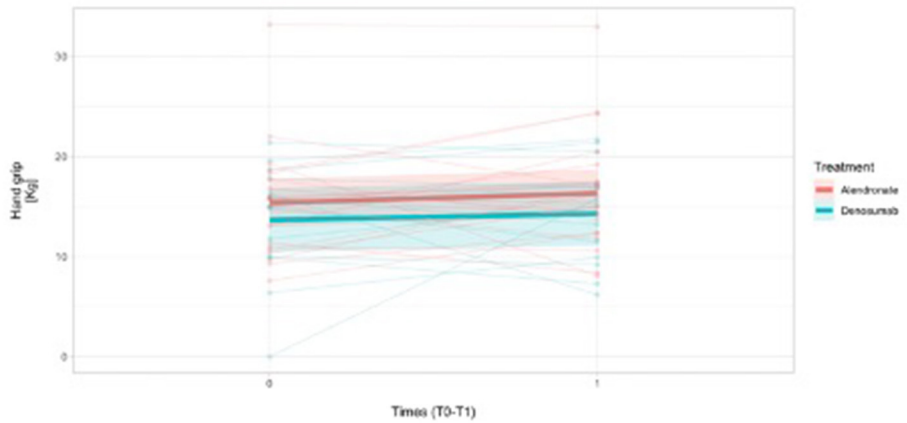

FIGURE 3 | Handgrip measurements trend over time (1 year time-frame observation) in females ($N = 31$) on the basis of the treatment assignment.

This scientific background may represent the biological plausibility of our findings and, in particular, the positive longitudinal trend for sarcopenia in the denosumab group may be the platform for further longitudinal assessment and intervention trials in such a highly vulnerable population.

However, the clinical complexity of frail old-age patients, the lack of systematic assessment of clinical, and/or exercise-based intervention targeting osteosarcopenia after hospital discharge and in between the observational period limited the generalization of the findings. Indeed, all patients received postsurgical rehabilitation on the basis of the best clinical practice (44, 45).

However, multiple intervening clinical variables, in between interventional pharmacological and non-pharmacological approaches (e.g., rehabilitation and/or physical therapy) in the time frame observation, may count for substantial clinical instability and heterogeneous frailty trajectories, affecting our ability to understanding the role of both denosumab and alendronate on osteosarcopenia in very old individuals.

In addition, several evidence gaps remain in this area of osteosarcopenia in very old individuals, including a paucity of data on the long-term effects of denosumab or other anti-resorptive agents on matrix mineralization variables, sarcopenia, and clinical outcomes, including any associations between treatment-related changes in bone density, microarchitecture and muscle strength, and long-term fracture outcomes.

Long- and short-term data on the effects of denosumab on bone quality, density, and on sarcopenia variables in very old individuals is warranted. Such a better understanding could help refining the conceptual framework of osteosarcopenia with regard to this highly vulnerable population. In turn, the potential identification of dual anti-resorptive drugs targeting both osteoporosis and sarcopenia is still at its infancy, but if appropriately tested in real-world geriatric trials, it could shed new light on potentially key relevant implications of such dyadic changes on fracture rates and skeletal adverse events over an extended period of uninterrupted denosumab treatment, serving as platforms for therapeutic achievements.

So far, the main limitations of the study are the small sample size and the high discontinuation rate that limited the longitudinal observation and the single population center that may represent a selection bias. In particular, it could be hypothesized that the high drop-put rate of patients relies on their frailty status, including higher posthospital discharge, functional disability, multimorbidity, and poorer social support with increased clinical instability and poorer access to health-care resources and services in the long-term period.

Moreover, there was no randomization and the group assignment was the result of the AIFA regulatory law, that might also count for further assignment biases.

Moreover, we cannot exclude that the improvements of glucose metabolism, neuromuscular function, and overall general health condition and frailty status in old-age patients within the observational period may be at least partially responsible for the improvement in bone and muscle strengths. Second, we did not test for physical performance in order to better understand the severity of sarcopenia and the degree of clinical benefits at the follow-up.

The strengths of the study are the real-world assessment of very old patients after hip fracture and their longitudinal assessment of osteometabolic and sarcopenic parameters for the definition of osteosarcopenia along with the systematic assessment of their clinical phenotypes, based on the comprehensive geriatric assessment. This study is part of an ongoing 3-year longitudinal clinical, and it could be hypothesized that the definition of long-term trajectories along with different time to response and sensitivity analyses for the two treatment groups may add knowledge to the field.

In conclusion, the present preliminary findings, although speculative in nature, moved a step forward in the understanding of "real world" old-age hip fracture patients from a therapeutic standpoint and might help in the identification of the best osteometabolic therapy for long-term treatment, exploring as well the potential dual role of denosumab as an anti-resorptive and muscle-strength-specific drug for osteosarcopenia in this highly vulnerable population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Liguria Regional ethical Commette IRCSS Policlinico san martino, Genoa, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP, MN, and AC: conceptualization and validation. CG and LP: data analysis and validation. LC: methodology, software, and formal statistical analysis. LM: data curation and validation. GB and AG: investigation and data analysis/interpretation. AN: writing, review, and editing. FS and FM: writing, review, editing, and supervision. All authors contributed to the article and approved the submitted version.

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Mapping Knowledge Structure and Themes Trends of Osteoporosis in Rheumatoid Arthritis: A Bibliometric Analysis

Haiyang Wu[1†], *Kunming Cheng*[2†], *Qiang Guo*[3†], *Weiguang Yang*[1], *Linjian Tong*[1], *Yulin Wang*[1] *and Zhiming Sun*[1,4*]

[1] Department of Clinical Medicine, Graduate School of Tianjin Medical University, Tianjin, China, [2] Department of Intensive Care Unit, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [3] Department of Orthopaedic Surgery, Baodi Clinical College of Tianjin Medical University, Tianjin, China, [4] Department of Orthopaedic Surgery, Tianjin Huanhu Hospital, Tianjin, China

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Barbara Ruaro,
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***Correspondence:**
Zhiming Sun
szhm618@163.com

[†]*These authors have contributed equally to this work*

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Background: Rheumatoid arthritis is a chronic disabling disease characterized by chronic inflammation, articular cartilage destruction, and reduced bone mass. Multiple studies have revealed that the development of osteoporosis in rheumatoid arthritis (RA; ORA) patients could be led to a reduced quality of life and increased healthcare costs. Nevertheless, no attempt has been made to analyze the field of ORA research with the bibliometric method. This study aimed to provide a comprehensive overview of the knowledge structure and theme trends in the field of ORA research from a bibliometric perspective.

Methods: Articles and reviews regarding ORA from 1998 to 2021 were identified from the Web of Science database. An online bibliometric platform, CiteSpace, and VOSviewer software were used to generate visualization knowledge maps including co-authorship, co-citation, and co-occurrence analysis. SPSS, R, and Microsoft Excel software were used to conduct curve fitting and correlation analysis, and to analyze quantitative indicators, such as publication and citation counts, *h*-index, and journal citation reports.

Results: A total of 1,081 papers with 28,473 citations were identified. Publications were mainly concentrated in North America, Western Europe, and Eastern Asia. Economic strength is an important factor affecting scientific output. The United States contributed the most publications (213) with the highest *h*-index value (46) as of September 14, 2021. Diakonhjemmet Hospital and professor Haugeberg G were the most prolific institution and influential authors, respectively. *Journal of Rheumatology* was the most productive journal concerning ORA research. According to the burst references, "anti-citrullinated protein antibodies" and "preventing joint destruction" have been recognized as the hot research issues in the domain. The keywords co-occurrence analysis identified "teriparatide," "interleukin-6," "Wnt," and "vertebral fractures" as the important future research directions.

Conclusion: This was the first bibliometric study comprehensively summarizing the trends and development of ORA research. Our findings could offer practical sources for scholars to understand the key information in this field, and identify the potential research frontiers and hot directions in the near future.

Keywords: rheumatoid arthritis, osteoporosis, bibliometrics, CiteSpace, VOSviewer

INTRODUCTION

Rheumatoid arthritis is an autoimmune disorder with a nearly 1% prevalence in the global population and is generally associated with significant morbidity and mortality (1). Chronic inflammation, a hallmark feature of rheumatoid arthritis (RA) disease, causes articular cartilage destruction and bone erosion, which subsequently leads to generalized osteoporosis with reduced bone mass (2, 3). Development of osteoporosis in RA (hereafter ORA) patients results in a further reduced quality of life and increased healthcare costs. Apart from that, abundant studies have demonstrated that the incidence of osteoporotic fractures in patients with RA is higher than in the matched non-RA population (4–7). It was estimated that the occurrence of femoral neck fractures and vertebral compression fractures in these patients was increased 2-fold than a healthy population of the same age (6). Data from the National Data Bank for Rheumatic Diseases in the USA suggested that osteoporotic fracture was the third leading cause of mortality in RA patients (1). Therefore, the updated American College of Rheumatology (ACR) guidelines and recommendations for RA treatment have stressed the prevention and control of ORA patients.

In view of the aspects described above. ORA has received increasing attention from scholars. However, to date, relatively little is known about the exact pathogenetic mechanisms that determine the severity of bone loss (8). In addition, there are still some controversies derived from ORA, such as the fracture risk assessment and risk factors, the effectiveness of disease-modifying antirheumatic drugs (DMARDs) on preventing bone loss, time-window for fracture prevention, and the optimal anti-osteoporotic protocols, and so on (9–12). Motivated by these concerns, a considerable amount of research related to ORA was published and this topic has gained increasing attention among scholars. Nevertheless, the rapidly increasing number of publications makes it more and more difficult for researchers to keep up with the latest findings, even inside their domain of expertise. Although several systematic reviews and meta-analyses surrounding this topic could offer innovations and basic information to researchers, these summative reviews merely focus on a unique perspective of ORA research, while some meaningful information such as the numerical growth trend, the contributions of countries, institutions, and authors, prediction of future research hotspots are not included (10, 13). Some studies pointed out that early-career researchers could benefit from the overview analysis of knowledge structure and current hotspots in a certain field (14, 15). Given this, bibliometric analysis has become an increasingly popular approach to acquiring the above-mentioned parameters.

Bibliometrics is a feasible method to analyze the scientific production quantitatively and qualitatively and the current status of a given research field. With the development of information technologies, the information visualization of bibliometrics has been achieved and several freeware bibliometric tools including CiteSpace (16), VoSviewer (17), R-bibliometrix (18), and HistCite (19) have been widely used medical fields such as orthopedics (20), neurology (21), oncology (22, 23), and rheumatology (24). Taking RA and osteoporosis as examples, Schöffel et al. (24), have performed the first bibliometric analysis of 78,128 documents regarding RA during the period 1901–2007. And their analysis has revealed the most prolific authors, institutions, and journals dealing with the topic. Wang et al. conducted a bibliometric study based on the WoS database to explore the publication status and research hotspots in the field of RA-related depression (25). Additionally, several scholars also investigated the publications on osteoporosis by using bibliometric methods and mapped the overall knowledge structures of the field (26, 27). However, as far as we know, although there had been several bibliometric studies on RA or osteoporosis, no attempt has been made to analyze the field of ORA to date. In order to fulfill this knowledge gap, this study aimed to make an overall analysis of scientific publications on ORA research from 1998 to 2021, thus identifying the main contributors and current research status, as well as presenting prospects for future development of this field.

MATERIALS AND METHODS

Data Acquisition and Search Strategy

Web of Science (WoS, Clarivate Analytics, Philadelphia, PA, USA), which contains more than 12,000 international academic journals, is one of the most comprehensive and authoritative database platforms to obtain global academic information (28). Apart from the general literature search, it also possesses an important function of citation index searching, which is helpful for assessing the academic performance of literature in a specific field. In our study, all the documents were retrieved and downloaded from the Science Citation Index Expanded (SCI-Expanded, 1998-present) of the WoS Core Collection (WoSCC) database on September 14, 2021, to avoid bias due to daily updates of the database. The search formula was set with reference to previous studies. Among these, as RA was the main research subject of this study, in order to achieve more precise results, terms related to "rheumatoid arthritis" were searched based on the titles (TI) and author keywords (AK). While terms related to "osteoporosis" were searched based on the TI, abstracts (AB), and AK. The specific search formula was as

follows (**Figure 1**): #1: TI=("rheumatoid arthritis") OR AK = ("rheumatoid arthritis"); #2: TI = (osteoporosis OR osteopenia OR osteoporotic OR "bone loss*" OR "low bone mass" OR "low bone density") OR AK = (osteoporosis OR osteopenia OR osteoporotic OR "bone loss*" OR "low bone mass" OR "low bone density") OR AB = (osteoporosis OR osteopenia OR osteoporotic OR "bone loss*" OR "low bone mass" OR "low bone density"); final dataset: #1 AND #2. A total of 1,597 publications were retrieved, of which 516 invalid records including proceedings paper, editorial material, correction, meeting abstract, letter, early access, retracted publication, and non-English works of literature were excluded. Ultimately, 1,081 valid documents were obtained as the final dataset and exported in the form of "full record and cited references" for further analysis. Afterward, the plain text files were renamed for further analysis as CiteSpace software can only recognize files named with the specified name of "download*.txt".

Data Extraction

The final dataset was first imported into CiteSpace software (Chaomei Chen, Drexel University, USA) to remove duplicates. Then two independent researchers (WHY and CKM) performed the data extraction to ensure the accuracy and reliability of the results. Any disagreements among the two investigators were discussed until consensus was reached. The extracted data included publication counts, citation times, countries, institutions, authors, funding agencies, subject categories, journals, highly-cited articles, and keywords. By using the function of "Create Citation Report" in WoSCC, the Hirsch index (*h*-index), and Average Citations per Item (ACI) of counties, institutions, and authors were acquired. The journal information including impact factor (JIF) and Quartile in category (Q1, Q2, Q3, and Q4) was obtained from the 2020 Journal Citation Reports (Clarivate Analytics, Philadelphia, PA, USA). Moreover, in consideration of the differences in economic and demographic conditions in different countries, several ratio indices including the number of papers per million people, and several papers per trillion Gross Domestic Product (GDP) was introduced (28).

Data Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 21, Inc., Chicago, IL, USA), R software (v3.6.3., R Foundation, Vienna, Austria), and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). Categorical data were expressed as count (percentage). The growth rate of publications over time was calculated with the following formula reported by Guo et al. (29). Growth rate = [(number of documents in the last year ÷ number of documents in the first year)$^{1/(\text{last year} - \text{first year})}$ – 1] × 100. The strength of correlation between continuous variables was assessed using Pearson's correlation coefficient. The strength of correlation coefficients was interpreted as follows: 0.00–0.25 as little if any correlation, 0.26–0.49 as low correlation, 0.5–0.69 as moderate correlation, 0.7–0.89 as high correlation, 0.9–1 as very high correlation. Correlations were considered statistically significant when the *p*-value was <0.05.

Bibliometric and visualization analyses were conducted by three bibliometric tools. CiteSpace, free Java-based software developed by Chen (16), is one of the most popular bibliometric tools for visualizing and analyzing the scientific literature and is often used to ascertain the knowledge structure, distribution, as well as evolution of a given field. In our study, CiteSpace was utilized to (a) perform a cooperation analysis of institutions; (b) analyze the co-citation relationship of authors; (c) conduct a dual-map overlay of scientific journals; (d) perform a co-citation analysis of references; (e) identify the top 25 references with the strongest citation bursts. In the network maps, the nodes represent various items such as institutions, authors, and references. The node size and color rings indicate the number of these items and different years, respectively. The lines between the nodes reflect the cooperation or co-citation relationships of items (28, 30).

VOSviewer, another bibliometric software developed by Professor van Eck and Waltman (31), has text mining capabilities to extract important parameters from a large pool of scientific publications for construction and visualization of co-authorship, co-citation, and co-occurrence network (32). In this research, this software was mainly applied to conduct visualization networks including institution co-authorship analysis, author co-authorship analysis, journal co-citation analysis, and keywords co-occurrence analysis. In addition, VOS viewer is able to provide three types of network maps, including the network visualization map, the overlay visualization map, and the density visualization map. For detailed descriptions of these maps, one can find the software manual at https://www.vosviewer.com/documentation.

Moreover, an online bibliometric platform (https://bibliometric.com/) was also applied to conduct the collaboration analysis of countries and annual publication trend analysis.

RESULTS AND DISCUSSION

Publication Outputs and Citation Trends

The number of publications and citations in each period can be a direct reflection of the development trend of scientific knowledge in a particular area. After the above-mentioned literature screening, a total of 1,081 publications, including 881 original articles and 200 reviews, were included in the final analysis. The specific distribution of annual publications of ORA research is shown in **Figure 2A**. As can be seen, despite the appearance of the volatility to decrease at some time points, the annual number of publications related to ORA showed an ascending tendency as a whole and reached its peak in 2019 with a total of 85 documents, which comprised 7.86% of the total quantity. From 1998 to 2019, the average growth rate of scientific publications regarding ORA research was 21.81%. The number of papers in this year, 2021, has reached a count of 75 as of September 14, 2021. When it comes to the number of citations, the cumulative total citations of these publications were 28,473 times (23,692 times after the removal of self-citations), with an average of 26.34 times per publication. As can be seen from the distribution of the annual number of citations (**Supplementary Figure 1**), it exhibited a linearly increasing trend ($R^2 = 0.9508$). There were over 2,000 citation frequencies per year in the past 5 years. Collectively,

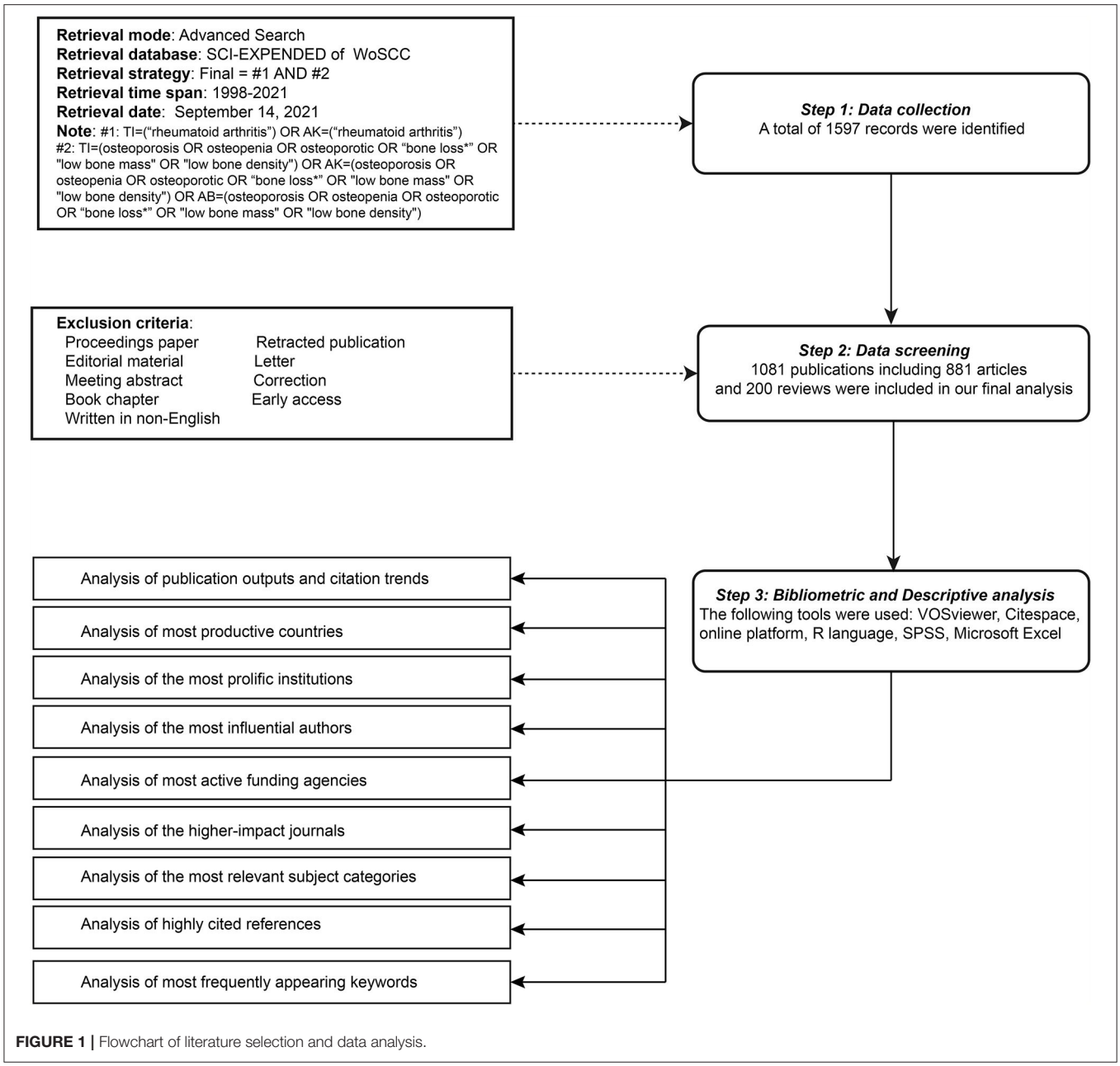

FIGURE 1 | Flowchart of literature selection and data analysis.

with an in-depth understanding of RA and osteoporosis, the role of osteoporosis in RA has gradually attracted the attention of scholars as reflected from both annual publications and citations quantity. And in recent years, an increasing number of studies in the pathogenesis of osteoporosis in RA have been revealed.

Basic Knowledge Structures of ORA Field

Analysis of Most Productive Countries

A world map depicting the contribution of each country was shown in **Figure 2B**. According to the indicated color gradient, we can clearly observe that the vast majority of the works of literature were published by researchers from regions such as North America, Western Europe, and Eastern Asia. Comparison of the total number of scientific publications between the three regions showed that authors from Western Europe have published 2.05 times more papers than Eastern Asian authors, and 2.48 times higher than North American authors. Thus, it could be concluded that Western European countries were the most active regions for the ORA-related research. Although the previous bibliometric studies about RA did not compare the number of documents from the three regions, similar findings have been reported by a bibliometric study on postmenopausal osteoporosis, which found that the number of papers published by Western European authors was about 75% greater than North America authors (24–26).

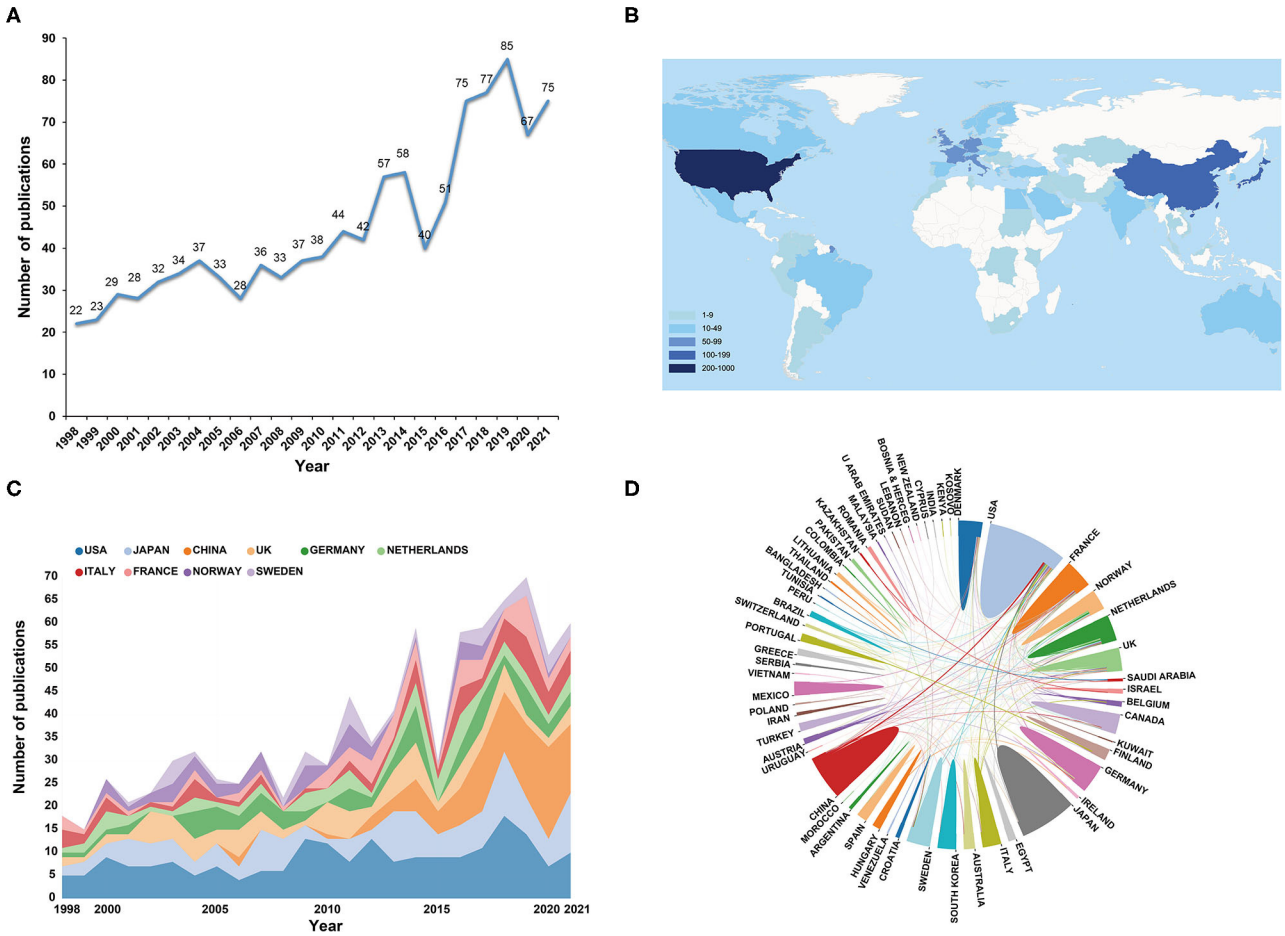

FIGURE 2 | (A) The annual number of publications regarding osteoporosis in RA research from 1998 to 2021. **(B)** A world map depicting the contribution of each country based on publication counts. **(C)** The annual number of publications in the top 10 most productive countries from 1998 to 2021. **(D)** International collaboration analysis among different countries.

In specific, as displayed in **Table 1**, the USA has published the most publications in this domain, with 213 (19.7%) documents, followed by Japan and China, and the remaining countries have published <100 articles. In addition, after adjusting by population size and GDP, Norway both occupied the first position with 8.41 papers per million people and 112.5 papers per trillion GDP. As we all know that Norway is a welfare state, where both primary and specialist health care is provided by well-developed publicly funded services. Statistics have revealed that apart from Luxembourg, there is no country spending more on publicly financed health care per capita than Norway (33). Medical investment from the government may be a key incentive for scientific research output. Moreover, our correlation analysis results showed that there was no significant correlation between the number of publications and demographic data ($r = 0.404$, $p = 0.077$), while publication counts and GDP has a high positive correlation ($r = 0.852$, $p < 0.001$). This outcome further illustrates that economic strength is an important factor affecting scientific output. As for the *h*-index, it is defined as the number of publications for an individual, *h*, each acquiring at least *h* citations. The metric thus enables an assessment of the quality and quantity of publications from a country, author, or journal. In this study, the USA (34), UK (35), Netherlands (33), Germany (28), and Italy (28) were the top five countries with the highest *h*-index. The value of this metric might be influenced by the time factor, that is, the relatively new entrants in this field have not accumulated sufficient citations. As can be seen from **Figure 2C**, prior to 2011, the USA, Japan, and the UK dominated in this field in terms of publications counts, while China experienced rapid growth since 2015, and even surpassed the USA for the first time in 2019. This tendency seems consistent with that of the economic growth process in China. Predictably, the *h*-index in China may further increase in the near future.

Additionally, ACI is another indicator that reflects the value of the paper and its contribution to science. It is evident from **Table 1** that China and Japan have occupied the second and third positions with regard to the number of publications, but the ACI was much lower than that of some European and American countries. As a result, except for quantity increase, there is still a need for improving the quality of publications. **Figure 2D**

TABLE 1 | Top 20 countries with the most publications related to ORA research.

Rank	Country	Contribution	% of 1,081	Number of papers per trillion GDP	Number of papers per million people	*h*-index	ACI
1	USA	213	19.70	9.94	0.65	46	33.5
2	Japan	145	13.41	28.54	1.15	24	16.54
3	China	109	10.08	7.09	0.08	23	17.11
4	UK	96	8.88	33.92	1.44	36	48.03
5	Germany	72	6.66	18.65	0.87	28	38.21
6	Netherlands	65	6.01	71.43	3.75	32	54.09
7	Italy	63	5.83	31.50	1.04	28	41.86
8	France	62	5.74	22.79	0.92	26	34.15
9	Norway	45	4.16	112.50	8.41	25	47.31
10	Sweden	43	3.98	81.13	4.18	19	32.28
11	South Korea	41	3.79	24.85	0.79	13	22.66
12	Canada	31	2.87	17.82	0.82	18	28.71
13	Denmark	29	2.68	82.86	4.98	19	29.21
14	Australia	28	2.59	20.00	1.10	16	53.32
15	Spain	23	2.13	16.55	0.49	13	34.39
16	Finland	22	2.04	81.48	3.99	14	20.18
17	Turkey	21	1.94	27.63	0.25	11	14.81
18	Austria	20	1.85	44.44	2.25	15	66.6
19	Belgium	20	1.85	37.74	1.74	15	41.65
20	Brazil	17	1.57	9.24	0.08	12	19.59

Rank, based on the number of total publications; GDP, Gross Domestic Product; ACI, Average Citations per Item.
Publications from Taiwan, Hong Kong, and Macau were assigned to China, and those from England, Northern Ireland, Scotland, and Wales were reclassified to the UK. The Demographic and GDP data were downloaded from the official website of the People's Republic of China, and the World Bank official website (https://data.worldbank.org.cn/).

displays the international cooperation among different countries. The line thickness between the two countries indicates the strength of cooperation. It can be seen that the USA collaborated most closely with China, Japan, the UK, and Italy. Overall, most of the collaborative relationships are mainly confined to European, American, and East Asian countries. Cooperation in less developed nations needs to be further enhanced.

Analysis of the Most Prolific Institutions

As for the analysis of institutions, it was roughly estimated that more than 1,500 institutions have made contributions to this field. The bar graph of **Figure 3A** demonstrated the publication counts, *h*-index, and ACI of the top 10 most prolific institutions in detail. Of these, three are from the USA, three are from Norway, and the remaining four are from Japan, Germany, Netherlands, and China. To be specific, Diakonhjemmet Hospital in Norway ranked first with 28 articles. The University of Alabama Birmingham from the USA was in second place with 21 publications, while Sørlandet Hospital from Norway and Tokyo Women's Medical University from Japan tied for third place with 18 publications. In terms of other quantitative indices, like *h*-index and ACI, Diakonhjemmet Hospital has the highest *h*-index of 20, and Sørlandet Hospital followed suit (16). The top three institutions with the highest value of ACI were the University of Massachusetts System (74.21 times), Diakonhjemmet Hospital (57 times), and the University of Erlangen Nuremberg (50.5 times). It is interesting to notice that despite the publication counts and *h*-index being not high, the ACI in the University of Massachusetts System was much higher than other institutions. One possible reason is that several studies from this institution have attracted enormous attention. We observed that a multicenter study including participants from the University of Massachusetts System, which explored the prevalence of comorbidities in RA has received more than 406 citations (36). Due to this, as mentioned in previous studies, citations or ACI may not fully capture the impact of scientific work, and evaluate the impact of an individual or institution (37).

Additionally, in our increasingly interdependent and globalized world, it is generally accepted that cross-country and inter-organizational collaboration is important ways to improve research quality and productivity. In this study, institution cooperation analysis was also conducted by CiteSpace software. As seen in **Figure 3B**, collaborations between institutions are scattered within high-income countries such as North America and Western European countries. Despite the fact that some Asian countries have made great contributions in the case of publication counts, institutions in these regions do not form a cooperation network, indicating a lack of academic exchange among Asian countries as well as research institutions. In addition, of all these institutions, the University of Alabama Birmingham had the highest centrality, with a betweenness centrality (BC) value of 0.13. BC is an indicator of the centrality of a node, which can reflect the importance of nodes within the networks. Generally, nodes with a BC value of more than 0.1 occupy pivotal positions connecting a large number of nodes and are usually identified as hubs of nodes displayed in purple

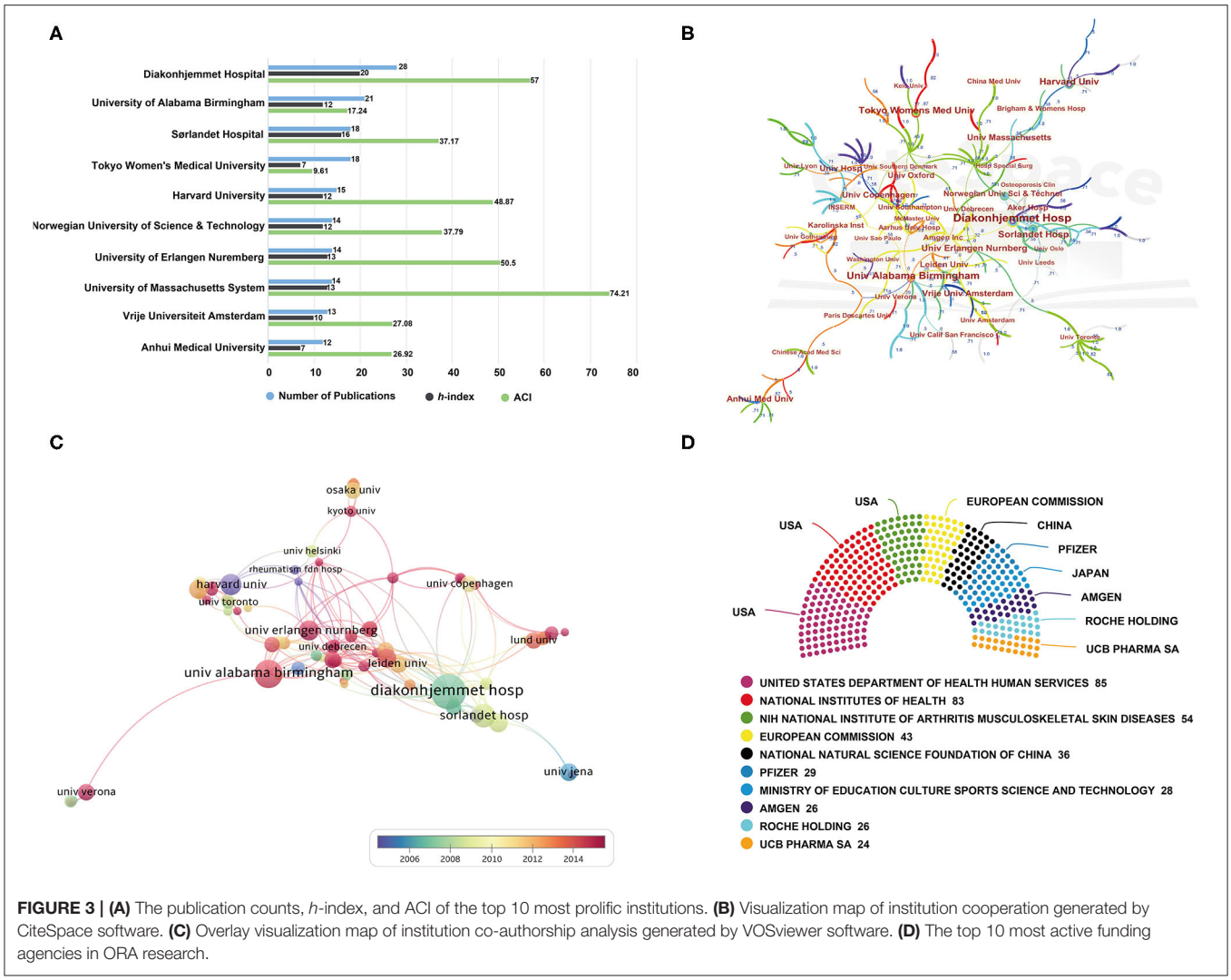

FIGURE 3 | (A) The publication counts, *h*-index, and ACI of the top 10 most prolific institutions. **(B)** Visualization map of institution cooperation generated by CiteSpace software. **(C)** Overlay visualization map of institution co-authorship analysis generated by VOSviewer software. **(D)** The top 10 most active funding agencies in ORA research.

rings (21, 30). It can be seen that the University of Alabama Birmingham was the only institution with a BC value of more than 0.1, which suggests that other institutions have not formed a strong influence in the field. Therefore, as pointed out by other researchers, there is an urgent need to remove academic barriers, improve cooperation and communication in different research institutions and teams (35, 38).

Apart from CiteSpace software, we also performed a co-authorship analysis of institutions by VOSviewer. Co-authorship analysis is a commonly used method to establish similarity relationships among individuals or groups through the number of co-authored publications (28, 39). As illustrated in the overlay visualization map in **Figure 3C**, nodes that represent institutions were marked by different colors based on the average appearing year (AAY) of each institution. According to the color gradient indicated in the lower right corner, it could be found that several institutions, e.g., Harvard University, Tampere University Hospital, and University of California San Francisco, were given purple color with the smaller values of AAY, suggesting that most of the researchers in these institutions were the relatively earlier entrants in this field. By contrast, many institutions marked with red or dark red color could be the relatively new participants of ORA research.

Analysis of Most Active Funding Agencies

As noted above, the economic foundation plays an important role in scientific development. In view of this, a brief summary of the top 10 most active funding agencies and sponsors in this area is provided in **Figure 3D**. In the case of distribution, funding organizations from the USA including the United States Department of Health Human Services, National Institutes of Health, and NIH National Institute of Arthritis Musculoskeletal Skin Diseases, occupied the top three positions contributed to ORA research, with 85, 83, and 54 studies, respectively. The remaining were from European Union, China, and Japan, and some pharmaceutical companies such as Pfizer and Amgen, among others. As is evident from these results, in addition to the well-established institutions, the USA maintained its leading position in the domain of ORA research cannot be separated from the support of adequate funding.

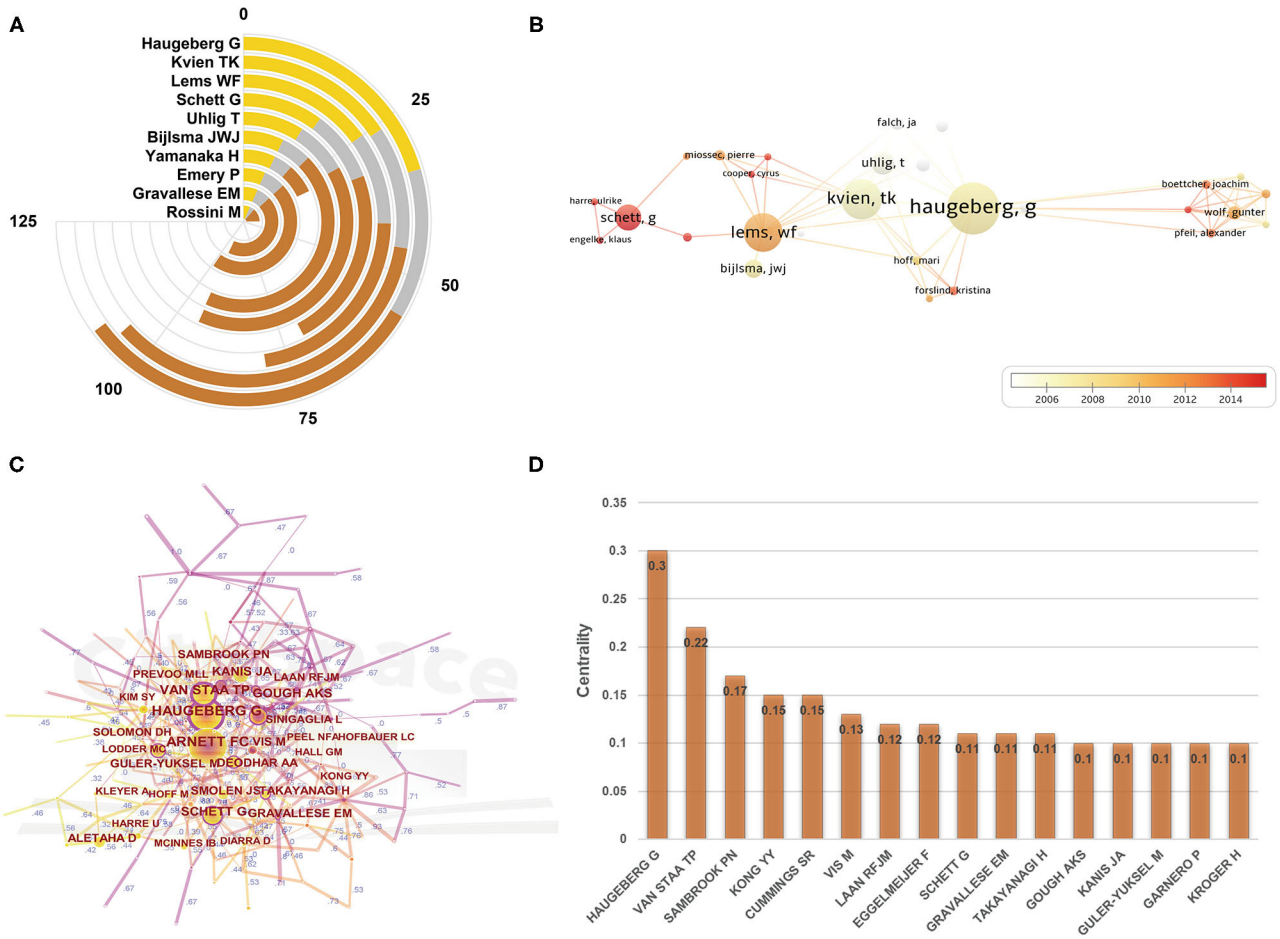

FIGURE 4 | (A) The publication counts, *h*-index, and ACI of the top 10 most prolific authors. **(B)** Overlay visualization map of author co-authorship analysis generated by VOSviewer software. **(C)** Visualization map of author co-citation analysis by using CiteSpace software. **(D)** All the authors with a centrality value of more than 0.1 (author co-citation analysis).

Analysis of the Most Influential Authors

The number of scientific publications written by one author is able to represent the degree of research activity and contribution in the field. More than 5,000 authors participated in the publication of these 1,081 documents. From the perspective of publication counts (**Figure 4A**), Haugeberg G from Norway was the author with the highest number of publications, followed by Kvien TK, and Lems WF. Apart from that, they were also the top three authors with the highest *h*-index. Of them, Haugeberg G and Kvien TK came from the same research institution. In the year 2000, they published work about bone mineral density (BMD) and frequency of osteoporosis in women RA patients aged 20–70 years. The results of their study reported that a 2-fold increase in osteoporosis was found in this population (4). This report has risen much attention in the field of ORA research and has been cited over 350 times up to now. In addition, Haugeberg and colleagues have also completed several population-based cohort studies that evaluated the impact of drug interventions including prednisolone, and infliximab combined with methotrexate on the bone density of RA patients. The results revealed that RA-related bone loss in hand bone can be decelerated by prednisolone (40). In the meantime, they also found that infliximab was potent enough to arrest inflammatory-related loss of hip bone density in early RA patients (41).

Scholars devoted to different research priorities have unique professional knowledge, among which cross-cooperation can promote communication and productivity of a certain research subject. In addition, an analysis of the co-authorship of authors is advantageous for researchers to learn existing partnerships and develop potential cooperative subjects. In **Figure 4B**, an overlay visualization map of author co-authorship analysis was generated by VOSviewer software. As can be seen that several research clusters were created, and each cluster was radiated by one or two core authors such as Haugeberg G, Kvien TK, Lems WF, and Schett G. Overall, there were only a few links between different clusters, indicating that the communication and collaboration in this domain have not been well developed. Besides, according to the color gradient indicated in the lower right corner, one can also understand the AAY of each author, that marked with different

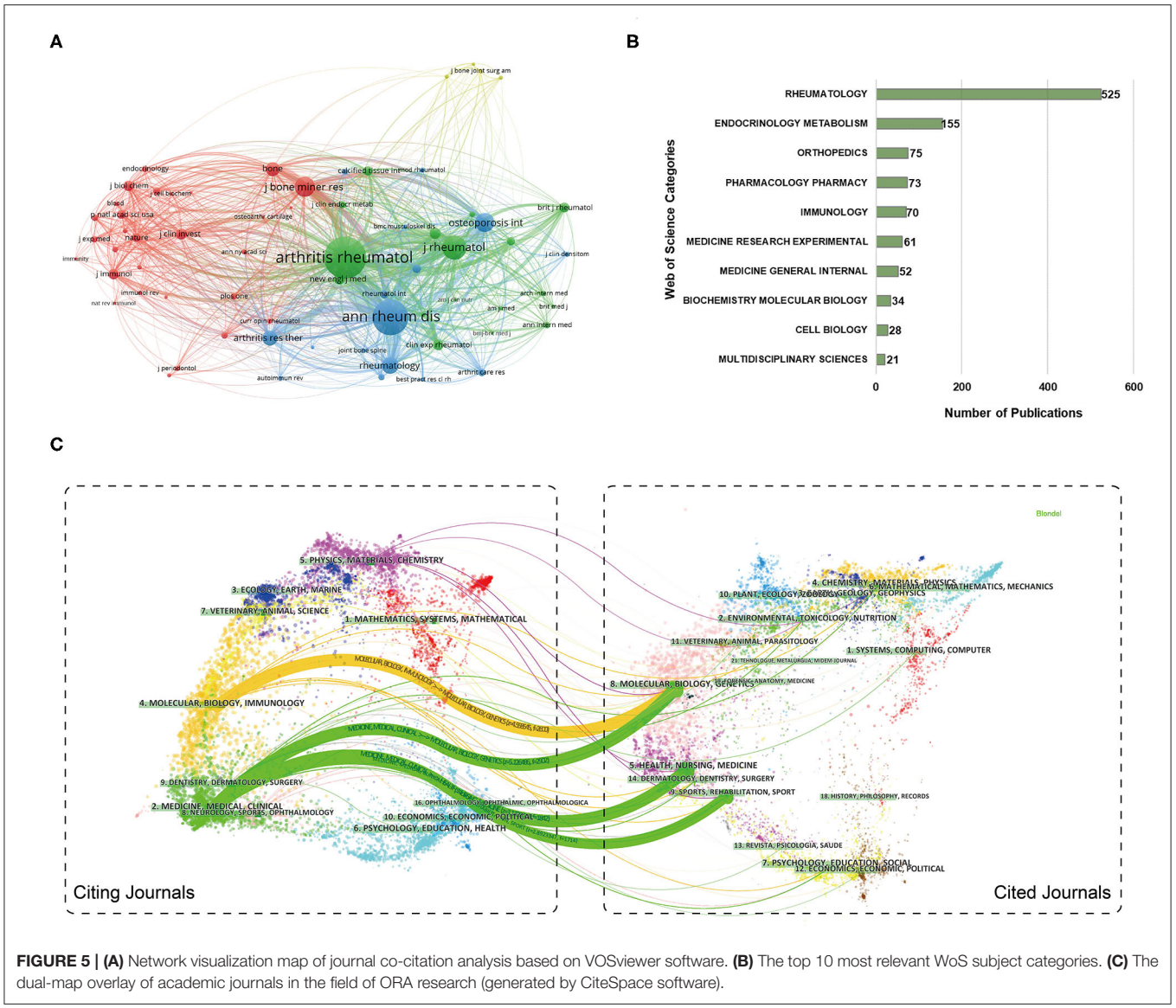

FIGURE 5 | (A) Network visualization map of journal co-citation analysis based on VOSviewer software. **(B)** The top 10 most relevant WoS subject categories. **(C)** The dual-map overlay of academic journals in the field of ORA research (generated by CiteSpace software).

colors. As it can be noticed, the cluster centered on Schett G seems to be relatively younger researchers in this field.

The co-citation relationship refers to two authors/works of literature appearing together in the reference list of a third document (28). The author co-citation analysis is often used to reveal the key authors in a co-citation network of a particular field. Generally, frequently cited authors are thought to have a greater influence than those less cited. And authors who are jointly cited are likely to focus on similar research areas. As displayed in **Figures 4C,D**, Haugeberg G had the largest BC value (0.3), ranked first among the top 10 co-cited authors, followed by Van Staa TP (0.22) and Sambrook PN (0.17). Professor Van Staa TP works at the University of Southampton. He and co-workers published a study estimating the long-term absolute fracture risk of RA patients (9). The study found that patients with RA were at increased risk of osteoporotic fractures, and they suggested this could be due to the use of oral glucocorticoids, which seems to be inconsistent with some previous studies (40). As for professor Sambrook PN from Garvan Institute of Medical Research, he and colleagues primarily devoted to the potential pathogenetic mechanisms that cause generalized osteoporosis in RA (42, 43). From the above results, it is clear that Haugeberg G was the most influential author in the ORA field, either from the volume of publications or the co-authorship and co-citation perspective.

Analysis of the Higher-Impact Journals

For centuries, scientific publications have always been essential tools for science communication of scientists and researchers in all fields. The presentation of research results in an international peer-reviewed journal is an essential component to establish effective scientific communication (23, 28). The analysis of the distribution of journal sources is helpful for researchers to quickly find the most appropriate journals for their articles. With preliminary statistics, all these publications related to ORA

TABLE 2 | Top 20 journals with most publications in the field of ORA research.

Ranking	Sources title	Output	% of 1,081	JIF (2020)	Quartile in category (2020)
1	*Journal of Rheumatology*	64	5.92	4.666	Q2
2	*Rheumatology*	47	4.35	7.58	Q1
3	*Clinical Rheumatology*	44	4.07	2.98	Q3
4	*Osteoporosis International*	44	4.07	4.507	Q2
5	*Rheumatology International*	44	4.07	2.631	Q4
6	*Annals of the Rheumatic Diseases*	43	3.98	19.103	Q1
7	*Arthritis Research Therapy*	35	3.24	5.156	Q2
8	*Clinical and Experimental Rheumatology*	32	2.96	4.473	Q2
9	*BMC Musculoskeletal Disorders*	25	2.31	2.362	Q2/Q4
10	*Modern Rheumatology*	23	2.13	3.023	Q3
11	*Arthritis and Rheumatology*	24	2.22	10.995	Q1
12	*Calcified Tissue International*	21	1.94	4.333	Q2
13	*Journal Of Bone and Mineral Metabolism*	20	1.85	2.626	Q3/Q4
14	*Best Practice Research in Clinical Rheumatology*	15	1.39	4.098	Q3
15	*Bone*	15	1.39	4.398	Q2
16	*Joint Bone Spine*	15	1.39	4.929	Q2
17	*Scandinavian Journal of Rheumatology*	14	1.30	3.641	Q3
18	*Arthritis Care Research*	13	1.20	4.794	Q2
19	*Current Opinion in Rheumatology*	13	1.20	5.006	Q2
20	*Frontiers in Immunology*	12	1.11	7.561	Q1

After checking the names of the journals, we ascertained that Arthritis and Rheumatism changed their name to Arthritis and Rheumatology. This was also found in the Journal of Bone and Joint Surgery Br and Bone and Joint Journal. The data from the same journals were merged.

research were distributed in more than 1,000 journals, and **Table 2** summarized the basic information on the top 20 most prolific journals. Of these, *Journal of Rheumatology* (64, 5.92%) had the highest number of outputs, followed by *Rheumatology* (47, 4.35%), *Clinical Rheumatology* (44, 4.07%), *Osteoporosis International* (44, 4.07%), and *Rheumatology International* (44, 4.07%). Furthermore, the JIF of a journal is an important factor parameter to evaluate its value and that of included publications. This concept of the JIF of the journal developed by Garfield (44), was intended to be a measurement of a 2-year moving average citation of a journal. Among the top 20 academic journals, *Annals of the Rheumatic Diseases* (19.103) has the highest JIF, followed by *Arthritis & Rheumatology* (10.995), and *Frontiers in Immunology* (7.561). Journal Citation Reports also split journals belonging to the same WoS categories into four equal parts based on JIF value, among which the top 25% attributed to Q1 and the top 25–50% being Q2, and so forth. It can be seen from **Table 2** that 20% of journals belong to Q1. As for the research domain of these journals, 70% of them were classified into rheumatology.

In terms of the publisher, of these top 20 journals, eight were from England, six were from the USA, and the others came from Canada, Germany, Italy, Japan, France, and Switzerland. Remarkably, the majority of these active journals were based in Western Europe and North America. Although the East Asiatic region was also one of the predominant contributors in this field, there was only one publisher from Japan, and even no one Chinese journal, indicating that Asian countries, especially China should strengthen the development of international journals to further improve the academic influence in the field. It is laudable that the Chinese government has invested a large number of resources into international journals construction, and multiple incentives have been promulgated in recent years (45). With the exception of publication counts, the influence of a journal also depends on the number of times they are co-cited in a particular research field. In this work, co-citation analysis of journals was performed by using the VOSviewer software. As shown in **Figure 5A**, journals with a minimum of 100 citations were included in the visualization analysis. There were 66 nodes, four clusters, and 2,144 links in the network map. The top five journals with the largest citations were *Arthritis & Rheumatology*, *Annals of the Rheumatic Diseases*, *Journal of Rheumatology*, *Journal of Bone and Mineral Research,* and *Osteoporosis International*. The results indicated that these journals have published numerous high-profile studies that attracted great attention from researchers interested in this field. Of these, *Arthritis & Rheumatology*, *Annals of the Rheumatic Diseases*, and *Journal of Rheumatology* mainly focus on studies of the rheumatic diseases, while *Journal of Bone and Mineral Research*, and *Osteoporosis International* are the primary journal containing bone and metabolism-related studies. It is therefore predictable that there may be more high-quality research published in these journals.

Analysis of the Most Relevant Subject Categories

In the WoSCC database, each article was labeled with one or more subject categories to facilitate rapid search. The top 10 subject categories in terms of the number of publications were shown in **Figure 5B**. Consistent with the distribution of journals,

TABLE 3 | The top 20 most cited works of literature on ORA.

Title	Journal	First Author	Publication year	Total citations
Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis	*Rheumatology*	Choy E	2012	420
Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA)	*Annals of the Rheumatic Diseases*	Dougados M	2014	406
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 and Rheumatism*	Haugeberg G	2000	363
Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis	*Arthritis and Rheumatism*	van Staa TP	2006	359
Low-dose prednisone therapy for patients with early active rheumatoid arthritis: Clinical efficacy, disease-modifying properties, and side effects-A randomized, double-blind, placebo-controlled clinical trial	*Annals of Internal Medicine*	van Everdingen AA	2002	341
Involvement of receptor activator of NF kappa B ligand and tumor necrosis factor-alpha in bone destruction in rheumatoid arthritis	*Bone*	Romas E	2002	318
Biology of the RANKL-RANK-OPG system in immunity, bone, and beyond	*Frontiers in Immunology*	Walsh MC	2014	314
RANK/RANKL: Regulators of Immune Responses and Bone Physiology	*Annals of the New York Academy of Sciences*	Leibbrandt A	2008	280
Relationship between rheumatoid arthritis and periodontitis	*Journal of Periodontology*	Mercado FB	2001	255
Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate - A two-year randomized trial	*Arthritis and Rheumatism*	Svensson B	2005	251
IL-7 induces bone loss *in vivo* by induction of receptor activator of nuclear factor kappa B ligand and tumor necrosis factor a from T cells	*Proceedings of the National Academy of Sciences of the United States of America*	Toraldo G	2003	209
1,25-Dihydroxyvitamin D-3 Modulates Th17 Polarization and Interleukin-22 Expression by Memory T Cells From Patients With Early Rheumatoid Arthritis	*Arthritis and Rheumatism*	Colin EM	2010	204
Osteoblast physiology in normal and pathological conditions	*Cell and Tissue Research*	Neve A	2011	201
Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies	*Annals of the Rheumatic Diseases*	Kleyer A	2014	192
Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss	*Annals of the Rheumatic Diseases*	Krishnamurthy A	2016	184
Classical and paradoxical effects of TNF-alpha on bone homeostasis	*Frontiers in Immunology*	Osta B	2014	183
Bone remodeling in rheumatic disease: a question of balance	*Immunological Reviews*	Walsh NC	2010	166
Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NF kappa B ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis	*Annals of the Rheumatic Diseases*	Vis M	2006	164
Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor	*Rheumatology*	Dayer JM	2010	159
A multicenter cross sectional study on bone mineral density in rheumatoid arthritis	*Journal of Rheumatology*	Sinigaglia L	2000	155

Rheumatology, Endocrinology, and Metabolism, Orthopedics was the most predominant subject category that received the most attention in this field. In addition, the dual-map overlay of journals stood for discipline distribution of journals involving ORA research. In the dual-map overlays, the base map for citations was generated from 10,000 journals indexed in WoS (46). After the dataset was entered, the citing trajectories were built in the dual-map overlay module. With this approach, we can see clearly how knowledge flows in different disciplines and identify the hotspot of each discipline. As presented in **Figure 5C**, the citing journals were on the left, the cited journals were on the right, and colored paths represented the citation relationship. There were following four core citation paths shown in the map. The orange paths indicate that documents

FIGURE 6 | The cluster view map **(A)** and timeline view map **(B)** of reference co-citation analysis were generated by CiteSpace. **(C)** Visualization map of top 25 references with the strongest citation bursts involved in ORA.

published in Molecular/Biology/Immunology journals usually cited documents published in journals belonging to Molecular/Biology/Genetics. The green paths imply that the majority of papers published in the journals of Medicine/Medical/Clinical are likely to be biased to cite papers published in journals within Molecular/Biology/Genetics, Health/Nursing/Medicine, and Sports/Rehabilitation/Sport.

An Overview of Research Hotspots and Frontiers

Analysis of Highly-Cited Studies

The analysis of citations is one of the key methodologies in a bibliometric study. Although there remains some controversy on the value of citation rates (47), it is generally agreed that the number of citations could reflect the impact extent of a publication, and the higher citations frequency indicates a higher academic level in a field (27). **Table 3** listed the top 20 most cited papers on ORA. All these studies were published between 2000 and 2016, and 50% of them acquired more than 200 citation times. The majority of studies were published in rheumatology journals such as *Arthritis and Rheumatism*, *Annals of the Rheumatic Diseases*, and *Rheumatology*. Among them, 12 were original articles and eight were systematic reviews. Specifically, a review entitled "Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis" published in *Rheumatology* has been cited 420 times and is the top-cited paper in the field (13). This review made a detailed overview of various immune modulators including cytokines and effector cells, and signaling pathways are involved in the pathophysiology of RA. It also summarized the role of cytokines especially IL-6 in the osteoporotic manifestation of RA. The second and third highest cited papers were published by Dougados et al. (36) and Haugeberg et al. (4), which have been discussed in detail previously. In summary, topics of top 20 publications mainly include reviews regarding cytokines and the impact on bone homeostasis (13, 34, 48, 49), epidemiological and clinical assessment of ORA (4, 5, 9, 36, 50), the molecular mechanism underlying RA-associated bone loss (51–53), and pharmacologic intervention studies on ORA (54, 55).

References Co-citation Analysis

Furthermore, reference co-citation analysis was a valuable technique to assess the evolution and trace the developmental frontiers of any research field (21). After running the bibliometric analysis in CiteSpace, a visualization network of cited references was plotted in **Figure 6A**. By using the clustering function,

TABLE 4 | The clusters information of co-cited references.

Cluster ID	Size	Silhouette	Label	Mean (Year)
#0	41	0.919	Digital X-ray radiogrammetry	2005
#1	40	0.955	Anti-citrullinated protein antibodies	2013
#2	38	0.927	Bone destruction	2000
#3	37	0.926	Ankylosing spondylitis	2006
#4	36	0.881	Risk factor	2013
#5	33	0.912	Bone mineral density	2000
#6	25	0.989	Soluble marker	1994
#7	23	0.965	Steroid hormone	1995
#8	23	0.952	Non-vertebral osteoporotic fracture	2010
#9	22	0.943	Assessment tool	2001
#10	22	1	Menopausal status	1994
#11	16	0.952	Dangerous liaison	2018
#12	14	0.949	Preventing joint destruction	2016
#13	10	0.984	Noninvasive technique	2002
#14	8	1	University hospital	2003
#15	6	0.986	Benign metabolic bone disorder	2007

the whole network map could be divided into several different clusters, which studies within the same cluster might have similar research topics than studies from other clusters. It should be noted that the modularity value (Q-value) and mean silhouette value (S-value) are two important parameters to evaluate the significance of community structure, that is, a $Q > 0.3$ and $S > 0.7$ corresponds to a significant clustering (56). In this study, the Q value was 0.8097, indicating the reasonableness of this network. The mean S-value was 0.9418, in which all the S-values of clusters #0–#15 were larger than 0.88, suggesting the good homogeneity of these clusters. As can be seen from **Figure 6A** and **Table 4**, "digital X-ray radiogrammetry" was the largest cluster (#0), followed by "anti-citrullinated protein antibodies" (#1), and "Bone destruction" (#2). Along with this, we also provided the timeline view for the major clusters in **Figure 6B**, from which the evolution characteristics of each cluster could be told at a glance based on the time axis or the average year of the clusters in **Table 4**. One can see that the research focus has shifted from "soluble marker" (#6), and "menopausal status" (#10), and "steroid hormone" (#7) to "anti-citrullinated protein antibodies" (#1), "risk factor" (#4), "dangerous liaison" (#11), and "preventing joint destruction" (#12).

Analysis of References With Citation Burst

Moreover, burst detection, an algorithm developed by Kleinberg (57), was an effective analytic tool to capture the sharp increases of references or keywords popularity within a specified period. This function can serve as an efficient way to identify concepts or topics that were actively discussed during some period of time. In the present study, the burst detection algorithm was applied to extract key references and keywords for ORA research. **Figure 6C** illustrated the top 25 references with the strongest citation bursts. In this map, the blue lines indicated the time interval, and the red part represented the time period when the reference burst occurred. Among these references, the reference with the strongest burst value was written by Kleyer et al. (52). In this study, they found that structural bone damage had already begun before the clinical onset of arthritis in anticitrullinated protein antibodies (ACPA) positive individuals. This finding corrected the previous concept that bone destruction was an exclusive consequence of synovitis in RA patients. In addition, as also can be seen that the first burst of co-cited reference began in 1998 due to a review summarizing bone mass measurement especially of the hand in RA patients, and the burst lasted for 4 years (58). Notably, although the burst in the majority of references was over, the burst in several references is still ongoing, indicating that these research topics are being of continuous concern in recent years. Of these, most of these references involved ACPA and therapies preventing joint destruction. For instance, one phase II clinical trial evaluated the efficacy and safety of denosumab on RA patients with risk factors of joint destruction (59). The results indicated that denosumab was able to significantly inhibit the progression of bone erosion at 12 months in comparison with the placebo group. Zerbini et al. (60) summarized the evidence of biological therapies on BMD, bone turnover markers, and fragility fractures in RA patients. In terms of studies related to ACPA, Orsolini et al. (61) analyzed the effect of ACPA on systemic BMD in established RA patients. The multivariate analysis confirmed the negative effect of ACPA positive on BMD of femoral sites, but not at the lumbar spine. A similar result was also reported by Bugatti and colleagues (62). They suggested that systemic reduced BMD in patients with early RA was associated with ACPA positivity and high rheumatoid factor levels. While Krishnamurthy and collaborators further dissected the role of ACPAs in osteoclast in osteoclast activation and identified the key cellular mediators of this process (53). Their findings suggested that IL8-dependent osteoclast activation could be an early event of initiating joint-specific inflammation in ACPA-positive patients.

Analysis of Most Frequently Appearing Keywords

In addition to references, keywords are also representative of the main topics and core content of a specific subject (63). For bibliometrics, another prevalent way to identify hot research topics was keywords co-occurrence analysis. In a co-occurrence analysis, the relatedness of keywords is determined according to the number of documents in which they occur together (28). In this study, author keywords were extracted from 1,081 publications and analyzed by VOSviewer. After excluding several meaningless keywords, and merging keywords with the same meaning, 46 keywords were identified. **Figure 7A** presented the overlay visualization map of the most frequently used keywords in ORA research. The size of nodes is proportional to the occurrence times of keywords, and the relative distance between two nodes approximates the strength of their relationship. The thicker the lines between two nodes, the higher the frequency of their co-occurrence (28). **Figure 7B** showed the frequency distribution of the top 25 most common keywords. It can be seen that besides the keywords "rheumatoid arthritis" and "osteoporosis", the other common keywords mainly focused on

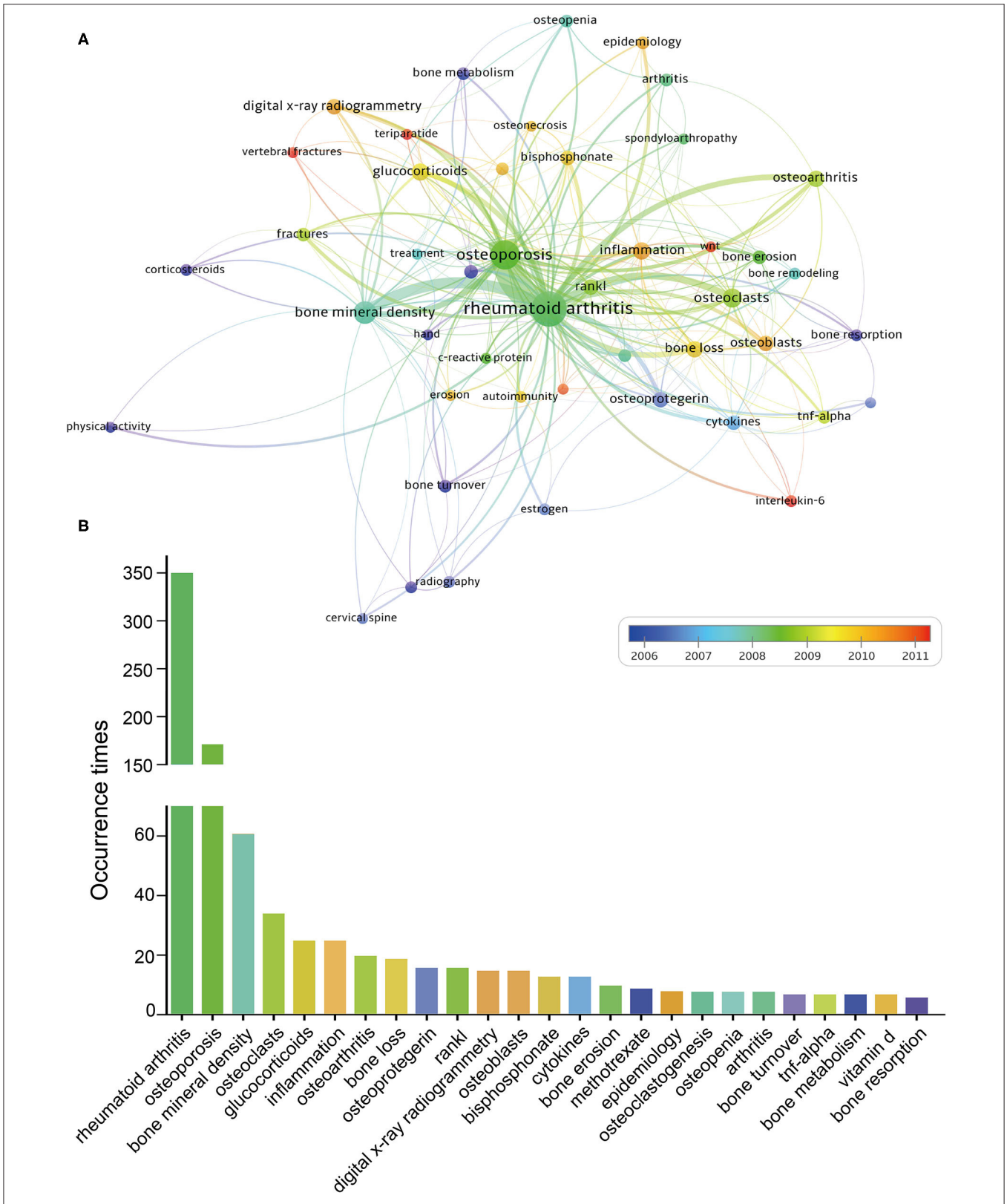

FIGURE 7 | (A) Overlay visualization map of keywords co-occurrence analysis. **(B)** The top 25 keywords with the largest occurrence times.

the molecular mechanisms and signaling pathways studies on ORA. It is commonly held that high levels of pro-inflammatory cytokines and immune system dysregulation played a critical role in the progression of ORA (1, 64). Thus, theoretically, the drugs that reduce inflammation, especially biological agents, may simultaneously alleviate inflammatory conditions and prevent bone loss (65). Although results are still debated, elucidation of these molecular mechanisms of ORA may facilitate the discovery of novel therapeutic strategies.

In addition, all these keywords were also marked with different colors according to the AAY by VOSviewer. Keywords that appeared relatively earlier were colored in blue, while keywords with a more recent appearance were colored in red. These keywords such as "bone turnover," "bone metabolism," "bone resorption," and "methotrexate" were the major topic during the early stage. While the keywords "teriparatide" (66), "interleukin-6" (67), "Wnt" (68), and "vertebral fractures" (69) showed a relatively latest AAY, which indicated that this topic may have gained increasing attention recently, and have the potential to become research hotspots in the near future. Take teriparatide as an example, it is an osteoanabolic agent that significantly increases cortical and trabecular bone microstructure indices and is also the only available anabolic agent for osteoporosis in many countries (70). Multiple previous studies have revealed that daily teriparatide treatment was able to significantly increase the BMD and bone strength of the lumbar spine and reduce the rates of clinical fractures (66, 71). However, results from large-sample randomized controlled studies are currently lacking, which could be the future direction of next research.

LIMITATION

The present study had some limitations inherent in bibliometrics as well. Firstly, the dataset consisted of only data from the WoSCC database but neglected the other large databases, which could miss a few related studies. However, as described in previous studies, WoSCC was the most commonly applied database for bibliometric analysis (17, 28, 39). And data from WoSCC was large enough to reflect the current state of ORA research. Moreover, different databases are characterized by different features including output formats of files and count of citations. Merging of the databases may not optimal choice. Secondly, we only selected studies published in the English language and ignored non-English language publications, which means that the contributions of non-English speaking countries are likely to be underestimated. Thirdly, since the WoSCC database is continually updated, the influence of recently published high-quality articles may also be underestimated as they may not accumulate sufficient citations.

CONCLUSION

To our knowledge, this was the first-ever study to conduct a comprehensive bibliometric analysis of publications related to ORA from 1998 to 2021. Our findings demonstrates that the role of osteoporosis in RA has gradually attracted the attention of scholars as reflected in both annual publications and citations quantity. So far, the United States has been the leader in this field, which cannot be separated from sufficient funding sources. Diakonhjemmet Hospital and professor Haugeberg G were the most prolific institution and influential authors, respectively. *Journal of Rheumatology* and *Arthritis & Rheumatology* were the most productive and influential journals in ORA research, with the largest number of publications and citations, respectively. According to the burst references, "anti-citrullinated protein antibodies" and "preventing joint destruction" have been recognized as the hot research issues in the domain. Besides that, a keywords co-occurrence analysis identified "teriparatide," "interleukin-6," "Wnt," and "vertebral fractures" as important future research directions, which deserves further attention. All in all, researchers especially new entrants could benefit from this bibliometric analysis as they could clearly understand the fundamental knowledge structure including countries, institutions, authors, and journals in this field, and be inspired by the analysis of research hotspots and frontiers. In addition, this study could also provide a valuable reference for policymakers and funders to make more correct investments.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HW, KC, and ZS designed the study. HW, QG, LT, and YW collected the data. HW, KC, YW, LT, and ZS analyzed the data and drafted the manuscript. HW, QG, and ZS revised and approved the final version of the manuscript. All authors have read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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