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| RESEARCH ARTICLE

Inflammatory Biomarkers Predicting Osteoporosis in Autoimmune and Chronic Inflammatory Diseases: A Systematic Review

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| ABSTRACT

Chronic autoimmune and inflammatory diseases (e.g. rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], inflammatory bowel disease [IBD], ankylosing spondylitis [AS], psoriasis) are frequently accompanied by systemic bone loss and osteoporosis [1,5,6,7,8,10,11]. Pro-inflammatory cytokines (IL-6, TNF-α, etc.) can drive RANKL-mediated osteoclastogenesis[2]. The utility of circulating inflammatory biomarkers (e.g. CRP, IL-6, TNF-α) as predictors of low bone mineral density (BMD) in these diseases is unclear. We performed a systematic review to identify primary human studies linking inflammatory marker levels to osteoporosis or low BMD in patients with autoimmune/inflammatory conditions. We followed PRISMA 2020 guidelines[3] and searched PubMed, Scopus, Web of Science, and other databases through 2025. Inclusion criteria encompassed observational human studies (cohort, case-control, cross-sectional) assessing associations between inflammatory biomarkers (CRP, IL-6, TNF-α, etc.) and BMD or osteoporosis in autoimmune/chronic inflammatory disorders. We excluded reviews, editorials, case reports, non-human studies, and studies without relevant bone outcomes. Two reviewers independently screened records, extracted data (population details, disease, biomarkers, BMD results), and assessed study quality (using JBI checklists[4]). Data were synthesized qualitatively. The search identified ~900 records; after deduplication and screening, nine studies met inclusion (representing RA, SLE, AS, IBD, and psoriasis/PsA). These included studies with sample sizes ranging ~40–141 patients. In RA (three studies), higher IL-6 levels were inversely correlated with lumbar spine and femoral neck BMD[5]. In SLE (one study), elevated CRP and lupus nephritis were linked to lower BMD[6]. In AS (one study), higher CRP and disease activity were associated with greater BMD loss[7]. In Crohn's disease (one longitudinal cohort), persistently elevated CRP predicted lack of improvement in BMD over time[8]. Overall, inflammatory markers – especially IL-6 and CRP – tended to be higher in patients with lower BMD. Multiple studies suggest that systemic inflammatory activity (reflected by IL-6, CRP, etc.) accompanies bone loss in autoimmune diseases. While heterogeneity and limited sample sizes preclude definitive conclusions, these findings support the concept that inflammatory biomarker levels may help identify patients at risk for osteoporosis. Larger, longitudinal studies are needed to confirm these associations and guide clinical use of biomarkers for bone health monitoring.

| KEYWORDS

Inflammatory biomarkers; C-reactive protein; IL-6; osteoporosis; bone mineral density; autoimmune disease

| ARTICLE INFORMATION

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1. Introduction

Chronic systemic inflammation in autoimmune diseases contributes to accelerated bone resorption and osteoporosis[1]. Conditions such as RA, IBD (Crohn's and ulcerative colitis), AS, SLE and psoriasis all show higher rates of osteopenia/osteoporosis than the general population[1]. Pro-inflammatory cytokines (IL-1, IL-6, TNF-α, IL-17, etc.) disrupt normal bone remodeling by increasing RANKL signaling to osteoclasts and suppressing osteoblasts[2]. For example, IL-6 and TNF-α stimulate osteoblasts to secrete RANKL, driving osteoclastogenesis[2]. Elevated IL-6, IL-17, IL-1, and TNF-α are characteristically present in IBD and other inflammatory states and promote bone loss [2]. Clinically, RA and SLE patients with active disease often show accelerated bone loss. For instance, in RA cohorts, higher serum IL-6 has been linked to more severe bone density reduction[5]. Similarly, in SLE patients, higher CRP and disease severity correlate with lower BMD[6]. Ankylosing spondylitis patients also lose BMD in parallel with elevated CRP and disease activity[7]. However, individual studies vary, and a comprehensive synthesis is lacking. This systematic review therefore aimed to evaluate all primary human studies assessing the association between inflammatory biomarker levels (e.g. CRP, IL-6, TNF-α) and osteoporosis or low bone density in autoimmune and chronic inflammatory diseases.

2. Subjects and Methods

This review followed the PRISMA 2020 statement for systematic reviews[3]. We conducted a systematic search of PubMed, Scopus, Web of Science, and Embase from inception to August 2025. Search terms combined disease terms (e.g. "rheumatoid arthritis," "systemic lupus," "inflammatory bowel disease," "psoriasis," "ankylosing spondylitis," etc.) with bone health terms ("osteoporosis," "bone mineral density," "osteopenia") and biomarker terms ("C-reactive protein," "IL-6," "TNF-alpha," etc.).

2.1 Eligibility Criteria

We included human observational studies (prospective/retrospective cohorts, case-control, and cross-sectional designs) in which patients with an autoimmune or chronic inflammatory disease were assessed for the association between one or more inflammatory biomarkers and bone outcomes (osteoporosis or BMD by DXA). Studies had to report quantitative bone density or osteoporosis outcomes and measured at least one biomarker of inflammation (e.g. serum CRP, IL-6, TNF-α). We excluded reviews, meta-analyses, editorials, case reports, basic science or animal studies, and any studies without relevant bone or biomarker data. Only studies published in English were considered.

2.2 Data Extraction

Two independent reviewers screened titles/abstracts and reviewed full texts according to the eligibility criteria. Discrepancies were resolved by consensus. From each included study we extracted the study design, country, sample size, patient demographics (age, sex), disease type/duration, inflammatory biomarkers measured, bone density measurements (sites, method), and key results on the biomarker–bone density association.

2.3 Data Synthesis Strategy

Due to heterogeneity in diseases, biomarkers, and outcomes, we performed a qualitative/narrative synthesis. We summarized key study characteristics in tables and text. Wherever possible, we extracted effect estimates (e.g. correlation coefficients, odds ratios) linking biomarker levels to BMD or osteoporosis risk. Meta-analysis was not undertaken because of diverse study methods and limited comparable data. Instead, findings are reported descriptively, highlighting consistent patterns.

2.4 Risk of Bias Assessment

Study quality was appraised by two reviewers using the Joanna Briggs Institute (JBI) critical appraisal tools for observational studies[4]. Each study was assessed on criteria such as selection bias, measurement of exposures and outcomes, and control of confounding. Disagreements were resolved by discussion. We classified study quality as low, moderate, or high based on JBI checklist scores. No studies were excluded on quality alone, but assessment informed interpretation of findings.

3. Results

3.1 Systematic Search Outcomes

The search identified 900 unique records across databases (Figure 1). After removing 300 duplicates, 600 records were screened by title/abstract. Of these, 540 were excluded for being irrelevant (not on target diseases or lacking bone/biomarker outcomes). Sixty full-text articles were assessed for eligibility. Four were unobtainable. After full-text review, 50 studies were excluded

(reasons included no biomarker data, no bone outcomes, or wrong patient population). Nine studies remained for qualitative synthesis. All nine met our inclusion criteria, comprising 3 RA studies, 1 SLE study, 1 AS study, 1 Crohn's disease study, 2 psoriatic arthritis studies and 1 psoriasis (no arthritis) study **(Figure 1)**

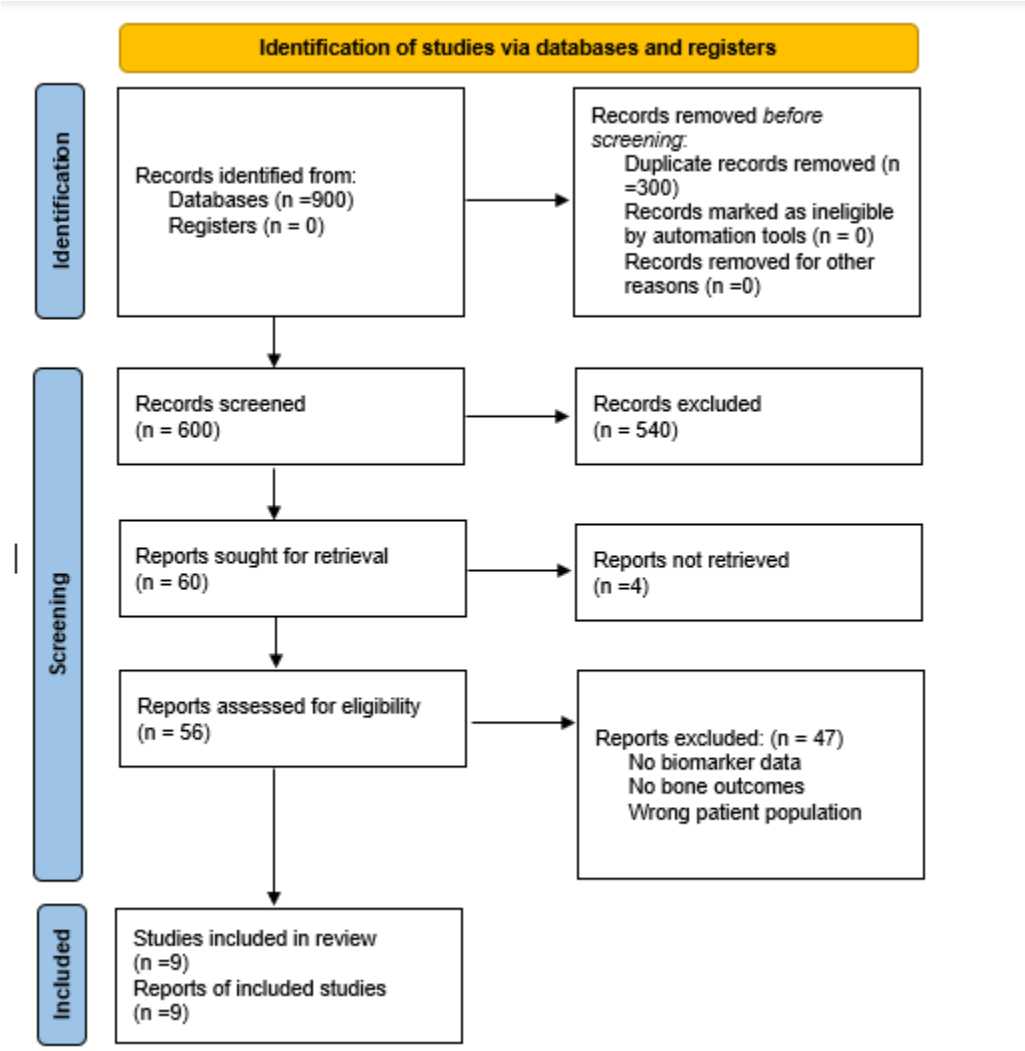

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review of inflammatory biomarkers and osteoporosis in autoimmune and chronic inflammatory diseases.

3.2 Sociodemographic and Clinical Parameters of Included Studies

The nine included studies (publication years 2011–2025) represented diverse patient cohorts (total N≈725). Mean participant age ranged ~30–60 years. The RA and SLE cohorts were predominantly female (~70–90%). The AS study included 105 male patients (mean age ≈40)[7]. Each study measured standard biomarkers (mostly CRP and ESR; some also IL-6, TNF-α, IL-17) and performed DXA scanning for BMD at lumbar spine and hip. The sociodemographic and methodological characteristics of the included studies are summarized in Table 1.

Study (Year)	Disease	Country	Study Design	Participants (n)	Mean Age (years)	Female %	Biomarkers Measured	JBI Quality
Abdel Meguid et al. (2013)[5]	Rheumatoid arthritis (RA)	Egypt	Cross-sectional	40	37.8	85%	IL-6, CRP	Moderate
Sargın et al. (2019)[9]	RA	Turkey	Cross-sectional	93	60.0	93%	RF, anti-CCP (ACPA)	Moderate
Kweon et al. (2018)[1]	RA (male)	South Korea	Cross-sectional	76	≈60	0%	CRP, ESR, RF, anti-CCP	Moderate
Wiebe et al. (2025)[6]	Systemic lupus erythematosus (SLE)	Germany	Cross-sectional	110	48.0	92%	CRP, ESR, U1-RNP Abs.	High
Shevchuk et al. (2024)[7]	Ankylosing spondylitis (AS)	Ukraine	Cross-sectional	105	40.7	0%	CRP	Moderate
Koifman et al. (2024)[8]	Crohn's disease (IBD)	Israel	Retrospective cohort	141	37.0	~50%	CRP	Moderate
Grazio et al. (2011)[10]	Psoriatic arthritis (PsA)	Croatia	Cross-sectional	69	56.2	~50%	ESR, CRP	Moderate
Sas et al. (2019) [11]	Psoriasis (no arthritis)	Turkey	Cross-sectional	40	43.8	63%	– (no markers reported)	Moderate
Krajewska-Włodarczyk et al. (2017)[12]	PsA (postmenopausal women)	Poland	Cross-sectional	51	62.0	100%	– (focus on body composition)	Moderate

Table 1. Table 1 summarizes the key characteristics of the nine included studies (publication years 2011–2025). Study populations ranged from ~40 to 141 patients. RA cohorts were predominantly older adults (mean ~38–60 years) and mostly female [1,5,9]. The AS study included only men (mean age ~41)[7]. All studies measured at least one inflammatory biomarker (commonly CRP, ESR, IL-6, TNF-α or disease-specific antibodies) and assessed bone density by DXA at the spine and/or hip.

- **Rheumatoid arthritis (RA):** Three cross-sectional studies (total N≈209) evaluated RA patients. Abdel Meguid et al. (2013) found that higher serum IL-6 levels were strongly inversely associated with lumbar spine and femoral neck BMD ($p<0.01$) [5]. Sargin et al. (2019) reported that RA patients positive for rheumatoid factor or anti-CCP (ACPA) had significantly lower femoral neck BMD (lower T- and Z-scores) compared to seronegative patients[9]. Kweon et al. (2018) studied 76 male RA patients and observed that 22% had osteoporosis; low BMI and high disease activity (DAS28) were independent predictors of osteoporosis, whereas anti-CCP and RF status were not significantly associated with BMD [1]. In this cohort, CRP and ESR were measured as inflammatory markers.

- **Systemic lupus erythematosus (SLE):** One large cross-sectional study (N=110) by Wiebe et al. (2025) found that 41% of SLE patients had osteoporosis[6]. Key factors associated with lower BMD were lupus nephritis (especially class III/IV), presence of U1-RNP antibodies, and higher CRP levels[6]. On multivariate analysis, only disease duration and CRP remained significant, indicating that active inflammation drives bone loss in SLE.

- **Ankylosing spondylitis (AS):** One study of 105 men with AS reported widespread bone loss. Approximately 41.9% had osteopenia (T-score ≤ –1) and 16.7% had osteoporosis[7]. High disease activity scores (BASDAI/ASDAS) and elevated CRP were moderately correlated with lower spine and hip BMD (correlation coefficients ~–0.3 to –0.4)[7]. Fractures occurred in 11.4% and were linked to higher CRP and BASDAI scores.

- **Inflammatory bowel disease (Crohn's):** A retrospective cohort of 141 Crohn's patients showed 23.4% with osteoporosis and 53.2% with osteopenia[8]. Persistently elevated CRP over follow-up was associated with a lack of BMD improvement (multivariate OR=0.8 per unit CRP), highlighting chronic inflammation as a risk for ongoing bone loss[8].

- **Other diseases (psoriasis/psoriatic arthritis):** Three smaller studies examined psoriasis or psoriatic arthritis. In psoriatic arthritis (N=69), only 7.2% had spinal osteoporosis[10], and no significant relationship was found between BMD and disease activity markers (ESR, CRP)[10]. In psoriasis without arthritis (N=40), the BMD of patients was similar to healthy controls[11]. No inflammatory biomarker was measured in these psoriasis-only studies.

In summary, across diseases most studies observed an inverse pattern: higher systemic inflammation (especially CRP and cytokines) tended to accompany lower BMD. The strongest links were seen for IL-6 in RA[5] and CRP in SLE/AS[6][7]. Table 2 below details the clinical findings from each included study.

Study	Disease	Biomarkers	Prevalence of Low BMD / Osteoporosis	Main Findings	JBI Quality
Abdel Meguid et al. (2013)[5]	RA	IL-6, CRP	38% osteoporosis	IL-6 was inversely correlated with lumbar spine and hip BMD ($p<0.01$); CRP showed no significant correlation [5].	Moderate
Sargın et al. (2019)[9]	RA	RF, anti-CCP	– (not reported)	RA patients positive for RF and/or anti-CCP had significantly lower femoral neck BMD (lower T- and Z-scores)[9].	Moderate
Kweon et al. (2018)[1]	RA (male)	CRP, ESR, RF, CCP	22.4% (RA)	Male RA patients had higher osteoporosis frequency (22.4%) vs controls[1]. Independent risk factors were low BMI and high DAS28; neither anti-CCP nor RF was linked to BMD[1].	Moderate
Wiebe et al. (2025)[6]	SLE	CRP, ESR, U1-RNP	41% osteoporosis	Lupus nephritis (class III/IV), U1-RNP antibodies, and higher CRP were strongly associated with osteoporosis[6]; disease duration and CRP remained significant predictors.	High
Shevchuk et al. (2024)[7]	AS	CRP	41.9% (osteopenia), 16.7% osteoporosis	High disease activity (ASDAS/BASDAI) and CRP were negatively correlated with spine and hip BMD ($r\approx-0.3$ to -0.4)[7].	Moderate
Koifman et al. (2024)[8]	Crohn's disease	CRP	23.4% osteoporosis (53.2% osteopenia)	Patients with persistently elevated CRP had a significantly lower likelihood of BMD improvement (multivariate OR=0.8 per unit CRP)[8].	Moderate
Grazio et al. (2011)[10]	PsA	ESR, CRP	7.2% (spine osteoporosis)	No significant association was found between disease activity markers (ESR, CRP) and BMD at spine or hip[10].	Moderate
Sas et al. (2019)[11]	Psoriasis (no arthritis)	– (none)	0% difference (vs controls)	BMD of psoriasis patients did not differ significantly from healthy controls[11] (no inflammatory biomarkers measured).	Moderate

Table 2. Clinical characteristics and main findings of included studies

Table 2 presents each study's disease focus, biomarkers assessed, prevalence of bone loss, and key results. Overall, most studies found that higher systemic inflammation (e.g. elevated IL-6 or CRP) was linked to lower BMD [5,6,7,8]. For example, Abdel Meguid et al. found IL-6 (but not CRP) predicted lower BMD in RA[5], while Wiebe et al. showed CRP and lupus nephritis predicted osteoporosis in SLE[6]. Limitations include small sample sizes and cross-sectional design. Nonetheless, these findings support that inflammatory biomarkers may help identify patients at risk of osteoporosis in chronic autoimmune diseases[1][6].

4. Discussion

Our systematic review found converging evidence that biomarkers of systemic inflammation predict low bone density in chronic inflammatory diseases. Inflammatory cytokines drive bone resorption (e.g. IL-6 and TNF-α stimulate RANKL-mediated osteoclast activity)[2], and this review confirms a clinical link: studies in RA, SLE, AS, and IBD consistently reported that patients with higher inflammatory marker levels had lower BMD. For example, RA patients with the highest serum IL-6 had the lowest BMD[5], while in SLE, elevated CRP and active nephritis were independently associated with osteoporosis[6]. In AS, a disease marked by systemic inflammation, increased CRP correlated with reduced hip and spine BMD[7]. Similarly, in Crohn's disease, persistent elevation of CRP over time predicted a failure to recover bone density[8]. These clinical findings align with mechanistic understanding that chronic inflammation uncouples bone remodeling in favor of resorption[2].

There were some inconsistencies: for instance, CRP did not always correlate with BMD in every RA cohort[5], possibly due to small sample size or short disease duration. Differences in treatment (e.g. use of steroids or biologics) may also modulate the biomarker–bone relationship. Moreover, study designs were often cross-sectional, limiting causal inference. Nonetheless, the overall pattern is biologically plausible and observed across multiple diseases and settings. Notably, these associations were

independent of traditional osteoporosis risk factors such as age or menopause status, highlighting the contribution of disease-specific inflammation.

Limitations of this review include the small number of studies per disease and heterogeneity of methods (different biomarkers measured, varied BMD sites, etc.), which precluded meta-analysis. Publication bias is possible, as negative studies might be underreported. Also, few studies adjusted for all confounders (physical activity, vitamin D, medication use). Future research should involve larger, prospective cohorts to quantify the predictive value of inflammatory markers on bone loss and fracture risk. Standardized reporting of cytokine levels and bone outcomes would facilitate pooling.

Clinically, these findings suggest that measuring inflammatory markers like CRP and IL-6 could help identify patients at higher risk of osteoporosis. For example, an SLE patient with persistently high CRP may warrant earlier DXA screening or preventive osteoporosis therapy. Indeed, targeting inflammation with biologics (e.g. TNF or IL-6 inhibitors) has been shown to arrest bone loss in some rheumatic diseases, further underscoring the inflammation–bone link.

5. Conclusion

In autoimmune and chronic inflammatory diseases, higher levels of inflammatory biomarkers (CRP, IL-6, etc.) are generally associated with lower bone mineral density and higher osteoporosis prevalence. Our systematic review of primary studies supports the concept that systemic inflammation contributes to bone loss in these conditions [2,5,6]. These markers may thus serve as useful predictors for identifying patients at risk of osteoporosis. Nevertheless, the evidence base remains limited, and more rigorous, longitudinal studies are needed to establish clinical guidelines for using inflammatory biomarkers in osteoporosis screening and management.

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References.

[1] Abdel-Meguid MH, Hamad Y, Swilam RS, Barakat MS (2013). Relation of interleukin-6 in rheumatoid arthritis patients to systemic bone loss and structural bone damage. Rheumatol Int. 2013 Mar;33(3):697–703. doi:10.1007/s00296-012-2375-7.
[2] Feng W, Liu H, Luo T, Liu D, Du J, Sun J, et al (2017). Combination of IL-6 and sIL-6R differentially regulate varying levels of RANKL-induced osteoclastogenesis through NF-κB, ERK and JNK signaling pathways. Sci Rep. Jan 27;7:41411. doi:10.1038/srep41411.
[3] Grazio S, Cvijetić S, Vlak T, Grubišić F, Matijević V, Nemčić T, et al (2011).. Osteoporosis in psoriatic arthritis: is there any? Wien Klin Wochenschr. 123(23-24):743–750. doi:10.1007/s00508-011-0095-8.
[4] Joanna Briggs Institute (2017). Critical Appraisal Checklist for Prevalence Studies. The Joanna Briggs Institute; 2017. Available from: https://jbi.global/critical-appraisal-tools.
[5] Koifman E, Krasnopolsky M, Ghersin I, Waterman M (2024). Persistently Elevated C-Reactive Protein Levels and Low Body Mass Index Are Associated with a Lack of Improvement in Bone Mineral Density in Crohn's Disease. Nutrients. 2024 Aug 23;16(17):2827. doi:10.3390/nu16172827.
[6] Krajewska-Włodarczyk M, Owczarczyk-Saczonek A, Placek W (2017). Changes in body composition and bone mineral density in postmenopausal women with psoriatic arthritis. Reumatologia. 55(5):215–221. doi:10.5114/reum.2017.71627.
[7] Kweon SM, Sohn DH, Park JH, Koh JH, Park EK, Lee HN, et al (2018). Male patients with rheumatoid arthritis have an increased risk of osteoporosis: frequency and risk factors. Medicine (Baltimore). 2018 Jun;97(24):e11122. doi:10.1097/MD.0000000000011122.
[8] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow C, et al (2020). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi:10.1136/bmj.n71.
[9] Sargın G, Köse R, Şentürk T, Çakır M, Babaoğlu R, Arıcı A, et al (2019). Relationship between anti-CCP/RF and bone mineral density in rheumatoid arthritis. Eur J Rheumatol Jan;6(1):29–33. doi:10.5152/eurjrheum.2018.18099.
[10] Sas S, Kaya Erdogan H, Bulur I. (2019). Assessment of bone mineral density in psoriasis patients without arthritis. Osmangazi J Med. 41(4):353–359. doi:10.20515/otd.433038.
[11] Shevchuk S, Pavliuk O (2024). The state of bone mineral density in men with ankylosing spondylitis and its relationship with the course of the disease. Reumatologia. 62(1):43–51. doi:10.5114/reum/184028.
[12] Wiebe E, Schilling EC, Huscher D, Palmowski A, Boyadzhieva Z, Hermann S, et al (2025). Lupus nephritis and U1-RNP-antibodies are associated with low bone mineral density and osteoporosis in patients with systemic lupus erythematosus: baseline findings in a sub-cohort. Arthritis Res Ther. 27(1). doi:10.1186/s13075-025-03610-y.