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Bone Mineral Density Changes and Metabolic Risk Factors in Patients with Rheumatoid Arthritis on Long-Term Therapy

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ABSTRACT
Chronic systemic inflammation and prolonged immunomodulatory treatment in rheumatoid arthritis (RA) predispose patients to accelerated bone loss and metabolic dysregulation, yet comprehensive data on long-term bone mineral density (BMD) changes and associated metabolic risk factors in the context of cumulative therapy remain limited. This prospective cohort study evaluated BMD alterations, metabolic risk profiles, and renal function markers in RA patients undergoing long-term disease-modifying antirheumatic drug (DMARD), biologic, and glucocorticoid therapy over three years. Dual-energy X-ray absorptiometry (DXA) was employed to measure BMD at lumbar spine and femoral neck, accompanied by serial assessment of metabolic parameters including glucose, lipids, vitamin D, parathyroid hormone, and renal biomarkers. We hypothesized that long-term biologic therapy modulates bone loss more effectively than conventional therapy and that metabolic risk factors correlate with both BMD changes and renal functional decline. Results demonstrated statistically significant preservation of BMD in patients receiving biologic/targeted synthetic DMARDs compared to conventional DMARDs ($p < 0.01$), while higher BMI, elevated inflammatory burden, and impaired renal function independently predicted greater bone loss and metabolic risk clustering. Multivariate regression highlighted renal impairment (eGFR decline) and dyslipidemia as significant contributors to lower BMD ($\beta = -0.42$, $p < 0.01$). These data suggest that integrated management of metabolic risk and renal health may mitigate bone loss in RA during long-term therapy, representing a novel contribution to optimizing multidisciplinary care.
Keywords: *Rheumatoid arthritis, Bone mineral density, Metabolic risk factors, Long-term therapy, Renal function*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis, systemic inflammation, and progressive joint destruction. While the primary clinical focus has traditionally centered on articular symptoms, RA is increasingly recognized as a multisystem condition with significant extra-articular manifestations including generalized bone loss, osteoporosis, metabolic derangements, and increased cardiovascular and renal risk. Systemic inflammation, mediated by pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1, and interleukin-6, drives osteoclast activation, disrupts homeostatic bone remodeling, and enhances bone resorption, which accelerates bone mineral density (BMD) decline beyond age-related changes. Chronic inflammatory burden in RA thus predisposes to fragility fractures and decreased quality of life, making early detection and management of bone loss a clinical priority [1-4].

The dynamic interplay between inflammation and bone metabolism in RA is complex. Pro-inflammatory cytokines increase RANKL expression, enhance osteoclastogenesis, and suppress osteoblast activity, which collectively contribute to structural bone loss centrally and peripherally. This mechanism explains why RA patients exhibit higher rates of generalized osteoporosis compared with age-matched populations, with notable reductions in lumbar spine and femoral neck BMD. Furthermore, clinical data reveal that

osteoporosis risk patterns in RA are influenced not only by underlying immune mechanisms but also by disease duration, functional disability, and glucocorticoid exposure [5-7].

Therapeutic strategies for RA have evolved substantially, with the introduction of biologic and targeted synthetic DMARDs aimed at controlling inflammation and minimizing joint damage. In addition to disease control, emerging evidence suggests that biologic therapy may exert protective effects on bone metabolism by attenuating inflammatory signaling pathways. Longitudinal studies indicate that patients receiving long-term biologic therapy maintain more stable BMD compared with those on conventional therapy, although the degree of protection varies by agent and individual metabolic profile [8-10]. Nevertheless, bone loss may persist despite adequate inflammation control, highlighting the need for comprehensive evaluation of bone health in this population.

Metabolic risk factors such as insulin resistance, dyslipidemia, obesity, and metabolic syndrome are prevalent in RA and share overlapping inflammatory pathways with both bone loss and atherosclerotic disease. These metabolic abnormalities may further perturb bone homeostasis through adipokine secretion, altered calcium-phosphate metabolism, and endocrine influences, thereby compounding the risk of osteoporosis. Recent evidence has documented a significant prevalence of metabolic syndrome in RA patients, affirming the need for integrated assessment of metabolic and skeletal outcomes 9-12].

Renal function represents another critical dimension in RA management. Chronic inflammation, comorbid hypertension or diabetes, and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) and certain DMARDs can adversely impact kidney function over time. Impaired renal function influences calcium-phosphate metabolism, vitamin D activation, and parathyroid hormone regulation, all of which are pivotal determinants of bone health. Declining renal function, particularly in older RA cohorts, may synergize with inflammatory and metabolic risk factors to accelerate bone loss and fracture susceptibility. This nephrology-oriented perspective underscores the importance of evaluating kidney function in studies of BMD changes in RA.

Despite extensive research, there remain gaps in understanding the longitudinal evolution of BMD in RA relative to metabolic risk and renal function during long-term therapy. Most studies have either focused on short-term changes or lacked comprehensive metabolic and renal data, thus limiting translational insights for holistic patient management. This research aimed to address these gaps by evaluating long-term BMD changes, associated metabolic risk factors, and renal functional markers in a cohort of RA patients receiving contemporary therapeutic regimens.

By correlating BMD trajectories with metabolic and renal variables, this study contributes new evidence relevant to multidisciplinary care in RA, with implications for optimizing therapeutic strategies that not only control inflammation but also preserve bone health and metabolic homeostasis.

MATERIAL AND METHODS

This prospective, longitudinal observational study was conducted among adult patients diagnosed with rheumatoid arthritis and renal diseases at King Edward Medical University. A target sample size of 240 patients was calculated using Epi Info software (version 7), with assumptions of 80% power to detect a 0.5 SD difference in BMD change between groups ($\alpha = 0.05$) and anticipated attrition of 15%, ensuring adequate statistical precision for primary and secondary outcomes.

Patients aged 25–75 years who had been on stable RA therapy for at least six months and were willing to participate in three-year follow-up assessments were eligible. Exclusion criteria included known primary bone disorders (e.g., Paget's disease), active malignancy, chronic kidney disease stage IV or higher, current pregnancy or lactation, and use of medications specifically indicated for osteoporosis (bisphosphonates, teriparatide, denosumab) initiated within the past year. Verbal informed consent was obtained from all participants in accordance with institutional ethical standards.

Participants were stratified based on primary long-term therapy into three groups: (1) conventional synthetic DMARDs (csDMARDs) only, (2) biologic or targeted synthetic DMARDs (b/tsDMARDs), and (3) glucocorticoid-intensive cohort (≥5 mg/day prednisone equivalent for >3 months). Baseline demographic variables, disease activity scores, comorbid conditions, body mass index (BMI), and lifestyle factors were recorded.

BMD was measured at baseline and annually for three years using dual-energy X-ray absorptiometry (DXA) at lumbar spine (L1–L4) and femoral neck. Metabolic parameters including fasting glucose, HbA1c, lipid profile, vitamin D (25-OH), parathyroid hormone, calcium, and phosphorus were assessed at the same intervals. Renal function was evaluated through serum creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio. RA disease activity and severity indices were recorded contemporaneously to adjust for inflammatory burden.

All laboratory assessments were performed in a central accredited laboratory following standardized protocols. Adherence to RA therapy was monitored through pharmacy refill records and patient interviews.

Data Analysis

Statistical analysis included repeated-measures ANOVA to examine changes in BMD and metabolic parameters across time and therapy groups; multivariate regression models were employed to identify independent predictors of BMD change, adjusting for age, sex, BMI, disease activity, and renal function. Missing data were addressed through multiple imputation techniques.

RESULTS

Table 1: Baseline Demographics and Clinical Characteristics

Variable	csDMARD (n=78)	b/tsDMARD (n=82)	Glucocorticoid-intensive (n=80)	p-value
Mean age (years)	52.3 ± 10.1	50.8 ± 9.8	54.6 ± 11.2	0.12
Female (%)	65	71	68	0.62
BMI (kg/m^2)	27.1 ± 4.8	26.8 ± 5.1	28.3 ± 5.3	0.21
Mean disease duration (years)	8.9 ± 4.1	9.4 ± 4.7	10.2 ± 5.2	0.18
Baseline eGFR (mL/min/1.73m^2)	86.5 ± 14.3	88.2 ± 12.8	80.9 ± 15.6	0.03

Table 2: BMD Change (g/cm^2) Over 3 Years

Group	Lumbar Spine – Δ (Mean ± SD)	Femoral Neck – Δ (Mean ± SD)	p-value
csDMARD	-0.047 ± 0.018	-0.036 ± 0.015	<0.01
b/tsDMARD	-0.011 ± 0.012	-0.007 ± 0.010	0.34
Glucocorticoid-intensive	-0.063 ± 0.021	-0.049 ± 0.019	<0.001

Table 3: Metabolic and Renal Predictors of BMD Change

Predictor	β	95% CI	p-value
eGFR decline (per 10 mL/min)	-0.42	-0.65, -0.19	<0.01
BMI (per 1 kg/m^2)	0.15	0.07, 0.23	0.02
HbA1c (%)	-0.31	-0.52, -0.10	0.01
CRP (mg/L)	-0.28	-0.50, -0.06	0.03

Explanation: Table 1 confirms comparable demographic profiles across therapy groups, with a statistically significant but clinically modest difference in baseline eGFR. Table 2 demonstrates that patients on biologic therapy experienced relative preservation of BMD compared with declines seen in csDMARD and glucocorticoid-intensive cohorts. Table 3 identifies renal function decline, glycemic control, and systemic inflammation as significant independent predictors of BMD loss.

DISCUSSION

This study provides robust longitudinal evidence that long-term RA therapy with biologic or targeted agents confers greater preservation of bone mineral density compared to traditional csDMARDs or regimens heavily reliant on glucocorticoids. These findings corroborate and extend prior observations that biologic agents not only control systemic inflammation but also stabilize skeletal integrity, likely through modulation of cytokine-mediated osteoclastogenesis pathways [13-14].

Importantly, our results highlight renal function as a significant and independent predictor of bone loss, underscoring the nephrology perspective in RA management. Declining eGFR contributes to dysregulated calcium-phosphate balance, secondary hyperparathyroidism, and altered vitamin D metabolism, each of which negatively impacts BMD and fracture risk. The identification of eGFR decline as a key predictor reinforces the need for early nephrological evaluation and integrated management in RA, particularly for patients on long-term NSAIDs or DMARDs with potential renal implications [15, 16].

Metabolic risk factors including dysglycemia (HbA1c) and BMI further delineate the complex interplay between metabolic syndrome components and bone health in RA. Elevated HbA1c predicted greater BMD loss, aligning with evidence linking insulin resistance to increased inflammatory milieu and osteoclast activation. Similarly, higher BMI displayed a protective association—possibly due to mechanical loading—though obesity-related adipokines may contribute to metabolic abnormalities that adversely influence bone remodeling. The nuanced impact of BMI underscores the importance of individualized metabolic assessment rather than reliance on anthropometric indices alone [17-20].

Consistent with previous research, glucocorticoid-intensive therapy was associated with the most pronounced bone density loss, reinforcing established knowledge that chronic corticosteroid use remains a potent risk factor for osteoporosis in RA due to direct effects on osteoblasts and enhanced bone resorption. These findings reaffirm clinical recommendations to minimize glucocorticoid exposure and consider adjunctive bone-protective strategies where unavoidable.

The integration of renal and metabolic risk assessments within monitoring protocols could improve early identification of RA patients at heightened risk for accelerated BMD decline. This multidisciplinary insight advocates for collaborative care involving rheumatology, endocrinology, nephrology, and primary care to optimize skeletal, metabolic, and renal outcomes.

While inflammatory control remains a cornerstone of RA management, our data emphasize that therapeutic success cannot be fully appraised without addressing metabolic and renal determinants of bone health. This holistic perspective advances clinical understanding and may inform guideline development for comprehensive RA care.

CONCLUSION

Long-term biologic DMARD therapy mitigates bone mineral density loss more effectively than conventional treatment in rheumatoid arthritis, particularly when metabolic risk factors and renal function are optimally managed. Declining renal function and metabolic derangements independently predict greater BMD loss, highlighting the need for integrated approaches that extend beyond inflammation control.

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