Association between bone mineral density and vascular health in rheumatoid arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is associated with heightened cardiovascular disease and increased susceptibility to osteoporosis, with shared underlying mechanisms. This study aimed to investigate the association between vascular function and bone mineral density (BMD).

Methods: We conducted a cross-sectional study of 49 patients with RA at Tan Tock Seng Hospital, Singapore. Endothelial function was measured as reactive hyperaemia index (RHI)-endothelial peripheral arterial tonometry and aortic stiffness as carotid–femoral pulse wave velocity (cf-PWV) using SphygmoCor. Univariable and multivariable linear regression analyses were performed to evaluate the associations between BMD and vascular function. We used natural logarithm RHI (lnRHI) and cf-PWV as response variables, and each BMD as covariate, adjusting for body mass index, positive anti-cyclic citrullinated peptide, cumulative prednisolone dose, hydroxychloroquine use and Systematic COronary Risk Evaluation 2.

Results: We recruited 49 patients (mean age 61.08 ± 8.20 years), of whom 44 (89.80%) were women and 39 (81.25%) were Chinese. Significant associations were found between lnRHI and BMD at the lumbar spine ($\beta = 0.4289$, $P = 0.037$) and total hip ($\beta = 0.7544$, $P = 0.014$) in univariable analyses. Multivariable analyses confirmed these associations, showing that lower BMD at the lumbar spine ($\beta = 0.7303$, $P = 0.001$), femoral neck ($\beta = 0.8694$, $P = 0.030$) and total hip ($\beta = 0.8909$, $P = 0.010$) were significantly associated with worse lnRHI. No significant associations were found between BMD and cf-PWV.

Conclusion: Lower BMD is associated with endothelial dysfunction, but not aortic stiffness in patients with RA. Further longitudinal studies are needed to confirm these associations and understand the underlying mechanisms.

Keywords: Aortic stiffness, bone mineral density, endothelial dysfunction, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with a worldwide prevalence of 17.6 million.[1] Both cardiovascular morbidity and impaired bone health are elevated in RA.[2,3]

Cumulative evidence has demonstrated elevated cardiovascular disease (CVD) and associated morbidity and mortality in patients who have RA. The occurrence of these conditions is independent of traditional cardiovascular risk factors, with up to twofold increased risk of atherosclerosis in individuals with RA as compared to the general population.[2] Endothelial dysfunction is a state in which the endothelial cells lining the blood vessels lose their normal functions, leading to reduced vasodilation, increased inflammation and thrombogenicity. In RA, endothelial dysfunction is evident in both macrovascular and microvascular beds.[4] Endothelial dysfunction is a critical early event in the development of CVD in RA, preceding the formation of atherosclerotic plaques and predicting

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SUMMARY BOX

What is known?

Patients with rheumatoid arthritis (RA) have an elevated risk of cardiovascular disease and osteoporosis. There is a potential link between bone mineral density (BMD) and vascular function.

What is new?

Our study demonstrates significant associations between lower BMD and endothelial dysfunction in patients with RA. No significant associations were observed between BMD and aortic stiffness measured.

What is the impact?

Monitoring BMD and vascular health should be part of holistic care for patients with RA. Integrating BMD assessments into cardiovascular risk evaluations could potentially enhance patient management and outcomes in RA.

future cardiovascular events.[4] In addition, aortic stiffness, reflecting the arterial wall elasticity and compliance, has been recognised as a novel marker for early assessment of vascular dysfunction and subclinical vascular damage.[5] Aortic stiffness, measured by pulse wave velocity, is shown to be elevated in patients with RA. A meta-analysis by Wang *et al*.[6] found significantly increased levels of carotid–femoral pulse wave velocity (cf-PWV) in patients with RA as compared to controls, indicating higher aortic stiffness.

The risk of impaired bone health is increased and considered to be multifactorial in patients with RA.[7] Systemic inflammation has also been linked to bone loss across the axial skeleton, resulting in a doubling of the risk of osteoporosis in patients with RA as compared to healthy controls.[3] Hip bone mineral density (BMD) is inversely correlated with disease activity, while corticosteroid use further increases the fracture risk independent of BMD.[8] Receptor activation of nuclear factor kappa-B ligand (RANKL) is activated by the release of tumour necrosis factor-α and interleukin-6, which, in turn, enhances osteoclast formation and activation while simultaneously decreasing osteoblastogenesis.[8]

Although cohort studies have previously reported that BMD is inversely correlated with Framingham risk scores, the risk of adverse CVD outcomes (such as heart failure and myocardial infarction) and whether their pathogenesis interacts or they simply coexist through shared pathways remain an area of ongoing research.[9,10] The association between atherosclerosis and bone health has also been explored between women and men and in special populations with type 2 diabetes mellitus, advanced chronic kidney disease and primary Sjogren's syndrome.[11-14] However, thus far, there is scarce literature that explores this association in patients with RA. There are various shared risk factors of impaired bone health and vascular damage in RA, namely age, smoking, chronic inflammation, use of glucocorticoids and physical inactivity.[15] Therefore, we designed a study to investigate the associations between BMD and surrogates of vascular damage (endothelial function and aortic stiffness) in patients with RA.

METHODS

Study population and clinical data

Patients with RA were identified from the longitudinal RA registry at the Department of Rheumatology, Allergy and Immunology at Tan Tock Seng Hospital, Singapore, as previously described.[16] All patients fulfilled the American Rheumatism Association 1987 revised criteria or the 2010 American College of Rheumatology/European League Against Rheumatism criteria.[17,18] All study participants were between 21 and 80 years of age. Exclusion criteria were pregnancy/breastfeeding, diabetes mellitus as coronary artery disease equivalent,[19] severe chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²), known history of previous atherosclerotic disease in any of the large vessels, heart disease, cerebrovascular disease or peripheral artery disease, malignancy, and recent history of hospitalisation or other acute diseases. The study was approved by the National Healthcare Group Domain Specific Review Board (reference number: 2020/00974).

The disease registry collected the following at baseline and six monthly thereafter: sociodemographic data, clinical data including comorbidities, Disease Activity Score of 28 joints (DAS-28) and data on drug treatment and laboratory tests. The cumulative dose of prednisolone administered since the diagnosis of RA was calculated. Bone mineral density was assessed by Dual-Energy X-ray Absorptiometry (Hologic™ DXA system, Hologic Singapore Pte. Ltd., Singapore). Systematic COronary Risk Evaluation 2 (SCORE2) and the recalibrated Singapore-modified Framingham-based National Cholesterol Education Program Adult Treatment Panel III (SG-ATP III) models were calculated.[20,21]

Reactive hyperaemia index (Endo-PAT 2000) and pulse wave velocity (SphygmoCor XCEL)

Peripheral endothelial function was measured by digital pulse amplitude with endothelial peripheral arterial tonometry (Endo-PAT2000; Itamar Medical, Caesarea, Israel), as previously described.[22] The data were digitally analysed (Endo-PAT2000 software version 3.4.4) to obtain the reactive hyperaemia index (RHI). Values of RHI <1.67 (equivalent to natural logarithm RHI [lnRHI] <0.51) indicated the presence of endothelial dysfunction.[22]

Aortic stiffness was measured by the SphygmoCor XCEL (Atcor Medical, Sydney, Australia) device using cf-PWV and central aortic pressure. In the case of cf-PWV assessment, the XCEL device uses the volumetric displacement waveform from a cuff around the upper thigh in place of femoral artery

tonometry and tonometry for acquisition of the carotid pulse. We took two measurements for consistency. We recorded cf-PWV, central systolic and diastolic blood pressure, augmentation pressure, augmentation index and subendocardial viability ratio. The average of the two measurements was used in the analysis. We performed cf-PWV according to the consensus guidelines suggested by the Artery Society, and a cut-off of 10 m/s was used to define arterial stiffness.[23]

Statistical analyses

Demographics and clinical characteristics were summarised for all patients. Arithmetic mean and standard deviation were presented for continuous variables, and counts and percentages for categorical variables. We used univariable and multivariable linear regression models to investigate the associations between patient characteristics and cf-PWV or lnRHI. Coefficient estimates and 95% confidence interval (CI) were presented for independent variables. The significance level was set at 0.05 in this study. We used STATA software version 15 (Stata Corp LP, College Station, TX, USA).

RESULTS

Characteristics of patients

We conducted a cross-sectional study of 49 patients with RA (mean age 61.08 ± 8.20 years), who were predominantly female (89.8%) and Chinese (81.25%) [Table 1]. Twelve percent of patients were smokers. The mean body mass index (BMI) was 24.05 ± 4.90 kg/m². Hypertension and hyperlipidaemia were present in 24.49% and 38.78% of patients, respectively. Most patients (87.76%) were in RA remission; the mean DAS-28 C-reactive protein score was 1.92 ± 0.66. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibody were positive in 77.55% of patients. The mean cumulative prednisolone dose was 11.68 ± 11.49 g. Methotrexate and hydroxychloroquine (HCQ) were used by 95.92% and 55.10% of patients, respectively. Mean BMD values were 0.91 ± 0.20 g/cm² (lumbar spine), 0.66 ± 0.13 g/cm² (femoral neck) and 0.77 ± 0.13 g/cm² (total hip). Eleven (22.45%) patients fulfilled the criteria for osteoporosis. The mean lnRHI was 0.73 ± 0.26, with 11 (22.45%) patients showing endothelial dysfunction, and the mean cf-PWV was 6.87 ± 1.64 m/s, with two (4.08%) patients showing aortic stiffness [Table 1].

Table 1. Characteristics of patients with rheumatoid arthritis (*N* = 49).

Characteristic	*n* (%)/Mean ± SD
Demographics	
Age (yr)	61.08 ± 8.20
Female gender	44 (89.80)
Ethnicity	
Chinese	39 (81.25)
Malay	6 (12.50)
Indian	3 (6.25)
Others	1 (2.04)
Smoker	6 (12.24)
BMI (kg/m²)	24.05 ± 4.90
Clinical data	
Secondary Sjogren's syndrome	4 (8.16)
Hypertension	12 (24.49)
Hyperlipidaemia	19 (38.78)
Creatinine (μmol/L)	60.00 ± 10.63
CRP (mg/L)	6.36 ± 10.14
DAS-28 CRP	1.92 ± 0.66
Disease in remission	43 (87.76)
Positive rheumatoid factor	38 (77.55)
Positive anti-CCP	38 (77.55)
Cumulative prednisolone dose (g)	11.68 ± 11.49
Use of methotrexate	47 (95.92)
Use of hydroxychloroquine	27 (55.10)
BMD measurement	
Lumbar spine (g/cm²)	0.91 ± 0.20
Femoral neck (g/cm²)	0.66 ± 0.13
Total hip (g/cm²)	0.77 ± 0.13
Osteoporosis (T score <–2.5)	11 (22.45)
Vascular health/CVD risks	
lnRHI	0.73 ± 0.26
Endothelial dysfunction	11 (22.45)
cf-PWV (m/s)	6.87 ± 1.64
Aortic stiffness	2 (4.08)
SCORE2	0.04 ± 0.23
SG-ATP III	0.05 ± 0.04

anti-CCP: anti-cyclic citrullinated peptide, BMD: bone mineral density, BMI: body mass index, cf-PWV: carotid–femoral pulse wave velocity, CRP: C-reactive protein, CVD: cardiovascular disease, DAS-28: Disease Activity Score-28, lnRHI: natural logarithm reactive hyperaemia index, SCORE2: Systematic COronary Risk Evaluation 2, SD: standard deviation, SG-ATP III: Singapore-modified Framingham-based National Cholesterol Education Program Adult Treatment Panel III

Results of univariable analysis

In the univariable analysis, significant associations were observed between lnRHI and BMD at the lumbar spine (β = 0.4289, $P = 0.037$) and total hip (β = 0.7544, $P = 0.014$) [Table 2 and Figure 1]. No significant association was found between lnRHI and other variables, including SCORE2 and SG-ATP III, apart from ethnicity [Table 2]. Significant associations were found between cf-PWV and hypertension (β = 1.3581, $P = 0.011$), hyperlipidaemia (β = 1.0217, $P = 0.032$) and positive anti-CCP (β = –1.3024, $P = 0.022$) [Table 2]. However, no significant associations were observed between cf-PWV and each component of BMD.

Results of multivariable analysis

Multivariable linear regression analyses were performed using two models to evaluate the associations between BMD and vascular function, adjusting for clinically relevant variables [Table 3]. Model 1 was adjusted for BMI and SCORE2. As SCORE2 is a composite score of age, sex,

Table 2. Univariable analyses of risk factors of vascular damages (*N*=49).

Characteristic	lnRHI, β (95% CI)	*P*	cf-PWV, β (95% CI)	*P*
Demographics				
Age (yr)	−0.0013 (−0.0112 to 0.0086)	0.793	−0.0540 (−0.1105 to 0.0025)	0.061
Female gender	0.1873 (−0.0617 to 0.4362)	0.136	0.1620 (−1.4107 to 1.7349)	0.837
Ethnicity				
Chinese	reference		reference	
Others	−0.3075 (−0.4946 to 0.1203)	0.002*	−0.6778 (−1.8428 to 0.4871)	0.248
Smoker	0.1239 (−0.1289 to 0.3768)	0.328	-0.0279 (−1.4809 to 1.4251)	0.969
BMI (kg/m²)	−0.0004 (−173 to 0.0165)	0.959	0.0864 (−0.0105 to 0.1832)	0.079
Clinical data				
Hypertension	−0.1043 (−0.2891 to 0.0811)	0.263	1.3581 (−0.3247 to 2.3916)	0.011*
Hyperlipidaemia	−0.0007 (−0.1678 to 0.1677)	0.999	1.0217 (−0.0912 to 1.9521)	0.032*
Creatinine (μmol/L)	0.0029 (−0.0051 to 0.0110)	0.461	0.0255 (−0.0193 to 0.0704)	0.256
CRP (mg/L)	−0.0019 (−0.0101 to 0.0064)	0.664	0.0146 (−0.0323 to 0.0616)	0.537
DAS-28 CRP	−0.0158 (−0.1434 to 0.1119)	0.804	0.0686 (−0.7496 to 0.8867)	0.866
Positive rheumatoid factor	−0.0801 (−0.2726 to 0.1124)	0.405	−0.0329 (−1.1744 to 1.1086)	0.954
Positive anti-CCP	0.1369 (−0.0834 to 0.3571)	0.216	−1.3024 (−2.4070 to −0.1976)	0.022*
Cumulative prednisolone dose (g)	0.000 (−0.0001 to 0.0000)	0.439	0.0000 (−0.000 to 0.0000)	0.227
Methotrexate	0.0960 (−0.2923 to 0.4843)	0.620	1.7979 (−0.5509 to 4.1466)	0.130
Hydroxychloroquine	−0.1474 (−0.3047 to 0.0100)	0.066	−0.4629 (−1.4108 to 0.4851)	0.331
BMD measurement				
Lumbar spine (g/cm²)	0.4289 (−0.0269 to 0.8309)	0.037*	2.4444 (−0.0413 to 4.9300)	0.054
Femoral neck (g/cm²)	0.5802 (−0.0799 to 1.2404)	0.083	0.4828 (−3.3935 to 4.3591)	0.803
Total hip (g/cm²)	0.7544 (−0.1645 to 1.3442)	0.014*	0.3134 (−3.4364 to 4.0631)	0.867
CVD risks				
SCORE2	1.0161 (−2.5543 to 4.5865)	0.568	−1.6018 (−22.7785 to 19.5748)	0.880
SG-ATP III	−1.6222 (−4.4868 to 1.2424)	0.259	1.9246 (−10.3644 to 14.2137)	0.754

Univariable linear regression was performed. *Statistically significant at P <0.05. anti-CCP: anti-cyclic citrullinated peptide, BMD: bone mineral density, BMI: body mass index, cf-PWV: carotid–femoral pulse wave velocity, CI: confidence interval, CRP: C-reactive protein, CVD: cardiovascular disease, DAS-28: Disease Activity Score-28, lnRHI: natural logarithm reactive hyperaemia index, SCORE 2: Systematic COronary Risk Evaluation 2, SG-ATP III: Singapore-modified Framingham-based National Cholesterol Education Program Adult Treatment Panel III

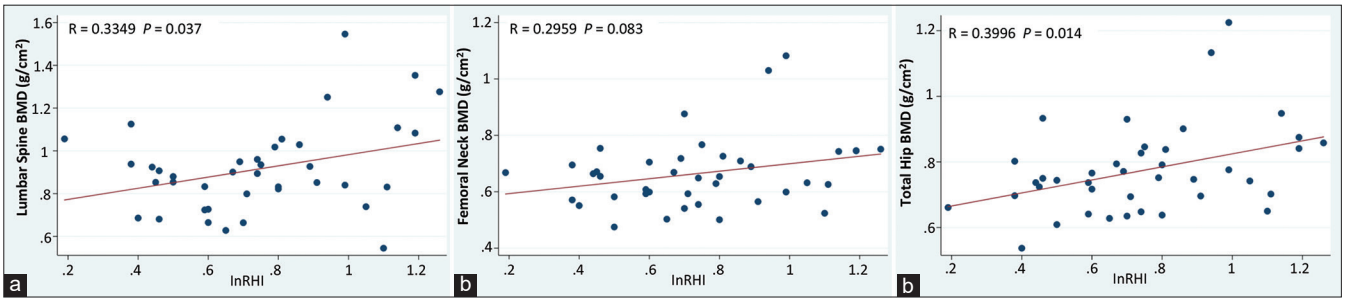

Figure 1: Graphs show the association of (a) lumbar spine BMD and lnRHI, (b) femoral neck BMD and lnRHI, and (c) total hip BMD and lnRHI. BMD: bone mineral density, lnRHI: natural logarithm reactive hyperaemia index

ethnicity, smoking, blood pressure and lipids, these individual variables were not included in the multivariable linear regression analyses. Model 2 was adjusted for the same variables as in Model 1, with additional variables in RA, including anti-CCP, cumulative prednisolone dosage and HCQ.

The multivariable analyses confirmed the significant associations observed in the univariable analysis. Lower BMD values at the lumbar spine (Model 1: β = 0.5707, P = 0.013; Model 2: β = 0.6998, P = 0.002) and total hip (Model 1: β = 0.8203, P = 0.011; Model 2: β = 0.8922, P = 0.009) were significantly associated with worse lnRHI after adjusting for the other confounders, indicating worse endothelial function. Femoral neck BMD was significantly associated with lnRHI in Model 2 (β = 0.8671, P = 0.028). No significant associations were found between BMD and cf-PWV in both models, indicating no association of aortic stiffness with our current data [Table 3]. This was consistent across the lumbar spine, femoral neck and total hip BMD measurements.

Table 3. Multivariable analyses of the association of bone mineral density with lnRHI and cf-PWV.

Variable	Model 1		Model 2	
	β (95% CI)	*P*	β (95% CI)	*P*
lnRHI				
Lumbar spine (g/cm²)	0.5707 (0.1302 to 1.0114)	0.013*	0.6998 (0.2882 to 1.1114)	0.002*
Femoral neck (g/cm²)	0.6715 (−0.0752 to 1.4183)	0.076	0.8671 (0.1005 to 1.6338)	0.028*
Total hip (g/cm²)	0.8203 (0.1970 to 1.4436)	0.011*	0.8922 (0.2453 to 1.5391)	0.009*
cf-PWV				
Lumbar spine (g/cm²)	2.1218 (−0.6744 to 4.9179)	0.133	2.1941 (−0.7026 to 5.0907)	0.132
Femoral neck (g/cm²)	0.0231 (−4.4365 to 4.4828)	0.992	−0.5092 (−5.2389 to 4.2205)	0.827
Total hip (g/cm²)	−0.1190 (−4.1729 to 3.9349)	0.953	−0.2054 (−4.4680 to 4.0571)	0.992

Model 1: adjusted for body mass index and SCORE2. Model 2: adjusted for body mass index, positive anti-cyclic citrullinated peptide, cumulative prednisolone dose, hydroxychloroquine and SCORE2. *Statistically significant at $P<0.05$. cf-PWV: carotid–femoral pulse wave velocity, CI: confidence interval, lnRHI: natural logarithm reactive hyperaemia index, SCORE2: Systematic COronary Risk Evaluation 2

DISCUSSION

In our cohort of patients with RA, we found that lower BMD values of the femoral neck, total hip and lumbar spine were associated with endothelial dysfunction, but not with aortic stiffness, independent of age, ethnicity and other traditional cardiovascular risk factors.

Our findings on the associations between BMD and endothelial dysfunction in RA align with previous studies conducted in postmenopausal women,[24-27] the very elderly[28] and those with early coronary atherosclerosis.[29] One study reported that endothelial dysfunction was associated with osteoprotegerin (OPG), an inhibitor of osteoclastogenesis, but not with BMD in RA.[30] However, our study demonstrated a consistent association between BMD and endothelial dysfunction in RA. There are several mechanisms to explain the associations between BMD and endothelial dysfunction. First, nitric oxide, synthesised by endothelial nitric oxide synthase (eNOS), is crucial for maintaining vascular homeostasis and endothelial function; it also affects bone remodelling by promoting osteoblast activity and inhibiting osteoclast activity.[31] A genetic variant of eNOS (CTAAAT) was found to predict the association between endothelial dysfunction and osteoporosis in postmenopausal women.[27] Second, the receptor activation of nuclear factor kappa-B (RANK)/RANKL/OPG system, which plays a significant role in both vascular health and bone metabolism, is involved.[32] Third, the association of endothelial dysfunction with BMD in postmenopausal women suggests a potential synergistic effect of oestrogen deficiency.[24-27] Oestrogen deficiency exacerbates oxidative stress and inflammation, increases reactive oxygen species and dysregulates the RANK/RANKL/OPG system.[33] An animal study demonstrated an endothelium-dependent vascular coupling mechanism in bone remodelling.[34] Endothelial dysfunction obstructs the blood supply carrying oxygen, nutrients and metabolites to the osteoid, hindering its calcification, mineralisation, repair and maintenance.[27,35] Oxidative stress and activation of the RANK/RANKL/OPG system are known in RA and may be exacerbated by glucocorticoids.[7] Furthermore, shared risks for endothelial dysfunction and bone health impairment are known in RA, that is, the use of glucocorticoids, HCQ and systemic inflammation.[15] Therefore, the finding of an association between endothelial dysfunction and decreased BMD is plausible in RA.

The association between arterial or aortic stiffness and impaired bone health is reported in various populations.[36] The Baltimore Longitudinal Study of Aging found that arterial stiffness, as measured by cf-PWV, is inversely related to cortical bone area in women, but not in men, independent of age and other risk factors.[37] The UK Biobank study reported that poor bone quality, assessed by bone speed of sound, is associated with greater arterial stiffness in both men and women. This relationship was consistent across different measures of arterial compliance, such as aortic distensibility and arterial stiffness index.[38] While the associations were reported in a healthy Chinese population, men with hypertension and patients with end-stage renal disease, no associations were found in postmenopausal women patients in Japan and patients with hyperhomocysteinaemia.[36] Conversely, bone loss increases the levels of matrix metalloproteinase-2 and transactivates the RunX promoter, transforming vascular smooth muscle cells into osteoblasts, subsequently resulting in vascular calcification and increased vascular stiffness.[10] The absence of association between aortic stiffness and BMD in our cohort may be due to the small sample size and the low prevalence of aortic stiffness. Nevertheless, further study is warranted in larger cohorts.

The elevated CVD risk in RA cannot be fully explained by the traditional risk factors, and existing CVD risk prediction models do not perform well in patients with RA.[39] Given the shared risk factors and the association between subclinical vascular damage and bone health, BMD results, which are easily accessible and well validated, could serve as potential predictors for CVD in RA, in conjunction with the traditional risk factors. This, in turn,

could prompt more aggressive screening and management of both cardiovascular risk factors and bone health in these patients. In non-inflammatory diseases, studies have shown an increased risk of CVD in patients with osteoporosis,[40,41] though some controversy exists.[42] Although the fracture risk assessment (FRAX) tool score was developed to predict fracture risks, it was found that the hazard ratio for major adverse cardiovascular events increased by 1.99 for each standard deviation rise in FRAX.[43] In RA, the risk of CVD is higher among patients with a history of fragility fractures, with a hazard ratio of 1.81.[44] Data from the Oslo RA Register indicated that patients who died from CVD had a higher prevalence of osteoporosis and fracture.[45]

Our study has a few strengths. First, the study employed RHI for endothelial function and cf-PWV for aortic stiffness, offering a thorough evaluation of vascular health. Secondly, our findings are based on routinely monitored parameters like BMD, which are accessible in clinical practice, making the results directly applicable to patient care. In addition, it included well-annotated and comprehensive clinical data, enhancing the robustness of the findings. A limitation of this study is its small sample size from a single centre. Because of the absence of patients on biologics and the majority being in remission, this study was unable to investigate the impact of these factors on vascular and bone health. In addition, despite adjusting for several confounders, residual confounding by unmeasured variables cannot be ruled out. The analyses did not account for factors such as diet, physical activity and genetic predispositions.

In conclusion, our findings demonstrate that lower BMD is associated with endothelial dysfunction, but not aortic stiffness in patients with RA. To validate the findings, future research should focus on longitudinal studies, mechanistic studies and broader vascular health assessments.

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Conflicts of interest

There are no conflicts of interest.

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