235 SERUM OSTEOEONPIN LEVELS ARE ASSOCIATED WITH THE SUBCLINICAL CARDIOVASCULAR DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: In the general population, altered levels of proteins which regulate bone metabolism such as osteopontin (OPN), are associated with cardiovascular disease (CVD) and atherosclerosis. In rheumatoid arthritis (RA), levels of these bone markers are associated with joint inflammation and erosions. We hypothesised that they may also be associated with subclinical CVD in RA.

Methods: Bone markers: OPN, osteoprotegerin, sclerostin, receptor activator of nuclear factor kappa-B ligand (RANKL) and osteocalcin were measured in serum of patients with established RA (disease duration<1year) and age/sex matched controls using a Milliplex Multiplex Assay for markers of bone metabolism. Clinical and serological assessment of disease activity and cardiovascular risk factors was undertaken. Subclinical CVD was evaluated using carotid ultrasound (atherosclerotic plaque) and pulse wave velocity (arterial stiffness). Differences in levels of bone markers in patients and controls were tested using Mann Whitney U test. In patients, the association of bone markers with subclinical CVD measures was assessed using non parametric statistics. If a significant association was observed between individual markers and subclinical CVD, multivariable regression models, adjusting for traditional cardiovascular risk factors and CRP, were used to test for independent associations.

Results: Bone markers were measured in 128 patients and 42 controls. Median (IQR) age was 55.4 (48.8, 61.8) vs 56.9 (49.7, 60.5) years and 97 (75%) vs 33 (78.5%) were female in patients and controls respectively (all p > 0.05). In patients, median disease duration was 10.2 (5.5, 20.7) years, disease activity (DAS28) score was 4.5 (3.72, 5.44) and CRP was 3.0 (1.01, 6.2) mg/L. Plaque was present in 69 (53%) patients and 15 (35.7%) controls (p = 0.04). Median PWV was 9.6 (7.5, 11.7) m/s and 8.6 (7.7, 10.9) m/s in patients and controls respectively (p = 0.77). RANKL levels were significantly higher and sclerostin levels significantly lower in patients compared to controls (both p < 0.01) but there was no association between these two markers and subclinical CVD in the patient group. Osteopontin levels were significantly associated with carotid plaque in patients (8.33 [3.33, 10.79] ng/ml vs 5.78 [3.61, 7.92] ng/ml, plaque and no plaque respectively, p = 0.003). Osteopontin levels also correlated with PWV in patients (spearman rho: 0.31, p = 0.002). On multivariable analysis the association between osteopontin and plaque was independent of CVD risk factors and CRP (odds ratio [95%CI]: 1.14 [1.03, 1.26]), p = 0.045 per 1ng/ml increase in osteopontin). The association with PWV was also independent on multivariable analysis (coefficient [95% CI]: 0.165 [0.044, 0.285], p = 0.008).

Conclusion: Osteopontin has been linked with joint inflammation and damage but to our knowledge this is the first study demonstrating a link with atherosclerosis in an RA cohort. The association was independent of systemic inflammation and CVD risk factors, suggesting proteins which regulate bone metabolism may also play an important role in the development of atherosclerosis in RA. However, we did not account for multiple testing and further studies are required to validate findings and interrogate mechanisms.

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