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DOI: https://doi.org/10.5114/reum/219206

# Investigation of the molecular background of early skeletal involvement in systemic sclerosis by serum osteoimmune mediators

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Key words: osteoimmunology, bone markers, SSc, biomarkers

**Introduction:** Systemic sclerosis (SSc) is a complex, autoimmune disease associated with reduced bone density and increased fragility.

The study aims to investigate the molecular background of early bone alterations in SSc using dual X-ray absorptiometry (DXA)-derived bone mineral density (BMD) parameters and their associations with osteoimmunological biomarkers.

**Material and methods:** The prospective cross-sectional study included 40 women with SSc of relatively short disease duration (≤ 7 years from diagnosis) and 45 age-, sex- and bone status-matched non-immune controls at the Department of Rheumatology and Immunology, Clinical Centre, University of Debrecen, Hungary. Bone status was assessed by DXA at the lumbar spine and femoral neck. Routine bone and mineral metabolism markers were measured, as well as a targeted panel of osteoimmunological mediators (osteoprotegerin [OPG], osteopontin [OPN], platelet-derived growth factor-BB [PDGF-BB], tartrate-resistance acid-phosphatase [ACP5], receptor activator of NF-κB ligand [RANKL], tumour necrosis factor [TNF], interleukin-6 [IL-6], IL-1β, Dickkopf-1 [DKK-1]), which were quantified by multiplex immunoassay. Ten-year probabilities of major osteoporotic fracture and hip fracture were calculated using the FRAX® algorithm.

**Results:** The DXA-defined bone status distribution did not differ between SSc patients and controls, yet FRAX estimates were numerically higher in SSc. Serum OC levels were significantly lower, while 25-hydroxy vitamin D levels were significantly higher in SSc compared to non-SSc group, reflecting more frequent supplementation (Mann-Whitney U test, $p = 0,05$). Whereas SSc exhibited a distinct osteoimmune serum profile, characterised by significantly elevated OPG, ACP5, RANKL, IL-6, IL-1β, DKK-1, and an increased RANKL/OPG ratio, remaining significant after false discovery rate correction. Subgroup analyses across osteoporosis, osteopenia, and normal bone status showed consistent elevation of DKK-1 in SSc patients, with additional subgroup-specific differences of OPG, ACP5, RANKL, IL-6, and IL-1β levels, which were preferentially featured with osteoporosis and osteopenia.

**Discussion:** Early diagnosis and molecular characterisation of bone metabolism alterations may be crucial for optimising therapeutic strategies and potentially reducing the extent of bone loss in patients with SSc.

**Conclusion:** In women with relatively early SSc, a distinct osteoimmunological biomarker profile differentiated SSc from controls and was associated with DXA-derived BMD parameters, supporting a link between osteoimmunological alterations and skeletal involvement in the first years of SSc.