

18 **GDF15, A DISTINCT TGF β FAMILY MEMBER, IS DIFFERENTIALLY REGULATED IN SPONDYLOARTHRITIDES COMPARED TO OTHER RHEUMATIC DISEASES**

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Introduction The transforming growth factor β (TGF β) superfamily consists of a number of cytokines that regulate a variety

of cellular processes. Growth differentiation factor 15 (GDF15) is a distant member of this TGF β family with limited sequence homology to other members of this group. Its role in inflammatory arthritis is unclear. This study aims to evaluate the role of GDF15 across various inflammatory rheumatic diseases.

Methods GDF15 levels were determined by ELISA in three different populations. An exploratory study included serum samples from a consecutive cohort of 555 patients where serum was collected initially during diagnostic investigation. A second population constituted of patients with an indication for an arthroscopic procedure for diagnostic purposes. A third consisted of a cohort of RA patients in which the efficacy of infliximab was evaluated. Synovial tissue biopsies and peripheral blood mononuclear cells (PBMC) were collected, RNA isolated and qPCR for GDF15 conducted.

Results In all cohorts, inflammatory rheumatic diseases showed elevated GDF15 levels, except SpA. Interestingly, these patients showed near normal GDF15 serum levels. PsA patients only, but not RA patients or non-PsA SpA patients, show a significant higher concentration of GDF15 in synovial fluid compared to serum, pointing to a local production of GDF15 in the synovial joint. In line herewith, GDF15 mRNA levels were markedly higher in synovial tissue versus PBMC.

In general, no significant correlations were observed between GDF15 serum levels and inflammation markers (CRP, ESR), indicating that GDF15 serum levels might be indicative for a distinct underlying disease process. Moreover, suppression of inflammation by antitumour necrosis factor α treatment does not affect GDF15 serum levels.

Remarkably, SpA patients only, showed a strong positive correlation between GDF15 synovial fluid levels and levels of MMP3 and MMP1. In these patients, GDF15 synovial fluid levels also correlated with inflammation parameters (CRP, ESR). Given the involvement of MMPs in joint degradation, the observed correlations demonstrate an intriguing relationship between synovial GDF15 levels and local disease activity in SpA patients.

Conclusion Overall, our results highlight a markedly distinct regulation of GDF15 in SpA as opposed to other inflammatory rheumatic disease. Based hereon and the knowledge that other members of the TGF β family, have been linked to the modulation of the immune system as well as to bone formation, a process that differentiates RA from SpA, the authors anticipate that the elevated synovial fluid levels of GDF15 might be related to the remodeling features that typically are associated with SpA associated arthritis.