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Serum calprotectin is increased in early axial spondyloarthritis with sacroiliitis and objective signs of inflammation: results from the DESIR cohort

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Axial Spondyloarthritis (axSpA) is a chronic inflammatory disease that affects spine and sacroiliac joint (SIJ) leading to highly variable spinal radiographic damages in the individual patient [1]. Inflammation appears to be a determining factor of developing future structural damage [2, 3]. The quantification of inflammation in axSpA remains a challenge [4]. Calprotectin, an alarmin secreted by activated myeloid cells, has been suggested as a biomarker predicting radiographic spinal progression at 2 years in established ankylosing spondylitis (AS) [5-7]. The aim was to assess whether serum calprotectin was associated with inflammation and spinal radiographic progression within 2 years in early axSpA.

Patients with recent-onset inflammatory back pain, suggestive of axSpA from the DESIR cohort (NCT01648907) were included [8]. Assessment in SpondyloArthritis Society (ASAS) and modified New York criteria were respectively used for classification of axSpA and AS patients. Serum calprotectin was assessed at baseline (Calprotectin ELISA kit, Hycult Biotech). Radiographic spinal progression was defined as worsening by ≥2 units of the modified Stoke Ankylosing Spondylitis Spine Score 2 years after the inclusion. Spine and SIJ magnetic resonance imaging (MRI) inflammation were graded with the Spondyloarthritis Research Consortium of Canada (SPARCC) score.

At baseline, calprotectin was assessed in 426 early axSpA, including 149 patients with AS (**Table 1**). Serum calprotectin level was not significantly different between patients with recent-onset inflammatory back pain fulfilling *vs.* those not the ASAS criteria. High level of calprotectin was observed in axSpA with sacroiliitis, non-radiographic axSpA with objective signs of inflammation (*i.e.* with sacroiliitis on MRI and/or elevated CRP levels) and AS (**Figure 1A-B**). A total of 211 axSpA and 77 AS patients had both baseline and 2 years mSASSS scoring. Fifteen (15/211, 7.1%)

axSpA and seven (7/77, 9.1%) AS had a radiographic spinal progression within 2 years. Serum calprotectin levels did not identify patients with subsequent radiographic progression and was not increased in axSpA with syndesmophytes (≥1) or with significative SIJ erosions (≥3) and fat lesions (≥3) on MRI. axSpA patients with high disease activity index score (BASDAI>4 and ASDAS>3.5) and high SIJ and spine SPARCC scoring (≥5) showed an elevated calprotectin level (**Figure 1 C-F**). Calprotectin correlated with inflammatory parameters as CRP (r_s = 0.32, p<0.01), ESR (r_s = 0.23, p<0.0001), IL-6 (r_s = 0.24, p<0.0001), IL-31 (r_s = 0.17, p<0.001), sCD40L (r_s = 0.13, p<0.05) but not with TNF.

The present study shows that calprotectin is associated with inflammatory parameters, MRI inflammation rather than structural lesions in early axSpA. These results are in line with previous study [9]. We do not confirm, as observed in establish AS patient [5], that calprotectin level is a factor associated with spinal radiographic progression in early axSpA and AS. Nevertheless, this analysis is limited by a lack of statistical power to detect small effect size. Structural damage in axSpA is definitely a complex phenomenon hardly captured by a single biomarker assay compared to a biomarker combination strategy [10].

In conclusion, calprotectin in early axSpA seems to reflect the local inflammatory process involving myeloid cells in SIJ and spine.

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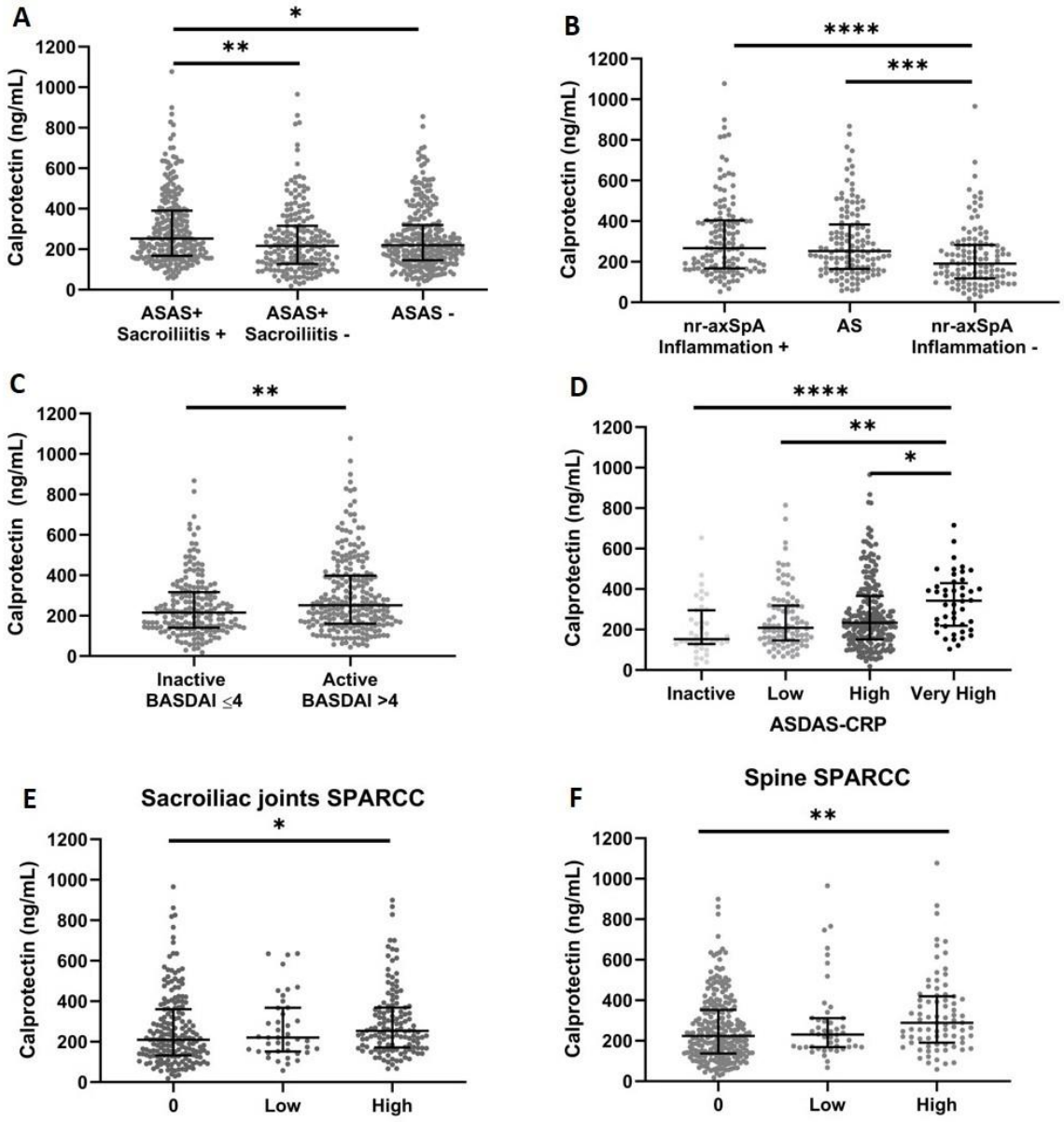

Figure 1. Serum calprotectin level is increased in early axial spondyloarthritis with sacroiliitis and objective signs of inflammation

Serum calprotectin levels at baseline (A) in early axial SpA (axSpA) patients fulfilling axial ASAS criteria (ASAS+) with sacroiliitis (sacroiliitis +) or not (sacroiliitis -) on X-ray or magnetic resonance imaging (sacroiliitis +) compared to those not fulfilling (ASAS-) and (B) in non-radiographic axSpA (nr-axSpA) patient with objective signs of inflammation (sacroiliitis + or elevated C-reactive protein level) (inflammation +), AS and those without objective signs of inflammation (inflammation -). (C) Serum calprotectin levels according to disease activity assessed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), (D) Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) and Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging score of the (E) sacroiliac joints and (F) spine. Inactive: ASDAS<1.3, Low: 1.3-2.1, High: 2.1-3.5 and Very High: ASDAS>3.5. 0: SPARCC score=0, Low: 2≤SPARCC score<5 and High: SPARCC score≥5. Each point represents a subject, horizontal and vertical lines show the median and interquartile range. * p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 with Mann-Whitney U test or Kruskal-Wallis one-way test with post hoc Dunn's test.

Table 1. Baseline characteristics of axial spondyloarthritis patients included from the DESIR cohort.

Baseline characteristics	axSpA ASAS+ (n=426)	AS mNY+ (n=149)	p-value
Males (%)	51.9	62.8	<0.05
Age (years, mean±SD)	31.4±7.2	32.1±8.5	NS
Disease duration (months, mean±SD)	10.4±23.0	13.1±24.5	NS
HLA B27 positivity (%)	86.1	74.3	<0.01
CRP level baseline (mg/L, mean±SD)	8.9±14.0	12.7±17.0	<0.01
elevated CRP	34.1	48.6	<0.01
BASDAI (mean±SD)	42.7±20.3	40.3±19.2	NS
ASDAS-CRP (mean±SD)	2.6±1.0	2.7±1.0	NS
BASFI (mean±SD)	28.8±22.1	30.2±23.2	NS
mSASSS (mean±SD)	1.5±4.0	1.9±4.2	<0.05
Serum calprotectin (ng/mL, mean±SD)	271.4±170.0	268.0±156.1	NS
Total Berlin score	1.2±2.9	2.7±4.5	<0.0001
SIJ SPARCC score	5.6±9.3	10.0±12.0	<0.0001
Spine SPARCC score	4.6±13.1	10.6±20.8	<0.0001

axSpA ASAS+: axial Spondyloarthritis fulfilling axial Assessment of Spondyloarthritis international Society criteria, AS mNY+: Ankylosing Spondylitis fulfilling modified New York criteria, HLA B27: Human Leukocyte Antigen B27, CRP: C-reactive protein, elevated CRP: CRP above 5mg/L, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASFI: Bath Ankylosing Spondylitis Spine Score, mSASSS: modified Stoke Ankylosing Spondylitis Spine Score, SIJ: sacro-iliac joint, SPARCC: Spondyloarthritis Research Consortium of Canada. P-values refer to Mann-Whitney U test result and Fisher's exact test. NS: non-significant

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