Added Value of Fecal Calprotectin to Support the Diagnosis of Spondyloarthropathies

To the Editor:

We read with interest the article by Kopylov, *et al*, who reported small bowel inflammation consistent with Crohn disease (CD) in 42.2% of patients with spondyloarthropathy (SpA) by video capsule endoscopy[1].

The link between bowel and joint in SpA has been established for several decades. Already in the 1980s, it was demonstrated that up to 50% of all patients with SpA have microscopic bowel inflammation, without associated gastrointestinal (GI) symptoms[2]. Calprotectin is a heterodimeric complex of two S100 calcium-binding proteins, myeloid-related protein (MRP)-8 (S100A8) and MRP-14 (S100A9), expressed in granulocytes and monocytes[3]. Fecal calprotectin (FC) is a sensitive and specific biomarker of intestinal inflammation, and quantification of FC is useful for diagnosis and followup of inflammatory bowel diseases (IBD)[4,5]. Also in patients with SpA, FC has been shown to reveal GI inflammation before clinical onset[6], which was confirmed by Kopylov and colleagues.

In daily practice, the diagnosis of SpA based on the Assessment of Spondyloarthritis international Society (ASAS) criteria is hampered by a relative low sensitivity of 79.5%[7]. We wondered whether the analysis of FC could add value to the diagnostic process of SpA.

We therefore quantified FC in 99 adult patients who for the first time presented with a clinical suspicion of SpA. Final SpA diagnosis (n = 52) was based on expert opinion. Patients were asked to discontinue intake of nonsteroidal antiinflammatory drugs 2 weeks before sample collection, and patients previously diagnosed with IBD were excluded. Three commercially available FC assays (Quantum Blue Calprotectin, Bühlmann; QUANTA Lite Calprotectin Extended Range, Inova Diagnostics; LIAISON Calprotectin, DiaSorin) were performed on each sample.

A summary of the diagnostic performance of the different FC assays in SpA diagnosis is shown in Table 1. In concordance with the findings of Kopylov, *et al*, FC levels were significantly higher in the SpA group versus the non-SpA group (Supplementary Figure 1, available from the authors on request). A receiver-operating curve analysis was performed to reveal the diagnostic performance for the different FC assays for SpA. The area under the curve did not differ significantly among assays, but there was a significant difference in sensitivity and specificity for SpA when the manufacturer's cutoffs were applied. At a cutoff of 98% specificity for SpA, sensitivities of 13%, 21%, and 8% were obtained for, respectively, the FC assays Quantum Blue Calprotectin, LIAISON Calprotectin, and QUANTA Lite Calprotectin Extended Range. Only for the FC LIAISON Calprotectin assay was a significant OR between the SpA and non-SpA patient group revealed, increasing the probability for SpA 6.8-fold for a patient with a positive FC test with the LIAISON Calprotectin assay (Table 1). Likelihood ratios [LR; i.e., the likelihood (%) for patients with SpA divided by the likelihood (%) for controls] were calculated for different FC test result intervals. The probability of SpA increased with FC, and LR of 0.5, 2.0, and 9.9 for FC of ≤ 20, 21–62, 63–200 μg/g were obtained for the LIAISON Calprotectin FC assay. These results show that on the one hand, low FC cannot exclude the diagnosis of SpA (LR of 0.5), and on the other hand, that high FC cannot be used to diagnose SpA (LR of 9.9). Nevertheless, as shown in Table 2, FC improved diagnostic sensitivity if combined with radiology and HLA-B27 analysis in the diagnostic process of patients with suspicion of SpA. For 67 of 99 patients, imaging [radiograph and/or magnetic resonance imaging (MRI)] and HLA-B27 analysis were available and both examinations resulted in an overall sensitivity and specificity for SpA of 67% and 84%, respectively. Adding FC improved the diagnostic sensitivity to 74% (Table 2), without reducing specificity. The corresponding LR was 4.6 (indicating a moderate difference in pretest to posttest probability).

Further, FC results could also be used to guide patient management in SpA[8]. Bowel inflammation seems to be an important prognostic factor in SpA; it was shown to be associated with more extensive bone marrow edema of the sacroiliac joints, a higher risk of progression to ankylosing spondylitis, and a higher risk of developing CD[9]. Even in the absence of clinical symptoms, endoscopic investigation of patients with elevated FC is advocated. If endoscopy and histologic analysis reveal evidence of active CD, therapeutic management of patients with SpA could be changed, by choosing a treatment option that is effective for both CD and SpA (e.g., adalimumab, infliximab, ustekunimab)[10]. In the study by Kopylov, *et al*, the finding of CD led to a change in patient management in 65.2% of cases[1]. The guidance of SpA management based on FC results is promising and merits further investigation.

FC analysis in combination with imaging and HLA-B27 analysis improves the diagnostic sensitivity in SpA.

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Table 1. Diagnostic performance of different fecal calprotectin assays to support the diagnosis of SpA.

	Quantum Blue Calprotectin		LIAISON Calprotectin	QUANTA Lite Calprotectin Extended Range	
AUC (95% CI)	0.658 (0.556–0.750)		0.684 (0.583–0.774), p = 0.2964*	0.661 (0.559–0.754), p = 0.9056*	
Median (95% CI) in SpA (n = 52)	59.0 μg/g (39.9–82.0)		25.4 μg/g (15.8–38.7)	24.6 μg/g (15.2–32.6)	
Median (95% CI) in non-SpA (n = 47)	32 μg/g (15.0–45.4), p = 0.0056§		11.5 μg/g (7.9–16.6), p = 0.0017§	13.0 μg/g (10.9–15.6) p = 0.0057§	
Manufacturer's cutoff	50 μg/g	200 μg/g	50 μg/g	50 μg/g	120 μg/g
Sensitivity for SpA (95% CI)	56% (41–70)	6% (1–16)	29% (17–43)	15% (7–28)	0% (0–7)
Specificity for SpA (95% CI)	68% (53–81)	98% (89–100)	94% (83–99), p < 0.0001**	96% (86–100), p < 0.0001**	98% (89–100)
Cutoff at 98% specificity for SpA	157 μg/g		62 μg/g	60 μg/g	
Sensitivity for SpA (95% CI)	13% (6–26)		21% (11–35)	8% (2–19)	
Likelihood ratio for SpA (95% CI)	6.3 (0.8–49.5)		9.9 (1.3–74.1)	3.6 (0.4–31.2)	
OR for SpA (95% CI)	7.2 (0.8–60.5), p = 0.1308§§		12.3 (1.5–99.8), p = 0.018§§	3.8 (0.4–35.6), p = 0.2372§§	

* Evaluation performed versus AUC Quantum Blue Calprotectin using the method of DeLong, *et al*, in MEDCALC software (version 17.1). § Mann-Whitney U test (independent samples). ** McNemar test (paired proportions) versus Quantum Blue Calprotectin. §§ OR calculated using the method of Altman, *et al*, in MEDCALC: if the associated p value is < 0.05 it can be concluded that the OR is significantly different from 1 and that the odds in 1 group are significantly higher than in the other. SpA: spondyloarthropathies; AUC: area under the curve.

Table 2. Performance of different tests to support the diagnosis of SpA.

	R, n = 80	R + HLA-B27, n = 67	R + HLA-B27 + FC, n = 67	FC, n = 99	HLA-B27 + FC, n = 81	R + FC, n = 80
Sensitivity (95% CI)	36% (24–50)	67% (52–79)	74% (59–85), p = 0.2482*	21% (11–35)	71% (57–82)	55% (41–68) p = 0.0026**
Specificity (95% CI)	94% (80–98)	84% (65–94)	84% (65–94)	98% (89–100)	78% (62–88)	88% (73–95)
LR (95% CI)	6.0 (1.5–24.1)	4.2 (1.7–10.5)	4.6 (1.8–11.5)	9.9 (1.3–74.1)	3.2 (1.7–6.1)	4.6 (1.8–11.8)
OR (95% CI)	8.8 (1.9–41.3)	10.5 (3.0–36.5)	14.8 (4.1–52.8)	12.3 (1.5–99.8)	8.6 (3.1–23.8)	9.0 (2.7–29.6)

* McNemar test (paired proportions) versus R + HLA-B27. ** McNemar test (paired proportions) versus R. With n = no. patients for which the test(s) was/were performed. SpA: spondyloarthritis; R: radiology (radiograph and/or MRI); FC: fecal calprotectin analysis with LIAISON Calprotectin performed at cutoff of 62 μg/g, corresponding to a 98% specificity for SpA; LR: likelihood ratio; MRI: magnetic resonance imaging.

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