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## Antibodies against collagen type II are not a general marker of acute arthritis onset.

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The fibrillar protein collagen type II (CII) is essentially confined to hyaline cartilage in diarthrodial joints. Antibodies against CII (anti-CII) were previously described in 3-27% of rheumatoid arthritis (RA) patients, and Kim et al. described anti-CII to be associated with elevated levels of CRP and ESR in a heterogeneous group of RA patients with 2-432 months of disease duration. [1] Contrary to anti-citrullinated protein antibodies, anti-CII are not detected before RA onset. [2] We have shown that anti-CII levels are highest at the time of RA diagnosis and thereafter decline, and that elevated anti-CII levels at diagnosis associate with elevated CRP, ESR, swollen joint count, disease activity score and radiological destruction at the time of diagnosis but not later, thus representing an acute onset RA phenotype. [3-5] It is plausible that production of pro-inflammatory cytokines by macrophages is stimulated by anti-CII-containing immune complexes (IC) in RA joints, as anti-CII producing B cells are detectable in synovial fluid but not in the circulation. [6, 7] Analogously, in rodents, collagen antibody-induced arthritis (CAIA) develops soon after injection of a defined blend of anti-CII antibodies. [8] Polymorphonuclear granulocytes (PMN) are central in CAIA pathogenesis, and we have recently shown that PMN induce chemokine production after stimulation with IC containing anti-CII from RA patients. [9]

In patients with very early synovitis with  $\leq 3$  months duration, anti-CII are not more common in patients developing RA than in patients developing other diagnoses during the following year. [10] Post-publication subgroup analysis showed that 3/11 (27%) of reactive arthritis and 2/7 (29%) of gouty arthritis patients had elevated anti-CII levels at the early synovitis stage (unpublished). As both reactive arthritis and gouty arthritis often have an acute arthritis onset, we hypothesized that high levels of anti-CII might not only be a marker of acute onset RA, but a marker of acute onset arthritis in general.

To investigate the hypothesis that high anti-CII levels might be a general marker of acute onset arthritides we collected first visit sera from 26 patients with gouty arthritis, 3 patients with pseudogout, 44 patients with reactive arthritis, and 33 patients with remitting seronegative symmetrical synovitis with pitting edema (RS3PE), diagnoses that often start with acute onset arthritis. Patient

characteristics are described in table 1. Antibodies against native human CII were measured with ELISA, and levels above the 95<sup>th</sup> percentile among controls were regarded as positive in agreement with our previous studies. [4-6] Serially followed internal laboratory controls showed that the analysis performance remained unaltered. [3, 4]

Eight of the 106 (7.5%) first visit non-RA patients were anti-CII positive, very similar to our previously published data on early RA (6.6-8.8%). [3, 4] There was no significant difference between any diagnostic groups (table 1). Only moderately elevated anti-CII levels were found; no non-RA patients exhibited very high anti-CII levels comparable to the high outlier group that we have described in early RA patients (figure 1). [4, 5]

We conclude that although high anti-CII levels are associated with acute onset in RA, this cannot be generalized to most patients with other acute onset arthritides.

Competing interests: None declared.

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Table 1. Patient characteristics for the investigated patients. Not all patients had data on RF and ACPA.

	Gouty arthritis	Pseudogout\$	Reactive arthritis	RS3PE	All non-RA	RA (from [4])
Number	26	3	44	33	106	274
Female; number (%)	9 (34)	1 (33)	17 (39)	17 (52)	44 (42)	193 (70)
Age, years; median (IQR)	62 (48-69)	80 (74-80)	33 (27-47)	52 (28-72)	46 (30-66)	56 (46-70)
CRP; median (IQR)	7 (3-30)	52 (0-100)	13 (3-38)	5 (3-11)	7 (3-26)	14.5 (7-31)
ESR; median (IQR)	16 (10-37)	60 (17-77)	19 (8-63)	11 (6-26)	16 (8-39)	21 (12-40)
SJC (66 joint count); median (IQR)	3 (1.5-9.5)	11 (1-12)	2 (1-4)	3 (1-6)	2 (1-6)	9 (5-13)
TJC (66 joint count); median (IQR)	4 (1-6)	13 (1-17)	3 (2-5)	5 (2-10.5)	4 (2-6)	7 (4-12)
RF positive/total measured (%)	4/26 (15.4)	0/3 (0)	3/44 (6.8)	4/33 (12.1)	11/106 (10.4)	172/272 (63.2)
ACPA positive/total measured (%)	0/19 (0)	0/3 (0)	1/12 (8.3)	0/6 (0)	1/41 (2.4)	157/274 (57.3)
Anti-CII* positive/total measured (%)	2/26 (7.7)	0/3 (0)	3/44 (6.8)	3/33 (9.1)	8/106 (7.5)	24 (8.8)

\* samples yielding > 29 AU/ml of anti-CII and showing lower OD in bovine serum albumin blocked control wells without CII than in anti-CII coated and subsequently blocked wells. \$ patients presenting with an inflammatory arthritis of at least one joint in which calcium pyrophosphate crystals were identified in synovial fluid microscopy and in whom no alternative diagnosis was made.

Figure 1. Levels of antibodies against native human collagen type II. The dotted horizontal line represent the cutoff based on the 95<sup>th</sup> percentile among healthy controls (29 arbitrary units/ml). Values above the cutoff are divided into true positive samples (triangles) and samples with non-specific binding (stars) reacting with higher OD levels in control wells coated only with bovine serum albumin. Only true positive values are reported as positive in table 1. Solid horizontal bars represent median values in each group. ReA= reactive arthritis, RS3PE= remitting seronegative symmetrical synovitis with pitting edema, RA=rheumatoid arthritis. Data on the 274 RA patients were published previously. [4, 5]