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Anti-cyclic citrullinated peptide antibody and pain sensitization in patients with rheumatoid arthritis: A cross-sectional analysis

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Pain and inflammation are often discordant among patients with rheumatoid arthritis (RA). In a mouse model, systemic injection of polyclonal autoantibodies against citrullinated

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proteins (ACPA) induced pain-like behaviors.[1] A recent study also suggested that specific monoclonal ACPAs may be responsible for tenosynovitis and pain behaviors in mice.[2] Given these findings, our goal was to examine the association between a subset of ACPA, anti-cyclic citrullinated peptides (anti-CCP), and pain in humans with RA.

Patients with active RA were enrolled in the Central Pain in Rheumatoid Arthritis study. Anti-CCP positivity was categorized as positive/negative and into quintiles. Experimental measures of peripheral sensitivity were pressure pain thresholds (PPTs) at the wrists and knees. Measures of central sensitivity were PPT at the trapezius muscles, PPT at the thumbnails, temporal summation (TS), and conditioned pain modulation (CPM). Patient-reported measures included pain intensity on a numeric rating scale and pain interference assessed by the PROMIS computerized adaptive test. Associations between anti-CCP positivity and pain were examined using multiple linear regression and linear trend tests. Exploratory subgroup analyses were performed, stratified by sex, hsCRP (≤ or >3 mg/L), and swollen joint count (SJC ≤ or >1) (See Supplemental Materials).

Among the 255 participants, 159 (62.4%) were positive for anti-CCP antibody. Mean (SD) DAS-28 score was 4.4 (1.2) (Supplemental Table 1). Comparing anti-CCP positive and negative groups, no differences in wrist PPT, knee PPT, trapezius PPT, thumbnail PPT, TS, and CPM were observed (Figure 1A, Supplemental Table 2). No dose responses were noted (Figure 1B), except for a trend in knee PPT in the adjusted model ($p = 0.0275$). Patient-reported pain intensity and pain interference were similar between anti-CCP positive and negative groups (Figure 1C, Supplemental Table 3). No consistent relationships were noted in analyses stratified by sex, hsCRP, or SJC.

Our results contrast with initial findings by Wigerblad et al., who demonstrated that intravenous administration of ACPA led to peripheral pain sensitivity in mice.[1] However, the monoclonal ACPAs used in the initial experiments were subsequently determined to lack specific binding to citrullinated peptides.[3] Alternative mechanisms of action were proposed, including ACPAs acting as immune complexes and/or cross-reactivity with other moieties (e.g., carbamylated proteins/peptides). Ultimately, the mechanisms underlying associations between ACPA and pain in mice remain elusive. Additional studies are needed to determine if autoantibodies in pre-RA or early RA could explain clinically suspect arthralgia without inflammation in humans.

Our results corroborate findings from the Better Anti-Rheumatic Pharmacotherapy study, which showed that ACPA positivity was not associated with unacceptable pain among DMARD-naïve patients with early RA.[4] Our study expands the generalizability of these findings by including DMARD-treated patients with a range of disease durations. In addition, we assessed experimental pain sensitivity, which provides information on neurobiological mechanisms and suggests our findings are not simply due to factors confounding self-reported pain.

Limitations include the small number of men and complexities in interpreting experimental pain sensitivity. Although we considered articular PPTs as measures of peripheral sensitization, they may also reflect a component of CNS pain dysregulation. However, we

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have shown that wrist PPTs are lower among patients with RA compared to controls and associated with peripheral inflammation.[5,6] Thus, we expect the peripheral contribution to be larger than the CNS contribution.

To our knowledge, this is the first study to demonstrate that anti-CCP antibodies are not associated with experimental pain sensitivity or patient-reported pain in patients with active RA and long disease duration. While more studies are needed to determine if anti-CCP antibodies may be direct effectors of pain in subgroups of patients, our results suggest that anti-CCP antibodies are unlikely to have a large impact on pain in most patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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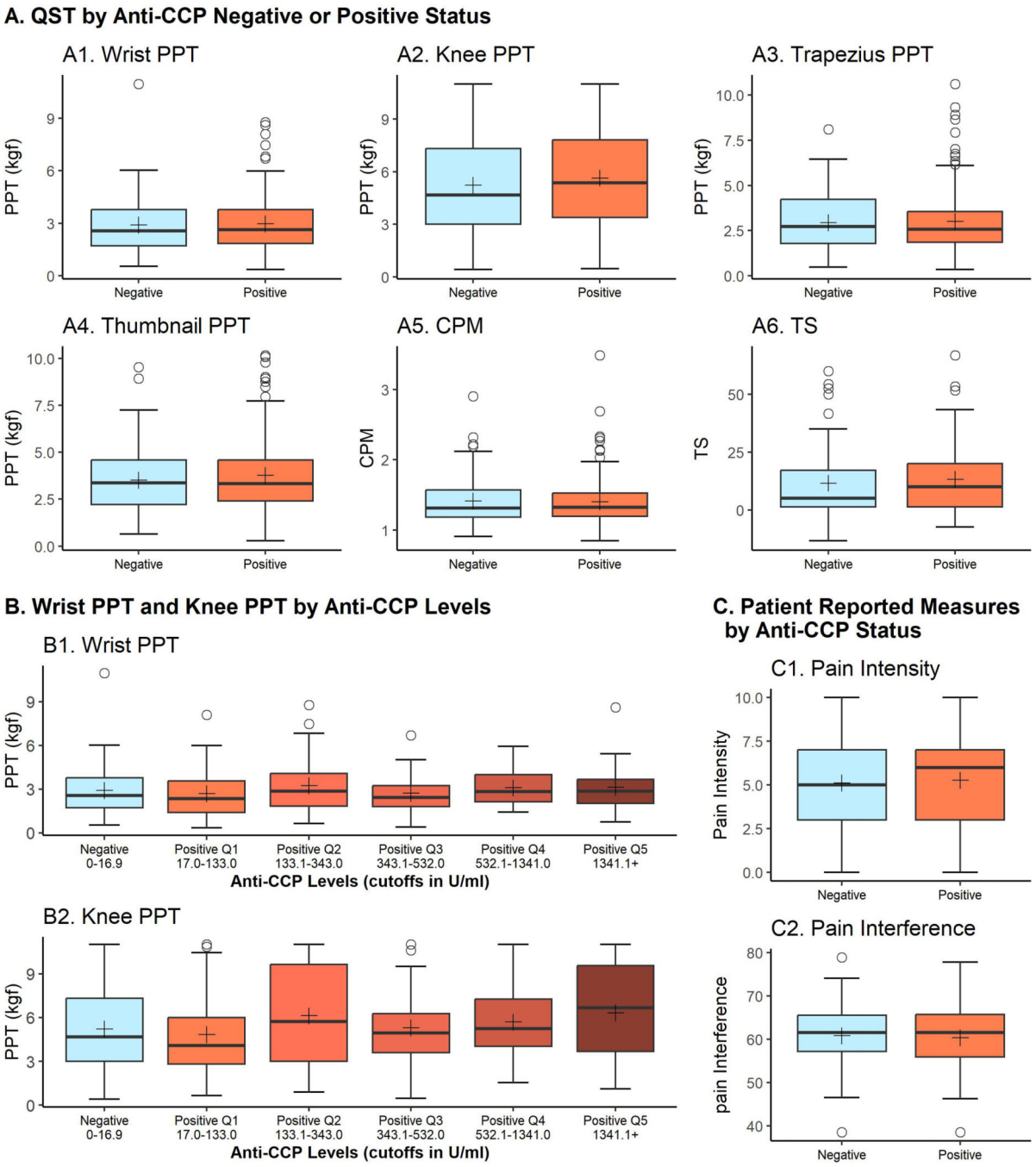


Figure 1.

Relationship between pain measures and anti-CCP positivity. (A) Association between experimental pain sensitivity and anti-CCP positivity; (B) Dose response between measures of peripheral experimental pain sensitivity and quintiles of anti-CCP positivity; (C) Association between patient-reported measures of pain and anti-CCP positivity. CCP, cyclic citrullinated peptide; CPM, conditioned pain modulation; PPT, pressure pain threshold; TS, temporal summation.