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## **Onset of rheumatoid arthritis after COVID-19: coincidence or connected?**

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26 COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can lead to  
27 severe inflammation and has been suggested to induce autoimmune phenomena. Multiple studies  
28 have reported autoantibodies in patients with COVID-19, particularly anti-cardiolipin, anti- $\beta$ 2  
29 glycoprotein I and anti-nuclear antibodies.[1, 2] Anti-citrullinated protein antibodies (ACPA) and  
30 flaring of rheumatoid arthritis (RA) after SARS-Cov-2 infection have also been described.[1, 3]  
31 However, it is unclear how often ACPA occur after COVID-19 and whether they differ from ACPA  
32 normally found in RA patients.

33 We have therefore performed a detailed investigation into ACPA-positivity after COVID-19. To  
34 determine the seroprevalence of ACPA after COVID-19, ACPA was measured using routine tests or  
35 in-house enzyme-linked immunosorbent assay (ELISA) in 61 patients visiting the post-COVID  
36 outpatient clinic of the LUMC 5 weeks after hospitalization. None of the patients tested positive for  
37 ACPA, except two patients previously diagnosed with ACPA-positive RA. Thus, we could not observe  
38 an increase in ACPA-positivity after COVID-19.

39 Furthermore, we identified five patients across various Dutch rheumatology clinics presenting with  
40 polyarthritis compatible with RA after SARS-CoV-2 infection. To study the impact of COVID-19 on  
41 disease presentation, we closely examined their clinical phenotype and autoantibody characteristics  
42 (Supplementary table S1). All had suffered from moderate to severe COVID-19. On average, joint  
43 complaints started 6.6 weeks after infection, although two patients reported symptoms before  
44 infection. 4/5 patients fulfilled the ACR 2010 criteria for RA. Three patients were phenotypically very  
45 similar to regular new-onset RA patients. Patient 3 had a history of seronegative RA and had been in  
46 DMARD-free remission for 5 years. She flared 6 weeks after SARS-CoV-2 infection. Patient 2 had a  
47 remarkably different presentation. He was admitted with acute polyarthritis and high inflammatory  
48 markers 6 weeks after COVID-19. Pneumonia with reactive polyarthritis or septic polyarthritis were  
49 considered and treatment was started accordingly. ACPA-level was low positive. The patient died  
50 unexpectedly after two days and autopsy revealed dilating myocarditis of unclear underlying cause.  
51 No causative pathogen, nor compelling evidence of autoimmunity, could be identified.

52 Previous studies have shown that RA-patients are most often either seronegative or triple-positive  
53 for rheumatoid factor, ACPA and anti-carbamylated protein antibodies. ACPA IgM and IgA are most  
54 frequently found within patients positive for ACPA IgG.[4] Autoantibody measurements on sera of  
55 the post-COVID polyarthritis patients using in-house ELISA's,[4] revealed patterns very similar to RA  
56 (figure 1A) with two patients being completely seronegative, and three patients positive for a range  
57 of autoantibodies at presentation. Sera prior to presentation to the rheumatologist are not  
58 available.

59 A unique feature of ACPA IgG in RA patients is that they harbour glycans not only in their Fc-part, but  
60 also in their variable domains (V-domains)[5]. We analysed the ACPA IgG V-domain glycosylation  
61 profiles of the above-mentioned 3 ACPA-positive post-COVID patients and established RA patients  
62 (Supplementary table S1) using UHPLC.[5] In all post-COVID samples, the percentage of ACPA V-  
63 domain glycosylation was increased compared to total IgG (figure 1B), similar to regular RA.  
64 Inflammatory conditions, among which COVID-19, can induces changes in the composition of  
65 antibody Fc-glycans[6]. A detailed examination of the specific ACPA IgG V-domain glycan traits  
66 revealed a significant decrease in bisecting N-Acetylglucosamine containing moieties (G2FBS1,  
67 G2FBS2) after COVID-19 (figure 1C), comparable to patterns described for total IgG Fc-glycosylation  
68 post-COVID.[6] The biological causes and consequences of these glycosylation changes currently  
69 remain unclear.

70 Limitations of this study include the small sample size and limited follow-up duration after COVID-19.  
71 Although autoantibody responses can develop rapidly after (SARS-Cov-2) infections, replication in a  
72 larger cohort with a longer follow-up would be valuable. Furthermore, part of the samples were  
73 measured on in-house instead of commercial tests. However, the characteristics of these assays  
74 appear very comparable based on previous experience.

75 In conclusion, we found that the seroprevalence of ACPA is not increased after COVID-infection and  
76 that patients presenting with polyarthritis post-COVID resemble regular RA patients, both regarding  
77 clinical phenotype and autoantibody characteristics. Based on these data, it appears that RA post-  
78 COVID may be coincidence rather than connected.

79

80 Figure legend: Figure 1. A Auto-antibody measurements using in-house ELISA's: Rheumatoid factor  
81 (RF), anti-citrullinated protein antibody (ACPA) and anti-carbamylated protein antibody (anti-CarP)  
82 isotype levels per patient. White – seronegative, Gradient light to dark blue – low to highest levels,  
83 normalized against maximum detection limit ELISA per antibody isotype. B Percentage of variable  
84 domain glycosylation (mean, SD). Average value of duplicates plotted. V- domain glycosylation in  
85 ACPA IgG post-COVID is significantly increased compared to total IgG ( $p < 0.05$ ; Mann-Whitney U test),  
86 no significant difference between ACPA IgG V-domain glycosylation post-COVID and in regular RA  
87 (disease characteristics in supplementary table S1). C Percentage of specific glycan traits of all ACPA  
88 IgG V-domain glycans (mean, SD). Average value of duplicates plotted. Glycan trait G2FS2 without  
89 bisecting N-Acetylglucosamine is significantly increased, while G2FBS1, a glycan traits with bisecting  
90 N-Acetylglucosamine is significantly decreased post-COVID-19 ( $p < 0.05$ ; Mann-Whitney U test). Blue  
91 square – N-Acetylglucosamine (B when bisecting), green circle – mannose, red triangle – Fucose (F),  
92 yellow circle – galactose (G), purple diamond – sialic acid (S).

93

94 **Statements**

95 Patient and public involvement Patients and/or the public were not involved in the design, or  
96 conduct, or reporting, or dissemination plans of this research.

97 Data Availability Statement All glycan analysis data are available upon reasonable request.

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100 Patient consent for publication Patients did not object to the use of their anonymized data.

101 Contributorship statement: VD, TH, RT and DvdW designed the study. FLK, AvdB, AV and AR  
102 collected the patient data and materials. VD and TK performed the experiments. VD, TK and DvdW  
103 analysed the data. VD drafted the manuscript. All authors revised the manuscript critically and gave  
104 approval of the version to be published.

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