Duration of pre-rheumatoid arthritis anti-CCP positivity is positively associated with age at seroconversion.
Introduction

Majka et al.\(^1\) have recently shown that higher age at the time of diagnosis of rheumatoid arthritis (RA) is associated with an increased period of pre-diagnosis antibody positivity for rheumatoid factor (RF) and anti-CCP. We have extended this observation using a previously described RA cohort (n=79) in which serial preclinical serum samples were available, in most cases preceding and following seroconversion, thereby enabling approximation of the age at seroconversion.\(^2\) Thirty-two patients were anti-CCP positive and 22 patients were IgM-RF positive in the preclinical period. The age at seroconversion and the period of seropositivity before onset of RA symptoms was calculated using the mean of the time points of the last seronegative and the first seropositive sample. When samples preceding seropositivity were unavailable (anti-CCP 6 patients; IgM-RF 3), the date of the first available sample was used. Patients positive for both antibodies were analyzed in both groups (n=14).

Results

In the anti-CCP positive patients, the mean age at seroconversion was 43.0 years (standard deviation [SD] 11.4). The median period between seroconversion and onset of RA symptoms was 4.7 years (range 0.3-12.7). Linear regression analysis using this period as the dependent variable and age at seroconversion as the independent variable revealed a relationship between these parameters (B 1.43; 95% confidence interval [95% C.I.] 0.22-2.64; \(P = 0.02\), see figure 1). Correcting for gender and subgroup analysis excluding the patients where the age at seroconversion could not be determined, or using the first positive sample as start of the seropositive period, did not alter these results. The same analysis was performed in the IgM-RF positive patients. The mean age at seroconversion was 45.7 years (SD 8.9). The median period between seroconversion and onset of RA symptoms was 2.0 years (range 0.2-9.1). Linear regression analysis did not show a correlation between age at seroconversion and period of seropositivity before onset of RA symptoms. Correcting for gender and subgroup analysis as described for the anti-CCP group did not alter these results. The median period between seroconversion and onset of RA symptoms was longer for anti-CCP than for IgM-RF (\(P = 0.02\)).
ACPA and age at seroconversion

Figure 1: age at seroconversion is associated with duration of pre-clinical anti-CCP positive period. The period between anti-CCP seroconversion and onset of RA symptoms is shown on the x-axis and the age at seroconversion on the y-axis.

\[ y = 35.6 + 1.43 \times \text{delta period} \quad (P = 0.022) \]

Conclusion

The novel finding in this study is that age at onset of seropositivity determines the period of anti-CCP positivity until symptoms preceding the diagnosis of RA appear. This result further extends the observation of a positive association between duration of pre-clinical antibody positivity and age-at-diagnosis of RA.\(^1\) As suggested by Majka et al, biological senescence and a differential relationship between genetic and environmental exposures as age increases may explain the longer duration of anti-CCP positivity before onset of RA symptoms. In contrast to others, the period between seroconversion and onset of RA symptoms was longer for anti-CCP than for IgM-RF.\(^1\) In parallel to the differential response of these antibodies to antirheumatic treatment, these results suggest that the presence of IgM-RF is inflammation-driven, whereas the earlier appearance of anti-CCP suggests pathophysiological properties.\(^3\) In conclusion, the period of pre-clinical anti-CCP, but not IgM-RF positivity, is associated with age at seroconversion.

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Reference list