CLINICAL SIGNIFICANCE OF ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES IN A COHORT OF JUVENILE IDIOPATHIC ARTHRITIS

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Abstract

Anti-cyclic citrullinated peptide (anti-CCP) antibodies are considered to be specific for rheumatoid arthritis. The aim of the study consists in assessment of prevalence and clinical significance of anti-CCP antibodies in a cohort of juvenile idiopathic arthritis (JIA). In 55 patients with JIA, and a age and sex-matched control group (21 children with no articular sign) IgG anti-CCP antibodies were measured in serum using a commercial chemiluminescent immunoassay (CMIA) method (Architect ABBOTT). Positive anti-CCP values (above the 5U/ml cut-off value of the method) were found in 5 patients (9.1%). Statistical significant positive correlation had been found between anti-CCP antibodies titer and acute phase reactants, disease activity score and radiographic damage, respectively. Reevaluation after 3 months of the anti-CCP antibodies titer revealed statistical significant change. Anti-CCP is less prevalent in JIA than in rheumatoid arthritis, but its positivity denotes an erosive course of disease.

Key-words: anti-CCP antibodies, juvenile idiopathic arthritis

Background

In order to diagnose an autoimmune disease, determination of autoantibodies in the serum of patients is a matter of course. However, most of the autoantibodies can be detected in other conditions also, therefore they are not specific. A typical example for this situation is the rheumatoid factor (RF), which is present in many inflammatory conditions. Nevertheless, there are antibodies which occurs specifically in a certain disease, giving the clinician a precise indication of the type of pathologic condition. For example, anti-double chained DNA antibodies are typically present in systemic lupus erythematosus, and the literature of the last decade confirms that there are autoantibodies which are linked almost exclusively to rheumatoid arthritis (RA). These RA-specific autoantibodies are the so called anti-citrullinated peptide/ protein (anti-CCP) antibodies.

Citrullination (deimination) consists in a post-translational modification of arginine into citrulline. During this oxidation process, the positively charged arginine becomes neutrally charged citrulline, which increases hydrophobicity and leads to alteration of the protein structure. Secondly, citrulline is not coded by DNA, and consequently is not included in protein synthesis. Thereby, deimination, through alteration of protein structure and protein unfolding, probably leads to aberrant recognition of the citrullinated proteins by the immune system (1,2). Citrullination is preceded and up regulated by inflammation, and possibly leads to activation of CD4+ T cells (3) and initiation of autoimmunity. Studies performed in animal models with collagen-induced arthritis, proved that the anti-citrulline IgG response targeted not only the altered protein, but also caused cross-reactivity to unmodified peptide (3).

The anti-citrullinated peptide autoantibodies positivity can be searched via the anti-CCP antibody test. The first generation CCP test (CCP1) contained a single cyclic citrullinated peptide derived from fillagrin as the substrate (4). Second generation CCP test (CCP2) incorporates numerous novel citrullinated peptides with epitopes for detection of anti-CCP antibodies. The anti-CCP2 test demonstrated an RF-like sensitivity (70-75%) with a very high (95-99%) specificity for RA (5,6).

Objective

The present study was undertaken to determine the prevalence of anti-CCP antibodies in a cohort of children with JIA, and to observe possible correlations of these antibodies with subtype of JIA, disease activity and joint lesions. Basically, the main objective of the study was to estimate the clinical and prognostic significance of anti-CCP antibodies in JIA.

Patients and Methods

A cohort of 55 patients with JIA was recruited from First Pediatric Clinic of "Louis Țurcanu" Clinical Emergency Hospital for Children, Timisoara, Romania and participated in the prospective study. The JIA group consisted in 32 girls and 22 boys, with median age of 11.3 ± 1.2 years. Diagnosis and classification was performed according to International League Association for Rheumatology (ILAR) criteria. Figure 1 presents the distribution of patients in subtypes of JIA.

Control group consisted in 21 children with no articular symptom or sign, 12 girls and 9 boys, and median age of 12.1± 1.8 years.

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Measurement of disease activity

Acute-phase reactants, including erythrocyte sedimentation rate (ESR, mm/h) and plasma concentrations of C reactive protein (CRP, mg/dl) were determined both in children with JIA and control group. At the same time points, clinical examination of studied group included a 27 joint count for tender and swollen joints. Assessment with a global visual analogue scale (VAS with range 0 to 10cm) was undertaken both by physician and parents or patients according to the age of child with JIA. ESR value was normalized to a 0-10 scale according to the following formula: [ESR (mm/hour) – 20] divided to 10. Before performing the calculation, ESR values < 20mm/hour were converted to 0 and ESR values > 120 mm/hour were converted to 120 (7). The Juvenile Arthritis Disease Activity Score (JADAS) was calculated as the simple linear sum of the scores of its four components: physician global assessment (VAS), parent or patient global assessment (VAS), active joint count (swollen joint count and tender joint count), normalized ESR (range 0 to 10).

Immunological assessment

IgG rheumatoid factor (RF) were determined by a nephelometric commercial test. Presence of antinuclear antibodies (ANA) was tested by a standard indirect immunofluorescence technique on HEp-2 cells. ANA were considered positive at serum titers >1/40.

Anti-CCP measurement

IgG anti-CCP antibodies were measured in serum using a commercial chemiluminescent immunoassay (CMIA) method (Architect ABBOTT) with 5 units/ml cut-off value. In all JIA cases titer of anti-CCP antibodies had been reassessed after 3 months.

Imagistic

X-ray was performed in order to evaluate the radiographic damage (erosions or joint space narrowing) in the affected joints (no).

Ethics

The study was approved by the ethics committees of the institution. Informed consent was obtained from parents or guardians of all participating children.

Results and Discussions

Prevalence of anti-CCP antibodies

Positive anti-CCP values (above the 5U/ml cut-off value of the method) were found in 5 patients (9.1%) in the cohort with JIA (figure 3), in comparison with the control group, with negative anti-CCP in all children (figure 4).

In comparison with the prevalence of anti-CCP antibodies in rheumatoid arthritis, we found a much lower rate of positivity in our juvenile cohort. Most of the studies from literature confirm our data, that anti-CCP can be detected also in patients with JIA, but they are generally present at low levels and less common than in adults with RA (8,9). Prevalence of anti-CCP in JIA is still a controversial issue; Avcin and co. (8) found a lower prevalence (2%) than ours, while a recent study performed on a large cohort of JIA patients (334) showed a prevalence of 14% of anti-CCP positivity (10). However, the absence of

anti-CCP antibodies in control group states the question of the anti-CCP antibodies pathogenic role in JIA.

If we try to conclude the answer to the question "Should we test currently JIA children for anti-CCP antibodies?" is important to study concisely the predictive value of anti-CCP antibodies for rheumatoid arthritis. Clinical research studies show that anti-CCP is present in serum of a portion (55%-69%) of patients with rheumatoid arthritis and has been identified at all stages of RA: preclinical, early and established. Furthermore, blood bank studies proved that anti-CCP antibodies are present in the serum of patients as many as 12 to 14 years prior to the development of RA (11-14). The length of time that anti-CCP antibodies are detectable in patient serum prior to disease onset appears to be age related (15). Anti-CCP antibodies are present in the serum of older patients well before the developmental of clinical symptoms, while in younger patients, the detection of anti-CCP occurs closer to the time of disease onset (16). Clinical research showed that a combination of anti-CCP antibodies and RF had a high specificity and positive predictive value for the development of persistent RA. This autoantibody combination can be used to identify patients with disease destined to develop RA who may be appropriate for very early intervention (17).The results of these researches highlight the importance of anti-CCP testing, in spite of the low prevalence of anti-CCP positivity in JIA.
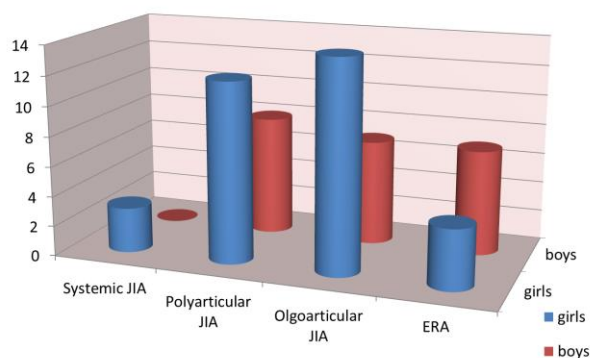

Figure 1. Distribution of cohort in types of JIA according to ILAR criteria

Distribution of anti-CCP positivity in JIA subtypes

In serum of 2 cases with extended ANA-positive oligoarthritis anti-CCP was found positive, but both cases were numbered into the polyarticular group, due to the extensive pattern of evolution. In 2 patients with seropositive (RF-positive) polyarticular onset JIA, we found positive anti-CCP antibodies, both with impressively high titers (≥200U/ml). Anti-CCP was not found positive in any case of persistent oligoarthritis or systemic JIA. In one case (1/11) with enthesitis-related-arthritis (ERA) anti-CCP titer was found higher than 5U/ml. Summarizing, in our cohort we found an association between anti-CCP positivity and a polyarticular course of disease (4/5, 2 seropositive, 2 seronegative), but the presence of anti-CCP antibodies was not exclusively linked to this subtype of JIA.

Figure 2. Anti-CCP antibodies in JIA patients

Figure 3. Prevalence of anti-CCP antibodies in control group
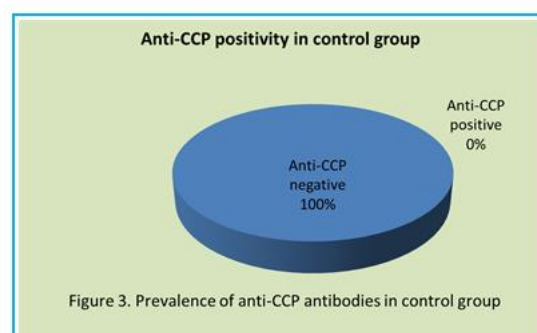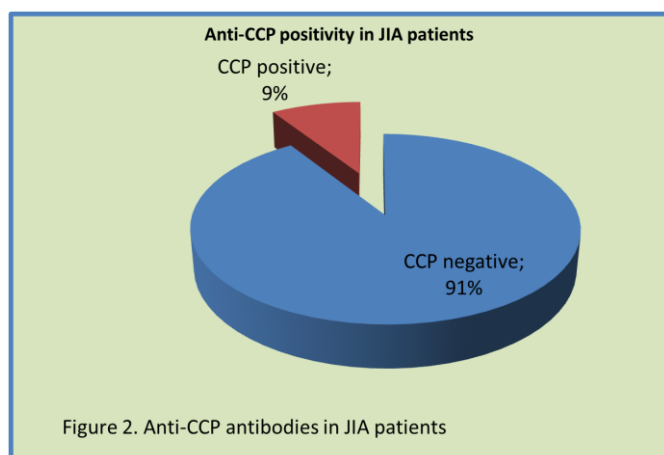
Type of JIA (number)	Median ESR (mm/1h)	Median CRP (mg/dl)	ANA+ (no cases)	Anti-CCP+ (no cases)	Median JADAS
Systemic (3)	49.8±12.7	12.2±5.7	0	0	19.8±3.5
Oligo (21)	27.5±11.9	7.35±4.3	2	0	6.3±2.9
RF+ Poly (6)	47.1±19.6	11.2±3.9	0	2	17.5±4
RF- Poly (14)	31.9±11.2	10.6±2.7	2	2	14.9±2.8
ERA (11)	20.1±7.1	4.8±1.3	0	1	11.7±4.7

Table 1. Description of clinical and paraclinical characteristics of the cohort
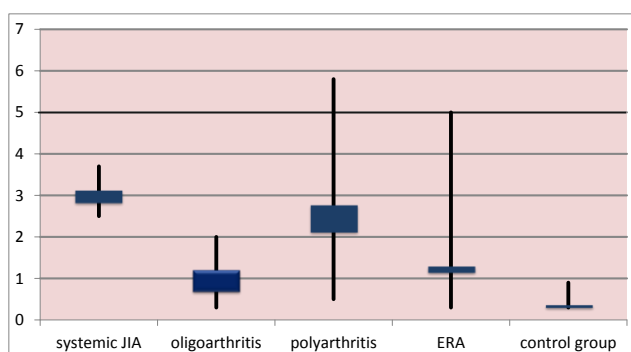

Figure 4. Median values of anti-CCP titers in different types of JIA and control group
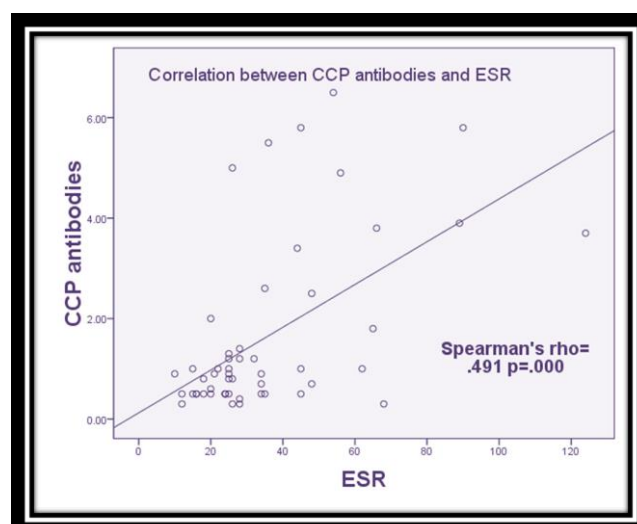

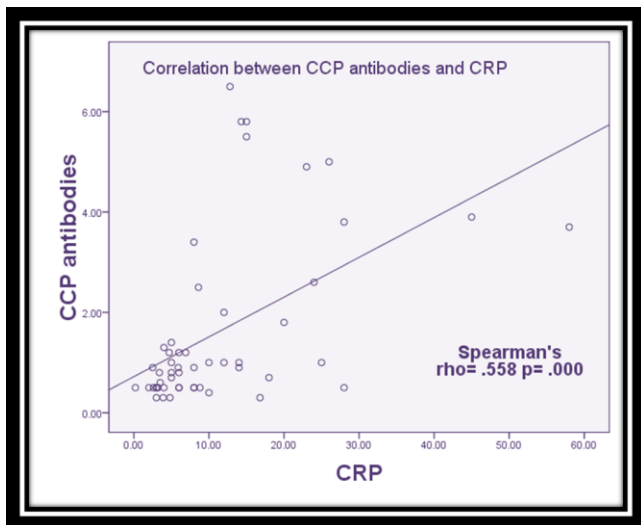Fig. 5 Correlation between CCP antibodies and ESR

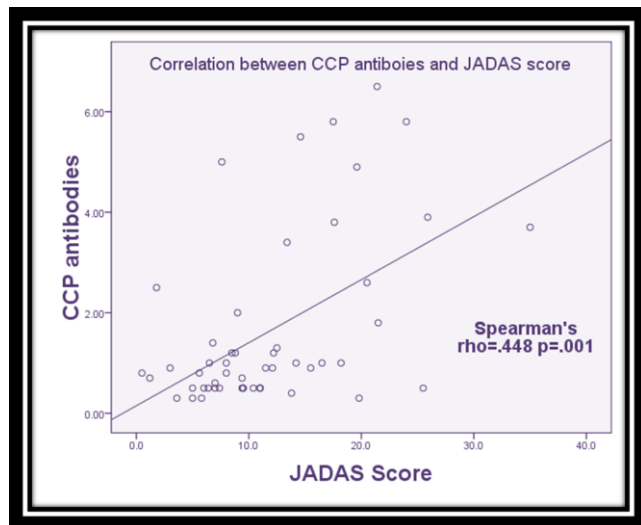Fig. 6 Correlation between CCP antibodies and CRP

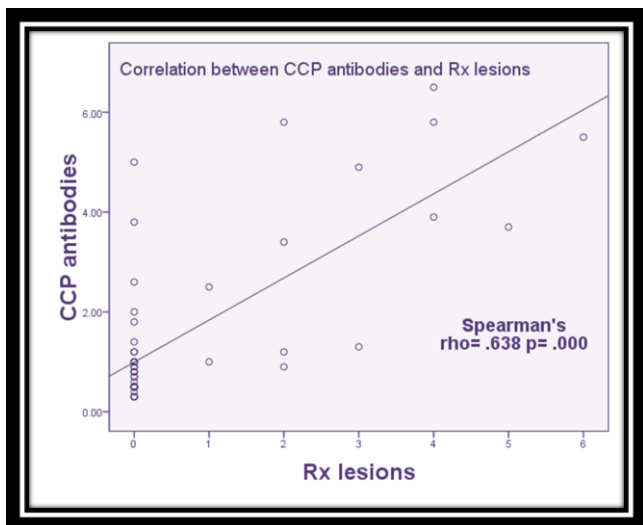Fig. 7 Correlation between CCP antibodies and jadas SCORE
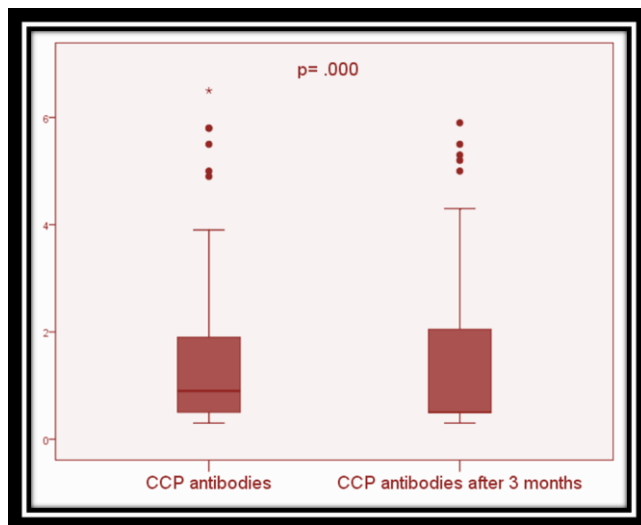

Fig. 6 Correlation between CCP antibodies and CRP

Fig. 7 CCP antibodies

Association between anti-CCP positivity and subtype of JIA is still debated. Habib and co. showed by his study that anti-CCP antibodies are detectable in a significant proportion of RF-positive patients with polyarticular-onset JIA, and are negative in patients with oligoarticular-onset and systemic-onset disease (18). Concordant with the previously mentioned study, Brunner found that anti-CCP antibodies are associated with RF-positive polyarticular course of JIA (19), they are not relevant for other subgroups of JIA, and therefore should not be investigated routinely. However, another important study (8) found no association between anti-CCP and disease subtype. Tebo and co. proved anti-CCP positivity in seronegative JIA patients as well, claiming that children with positive anti-CCP antibodies but negative RF are frequent, and may define a distinct subset of children with JIA (10). Similarly, clinical trials in adults suggest that anti-CCP antibodies are of particular diagnostic use in patients with rheumatoid arthritis who are negative for RF (20,21). Current research supports the hypothesis that rheumatoid arthritis patients who are negative or positive for anti-CCP antibodies may constitute two subsets of the disease with different clinical outcome (20). Therefore, testing of anti-CCP antibodies presence is mandatory in serum of all types of JIA patients.

Table 1 presents the median values of inflammatory biomarkers (ESR, CRP), the median disease activity score (JADAS), and the number of ANA, respectively anti-CCP positive cases severally for each subtype of JIA patients.

Disregarding the cut-off value of anti-CCP determination, we calculated the median titer for each type of JIA (figure 4), and the control group respectively. For a better analyze of the mean values, we excluded from the chart the two cases with high levels of anti-CCP (≥200U/ml). Figure 4 shows that in all types of JIA, the median anti-CCP titer was below the cut-off value of the commercial method, however permits a comparison between the median level of anti-CCP titer in JIA subtypes and the control group. We found a statistically significant difference (p<0.005) between median anti-CCP titer of all subtypes of JIA and anti-CCP values of control group.

These observations raise the issue of adjusted cut-off value in juvenile patients. The cut-off point should be calculated according to the mean value of anti-CCP titers of the control group. Similarly, in the study of Avcin and co. (8), the cut-off point was calculated as the mean plus three standard deviations of the values in the healthy children group (30 subjects matched for age and sex). In the assessment of rheumatoid arthritis also exists huge variation in cut-off values and performance characteristics of anti-CCP tests, highlighting the need for harmonization of these tests (15). There is a current effort at harmonization of anti-CCP tests in adult rheumatology, which includes the development of international reference reagents by the Centers for Disease Control and Prevention (20) and the Autoantibody Standardization Committee (22). Analogously, a standardization of the anti-CCP antibody cut-off value in juvenile arthritis would be mandatory. Perhaps, a lower cut-off level for anti-CCP antibodies in pediatric patients with an increased sensitivity would be more appropriate in JIA assessment.

Correlations between anti-CCP titer and disease activity

Using Spearman's test in order to investigate correlation between anti-CCP titer and the inflammatory biomarkers, we found a statistically significant moderate correlation between anti-CCP titer and ESR values (rho=0.491; p=0.000) (figure 5), and a good correlation between anti-CCP and CRP values (rho=0.558; p=0.000) respectively (figure 6).

Statistically significant moderate correlation was found between anti-CCP titer and disease activity score (JADAS) as well (rho=0.448, p=0.001) (figure 7).

In conclusion, our study found a positive correlation between anti-CCP titer and disease activity in JIA, which is not concordant with the results of the majority of published studies (8,9,11). This discrepancy may several explanations. First of all, all studies investigated the correlation between biomarkers of disease activity and exclusively the titer of anti-CCP which exceeded the cut-off point of the used method, reducing thus the number of tested patients. We searched the correlations disregarding the cut-off point of anti-CCP determination, including in trial all patients. Secondly, the two seropositive polyarticular cases with elevated titer of anti-CCP had a disease course with prolonged intense activity (high values of ESR, CRP). The low number of cases could be another reason of limitation. On the other hand, there are clinical trials which suggest that in patients with rheumatoid arthritis, anti-CCP positivity is

associated with a more intense inflammatory response (15), synovial tissue from anti-CCP positive patients expresses higher concentrations of immune cytokines, has higher numbers of infiltrating lymphocytes (23). Berglin and his coworkers proved that anti-CCP levels are correlated to inflammatory activity (24).

Correlation between anti-CCP titer and radiographic damage

We counted the number of joints with radiographic lesions (erosions or joint space narrowing) at the time point of anti-CCP determination and investigated the correlations between them. A statistically significant good correlation (rho=0.638, p=0.000) was found (figure 8). Furthermore, all five anti-CCP positive cases presented severe radiographic damage, and the most dramatic joint deformations were found in the 2 patients with seropositive polyarticular JIA and impressively increased titers of anti-CCP antibodies (≥200U/ml).

This correlation is concordant with the results of most of the published studies (9,10,11,24,25). Gilliam and co. showed that JIA patients with radiographic damage had significantly elevated levels of anti-CCP antibodies in comparison with children with JIA, but no radiographic joint lesions. Similarly, several clinical trials have demonstrated a strong association between anti-CCP positivity and joint damage in rheumatoid arthritis (24-29). In a large, prospective study of rheumatoid arthritis patients, the positivity of anti-CCP was the most important single predictor of radiographic progression in patients with early RA, and patients with high levels of anti-CCP were especially prone to radiographic progression (30). Consequently, IgG anti-CCP antibodies have demonstrated increasing importance in assessment of both of rheumatoid arthritis and juvenile arthritis to determine which patients have or will have more aggressive or severe disease and to be a useful tool in therapeutic attitude to prevent joint damage and disability (31). Furthermore, in 2011 ACR Recommendations for the treatment of JIA included anti-CCP positivity as a feature of poor prognosis in the treatment group of JIA patients with history of arthritis of 5 or more joints (32).

Evolution of anti-CCP titer

Reevaluation of anti-CCP antibodies titer after 3 months revealed statistical significant change (figure 9).

In rheumatoid arthritis, evolution of anti-CCP antibody titer following therapy is still controversial. Some studies showed that anti-CCP antibody levels in RA patients following treatment tended to remain stable or decreased only slightly (11,33,34). Other studies proved an association between modification of anti-CCP antibody titer and the disease duration: only in patients with RA whose disease duration was less than one year, there had been observed significant reduction in anti-CCP levels following treatment (35, 36). Significant reduction of anti-CCP antibodies levels have been reported in RA patients with positive clinical response following treatment with TNF-α blockers (24,33-40). On the other hand, several studies have shown that treatment with TNF-α blockers in established RA patients produced a significant reduction of IgM rheumatoid factor

levels, while had significantly less effect on anti-CCP levels (41-44).

There are very few studies concerning profile of anti-CCP antibodies titer in patients with JIA following treatment. Syed and coworkers found no significant correlation between anti-CCP titer and disease activity, with no significant reduction of anti-CCP titer following JIA treatment (31). A possible explanation is that an analysis of a small number of individuals with positive anti-CCP antibodies decreases the possibility of obtaining statistically significant differences. We tested the outcome of anti-CCP titer disregarding the cut-off value of the used method (both anti-CCP positive and negative patients).

Researches in rheumatoid arthritis show that the baseline titer of anti-CCP antibodies was higher in patients with radiological progression and decreased significantly in those with response to therapy, titre of anti-CCP antibodies being related to disease severity (24).

Conclusions

Anti-CCP is less prevalent in JIA than in rheumatoid arthritis, but its positivity denotes an erosive course of disease. Therefore, anti-CCP determination is a valuable tool in JIA assessment and promotes a correct therapeutic attitude to prevent disability and joint damage. Anti-CCP concentration remains unchanged during the course of disease, with no role as indicator of response to treatment. Because of low number of cases, conclusions are limited.

Standardization of anti-CCP tests with adjusted cut-off value for children is required.

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