

Cartilage proteoglycan aggrecan as a predictor of joint damage in juvenile rheumatoid arthritis

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قياس بروتيوغليكسان الأغريكان العَضْرُوفِي كعامل مسبب عن تخرب المفاصل في التهاب المفاصل الروماتويدي اليَقِي

زينب عوض السيد، مياسة توحيد صالح، أماني صلاح الدين الرقاد، لبنى سيد شريف وأني محمد ناصر الدين

خلاصة: تم قياس الأغريكان في مصل 31 طفلاً مصاباً بالتهاب المفاصل الروماتويدي وفي السائل الزليلي لعشرة منهم، وتم تقييم المرضى في بدء الدراسة وبعد مضي ثلاثة شهور، وأعيد إجراء الصور الشعاعية أيضاً بعد مضي سنة، ودرست للمقارنة مجموعة من الأطفال الأصحاء عددهم 15 طفلاً مع 10 أطفال مصابين بالتهاب مفصلي ناجم عن أمراض وعائية كولاجينية. وقد وجد أن قيمة الأغريكان في بداية الدراسة أكثر ارتفاعاً لدى مرضى التهاب المفاصل الروماتويدي منه لدى الأطفال الشواهد والمرضى بأسباب أخرى. ولدى إعادة التقييم لوحظ هبوط ملحوظ في مستوى الأغريكان المصلي عما كان عليه في بدء الدراسة، وترافق ذلك مع انخفاض ملحوظ أيضاً في المناسبات المختبرية والسريرية (الإكلينيكية) التي تدل على التهاب فعال. فمستوى الأغريكان المصلي يمكن أن يساعد على تقييم مدى تخرب العَضْرُوف، وهو يفيد كأداة إنذارية لتحديد مآل المرض والتنبؤ بتخرب المفصل لدى مرضى التهاب المفاصل الروماتويدي اليَقِي.

ABSTRACT Aggrecan was measured in the sera of 31 children with juvenile rheumatoid arthritis and in the synovial fluid of 10 of them. Patients were evaluated at baseline and 3 months later. Radiographs were repeated also after 1 year. As comparison, 15 apparently healthy children with no disease and 10 children with arthritis due to other collagen vascular diseases were studied. Baseline serum aggrecan was significantly higher in juvenile rheumatoid arthritis patients compared to controls and other patients. On re-evaluation, a significant drop in serum aggrecan from baseline values coincided with a significant drop in clinical and laboratory indices of active inflammation. Serum aggrecan can help to assess the extent of cartilage destruction and is useful as a prognostic tool to predict joint damage in patients with juvenile rheumatoid arthritis.

L'aggrecan, protéoglycane du cartilage, en tant que prédicteur d'une atteinte articulaire dans la polyarthrite rhumatoïde juvénile

RESUME L'aggrecan a été mesurée dans le sérum de 31 enfants souffrant de polyarthrite rhumatoïde juvénile et dans le liquide synovial de 10 d'entre eux. Les patients ont été évalués au début de l'étude et trois mois plus tard. De nouvelles radiographies ont été effectuées un an plus tard. A titre de comparaison, 15 enfants apparemment en bonne santé et n'ayant pas de maladie et 10 enfants atteints d'arthrite due à d'autres maladies vasculaires du collagène ont été étudiés. La valeur de référence de l'aggrecan dans le sérum était significativement plus élevée chez les patients atteints de polyarthrite rhumatoïde juvénile que chez les témoins et les autres patients. Lors de la réévaluation, une baisse significative de l'aggrecan dans le sérum par rapport aux valeurs de référence coïncidait avec une baisse significative des indices cliniques et biologiques d'inflammation active. L'aggrecan dans le sérum peut aider à évaluer l'ampleur de la destruction du cartilage et prévoir les atteintes articulaires chez les patients souffrant de polyarthrite rhumatoïde juvénile.

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Introduction

Rheumatoid arthritis is the dominant form of destructive chronic arthritis and can cause substantial disability and permanent functional impairment especially in children [1]. However, it is well known that the extent and the rate of tissue damage vary considerably among rheumatoid arthritis patients [2]. There is a lack of sensitive and specific biochemical markers for disease progression, and front-line biochemical research is devoted to characterizing molecules that are indicators of the degree of joint destruction [3].

With increasing knowledge of the composition and metabolism of the cartilaginous matrix, new assays have emerged permitting the study of the pathogenesis of joint damage. Metabolites of cartilage interstitial molecules, liberated into the synovial fluid (SF) and subsequently into the serum during cartilage turnover, have attracted special attention as possible markers of joint disease.

Aggrecan is the major proteoglycan in cartilage and provides it with its mechanical characteristics, such as compressibility and elasticity. Aggrecan metabolism is markedly altered in joint diseases such as osteoarthritis [4]. Epitopes within fragments of aggrecan are detectable in SF and serum [5]. These fragments, particularly those containing keratan sulfate, have been used to monitor cartilage turnover but have not hitherto proved useful as markers of rheumatoid arthritis [6]. The current study aimed to evaluate serum and SF aggrecan as a metabolic marker and predictor of cartilage destruction in juvenile rheumatoid arthritis.

Methods

Subjects

We randomly selected 31 children suffering from juvenile rheumatoid arthritis diagnosed according to the criteria of the American College for Rheumatology [7]. They presented at the Paediatric Allergy and Immunology Clinic of Ain Shams University, Cairo. Their age ranged from 4 to 17 years (mean 10.6 ± 4.2 years), with a male to female ratio of 1:1.06. The disease duration ranged from 6 to 156 months (mean 56.5 ± 42.2 months). As regards type of juvenile rheumatoid arthritis, 20 patients had the polyarticular variety, 5 the pauciarticular type and the rest (6) the systemic onset form of the disease. Current treatment was recorded as follows: 29.0% were treated with non-steroidal anti-inflammatory drugs (NSAIDs) alone, 51.6% with methotrexate, while oral steroids were used in 19.3% of the patients.

For the sake of comparison, 10 patients with arthritis due to other collagen vascular diseases were studied. This group comprised 6 patients with systemic lupus erythematosus, 2 patients with scleroderma, 1 with dermatomyositis and 1 with mixed connective tissue disease. Their age ranged from 4 to 17 years (mean 11.5 ± 5.1 years), with a male to female ratio of 2:3. Also, 15 apparently healthy children without disease were studied as a control group. Their age ranged from 4 to 17 years (mean 9.8 ± 4.7 years), with a male to female ratio of 1.1:1.3.

Study design

Baseline evaluation of the 31 juvenile rheumatoid arthritis patients was carried out clinically for active inflammation of all

joints. Radiographs were obtained for the knees, hands and feet. At this stage, blood samples were obtained from all of the juvenile rheumatoid arthritis patients as well as samples of SF aspirate from 10 of them.

Follow-up of the juvenile rheumatoid arthritis patients was carried out with close supervision of their compliance with therapy. Clinical, radiological and laboratory re-evaluation was carried out 3 months after the baseline assessment. Radiological re-evaluation was also performed 1 year later.

Clinical evaluation

Juvenile rheumatoid arthritis patients were evaluated for active joint inflammation. The clinical indices of articular inflammation used were as follows:

- joint swelling (graded as 0 = none, 1 = mild but obvious synovial swelling or effusion and bony landmarks visible; 2 = moderate swelling and definite obscuring of bony landmarks; 3 = severe swelling and no discernible bony landmarks);
- limitation of motion (graded as 0 = full range of motion; 1 = 25% limitation; 2 = 50% limitation; 3 = 75% limitation, 4 = no motion possible);
- pain on motion and/or joint tenderness (graded as 0 = none; 1 = mild pain; 2 = moderate pain; 3 = marked pain).

In addition to these indices, the total number of joints with active arthritis and the sum of the three clinical indices of articular inflammation, referred to as articular severity score, were recorded [8].

Radiological assessment

This was done at the beginning of the study, and after 3 months and 1 year for the knees, hands and feet. The method of Rau and Herborn [9] (modified Larsen scoring method) for scoring soft tissue swelling, joint space narrowing, osteoporosis and

erosions, as well as that of Fuchs et al. [10] for scoring joint malalignment, were applied for each radiograph. The Larsen index of each patient was then expressed as the mean of the gradings of all the examined areas of hands and feet (32 areas according to Larsen) [11] as well as of the knees. Similarly, the malalignment score was expressed as the mean value of the score of the above-mentioned joints. A composite score was then adopted merging both scores together as a mean value for each patient and termed total radiographic score. Two radiographs of the same joint were compared and scores were assigned to reflect the evolution of the change in joints, (score 00 = unaffected, or normal; score 0 = affected, but unchanged; score +1 = improvement; and score -1 = deterioration) (van Rossum score) [12].

Laboratory methods

The following assays were performed.

- Complete blood counts on a Coulter counter (model MD T660, Coulter Corporation, Miami, Florida, United States of America).
- Erythrocyte sedimentation rate (ESR) by the Westergren method.
- C-reactive protein by the Diamo CRP latex agglutination method.
- Serum rheumatoid factor (RF) by the latex agglutination test.
- Antinuclear antibodies (by immunofluorescence) and serum complement 3 and 4 (C₃ and C₄) (by turbidimetry) were measured as a part of the routine work-up of the patients.
- SF analysis for RF by the latex agglutination test; and for glucose, lactate dehydrogenase and protein concentrations on a Beckman Synchron CX5 automated system (Beckman Instruments In-

corporated, Fullerton, California, United States of America).

- Assay of serum and SF aggrecan: blood samples were obtained from all the children, serum was separated and divided into aliquots in multiple small plastic tubes and then stored at -70°C until assayed. SF from knee joints of 10 patients was collected in plastic tubes containing EDTA, centrifuged at 2000 g for 10 minutes. The supernatant was divided into small aliquots in multiple small plastic tubes then frozen at -70°C .

Aggrecan was measured by using Medgnix proteoglycan EASIA kit (Bio-source Europe SA, Belgium), which is a solid-phase enzyme amplified sensitivity immunoassay. The assay is based on an oligoclonal system in which a blend of monoclonal antibodies directed against distinct epitopes of proteoglycan are used. Briefly, each 50 μL sample was incubated in microtitre wells coated with monoclonal antibodies 1 after the addition of monoclonal antibodies 2 labelled with horseradish peroxidase, to allow the formation of a sandwich. After washing to remove the unbound enzyme, the bound enzyme was measured by incubation with a chromogenic solution. The reaction was stopped after the incubation period by adding a stop solution. A standard curve was plotted, and the aggrecan concentration in the sample was determined by interpolation from the standard curve. The minimum detectable concentration was estimated to be 0.9 ng/mL.

Statistical analysis

Analysis of the data was carried out using standard computer software (*Statview* for Apple Macintosh). Because of their non-parametric distribution, some data were analysed using the Wilcoxon signed rank

test for comparison of paired observations. For unpaired data, the Mann-Whitney test was employed. Normally distributed results were compared using the Student *t*-test. The Spearman rank correlation test was used for correlations. A probability of less than 0.05 was considered significant.

Results

The clinical, laboratory and radiological evaluation of the patients is shown in Table 1. This revealed that, at baseline, 16 patients (51.6%) had active disease with an overall mean articular severity score of 73.8 ± 13.6 .

In 23 patients (74%) haemoglobin concentration was below 10.5 g/dL. Leukocytosis was seen in 14 patients (45%) (counts above 11 000 cells/mL) and thrombocytosis in 15 patients (48%). C-reactive protein was positive in 51.6% of patients.

SF analysis as shown in Table 1 showed a low mean glucose concentration (levels were low in 40% of SF samples), and a high mean protein concentration. Mean lactate dehydrogenase was considered high in 60% of the SF samples. RF was positive only in one of the 10 samples with a concomitant positive serum RF. In one patient RF was negative in SF but positive in serum.

At re-evaluation, the articular severity score, ESR, total leukocytic count and platelet counts showed a statistically significant drop. This was associated with a significant rise in patients' haemoglobin concentration as well as in the haematocrit value.

Radiological assessment of joints

The Larsen index, malalignment score and total radiographic score at baseline and after one year are shown in Table 1. At 3

Table 1 Clinical, laboratory and radiological data of patients with juvenile rheumatoid arthritis

Variable	Baseline	3-month follow-up	P-value
No. of active joints	0.7 ± 0.1	2.0 ± 1.2	< 0.05
Articular severity score	73.80 ± 13.60	51.6 ± 11.2	< 0.001
Radiological score ^a			
Larsen index	1.38 ± 0.88	1.52 ± 0.99	> 0.05
Malalignment score	0.41 ± 0.86	0.53 ± 0.94	> 0.05
Total radiographic score	0.88 ± 0.79	1.02 ± 0.88	< 0.05
Haemoglobin (g/dL)	9.55 ± 1.53	10.51 ± 1.01	< 0.001
Total leukocytic count (× 10 ⁹ /L)	10.55 ± 2.97	7.76 ± 2.74	< 0.001
Platelet count (× 10 ⁹ /L)	429.55 ± 164.60	320.45 ± 112.45	< 0.001
Erythrocyte sedimentation rate (mm/hour)	45.68 ± 29.40	20.17 ± 9.21	< 0.001
Serum aggrecan (ng/mL)	69.96 ± 68.85	51.55 ± 67.68	< 0.01
Synovial fluid analysis (n = 10)			
Protein (g/dL)	213.75 ± 380.09	—	
Lactate dehydrogenase (IU/L)	458.64 ± 379.33	—	
Glucose (mg/dL)	55.71 ± 25.02	—	
Aggrecan (ng/mL)	40.10 ± 34.39	—	

^aRadiological evaluation after 1 year; the 3-month evaluation showed no change from the baseline.

Data are presented as mean ± standard deviation.

months, no obvious radiological changes were seen, whereas the mean Larsen index and the mean malalignment score of the juvenile rheumatoid arthritis patients showed deterioration at the 1-year follow-up, but the changes were statistically insignificant. The increase in the total radiographic score, which denotes radiographic deterioration, was significant. According to the van Rossum score for evaluation of changes in joints, 6 patients (19%) showed deterioration (score -1) while the remainder did not exhibit any obvious changes (score 0) [12].

Serum aggrecan in the different groups of the study

Baseline serum aggrecan was significantly higher in juvenile rheumatoid arthritis patients as compared to controls ($P < 0.001$) and to patients with other collagen vascular diseases ($P < 0.001$) (Table 2). This held true when the different forms of juvenile rheumatoid arthritis (polyarticular, pauciarthritic and systemic onset forms) were compared with controls and other collagen vascular diseases. No significant differences were observed between the different forms of the disease, although higher levels

Table 2 Mean serum aggrecan levels in the different groups of the study

Serum aggrecan (ng/mL)	Juvenile rheumatoid arthritis	Other collagen vascular disease	Controls
Mean	69.96	9.40	6.13
s	68.85	4.72	4.16
Z-value		4.36*	5.25*

*Significantly different ($P < 0.001$) compared with juvenile rheumatoid arthritis patients.

Other collagen vascular diseases versus control, $P > 0.05$.

s = standard deviation.

tended to be seen in the systemic form when compared to other forms (Figure 1). Also, serum aggrecan was not influenced by RF positivity. Age and sex did not seem to influence serum aggrecan levels significantly. Also, the levels did not correlate significantly with the duration of the disease.

Diagnostic performance of serum aggrecan as a laboratory marker of juvenile rheumatoid arthritis

At a cut-off level of 18.6 ng/mL (control mean + 3 SD), serum aggrecan showed a sensitivity and specificity as a marker of

juvenile rheumatoid arthritis of 93% and 100% respectively. The receiver operating characteristic (ROC) curve of serum aggrecan was very close to the upper left corner, at which a test can be considered a reliable marker.

Serum aggrecan in relation to SF analysis

No significant differences were observed between aggrecan concentrations in the patients' serum and in corresponding SF, nor did serum aggrecan correlate significantly with the glucose concentration in SF. Wor-

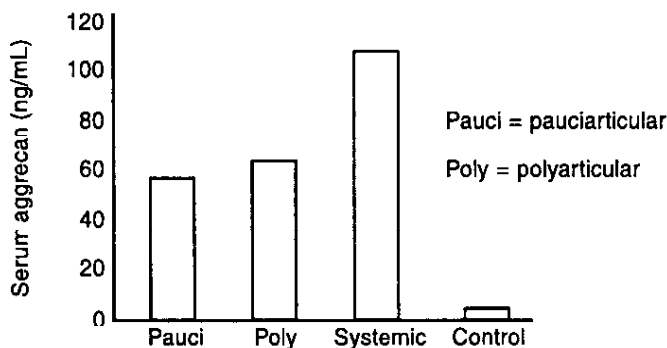


Figure 1 Serum aggrecan levels in different forms of juvenile rheumatoid arthritis

thy of note is the significant positive correlation of serum and SF aggrecan with SF protein concentration.

Serum aggrecan in relation to clinical and laboratory markers of disease activity

A significant drop in serum aggrecan of patients with juvenile rheumatoid arthritis was observed after 3 months, which coincided with the drop in clinical and laboratory indices of disease activity (Figure 2). However, it remained significantly higher than that of controls. Serum aggrecan did not correlate significantly with the number of active joints and was not influenced by the presence or absence of morning stiffness or by C-reactive protein positivity.

Its levels also did not correlate significantly with ESR, C_3 and C_4 total leukocyte count, haemoglobin concentration or platelet count. Similarly SF aggrecan did not correlate with ESR ($P > 0.05$).

Serum aggrecan in relation to the radiological indices of joint destruction

Patients with radiological evidence of joint erosions and narrowing (Larsen score > 1) had insignificant higher mean serum aggrecan levels than those with Larsen score > 1 . On the other hand, malalignment scores > 1 were associated with significantly lower mean serum aggrecan as compared to scores ≤ 1 (Table 3).

To rule out the influence of disease activity, data of patients with quiescent disease only (at follow-up after 3 months) were analysed for the relation of joint destruction to serum aggrecan. This revealed that patients with total radiographic score above 1 (destructive group) had lower serum aggrecan as compared to those with scores ≤ 1 (non-destructive group).

A minor predictive value for serum aggrecan was noticed in the sense that patients with radiological evidence of joint

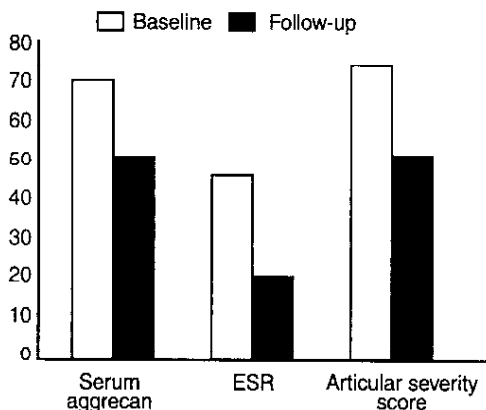


Figure 2 Effect of disease activity on articular severity score, erythrocyte sedimentation rate (ESR) (mm/hour) and serum aggrecan (ng/mL)

Table 3 Serum aggrecan in relation to concomitant radiographic findings and later deterioration

Serum aggrecan (ng/mL)	Larsen index		Malalignment score		Total radiographic score		van Rossum score	
	>1	≤ 1	>1	≤ 1	>1	≤ 1	-1	0
Mean	60.0	42.78	27.42	19.29	22.57	11.14	51.17	11.53
s	50.4	32.6	12.42	74.68	12.26	78.42	57.84	79.25
P-value	> 0.05		< 0.05		< 0.05		> 0.05	

s = standard deviation.

deterioration after 1 year (van Rossum score -1) had lower serum aggrecan levels at baseline (in spite of being in active phase) as compared to those without radiological deterioration.

Influence of therapy on serum aggrecan

Although the serum aggrecan level was not generally influenced by the form of therapy, the group receiving steroids had higher levels when compared to those under treatment with methotrexate or NSAIDS ($P > 0.05$).

Discussion

There is evidence that conventional markers of inflammation may not correlate with future structural joint changes [13]. Cartilage-specific matrix proteins, liberated into the SF and subsequently into serum during cartilage turnover, have been proposed as possible markers of acute joint disease [14].

A hypothetical role of the dominant cartilage proteoglycan aggrecan in maintaining the integrity and function of synovial tissue, and its use as a potential indicator of joint damage, led us to investigate whether aggrecan could be considered a useful

marker and a predictor of later joint destruction in juvenile rheumatoid arthritis.

We found that sera from patients with juvenile rheumatoid arthritis had considerably elevated levels of aggrecan compared to controls ($P < 0.001$). This finding is consistent with the results of other investigators [15].

An imbalance in the synthesis and degradation of matrix components is a common characteristic feature of rheumatoid arthritis [16]. However, this net loss of aggrecan in juvenile rheumatoid arthritis probably reflects increased tissue turnover with a tendency towards predominance of matrix degradation causing gradual deterioration of the articular surface.

On re-evaluation of the patients, a significant drop of serum aggrecan from baseline values was noticed. This coincided with a significant drop in the over all articular severity score. Thus a drop of serum aggrecan might herald a remission of local articular inflammation with a slowing down of the rate of cartilage destruction. However, the lack of correlation of serum aggrecan with other laboratory markers of inflammation, namely ESR and haematological indices, such as total leukocyte count, haemoglobin concentration and platelet count, implies that there is no close

connection between markers of the generalized inflammatory response and aggrecan as a marker for the localized inflammatory process that damages the cartilage. This process may progress independently of more generalized inflammation as measured by conventional biochemical markers. This hypothesis has been found to be true by many investigators [13,17]. Nonetheless, both serum and SF aggrecan correlated positively with SF protein concentration, which supports the concept that the severity of cartilage destruction is determined by the degree of articular inflammation and that it is an inevitable sequela of the active inflammatory response in the joints.

There is evidence that cartilage proteoglycans are degraded early in the course of joint disease, and their release from cartilage changes with the progress of matrix destruction, i.e. it decreases when the cartilage mass diminishes. The fragments formed are liberated into the SF and may subsequently either reach the circulation, probably by the lymphatic system or be eliminated in the lymphatic system itself [13,18]. Hence, a drop in serum aggrecan might denote a diminution in cartilage mass which occurs in the late stages of matrix destruction. Meticulous clinical and radiological evaluation of affected joints could help to determine whether the drop in serum aggrecan is a result of regression of articular inflammation or is an ominous sign indicating complete destruction of the articular surface.

In the present work, baseline radiological studies as well as re-evaluation were conducted at 3 months and 1 year and were correlated with serum aggrecan levels. High serum aggrecan was noted in patients with bony erosions and joint narrowing (Larsen score > 1). These radiographic findings are considered relatively early

events in the time course of the disease and are observed in 67% of rheumatoid arthritis patients within the first 2 years [19] as bone is usually affected earlier than cartilage [17]. Aggrecan is known to originate from cartilage and it seems that these high levels in patients with bony erosions reflect the extent of the inflammatory process in the joints that destroys both their cartilaginous and bony components. A high aggrecan level, however, indicates that the patient still retains some cartilage mass and that prompt control of the inflammatory process at that stage may slow down/halt the progression of cartilage damage. Conversely, radiographic evidence of malalignment, which results from cartilage destruction at a later stage [19], was concomitantly associated with significantly lower serum aggrecan levels.

The fact that no radiographic changes were noticed in the 3-months interval whereas significant changes were noticed after 1 year indicates the urgent need for another tool that can help predict the damage earlier. Quantification of serum aggrecan seems promising in this regard based on the presence of lower levels in the destructive group (total radiographic score > 1) and in patients who showed radiographic deterioration (van Rossum score -1) later on.

Mansson et al. reported that levels of serum aggrecan dropped over time in the destructive group, which they defined as those patients in whom later joint replacements were needed [13]. At the same time, initially low levels that did not change with time were observed in their non-destructive group. They suggested that a higher initial aggrecan level can help identify patients with rapidly progressing destruction. However, in an earlier study, levels of a putative marker of aggrecan synthesis, chondroitin sulfate epitope 846, were increased only in

patients with slow joint destruction compared with those with rapid joint destruction [20].

It should be pointed out that there is considerable variation between the results of different studies, which is probably related to the point in the time course of the disease and the state of activity of the inflammatory process at which the study was undertaken. Therefore, it seems logical to consider serum aggrecan levels in relation to radiographic findings if reliable conclusions about joint prognosis are to be drawn.

The fact that serum aggrecan levels positively correlated with SF aggrecan levels indicates that there is an equilibrium between serum and SF aggrecan. Thus, serum aggrecan levels can give an overall idea about the intra-articular changes in proteoglycan metabolism. However, reports exist of SF aggrecan level as high as 100 times the serum level [15].

Recent evidence has shown the benefit of starting therapy early for rheumatoid arthritis patients with disease-modifying anti-rheumatic drugs [21]. Of these drugs, methotrexate is probably the drug of choice after NSAIDs [22]. In our study, the aggrecan level was found to be unaffected by the form of therapy. This is in accordance with what was found by Neidal et al. [23]. However, the serum aggrecan level tended to be higher in patients using steroids compared to other therapies. Saxne and colleagues reported the same finding [24].

This could be explained on the basis of more severe disease that necessitated the use of steroids, or the increase of aggrecan could indicate increased proteoglycan degradation and permanent cartilage destruction with the use of steroid therapy. Hunneyball found decreased glycosaminoglycan content in the menisci during systemic treatment with prednisolone probably reflecting their loss from joint cartilage [25]. Another possible explanation is the elimination of a factor that inhibits chondrocyte function, allowing more synthesis of proteoglycan.

Conclusion

Serum aggrecan analysis can help to assess the extent of joint inflammation and cartilage destruction in juvenile rheumatoid arthritis. It gives a better insight into the nature of cartilage metabolism in joint disease without the need for more invasive techniques such as SF analysis. Quantification of such a marker in relation to the radiographic findings represents a useful prognostic tool to forecast the development of joint destruction in juvenile rheumatoid arthritis and may help in the early identification of patients at risk of rapidly progressing disease.

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This meeting was part of a broader project dealing with the transformation of health care to better address the needs of patients with chronic conditions. WHO initiated the project in response to a number of challenges: 1) The global disease burden has changed towards chronic conditions worldwide but health systems have not; 2) For most major chronic conditions highly effective interventions exist, yet patients do not receive them; 3) Current health systems are designed to provide episodic, acute care while chronic conditions are lengthy and require continuity of care. The increasing burden of chronic conditions falls most heavily on the poor. The meeting focused on the following areas: the growing challenge of chronic conditions; the current systems of care; how health systems can respond to the challenge; models and experiences of innovative care; dissemination of innovative care; what WHO is doing to advance the agenda. This report can be obtained from: Management of Noncommunicable Diseases Department, World Health Organization, Avenue Appia 20, CH-1211 Geneva 27, Switzerland. It is also available free on the Internet at: http://www.who.int/chronic_conditions/jcccmeeting.pdf