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Relation Between Anti-CCP Antibodies and Sharp Score in Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic rheumatic disease, very complex, with many different forms, progressive course, with pronounced changes in the joints, still unknown etiology and poorly understood pathology. Assessing of structural change can be done with proposed scores which observe changes on wrist and wrist joints, as a Sharp score. Aim: To examine the correlation between Anti-Citrullinated Protein Antibodies (Anti-CCP) values and Sharp score, and to determine the importance of Sharp score in the progression of RA. Methods: The study had prospective character and followed patients in the period from January 1, 2017 to December 31, 2017. The study included 40 patients with RA. At the beginning of the follow-up of patients, X-ray of hands and feet were performed. Results: Out of total of 40 patients, 34 or 85% had a follow-up examination after one year. Of these, 14 patients (41.2%) were reported to have complications. The subjects were divided into two groups according to Anti-CCP values. First group included patients with Anti-CCP values <4 and second those who had Anti-CCP> 4. Statistical analysis of the number of patients with complications at first and repeated examination indicated that there were no significant differences and that the sample was consistent between the first and repeated results (p> 0.05). Patients with higher Anti-CCP values also had a higher Sharp score with statistically significant differences during repeated examination (p <0.05). Correlation analysis shows that there was statistically significant (p <0.05) positive correlation with Anti-CCP values, and that an increase in values leads to an increase in the Sharp score (first measurement rho = 0.193, p> 0.05; repeated measurement rho = 0.645, p <0.0001). No statistically significant differences in Sharp score values at the first examination were compared with the repeated examination, but there was a statistically significant difference after one year in patients with complications (X2 = 13,388; p = 0.001), indicating that the Sharp score reflects disease progression. Conclusion: Anti-CCP values are also directly correlated with the Sharp score, which should be routine in both initial and repeated examination of a patient with RA. Sharp's score represents a marker of progression as well as of therapeutic modality of RA.
Keywords: rheumatoid arthritis, Anti-Citrullinated Protein Antibodies, prognosis.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic rheumatic disease, very complex, with many different forms and progressive course, with pronounced changes in the joints, still unknown etiology and poorly understood pathology (1). Inflammation causes destruction of cartilage and bone erosion, which is a major characteristic of the disease (1). The course of the disease is highly variable. Patients may have mild oligo arthritis or severe progressive polyarthritis with major impairment, and prognosis of RA may be predicted based on the presence of some clinical and laboratory records (2). Citrulline antibodies (Anti-Citrullinated Protein Antibodies; anticyclic citrulline peptide; Anti-CCP) are present in most patients with RA (3). The citrulline antibody test is most useful in identifying cases of previously undiagnosed inflammatory arthritis when the standard test for rheumatoid arthritis is negative. Thus, citrulline antibodies are suitable for the recognition of early stage of the disease (4-6). The test for citrulline antibodies in the blood of a rheumatoid arthritis patient is extremely specific and when citrulline antibodies were found, the likelihood of the subject suffering from RA was 90-95% (7). It is possible to find changes on the X- ray result when it is already obvious by physical examina-

tion, when there is swelling of the soft tissue of the joint and effusion into the joint. Typical radiological changes are: periarticular osteoporosis, swelling of the soft tissues around the joints, narrowing of the joint space, marginal bone erosion, structural damage to the joint surfaces, subluxations, dislocations and ankylosis of the joints, and secondary degenerative changes, while loss of joint cartilage and bone erosion are visible after months of continuous activity (8). Radiographic methods are of great importance in the evaluation of therapy (8). In case of suspected rheumatoid arthritis, it is necessary to take X-rays of the hands and feet and other joints as needed. If radiological damage develops early, it represents a more serious course of the disease. There are a number of methods for assessing structural change. Some give a global estimate, such as Steinbrocker, while others evaluate individual joints, such as the Sharp and Larsen method and their variants (9). In 1971, Sharp et al proposed a system that includes observation of hands and wrists through twenty-nine areas in each hand and wrist are considered for erosions, and 27 for joint space narrowing (JSN). Erosions are observed and scored in 29 spaces and narrowing of the joint space in 27 spaces in each hand. Erosion is scored from 0 to 5 and the total score for erosion is from 0 to 290 (9). The narrowing of the joint space is scored with grade from 0 to 4 and the total score for them is from 0 to 216 (9). This version is no longer in use (10). Sharp score is an individual score for the wrist and wrist joints. This method has good sensitivity but requires training of staff to perform the test and is more time consuming. In 1985, a modification of Sharp score was done, and today that modification it is considered to be the gold standard in practice (11).

Van Der Heijde in 1989 proposed modification of Sharp score, and his proposal observed erosion through 16 joints for each hand and wrist, and six joints for each foot (12). One point is scored if erosions are discrete, rising to 2, 3, 4, or 5 depending on the amount of surface area affected (complete collapse of the bone is scored as 5 (12)). The erosion score ranges from 0 to 160 in the hands and from 0 to 120 in the feet (12). JSN was evaluated in 15 joints for each hand and wrist, and six joints for each foot (12). Radiography has many deficiencies, the largest of which is that it is not sensitive enough, and it may take several months for joint damage to be registered and radiological signs are delayed in comparison to pathological changes by 3 to 6 months (6). Rheumatologists consider it to be the "gold standard" for determining and managing therapy in rheumatoid arthritis, as well as for monitoring the effects of treatment (6).

2. AIM

To examine the correlation between Anti-CCP values and Sharp score, and to determine the importance of Sharp score in the progression of RA.

3. PATIENTS AND METHODS

The study had prospective character and the patients were follow up in the period from January 1, 2017 to December 31, 2017. The study included 40 patients with diagnosis of RA at first examination. After one year of follow up, 34

patients were still eligible for the study. All patients were treated for one year with antirheumatics, occasionally corticosteroids, at the same doses.

Patients were treated at the Department of Rheumatology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina. Verification of rheumatoid arthritis as well as Anti-CCP findings were performed at the Institute of Immunology, Clinical Center University of Sarajevo, while at the beginning of the study, X-ray of hands and feet were performed on Clinic for Radiology, Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina (for monitoring of the Sharp score).

The rheumatic factor was used as an eliminatory finding. Anti-CCPs served as a parameter for dividing patients into two groups. The criteria for inclusion in the study were: American Rheumatism Association (ARA) criteria for RA (13,14), which may be seropositive or seronegative and positive rheumatic factor and a positive Anti-CCP (Anti-CCP was performed by ELISA test). Exclusion criteria were as follows: patients under 30 and over 60, patients with liver or renal failure, patients with verified cardiovascular pathology. Patients who suffered from an acute illness during the study after which there was a contraindication for therapy with antirheumatic drugs, corticosteroids and methotrexate were excluded from the study although they initially they met eligibility criteria.

The Stanford Health Assessment Questionnaire Disability Index (HAQ) score and The Disease Activity Score using 28 joint counts score (DAS28 score) were assessed during physical examination. C-reactive protein (CRP), fibrinogen and sedimentation values were monitored on first and repeated examinations.

Patients who met the above eligibility criteria were interviewed during which they were thoroughly acquainted with the research plan. Patients who agreed to participate by signing a written consent were immediately included in the survey. Ethical approval was obtained from Ethics Committee of Clinical Center University of Sarajevo.

The IBM statistics SPSS v19.0 statistical package (Chicago, Illinois, USA) was used for data analysis. All data collected are presented in tables and graphs by the number of cases, percentage, arithmetic mean with standard deviation, standard error and range of values. Student's t-test for paired samples or chi-squared test depending on the data type was used to test differences between individual groups, while Pearson's linear correlation coefficient was used to test the interaction of individual parameters. The results of all tests at p <0.05 were considered statistically significant or at 95% confidence level.

4. RESULTS

Out of total of 40 patients, 34 or 85% had a follow-up examination after one year. Of these, 14 patients (41.2%) were reported to have complications. The subjects were divided into two groups according to Anti-CCP values. First group included patients had Anti-CCP values <4 and second group had Anti-CCP> 4. Statistical analysis of the number of patients with complications at first and repeated examination indicated that there were no significant differ-

		N		SD	SEM	Min	Max	t	p
DAS 28 score	<4	12	3.200	.6889	.1989	2.5	4.8		
	>4	22	4.173	.7225	.1540	2.8	5.1	-3.811	0.001
	Total	34	3.829	.8444	.1448	2.5	5.1		
HAQ score	<4	12	1.050	.3205	.0925	.8	2.0		
	>4	22	1.195	.2853	.0608	.9	2.0	-1.361	0.183
	Total	34	1.144	.3017	.0517	.8	2.0		
Sharp score	<4	12	1.50	.522	.151	1	2		
	>4	22	1.77	.685	.146	1	3	-1.199	0.239
	Total	34	1.68	.638	.109	1	3		
C-reactive protein	<4	12	18.215	9.4352	2.7237	3.1	38.1		
	>4	22	31.087	24.7071	5.2676	3.1	78.0	-1.727	0.094
	Total	34	26.544	21.3804	3.6667	3.1	78.0		
Fibrinogen	<4	12	5.408	.7994	.2308	4.4	6.8		
	>4	22	4.986	1.1230	.2394	3.1	7.2	1.149	0.259
	Total	34	5.135	1.0284	.1764	3.1	7.2		
Sedimentation	<4	12	46.50	22.809	6.585	12	85		
	>4	22	69.86	36.421	7.765	5	122	-2.010	0.053
	Total	34	61.62	33.853	5.806	5	122		

Table 1. Comparison of monitored parameters within the first examination. (N-number of patients, -mean, SD–standard deviation, SEM -standard error of the mean, Min-minimum value, Max-maximum value, t–t-test, p–level of significance)

ences and that the sample was consistent between the first and repeated results (p> 0.05). In both examinations, Sharp scores were higher for subjects with Anti-CCP values above 4 and higher for repeated scores (2.23 ± 0.685).

Statistically significant differences in the first examination were observed only in the case of DAS28 score, and during the second examination in all observed parameters except in the case of fibrinogen.

Statistically significant differences in the first examination were observed only in the case of DAS28 score, and during the second examination in all observed parameters except in the case of fibrinogen.

An analysis of the Sharp score over the percentage representation of individual values confirms the previous analysis, which indicates that subjects with higher Anti-CCP values also had a higher Sharp score with statistically significant differences against Anti-CCP values during repeated examination (p <0.05) (Table 1 and 2).

Correlation analysis shows that there is a statistically significant (p <0.05) positive correlation with Anti-CCP values, and that an increase in Anti-CCP values leads to an increase in the Sharp score (first measurement rho = 0.193, p> 0.05; repeated measurement rho = 0.645, p <0.0001). Comparison of the Sharp score on the first and repeated examination indicates that during the first examination the number of respondents has a score of

1 (41.2%) and during the second examination a score of 2 (50%), with no statistically significant difference between the first and repeated examination (t = -1,786 ; p = 0.079). Likewise, analysis of the Sharp score averages shows that it was lower during the first examination (1.68 ± 0.6) compared to the second examination (1.97 ± 0.7) with no statistically significant difference in terms of a significant increase in the Sharp score during of the second review (t = -1.786; p = 0.079).

Comparison by complications of first and repeated results

Sharp score in patients with complications

No statistically significant differences in Sharp score values at the first examination compared to the repeated examination was performed, but that there was a statistically significant difference after one year in patients with complications ($X2 = 13,388$; p = 0.001), indicating that the Sharp score reflects disease progression.

Sharp score versus complication

No statistically significant difference in Sharp score values at first examination compared to repeated examination was observed, but that there was no statistically significant difference after one year in terms of higher mean values (2.5 ± 0.5) in patients with subjects without complications (1.6 ± 0.6) (t = 6.671; p = 0.0001) (Table 3 and 4).

The Sharp score showed the highest correlation to the DAS 28 score, and also a statistically significant positive

		N		SD	SEM	Min	Max	t	p
DAS 28 score	<4	12	3.167	.6597	.1904	2.6	4.8		
	>4	22	4.518	.9292	.1981	2.6	5.8	-4.450	0.0001
	Total	34	4.041	1.0603	.1818	2.6	5.8		
HAQ score	<4	12	1.033	.3257	.0940	.8	2.0		
	>4	22	1.273	.2676	.0570	.9	2.0	-2.309	0.028
	Total	34	1.188	.3073	.0527	.8	2.0		
Sharp score	<4	12	1.50	.522	.151	1	2		
	>4	22	2.23	.685	.146	1	3	-3.196	0.003
	Total	34	1.97	.717	.123	1	3		
C-reactive protein	<4	12	17.100	8.7401	2.5230	4.2	35.2		
	>4	22	42.450	29.6004	6.3108	3.0	95.0	-2.881	0.007
	Total	34	33.503	27.0969	4.6471	3.0	95.0		
Fibrinogen	<4	12	5.192	.7465	.2155	4.2	6.2		
	>4	22	5.736	1.1927	.2543	3.2	7.8	-1.431	0.162
	Total	34	5.544	1.0774	.1848	3.2	7.8		
Sedimentation	<4	12	41.92	19.332	5.581	14	78		
	>4	22	84.32	42.349	9.029	8	150	-3.270	0.003
	Total	34	69.35	41.096	7.048	8	150		

Table 2. Comparison of monitored parameters within repeated examination. (N-number of patients, -mean, SD–standard deviation, SEM -standard error of the mean, Min-minimum value, Max-maximum value, t–t-test, p–level of significance)

	N		SD	SEM	Min.	Max.
			Sharp score			
Yes	14	1.79	.699	.187	1	3
No	20	1.60	.598	.134	1	3
Total	34	1.68	.638	.109	1	3

Table 3. Sharp score according to complications – first examination (N-number of patients, -mean, SD – standard deviation, SEM -standard error of the mean, Min.- – minimum value, Max.-maximum value, t – t-test, p – level of significance). t=0,831; p=0,412

	N		SD	SEM	Min.	Max.
			Sharp score			
Yes	14	2.50	.519	.139	2	3
No	20	1.60	.598	.134	1	3
Total	34	1.97	.717	.123	1	3

Table 4. Sharp score according to complications – repeated examination. (N-number of patients, -mean, SD – standard deviation, SEM -standard error of the mean, Min.- – minimum value, Max.-maximum value, t – t-test, p – level of significance). t=6,671; p=0,0001

		Anti-CCP	Complications	Length of disease	Sharp score	DAS 28 score	HAQ score
Complications	r	-.710**					
	p	.000					
Gender	r	.092	-.074				
	p	.455	.550				
Length of disease	r	.143	-.100				
	p	.244	.416				
Sharp score	r	.498**	-.390**	.666**			
	p	.000	.001	.000			
DAS 28 score	r	.697**	-.727**	.327**	.706**		
	p	.000	.000	.006	.000		
HAQ score	r	.315**	-.084	.136	.549**	.407**	
	p	.009	.495	.268	.000	.001	
Sedimentation	r	.498**	-.582**	.142	.359**	.497**	.365**
	p	.000	.000	.247	.003	.000	.002
C-reactive protein	r	.551**	-.623**	.212	.508**	.629**	.341**
	p	.000	.000	.083	.000	.000	.004
Fibrinogen	r	.327**	-.316**	.204	.381**	.444**	.238
	p	.006	.009	.095	.001	.000	.050

Table 5. Correlation between parameters (r- correlation coefficient)

correlation to the HAQ score, C-reactive protein values, fibrinogen and sedimentation (higher Sharp score is related to higher values of these parameters and vice versa).

5. DISCUSSION

RA occurs 0.5 to 1% of the general population worldwide, and in terms of gender, women are more prevalent, 2.5: 1 (15). The use of synthetic cyclic citrullinated peptides (CCP) as antigens in ELISA tests marks the beginning of a new era in the diagnosis of rheumatoid arthritis. Furthermore, these highly specific antibodies also proved to be valuable prognostic markers. Braschi et al stated that A positive An-ti-CCP result means RA is likely but a negative result does not rule out RA (16). Anti-CCP is present in 23% of patients with early stage RA, in about 50% of patients at diagnosis (17). Braschi et al stated that a positive Anti-CCP result is more reliable than a positive rheumatoid factor result for diagnosed RA (16). Chou et al cite Anti-CCP antibodies associated with the severity of RA and erosion (18).

Our study included 40 patients with rheumatoid arthritis (RA) treated with antirheumatic agents, Methotrexate 15-25 mg, occasionally corticosteroids at the same doses, both sexes, aged from 30 to 60 year.. Our study showed that the Sharp score at the first and repeated examination indicated that during the first examination the highest number of respondents had a score of 1 (47.5%) and during the second examination a score of 2 (50%), which was expected given that 14 patients had a worsening clinical picture due to the inability to use anti-rheumatic methotrexate therapy, as evidenced by repeated X ray. There has been a worsening of the clinical picture by influencing not only endogenous but also exogenous factors (poor living conditions, low level of education). The use of X- ray in early diagnosis of RA is essential. The monitoring of these patients and the success of the therapy can also be monitored through radiological monitoring. Boini et al. stated that hand and foot X- rays capture the early estimates of RA development, erosion, and JSN are suitable measures of RA severity and progression, and can be used to provide separate or combined scores (19).

The use of computer-based RA scoring methods is a modern approach based on already standardized scores (20), and is something that is already part of modern RA monitoring.

HAQ score is the gold standard functional status questionnaire in rheumatology, while DAS 28 score is used to monitor disease activity in daily clinical practice (21, 22).

Higher Sharp score correlates with higher HAQ score as well as with DAS 28 score. It also correlates with higher values of inflammatory parameters. All patients were treated with antirheumatic drugs, corticosteroids and methotrexate because biological therapy was not part of the daily treatment of patients with RA.

Although Sharp score is basic and there was no difference between the two groups at the start of the research, Sharp score correlates with Anti-CCP values and is still a useful tool in the daily work with RA patients and should be part of the objective review patient. Sharp score is still essential in monitoring the radiological progression of the disease. The rise of Anti-CCP is accompanied by an increase in Sharp score, and they are directly correlated which justifies the use of Sharp score in everyday practice.

Treatment of RA should be based on diagnostic treatment, disease progression and when selecting therapy and when monitoring patients with RA, it is necessary to take into account the safety profile of drugs and the presence of comorbidities (23).

6. CONCLUSION

Anti-CCP values are also directly correlated with the Sharp score, which should be routine in both initial and repeated examination of a patient with RA. Sharp's score represents a marker of progression as well as of therapeutic modality of RA.

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