Journal of Advances in Medicine and Medical Research

32(16): 62-69, 2020; Article no.JAMMR.60859
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Diagnostic Accuracy of Cartilage Oligomeric Matrix Protein (COMP), for Cartilage Damage in Rheumatoid Arthritis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SQ and FS designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors AIM and MA supported and supervised the data collection, data analysis and interpretation. Author SK performed the statistical analysis. Author MAS managed the analyses of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i1630631
Editor(s):
(1) Dr. Sevgul Donmez, Gaziantep University, Turkey.
Reviewers:
(1) Wildan Khairi Muhtadi, Sekolah Tinggi Ilmu Farmasi Riau, Indonesia.
(2) Mohsen Korani, Baqiyatallah University of Medical Sciences (BMSU), Iran.
Complete Peer review History: http://www.sdiarticle4.com/review-history/60859

Original Research Article

Received 28 June 2020
Accepted 04 September 2020
Published 17 September 2020

ABSTRACT

Background: Cartilage oligomeric matrix protein (COMP), is an extracellular matrix (ECM) non-collagenous glycoprotein that is mainly localized within the cartilage, and also be found in tendon and synovium.Recent studies in west and Asia Pacific region has shown that COMP, is a prognostic marker in Rheumatoid arthritis(RA).
Objective: To correlate serum COMP levels with disease severity and cartilage destruction in rheumatoid arthritis.
Methods: The study was conducted in Department of Pathology and Rheumatology, Ziauddin University Hospital, Karachi from June 2018 to May 2019. Patients were recruited as per American

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College of Rheumatology (ACR) 2010 classification criteria. The study population consists of 88 healthy subjects and 88 RA patients. Sandwich ELISA technique was used to assess serum COMP level. Other inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) antibodies like rheumatoid factor, and anti-cyclic citrullinated protein (anti-CCP) were also assessed. Results were analyzed using SPSS-20 and P-value ≤0.05 was considered as significant.

Results: Serum COMP levels were significantly higher in RA patients 51.35 ng/ml than controls 21.454 ng/ml with significant p value=<0.0001. There was strong positive correlation between COMP level and disease severity in RA patients with moderate as well as high disease activity score (DAS) with significant p value. Serum COMP showed 96% sensitivity and 83% specificity at level of 27.01 ng/ml for diagnosis of RA.

Conclusions: COMP has significant positive correlation with severity of RA. Serum COMP can be utilized as a biomarker to quantify cartilage destruction in RA patients.

Keywords: Diagnostic accuracy; Cartilage Oligomeric Matrix Protein (COMP); cartilage damage; rheumatoid arthritis.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune joint disease that prevail virtually 0.5–1.0% of the adult population worldwide [1]. The approximate prevalence of RA in developing countries is variable [2-4]. The prevalence of RA in Pakistan is 0.5% where it is 0.2–1% in India for both male and female [5]. The prevalence of RA in southern areas of Pakistan such as city of Karachi is 0.142%, where as in northern areas it is reported to be 0.55% [6]. The precise etiology of Rheumatoid joint inflammation is obscure, it might be hereditary and natural components appear to be associated with its pathogenesis [7]. The most common reported symptoms in patients with RA are joint pain and stiffness particularly severe in the morning [8].

RA preferentially involves symmetrical small joints [9]. Joint destruction in rheumatoid arthritis brought about by infiltration of synovial fibroblasts and inflammatory cells, for example, macrophages and T cells in the subchondral bone and cartilage, which brings about irreversible harm to involved joint that may lead joint disfigurement and stiffness [10].

Diagnosis of RA can be made by various antibodies such as rheumatoid factor (RF) and Anti-cyclic citrullinated peptide (anti-CCP) [11]. As per literature anti-CCP is considered as gold standard for RA diagnosis. Anti-CCP may be embroiled in the disease pathophysiology and joint disintegrations yet it does not tell us about the extent of cartilage damage [12]. Cartilage oligomeric matrix protein (COMP) is biological marker that can identify the extent of cartilage damage quantitatively. It is an ECM non-collagenous glycoprotein that is mainly localized within the cartilage, but can also be found in tendon and synovium. It is homopentameric multidomain protein that interacts with number of ECM proteins, cells as well as growth factors and act as adaptor molecule to guide ECM synthesis and tissue remodeling in various physiological and pathological conditions [13]. There is proof about the connection between COMP level and radiologic indications of RA [14]. This biomarker emphatically correlates with cartilage debasement [15,16]. However the outcomes of all studies are not compatible. Consequently we investigate the diagnostic accuracy of this bio marker in separating RA patients from healthy persons and to set up whether serum COMP can be utilized to analyze cartilage harm in RA characterized by radiographic findings.

2. MATERIALS AND METHODS

2.1 Study Setting

This study was conducted at Department of Pathology and Rheumatology, Ziauddin University Hospital, Karachi from June 2018 to May 2019. Three groups were established consisting of 44 RA patients with high DAS, 44 RA patients with moderate DAS and 88 controls having same age and sex.

2.2 Patients and Methods

This research enrolled 88 recently diagnosed RA patients and 88 age and sex matched controls. All patients fulfilled the ACR Criteria 2010. The inclusion criteria were as under:

(a) Confirmed diagnosed RA patients (b) RA patients without routine treatment (c) >18 years. Exclusion criteria were: (a) <18 years, (b) individuals already on RA treatment, (c) patients with osteoarthritis, or gouty arthritis, (d) suffered from any severe disease. All patients were selected from the outpatient clinic of rheumatology and inpatient wards, Ziauddin University Hospitals Karachi. There were 77 female and 11 male in each group.

The selected patients and controls were evaluated on:

- Full medical history.
- Complete clinical examination including DAS-28 [17].

The DAS-28 is widely used as a tool for disease activity and response to treatment in RA, it is the most approximate indicator of successful treatment. The joints evaluated through DAS-28 are bilateral proximal and distal inter phalangeal joints, metacarpo-phalangeal joints and major joints such as shoulder, elbow, wrist, knee joint. Examination of joints is performed on following criteria. (1)Tenderness upon touching, (2) number of swollen joints is performed. From this, the disease activity of the patient was measured. DAS-28 score can be classified as follows:

Patients with low disease activity have DAS-28 <3.2, patients with moderate disease activity have DAS-28 >3.2 - <5.1, patients with high disease activity have DAS-28 >5.1 and patients in remission have DAS-28 <2.6 [17].

In addition, venous blood was collected by means of venipuncture. The following laboratory investigations were carried out for all participants(a) ESR using the westergren method (b) CRP using nephelometry (c) Serum rheumatoid factor (RF) using nephelometry (d) Serum Anti-CCP antibody using high sensitive ELISA kit (e) COMP assay using Human (COMP) ELISA kit (Cloud Clone CO, USA, catalog no. SEB197Hu).

- plain x-rays of the hands and feet were taken at radiology department of Ziauddin Hospital and assessed for radiological changes by Van der Heijde modified Sharp score [18].

2.3 Statistical Analysis

SPSS-20 was used to analyze the data. The quantitative data like age were presented as mean ± S.D. Paired data of continuous variables like DAS28, CRP were calculated using paired t-test. Pearson correlation was used to measure the correlation between quantitative variables like DAS-28, CRP, RF, Anti-CCP and COMP levels. Receiver-operating characteristic (ROC) curve was used to check the sensitivity, specificity of the potential biomarker. P-value ≤0.05 was considered significant

3. RESULTS

Our study included 88 controls and 88 RA patients. There was no significant difference in the mean age of the both groups. Mean SD of disease duration, morning stiffness in hours, joint tenderness index score and joint swelling index score was 2.68±6.43 years, 2.01±0.32 hours, 12.11±9.52, and 9.97±13.43 respectively. Figs.1 and 2 shows some radiological findings of the involved joints in our study.

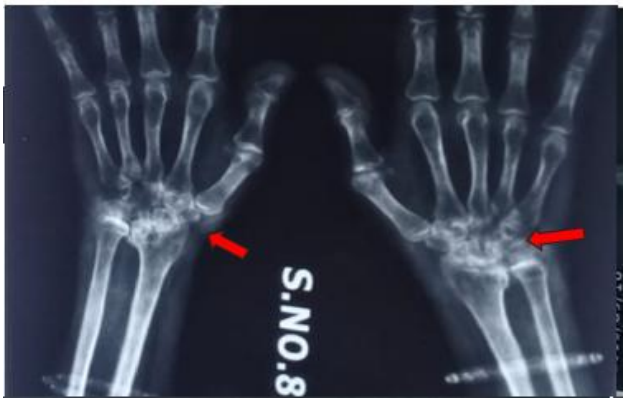

Fig. 1. X-ray of patient no 8 showing erosion and decrease in joint space and matting of carpal bones at wrist joints in both hand

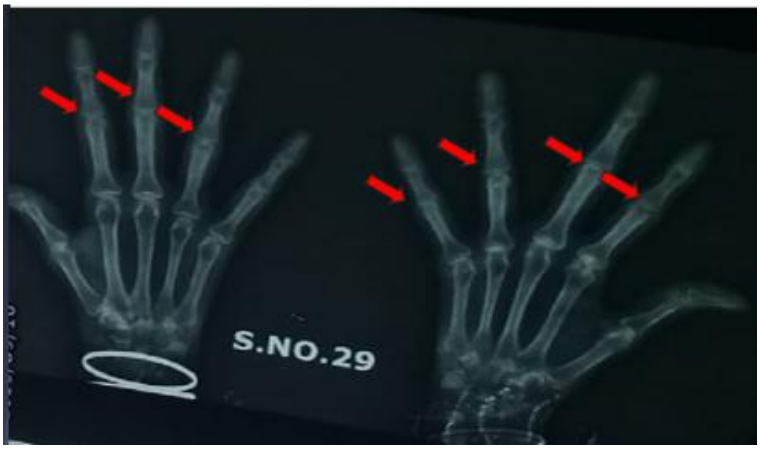

Fig 2. X-ray of patient no 29 showing mild erosion and decrease in joint space at proximal interphalangeal joints in both hand

Table 1 compares the mean values of variables in both groups, which shows significant difference in value of ESR, CRP, RF and Anti-CCP between patients and controls group P<0.0001. As it can be observed in Table 2 serum COMP levels are significantly higher in RA patients 51.35 ng/ml than controls 21.45 ng/ml and Table 3 shows serum COMP with high DAS 63.386 ng/ml is higher than COMP levels with moderate DAS 39.34 ng/ml in RA patients with in RA patients significant p value of <0.0001.

Table 4 and Figs. 3 & 4 shows the correlation between biomarkers and radiological damage severity (sharp scores). Serum COMP level shows strong positive correlation with Moderate DAS RA (r=0.932, p<0.001) and High DAS RA (r=0.952, p<0.001).

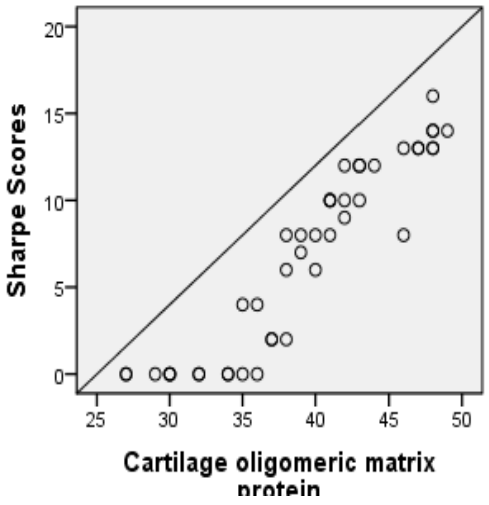

Fig. 3. Scatter plot COMP with sharp score in moderate DAS

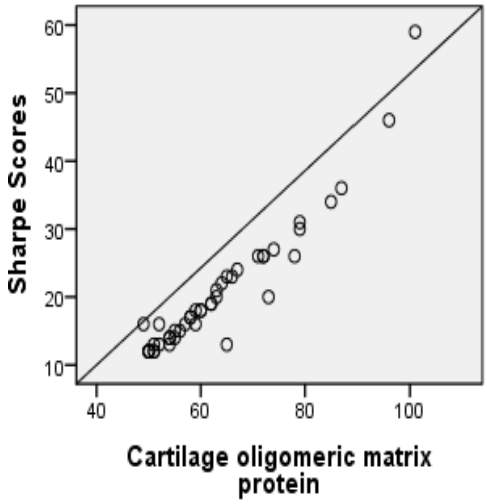

Fig. 4. Scatter plot COMP with sharp score in high DAS

To check the diagnostic ability of COMP for cartilage damage we plot ROC curve. The ROC curve clearly shows strong sensitivity and specificity of COMP levels with increased severity of disease.

Fig. 5 & Table 5 shows the receiver operating characteristic curve analysis for COMP in differentiating 88 Controls and 88 RA patients. Table 5 shows at level of 27.01 ng/ml serum COMP level had 96% sensitivity and 83% specificity to differentiate control from RA with AUC= 99%.

4. DISCUSSION

RA can be presented as a mellow and non-ruinous illness to a genuine and rapidly

dangerous joint sickness. Distinctive new proposed biomarkers are used to pick the best treatment procedure and anticipate RA prognosis [19,20]. These biomarkers could be applied in clinical practice and exploration settings to supervise accommodating response and joint harm and turnover movement. Taking into account the procured results, serum COMP level was essentially higher among RA patients stood out from control subjects. In the subset of RA patients, COMP not solely was higher in those with serious ailment, yet what's more had a satisfactory affectability and particularity to decide RA patients to have late-stage disease [15]. There is likewise proof that COMP has role in initiating complement cascade that adds to pathogenesis of disease. According to finding of Andersson et al in 2013 COMP is discharged because of catabolic response and when there is high damage of cartilage in RA [13]. Repair systems can't repay joint damage in late stages of disease [21,22]. In concurrence with our outcomes, a recent research led by Sakthiswary et al in 2017 which included RA patients and healthy individuals, revealed high levels of serum COMP in RA in contrast with healthy individuals [15]. In our study we used modified radiographic vender Heijde sharp scoring system to assess joint damage. Whereas a research by Sakthiswary et al in 2017, assessed joint damage by measuring knee cartilage thickness through ultrasound which revealed negative correlation between cartilage thickness and serum COMP levels. A previous research led by EL Defrawy et al in 2016 appeared, equivalent to our outcomes to, that serum COMP levels were higher in established RA than in early RA. This research likewise assessed synovial COMP level which demonstrated comparable outcomes to serum COMP level [23]. Our research uncovered that there is a strong positive correlation between this biomarker and joint decimation in late RA just as in early RA. Moreover, serum COMP had 96% sensitivity and 83% specificity at level of 27.01 ng/ml in diagnosing RA. A past report directed by Soderlin et al in 2004 uncovered that for diagnosing early RA serum COMP had 96% specificity and 44% sensitivity in contrast to healthy individuals [24]. In the view of this proof, serum COMP seems a specific test for RA. Our outcomes propose that serum COMP not exclusively can be utilized for diagnosis of RA, yet in addition, high levels recommend severe cartilage destruction. Additionally along with other clinical tools that are currently used to monitor the disease progression like DAS-28 and radiologic scores serum COMP levels can be objectively measured to check the disease progression in RA patients. Estimating biological markers to calculate cartilage development and breakdown disparity is an established practice to decide disease progress and treatment response [25]. Andersson et al. uncovered that at the time of diagnosis if levels of COMP are high they are associated with cartilage damage in RA patients over the next five years. This highlights that COMP is a good prognostic marker in RA [13].

Table 1. The Means (SD) of the variable in the studied groups.

Variables	Controls N=88	Patients N=88	P-value
Age years (mean SD)	42.44 ± 6.88	43.43 ± 9.4	0.429
ESR mm/h (mean SD)	7.55 ± 2.76	59.62 ± 28.44	<0.001
CRP mg/l (mean SD)	1.53 ± .48	27.02 ± 25.3	<0.001
RF U/ml (mean SD)	6.95 ± 3.12	59.84 ± 65.72	<0.001
Anti-CCP U/ml (mean SD)	6.69 ± 2.5	103.38 ± 98.95	<0.001

Table 2. Means (SD) of COMP between control and patients

COMP ng/ml	CONTROL(n=88)	PATINTS(n=88)	p-value
mean ± SD	21.454(±5.208)	51.35 (± 15.6)	<0.001

Table 3. Means (SD) of COMP between moderate DAS and High DAS in RA patients

COMP ng/ml	LOW DAS(n=44)	HIGH DAS(n=44)	p-value
mean ± SD	39.34(±6.258)	63.386(±12.675)	<0.001

COMP=Cartilage Oligomeric matrix Protein, CRP=C-Reactive Proteins, RF=Rheumatoid factor, Anti CCP= Anticyclic citrullinated. Protein, DAS=disease activity score.

. **Table 4. Correlation between the radiological sharp scores in rheumatoid arthritis and the measured markers**

Sharp Scores	Correlation coefficient and significance	COMP	CRP	RF	Anti CCP
High DAS	R	.952	.508	.055	.049
	p-value	.000	.000	.721	.753
Moderate DAS	R	.932	.566	.182	.010
	p-value	.000	.000	.238	.950

Table 5. Diagnostic accuracy of serum COMP

Area under curve	Cut-off point	Sensitivity	Specificity
0.994	COMP=27.01 ng/ml	96%	83%

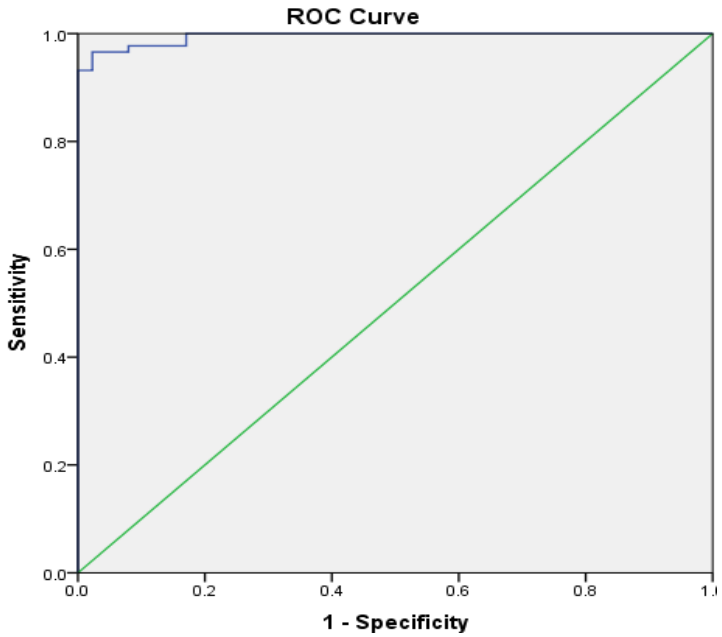

Fig. 5. Receiver operating characteristic curve analysis for COMP in differentiating 88 Controls and 88 RA patients

As our research was case control, so we were unable to find how serum COMP level can anticipate RA exacerbation and its relationship with radiographic scoring declining. A research led in 2013 described COMP as characteristic marker in RA and exhibited that patients with established RA will undoubtedly have progressively raised degrees of COMP [22]. Different studies showed that other biologic therapies and anti-TNF could prevent joint damage and reduce COMP levels in RA [26,27] In addition to that serum COMP level shows significant correlation with extensively used clinical tools like DAS-28 and radiographic scoring systems [15,28]. The present results are compatible with this reality, as the joint involvement increased the serum COMP levels became elevated. The ROC curve demonstrated that COMP, have acceptable sensitivity and specificity and can be utilized as diagnostic marker. This shows COMP didn't just mirror the cartilage damage, yet additionally it was related with disease seriousness. Utilizing COMP for diagnosis, prognosis and anticipating destruction of cartilage in patients with RA can unite a restorative manual for distinguish who may respond significantly to a particular treatment and for abatement of treatment related aftereffects.

5. CONCLUSIONS

Our results showed that serum COMP has significant positive correlation with severity of RA. Serum COMP can be utilized as a biomarker

to quantitatively measure cartilage destruction in RA patients. Further studies are recommended to see correlation between synovial thickness on ultrasound and COMP levels, and furthermore to decide prognostic value of serum COMP level by following participants over time.

6. LIMITATIONS

Firstly as study was case control so we cannot observe the patients to see the prognostic capability of COMP, secondly due to budget limitation we were unable to measure cytokines like IL and TNF which may show association with serum COMP levels and disease severity.

CONSENT AND ETHIC APPROVAL

Written and informed consents were taken from all participants.

Research approval was taken from Ethics Review Committee of Ziauddin Medical University (Ref.no:01604SKPATH).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Puchner R. Rudolf Puchner. Rheumatologie aus der Praxis: Entzündliche Gelenkerkrankungen–mit Fallbeispielen. 2017;199.
2. Riise T, Jacobsen BK, Gran J. Incidence and prevalence of rheumatoid arthritis in the county of Troms, northern Norway. The Journal of Rheumatology. 2000;27(6): 1386.
3. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheumatic Disease Clinics of North America. 2001;27(2):269-81.
4. Carmona L, Villaverde V, Hernández-García C, Ballina J, Gabriel R, Laffon A. The prevalence of rheumatoid arthritis in the general population of Spain. Rheumatology. 2002;41(1):88-95.
5. Rudan I, Sidhu S, Papana A, Meng SJ, Xin–Wei Y, Wang W, et al. Prevalence of rheumatoid arthritis in low–and middle–income countries: A systematic review and analysis. Journal of Global Health. 2015; 5(1).
6. Alam SM, Kidwai AA, Jafri SR, Qureshi BM, Sami A, Qureshi HH, et al. Epidemiology of rheumatoid arthritis in a tertiary care unit, Karachi, Pakistan. JPMA-Journal of the Pakistan Medical Association. 2011;61(2):123.
7. Hassan G, Aboelnour E, Ibrahiem O, Mohammed EF. Novel molecular diagnostic marker in the evaluation of cartilage destruction in patients with rheumatoid arthritis. Journal of Current Medical Research and Practice. 2016; 1(3):72.
8. Mok CC, Cha HS, Hidayat R, Nguyen LTN, Perez EC, Ramachandran R, et al. The importance of assessment and management of morning stiffness in Asian patients with rheumatoid arthritis: Recommendations from an expert panel. International Journal of Rheumatic Diseases. 2016;19(1):30-7.
9. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: Analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Research & Therapy. 2009;11(1): R7.
10. Mølbæk K, Hørslev-Petersen K, Primdahl J. Diagnostic delay in rheumatoid arthritis: A qualitative study of symptom interpretation before the first visit to the doctor. Musculoskeletal Care. 2016;14(1): 26-36.
11. Mocelin V, Nisihara RM, Utiyama SR, Kotze LM, Ramos Jr O, Messias-Reason I. Anti-CCP Antibodies and rheumatological findings in brazilian patients with crohn's disease. Digestion. 2015;91(4):303-6.
12. Vignesh APP, Srinivasan R. Ocular manifestations of rheumatoid arthritis and their correlation with anti-cyclic citrullinated peptide antibodies. Clinical Ophthalmology (Auckland, NZ). 2015;9:393.
13. Andersson ML, Svensson B, Petersson IF, Hafström I, Albertsson K, Forslind K, et al. Early increase in serum-COMP is associated with joint damage progression over the first five years in patients with rheumatoid arthritis. BMC Musculoskeletal Disorders. 2013;14(1):229.
14. Tseng S, Reddi AH, Di Cesare PE. Cartilage oligomeric matrix protein (COMP): A biomarker of arthritis. Biomarker Insights. 2009;4:BMI, S645.
15. Sakthiswary R, Rajalingam S, Hussein H, Sridharan R, Asrul AW. Cartilage

oligomeric matrix protein (COMP) in rheumatoid arthritis and its correlation with sonographic knee cartilage thickness and disease activity. Clinical Rheumatology. 2017;36(12):2683-8.
16. Skoumal M, Kolarz G, Klingler A. Serum levels of cartilage oligomeric matrix protein A predicting factor and a valuable parameter for disease management in rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2003;32(3):156-61.
17. Prevoo M, Van'T Hof MA, Kuper H, Van Leeuwen M, Van De Putte L, Van Riel P. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1995; 38(1):44-8.
18. Van Der Heijde D, Van Der Helm-Van AH, Aletaha D, Bingham CO, Burmester GR, Dougados M, et al. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. Annals of the Rheumatic Diseases. 2013;72(4):479-81.
19. Salaffi F, Carotti M, Carlo M. Conventional radiography in rheumatoid arthritis: New scientific insights and practical application. Int J Clin Exp Med. 2016;9(9):17012-27.
20. Christensen AF, Lindegaard H, Hørslev-Petersen K, Hetland ML, Ejbjerg B, Stengaard-Pedersen K, et al. Cartilage oligomeric matrix protein associates differentially with erosions and synovitis and has a different temporal course in cyclic citrullinated peptide antibody (anti-CCP)-positive versus anti-CCP-negative early rheumatoid arthritis. The Journal of Rheumatology. 2011;38(8): 1563-8.
21. Robinson WH, Lindstrom TM, Cheung RK, Sokolove J. Mechanistic biomarkers for clinical decision making in rheumatic diseases. Nature Reviews Rheumatology. 2013;9(5):267.
22. Algergawy SA, Abd El-Sabour M, Osman AS, Emam SM, Elham N. Early diagnostic and prognostic values of anti-cyclic citrullinated peptide antibody and cartilage oligomeric matrix protein in rheumatoid arthritis. Egypt J Immunol. 2013;20(2):11-20.
23. El Defrawy A, Gheita T, Raslan H, El Ansary M, El Awar A. Serum and synovial cartilage oligomeric matrix protein levels in early and established rheumatoid arthritis. Zeitschrift für Rheumatologie. 2016;75(9): 917-23.
24. Söderlin M, Kastbom A, Kautiainen H, Leirisalo-Repo M, Strandberg G, Skogh T. Antibodies against cyclic citrullinated peptide (CCP) and levels of cartilage oligomeric matrix protein (COMP) in very early arthritis: Relation to diagnosis and disease activity. Scandinavian Journal of Rheumatology. 2004;33(3):185-8.
25. Krabbe S, Bolce R, Brahe C, Døhn U, Ejbjerg B, Hetland M, et al. Investigation of a multi-biomarker disease activity score in rheumatoid arthritis by comparison with magnetic resonance imaging, computed tomography, ultrasonography, and radiography parameters of inflammation and damage. Scandinavian Journal of Rheumatology. 2017;46(5):353-8.
26. Acharya C, Yik JH, Kishore A, Van Dinh V, Di Cesare PE, Haudenschild DR. Cartilage oligomeric matrix protein and its binding partners in the cartilage extracellular matrix: Interaction, regulation and role in chondrogenesis. Matrix Biology. 2014;37: 102-11.
27. Wisłowska M, Jabłońska B. Serum cartilage oligomeric matrix protein (COMP) in rheumatoid arthritis and knee osteoarthritis. Clinical Rheumatology. 2005;24(3):278-84.
28. Algergawy S, Abd ME-S, Osman A, Emam S, Elham N. Early diagnostic and prognostic values of anti-cyclic citrullinated peptide antibody and cartilage oligomeric matrix protein in rheumatoid arthritis. The Egyptian Journal of Immunology. 2013; 20(2):11-20.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/60859