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Prognostic value of COMP a comparison with ACCP in rheumatoid arthritis patients in Iraq

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Abstract---comparison with Anti citrullinated peptide antibody (ACCP) and explore response to Methotrexate (MTX) , Etanercept and without treatment patients , with disease activity in rheumatoid arthritis Iraqi patients. Method of study was Case control. Measurement levels of biomarkers by ELISA. Results of ACCP and COMP levels in RA patients highly significantly than healthy control $p < 0.001$. highly significant ACCP and COMP levels in active disease than moderate and low activity $p < 0.001$. Without treatments Patients ACCP and COMP levels highly significant than on MTX or etanercept $p < 0.001$, Statistically non-significant between on MTX and etanercept $p > 0.05$. Significant positive correlation between ACCP and COMP ($r = 0.53, p < 0.001$) ACCP and CDAI ($r = 0.459, p < 0.001$) COMP and CDAI ($r = 0.519, p < 0.001$) ACCP and COMP cutoff ($> 13.13 \text{ U / ml}, > 0.21 \text{ ng / ml}$) Sensitivity (72 %, 78 %) Specificity (98%, 84% respectively). Suggestion COMP has potential prognostic ability a comparison with ACCP and to differentiation between RA patients and healthy and predict severity of disease with response to MTX or etanercept.

Keywords---COMP, ACCP, rheumatoid arthritis patients, biomarkers, Iraq

Introduction

Rheumatoid arthritis (RA) is inflammatory autoimmune chronic conditions unknown etiology disease due to immune cells interact with soluble mediators, Primary affects the small joints , extra articular manifestations of RA included skin , nerves , and eye diseases , as well as gastrointestinal , cardiovascular , pulmonary and renal diseases(Bullock et al, 2018 ; Marcucci et al, 2018; Smolen et al,2018; Testa et al,2021). Worldwide prevalence of RA approximately 0.5-1.0 % , Females are 2 – 3 times more affected than males (Ngo et al,2014;Bagherniya et al,2021).Pathogenesis of RA is by auto-reactive B cells which contribute on auto-antibodies production and T cells by release of cytokines after activation (Bugatti et al,2014).Antibodies against citrullinated protein /peptide including IgG, IgM, and IgA isotypes which are known as anti-citrullinated protein/ peptide antibodies (ACPA) , auto antibodies are associated with joint destruction and increase risk of disease progression (Chauhan et al, 2022) .

First line of treatments strategy isDisease-modifying anti-Rheumatic Drugs (DMARDs) to reduce Rheumatoid arthritis aggressiveness , If a patient does not respond to synthetic DMARDs , biological therapy should be initiated which have different targets such as interleukin-6 (IL-6) ,Tumor necrosis factor (TNF-a) (Lamers-Karnebeek et al,2019; Huang et al, 2021) .

Cartilage, synovium, tendon and other connective tissues all produce cartilage oligomeric matrix protein which is a non-collagen glycoprotein , COMP has been shown in recent research to be a good indicator of cartilage destruction ,the role ofCOMP in the pathogenesis of RA has already been established(Andersson et al, 2013;El Defrawy et al, 2016;Saghafi et al,2017 ;Posey et al,2018; Han,2020)COMP has predictive component in RA and role in pathologic mechanismwith progression of RA during the digestion and dissolving of connective tissue components by protease-derived hydrolysis (Liu et al,2016).The finding of abnormally high COMP in the serum of RA patients and T cell immunological abnormalities indicate that COMP may affect the Th17/Treg balance and therefore also play a role in the development of RA (Han,2020) .

Method

Study design

Case control study conducted in Baghdad teaching hospital/Rheumatology consultation clinic, recruited in the period from November 2021 to February 2022.

Inclusion criteria

Rheumatoid Arthritis patients according to (ACR/ELAR 2010 criteria of diagnosis) received DMARDs(Methotrexate 2.5 mg), or Biological DMARDs (Etanercept50 mg) and without treatments RA patients .

Exclusion criteria

Active infection and other rheumatologic autoimmune disease other than RA or systemic disorders and RA patients received (DMARDs) treatments other than methotrexate , patients received methotrexate (MTX) dose > 2.5 mg , Patients received Biological (DMARDs) other than Etanercept50 mg.

Patient's subgroups

1. Patients group : include (100) patients (83female and 17 male) age range (19 - 65) years RApatients which diagnosed by specialist rheumatologist by clinical examination and confirmed the diagnosis by laboratory investigation and radiology examination.

Patients group was subdivided into 3 sub groups

- A. First sub group included 37 Patients received DMARDs (MTX 2.5 mg).
 - B. Second sub group included 42 Patients received bDMARDs (etanercept 50 mg).
 - C. Third sub group included 21 without treatment patients for 2 month or more.
2. Healthy control group: included 50 apparently healthy persons(43 female and 7 male) age range between (22 -72) years were matched with age and gender with patients group.

Methods

Blood sample collection

Blood sample collected from patients and control five milliliters of venous blood.

Serum separation

Serum was obtained from the blood samples were left for 30 minutes at room temperature, then centrifuged at 3000 rpm for ten minutes.

The serum for each sample was collected in eppendorf tubes and stored at -20 °C until the time for using , then measured by using Enzyme-Linked Immune Sorbent Assay (ELISA), ACCP (Aeskulisa – Germany) , COMP (Sunlong-Biotech - China).

Data Collection

1. Patients questionnaire was about name , age , disease duration ,gender ,family history , full fill from American college of Rheumatology criteria 2010 (ACR 2010).
2. Clinical disease activity index (CDAI) for assessment of disease activity by clinical examination.
3. History of diseases and types of medication taken currently or previously.
4. Laboratory investigations : including ESR, CBC .

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 26 Used for statistical analysis of all data included in the study as mean, SD, range, independent T-test for determination of statically significant between groups, one way Anova test for determine any the statistically differences between the sub- groups.

Statistically significant when was $p < 0.05$,high p - value statistically significant when was $p < 0.001$, not statistically significant when was $p > 0.05$,used graphics and tables for the presentation of data , person correlation and regression analysis were used for determine correlation coefficient between study variables , receiver operating characteristic curve (ROC curve) was used for determined cutoff , the sensitivity and specificity of tests.

Results

The characteristics findings of the study

Genders in 150 participants were included in the study, Rheumatoid arthritis patients included n=100 (17% males) and (83% females), and healthy control n=50 (14% males) and (86% females), age of both groups shown no significant differences between RA patients and healthy control $p > 0.05$ age was sub divided into four age groups ≤ 35 years was (18%) between 36-45 years was (22%) between 46-55 was (35%) and ≥ 56 years was (25%). smoking status in RA patients was 87 % smokers and 13 % non-smokers. Disease duration in years was 9.13 ± 8.25 and range 6 months – 40 years, patients with family history and patients fever, redness, tender joints, swollen joints and VAS, demographic and clinical characteristics and related features of RA illness are shown in (Table 1). The medication of RA sub groups, 37 patients (37%) patients received DMARDs (MTX), 42 (42 %) patients received biological bDMARDs (etanercept) and 21 patients (21%) without any treatments patients for 2 months or more.

Table 1: Demographics and Clinical characteristics of RA

RA variables	Status	Values
Family history RA patients	With family history	18 (18 %)
	Without family history	82 (82 %)
Fever	With fever	64 (64 %)
	Without fever	36 (36 %)
Redness	With Redness	37 (37 %)
	Without Redness	63 (63 %)
Tender joints (Tj)	mean \pm SD	8.92 ± 5.53
Swollen joints (Sj)	mean \pm SD	1.13 ± 1.13
Visual analogue scale 0-10 (VAS)	mean \pm SD	5.44 ± 1.73

Clinical disease activity index (CDAI) of RA patients which are included in the study was 20.34 ± 8.89 and range (1-45), 12 RA patients (12%) Low disease activity CDAI was 5.92 ± 3.20 and CDAI range (1-9), 46 RA patients (46 %) moderate disease activity CDAI was 16.59 ± 3.84 and CDAI range (10- 22) and 42 RA patients (42%) high disease activity CDAI was 28.57 ± 5.11 and CDAI range (23-45) $P < 0.001$.

The investigations of RA patients and healthy control results are shown differences in means and levels of ESR, ACCP and COMP in RA patients were highly significant $P < 0.001$ than health control group (Table 2).

Table 2: The investigations of RA patients and healthy control

Investigations	Groups	Mean \pm SD	P – value
ESR mm / hr	RA patients	39.85 \pm 25.47	< 0.001
	Control	11.60 \pm 8.9	
ACCP U /ml	RA patients	58.98 \pm 13.04	< 0.001
	Control	5.05 \pm 1.70	
COMP ng/ml	RA patients	0.43 \pm 0.29	< 0.001
	Control	0.18 \pm 0.08	

ACCP level in RA patients according active disease CDAI , ACCP level in active disease was 93.08 ± 38.93 U /ml which highly significant $p < 0.001$ than the level in RA patients with moderate and low disease activity $CDAI \leq 22$ (38.29 ± 18.79 U /ml and 20.5 ± 5.12 U /ml respectively) .COMP level in RA patients with active disease was 0.57 ± 0.24 ng/ml which highly significant $p < 0.001$ than the level in RA patients with moderate and low disease activity (0.33 ± 0.15 ng/ml and 0.1 ± 0.04 respectively) .

The effect of treatments on ACCP level , patients without treatments ACCP level was 82.8 ± 35.53 U/ml which highly significant $p < 0.001$ than patients received treatments (MTX) 55.03 ± 14.31 U/ml or etanercept 51.46 ± 11.63 U/ml, but statistically non-significant $p > 0.05$ between patients received MTX or received etanercept. COMP level in Patients without treatments was 0.61 ± 0.18 ng/ml which highly significant $p < 0.001$ than patients received MTX 0.39 ± 0.17 ng/ml or etanercept 0.37 ± 0.2 ng/ml , statistically non-significant $p > 0.05$ between patients received MTX and patients received etanercept.

The Correlation between ACCP and study variables in RA patients group , significant positive correlation between ACCP and visual analog scale (VAS) $r = 0.305$ $p \leq 0.002$, significant positive correlation between ACCP and tender joints (TJ) $r = 0.469$ $p < 0.001$, significant positive correlation between ACCP and swollen joints (SJ) $r = 0.328$ $p \leq 0.001$. Significant positive correlation between ACCP and ESR $r = 0.258$ $p \leq 0.01$, Significant positive correlation between ACCP and disease activity (CDAI) $r = 0.459$ $p \leq 0.001$ Significant positive correlation between ACCP and COMP $r = 0.536$ $p < 0.001$ (Figure 1).

The Correlation between COMP and study variables in RA patients group , significant positive correlation between COMP and visual analog scale (VAS) $r = 0.379$ $p < 0.001$, significant positive correlation between COMP and tender joints (TJ) $r = 0.538$ $p < 0.001$, significant positive correlation between COMP and swollen joints (SJ) $r = 0.235$ $p < 0.05$, significant positive correlation between COMP and ESR $r = 0.227$ $p < 0.05$.Significant positive correlation between COMP and disease activity (CDAI) $r = 0.519$ $p < 0.001$.

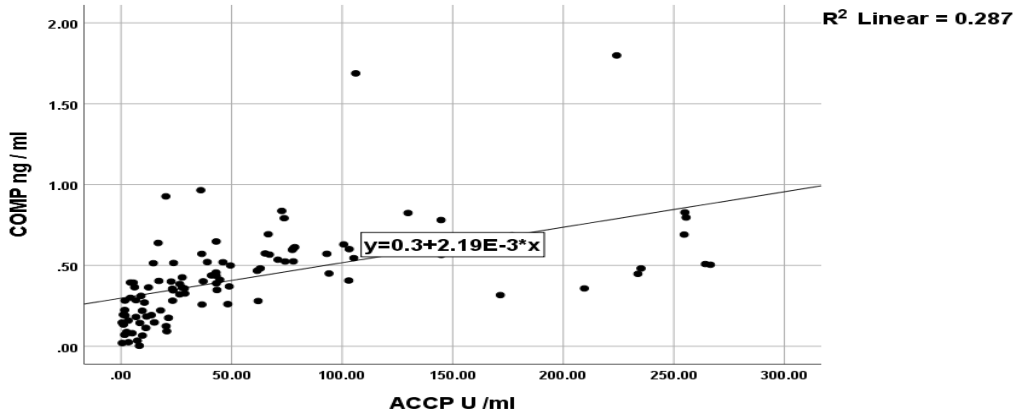


Figure 1: Scatter plot diagram show correlation between ACCP and COMP in patients group

Receiver operating characteristic curve (ROC curve) for comparison between ACCP and COMP for RA detection and evaluation of sensitivity, specificity and cutoff values.(AUC) of ACCP is large (0.87) cutoff value (> 13.13 U / ml)sensitivity (72 %) , high specificity (98 %) , (AUC) of COMP is large (0.82) cutoff value (> 0.21 ng / ml) sensitivity (78 %) , specificity (84 %)(Figure 2) .

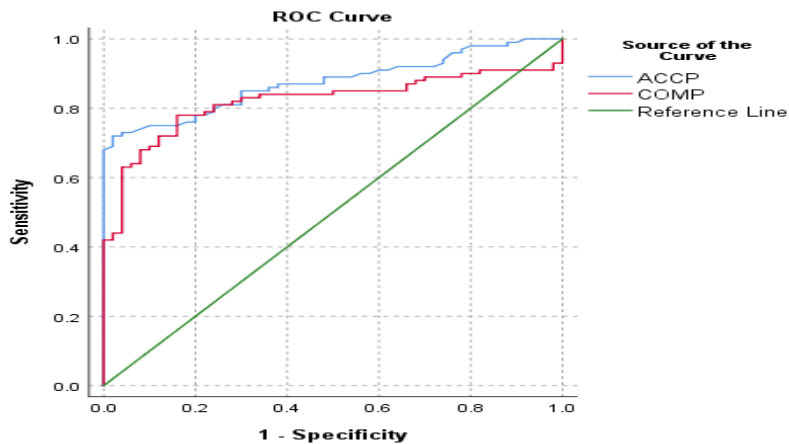


Figure 2: ROC curve of ACCP and COMP

Discussion

Rheumatoid arthritis (RA) is inflammatory condition that affect small and large joints with characteristics by symmetrical poly arthritis it does drastically affect the quality of life when untreated, medications include disease-modifying anti-rheumatic drugs (DMARDs) use to reduce inflammation, decrease damage and maintain function of joints and maintain the remission but no cure of disease ,

appropriate biomarkers are essential for early disease identification as well as monitoring disease activity and progression (Yap et al,2018). Incidence of RA in current study is more in females than males and ratio is 4.8:1, previous local studies mentioned ratio was 5.6:1 (Al -Yasiri et al,2014). international studies mentioned ratio was 3:1 and others shown females to males ratio was 4.5:1 (Machado-Alba et al,2015; Maranini et al,2022). The reason is due to the environment and role of females hormones including estrogen are associated with RA pathogenesis and inflammatory reactions and production of cytokines in the synovium which cause directly effect on cartilage (Yu et al,2020). RA patients were participants in the study distributed according age grouped into four age group and most age was affected by RA was between (46–55 years) previous local and international studies are shown age of RA patients is more than 40 years (Hussein et al,2018; Imari et al,2021; Jura-Póltorak et al,2021; Xu & Wu,2021). Increase age is associate with decrease of humoral immunity and immune defense mechanism lead to increase predisposition to autoimmunity, One of the main age-related alterations in compartments of B cell is accumulation of auto reactive B lymphocytes which known age-associated B cells also variation in B cells receptor and gene expression (Ma et al, 2019). Smoking is a risk factor of RA due to increase citrullination in the lung and production of ACPA and reduce response to DMARDs (Torrente-Segarra et al,2018; Regueiro et al, 2020). The disease duration of RA patients included in the study in years was 9.13 ± 8.25 in a line with local study which mentioned disease duration in years was 9.5 ± 3.7 (Albarzinji et al,2022). Mean of ESR in RA patients was higher than healthy control $p < 0.001$ (Table 2), other previous local shown similar result which indicate ESR of RA patients is highly significant in comparison healthy control (Khadim & Al-Fartusie, 2021).

Anti-citrullinated protein/peptide antibodies (ACPA) are found in Rheumatoid arthritis patients which produce in post translation modification against citrullinated protein, ACPA are associated with joint destruction and increase risk of disease progression and death (Chauhan et al,2022).

COMP is antigen that's mostly present in cartilage and bone and other tissues, function is mostly suggest the role as structural in extracellular matrix and for stabilization by interaction with other components such as collagen fibrils, in RA patients elevation of COMP level in synovial fluid and serum which indicate for cartilage destruction and can reflect particular metabolic processes of cartilage tissue (Ge et al,2022). In early stage of RA The damage of cartilage trigger an inflammatory immune reaction in the joint leading to gradual remodeling of the effected joints which explaining the disease's chronicity (Sweilam et al,2018).

The levels of ACCP and COMP in RA patients serum were highly significant $p < 0.001$ than healthy control (Table 2), other studies observed similar result which indicated ACCP and COMP level is highly significant in comparison with healthy control (Liu et al, 2016). and other studies observed COMP level is highly significant in RA patients than healthy control (Sakthiswary et al,2017; Tawfik et al, 2019).

ACCP level in the study was changed according disease activity, ACCP level in active disease is highly significant $p < 0.001$ than the level in RA patients with

moderate and low disease activity. local study shown serum ACCP level in RA patients is increase with increasing severity of disease , higher ACCP level in sever and moderate disease activity in comparison with mild severity (Alwan&Ghali, 2021). COMP level in active disease is highly significant $p < 0.001$ than the level in RA patients with moderate and low disease activity based on CDAI. Other study observed serum COMP level in RA patients is increase with increasing severity of disease in early and late of disease progression (Saghafi et al,2017).

ACCP level of patients without treatments in the study was highly significantly $p < 0.001$ than patients were received MTX or etanercept , similarly with local study which found the level of ACCP is significantly decrease in serum of patients received etanercept and lower than other RA patients whom without treatments (Chiad et al,2015). COMP level of patients without treatments was highly significant $p < 0.001$ than patients were received MTX or etanercept, previous study found the COMP level was decreased in serum of patients received etanercept after 6 months of administration in comparison with baseline value (Kawashiri et al,2010).The Correlation between COMP and ACCP in current study was significant positive correlation ($r = 0.536$ and $p < 0.001$) (Figure1).Other studies also reported significant positive correlation between COMP and ACCP (Aref& Ahmed, 2015 ; Sweilam et al,2018; Tawfik et al,2019).

Correlation between COMP and disease activity in RA patients was significant positive correlation between COMP and CDAI ($r = 0.519$ and $p < 0.001$).other study show significant positive correlation between COMP and disease activity (Qabulio et al,2020) .ROC curve forThe evaluation of accuracy and comparison of biomarkers for prognosis of RA patients in the study was done (Figure 2), ACCP (AUC) was 0.87 , cutoff > 13.13 U /ml , sensitivity (72 %) and high specificity (98 %) in a line with study observed Sensitivity and specificity of ACPA are (67% , 85-95%) respectively (Kwon&Ju, 2021). COMP (AUC) was 0.82 , cutoff > 0.21 ng/ml, Sensitivity and specificity of in the study was 78 % and 84 % respectively in a line with other studies which demonstrate Sensitivity and specificity of COMP was(74% and 83.33%) respectively (Sweilam et al,2018).

Conclusion

COMP has potential prognostic ability compared with ACCP, and to differentiation between RA patients and healthy control and predict severity of disease with response to MTX or etanercept. RApatients without treatments are higher levels of ACCP and COMP in comparison with patients received MTX or etanercept. Significant positive correlation between ACCP with COMP this enhance prognosis features of RA.

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