

Serum Pentraxin-3 Level in Patients with Rheumatoid Arthritis and its Association with Disease Activity

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Abstract

Background: The severity of rheumatoid arthritis (RA) is accompanied by the intensity of the inflammation and the joint damage. PTX-3 is a multifunctional protein with complex regulatory roles in inflammation and extracellular matrix organization and it is believed to more precisely present the actual inflammatory condition.

Aim of Study: The aim of the current work was to detect the serum PTX-3 level in RA cases and correlate its level with the clinical features, disease activity score (DAS28) and musculoskeletal ultrasound (MSUS) score.

Patients and Methods: Forty RA cases and 40 matched age and sex normal controls were comprised. Entire cases were subjected to history taking and clinical examination. Laboratory investigations, comprising CBC, ESR, CRP, RF, anti-CCP, random blood sugar, and serum PTX3 were estimated in all participants.

DAS -28 assessment and Musculoskeletal ultrasound for hands and feet according to novel 7 joint US score were done in RA cases.

Results: Serum PTX3 level were significantly increased in RA cases in comparison with control group. There was a significant positive correlation between serum PTX3 level and duration of morning stiffness, DAS 28 parameters. There was a significant positive association between serum level of PTX-3 and Synovitis GSUS score, Synovitis PDUS score, Tenosynovitis GSUS score and Tenosynovitis PDUS score.

Conclusion: Patients with RA exhibits a significant elevation in serum PTX3. Serum PTX3 level significantly correlates with clinical features, disease activity and MSUS parameter of inflammation and could act as a potentially efficient marker with for assessment of disease activity in RA

Key Words: *Rheumatoid arthritis – Pentraxins – Disease activity – Musculoskeletal ultrasound.*

Introduction

RHEUMATOID arthritis (RA) is the most common inflammatory arthropathy worldwide, with

an incidence of RA ranges from 0.5% to 2% globally, often affecting females being two folds more vulnerable than males [1]. In cases with RA, persistence of disease activity is eventually accompanied by permanent radiological alterations and permanent functional loss [2].

The management of RA had witnessed a considerable improvement in the past 15 years as the development of targeted biological and non-biological DMARDs due to the marked advancement in the identification of the mechanisms underlying the pathologic processes in RA. Consequently, “treat to target” has become a feasible objective. Accurate 'tight control' needs repeated measures of disease activity to facilitate the appropriate selection of therapeutic modality to obtain the goal of disease remission [3].

The proper evaluation of disease activity requires (a) Validated and quantitative method to reliably distinguish between different levels of disease activity in RA; (b) Quick and easy to conduct clinically to enhance repeated monitoring of disease activity [4]. However, both immune and inflammatory processes have essential roles in the context of RA pathogenesis [5], therefore, biologic markers such as autoantibodies and high level of inflammatory markers can be more appropriate indicator of RA activity for monitoring of treatment [6].

The acute-phase reactant which include ESR and CRP are often utilized to detect the degree of inflammatory condition clinically and are components of the DAS28, a frequently utilized tool to measure disease activity [7]. In contrast, such two markers have certain restrictions, which include short-term reflection of inflammatory activity, being increased in different microbial and inflammatory situations and they are normal in 40% of cases with RA [8].

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The innate immunity is triggered when conserved components on the surface of pathogens are identified by a certain receptors called pattern recognition molecules (PRMs). Pentraxins (PTX) superfamily of molecules are among the soluble PRMs. PTX are a group of acute phase proteins which plays an essential role in the inflammatory processes. Prototypes of the PTX family include CRP and SAP. Both are short PTX synthesized by the hepatic tissue owing to IL-6 [9].

Pentraxins-3 is the prototype of the long Pentraxins subfamily [10]. It is formed by innate immunity cells which include neutrophils and fibroblasts. Several researches have evaluated the serum concentrations of PTX3 in the context of RA and have demonstrated that; its level was significantly elevated among cases with RA compared to RA free ones [11,12].

Aim of the work:

To assess serum PTX3 levels in RA cases compared to normal controls and to assess its correlation with the DAS28 and musculoskeletal ultrasound (MSUS) score in RA cases.

Patients and Methods

This was a case-control study comprised 40 RA cases (case group) recruited from the outpatient clinics and inpatients unit of the Physical medicine, Rheumatology and Rehabilitation Department at Mansoura University Hospitals and 40 age- and sex-matched normal subjects act as control group within the period from July 2019 to July 2020. The normal controls were chosen from blood donors attending the blood bank. The study was approved by the ethical committee of the Faculty of Medicine, Mansoura University (IRB) (code:18.08.76). The aim and approaches were clarified to all members and an informed consent was acquired before their participation. We included cases fulfilling ACR / EULAR 2010 classification criteria for RA [13]. But we excluded patients with any medical conditions such as diabetes mellitus, thyroid, kidney disease, hepatic disease, Cushing syndrome, malignancies, autoimmune disorders & current or ex-smokers. Pregnant females, lactating females or females Receiving oral contraceptives were also excluded. Therapeutic, family and past history were also assessed.

Entire cases were subjected to history taking, comprehensive clinical examination with a focus on duration of disease, morning stiffness duration, number of tender joints, and existing drugs. Laboratory investigations were carried out comprising

ESR (mm/hr) using Westergren method, CRP (mg/dl) by latex agglutination, serum rheumatoid factor using latex agglutination slide method, anti-CCP using ELISA. The serum level of PTX3 level was quantified by commercial human ELISA kit) (Sun Red international trade company, Shanghai, china, catalog no.201-12-1939) based on the user manufacturer.

The DAS28 was assessed [14] which is based on a count of 28 swollen and tender joints, in addition to ESR or CRP as well as global health evaluation on Visual analogue scale (VAS), with a score ranging from zero to 9.4. The DAS-28 was demonstrated to be realistic in the context of follow up RA disease activity ever day [15].

Patients were evaluated by conventional gray-scale US and power Doppler using Acuson P300 with a multi-frequency linear ultrasonic probe (frequency 12-18 MHz). Power Doppler settings were standardized with a Doppler frequency of 6.7-7.5 MHz, pulse repetition frequency of 750 Hz, and low wall filter. Seven joints in the most clinically affected hands and feet were examined based on German US7 score and EULAR guidelines. It was utilized for detecting and grading of synovitis and presence or absence of tenosynovitis, Paratenonitis, tendinitis and erosions. The 7 joints of this score included wrist joint, 2nd MCP, 3rd MCP joints, 2nd PIP, 3rd PIP joints, 2nd MTP and 5th MTP joints. The interpretation of ultrasound findings was done according to Backhaus et al., [16].

GSUS was analysed semi quantitatively (zero =absence, I=mild, II=moderate, III=severe synovitis), tenosynovitis/paratenonitis and erosions were assessed (No=0, Presence=1). Tenosynovitis appeared as hypoechoic or anechoic thickened tissue in presence or absence of fluid within the tendon Sheath. Paratenonitis was recognized as an echo-poor halo surround the tendon and occasionally presented by an increase in vascularity. The semi-quantitative features of PDUS activity were scored as follow:

- Grade zero: No intra articular color signal.
- Grade I: Up to three color signals or two single and one confluent signal in the intra-articular region.
- Grade II: More than grade I to more than 50% of the intra-articular area occupied with color signals.
- Grade III: \geq 50% of the intra-articular are occupied with color signals.

Statistical analysis:

The collected data were evaluated by utilizing SPSS (version 20). Variables with continuous data were examined for normal distribution by the Shapiro-Wilk test. Variables with normally distributed data were evaluated in mean \pm SD while variables with abnormal distribution were evaluated as median and IQR. Categorical data were expressed in number and percentage. The comparisons were detected by utilizing Student's *t*-test for 2 variables with continuous data of normal distribution while Mann-Whitney test was utilized to compare two variables with data of abnormal distribution. Spearman correlation test was utilized for correlation between variable with continuous data. Statistical significance was set at $p < 0.05$.

Results

Results demonstrate that the mean age of case group was 51.2 ± 17.3 years while the mean age in the control group was 49.9 ± 17.1 years, there was no significant difference in the age between both groups ($p = 0.731$). There were 31 females (77.5%) and 9 males (22.5%) in the RA group while there were 30 females (75%) and 10 males (25%) in control group, there was no significant difference in the sex distribution between both groups ($p = 0.793$). In the cases group, the mean duration of RA was 10.5 ± 4.9 years with range between 3 and 19 years. The mean duration of morning stiffness was 128.3 ± 62.3 minutes with range between 30 and 240 minutes. The mean number of swollen joints was 10.6 ± 5.3 with range between 3 and 19 joints. The mean number of tender joints was 12.4 ± 4.9 with range between 4 and 19 joints. Steroids were used in 31 cases (77.5%) as the most frequently used drug, methotrexate was used in 25 cases (62.5%), leflunomide in 13 cases (32.5%), sulfasalazine in 5 cases (12.5%), hydroxychloroquine in 27 cases (67.5%) and biological treatment in 5 cases (12.5%).

In this cases the mean DAS28 ESR was 4.16 ± 1.42 with range between 2.30-7.50 and the number of cases with low disease activity was 15 (37.5%) and with moderate disease activity was 13 (32.5%) and with high disease activity was 12 (30%) this shown in Fig. (1), and the mean DAS28 CRP was 4.19 ± 1.16 with range between 2.71-6.39 and the number of cases with low disease activity was 13 (32.5%) and with moderate disease activity was 16 (40%) and with high disease activity was 11 (27.5%) as shown in Fig. (2).

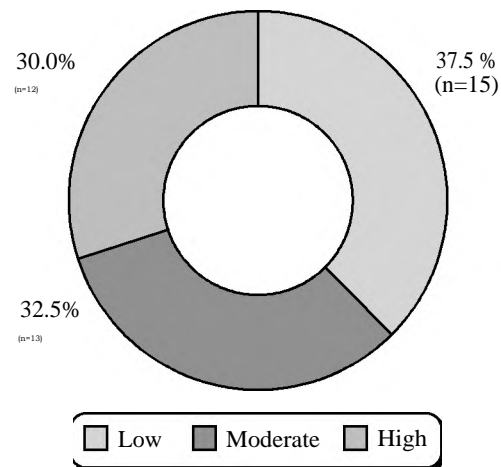


Fig. (1): Distribution of the RA activity according to the DAS28-ESR.

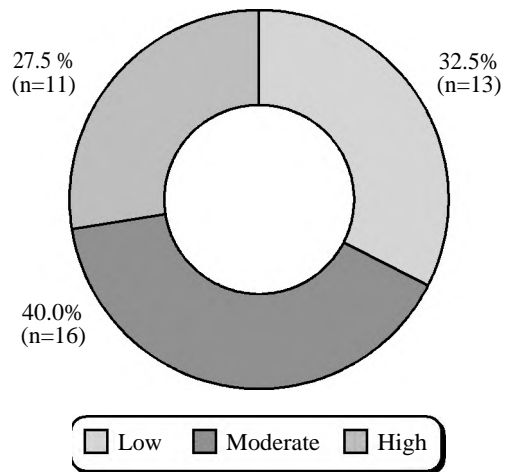


Fig. (2): Distribution of the RA activity according to the DAS28-CRP.

Regarding laboratory findings in our patients, the mean ESR in 1st hour was 67.2 ± 30.9 with range 18-112 and the median CRP was 51.9(44.2) with range 1.5-94.2, anti-CCP was positive in 27 cases (67.5%) with median value of 59 [132.0] and the range was between 9-173 (U/ml). RF was positive in 34 cases (85%) with median value of 234.5 [287.0] and the range was between 10 and 487 (U/ml). Table (1) shows the median level of serum PTX3 was 1.85ng/ml with IQR (1.48) and range between 0.3to 6.8ng/ml, whereas in the control the median level was 1.5ng/l with IQR (0.5) and range between 0.1 to 3ng/ml. The level of serum PTX3 was a statistically significant increase in the RA group compared to controls ($p < 0.05$). As regards Fig. (3), AUC for the serum level of PTX3 is excellent (0.796), sensitivity was 65%, specificity 72.5% and total accuracy 68.75%.

Table (1): Comparison of the serum PTX3 level between RA group and control group.

	RA group	Control group	P (Mann-Whitney U test)
<i>Serum PTX3 level (ng/ml):</i>			
Range	0.3-6.8	0.1-3.0	0.008
Median	1.85	1.50	
IQR	1.48	0.50	

PTX-3(pentraxin-3), IQR (inter quartile range).

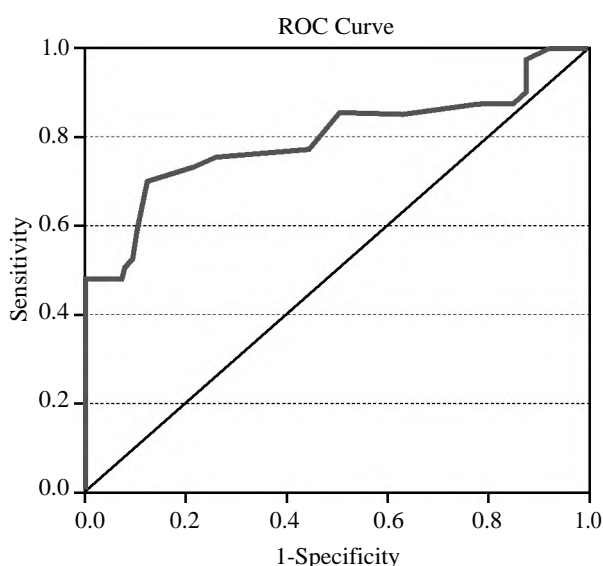


Fig. (3): ROC curve analysis for capability of the PTX3 for discrimination between the RA patients and controls (AUC=0.796).

There was a significant positive correlation existed between serum PTX3 and the duration of morning stiffness, SJC, TJC and VAS pain ($p < 0.05$).

However, no statistically-significant correlation between serum PTX3 value and age or duration of RA. There was no significant difference in the median (IQR) serum PTX3 level between the cases who received and who didn't receive different treatment including steroids, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine and biological treatment.

Table (2) shows that there was a significant positive association existed between serum PTX3 value and DAS28 ESR, DAS28 CRP ($p < 0.05$) and shows a significant positive association existed between serum PTX3 with ESR and CRP ($p < 0.05$). In contrast, there was no significant correlation between serum PTX-3 concentrations with Anti-CCP and RF titer.

There was a statistically-significant positive association existed between PTX-3 and grades of disease activity by DAS-28 ESR and DAS-28 CRP and shows that there was no significant correlation in the median concentration of serum PTX3 inter-quartile range (IQR) with Anti-CCP and RF positive or negative cases.

Table (2): Correlation of PTX3 serum level with DAS28, ESR, CRP, RF titer and anti-CCP of RA group.

	PTX3 serum level	
	<i>r</i>	<i>p</i>
DAS28-ESR	.345	.029
DAS28-CRP	.353	.025
ESR	.347	.028
CRP serum level	.345	.029
RF titer	.199	.219
Anti-CCP titer	.154	.342

Regarding our MSUS results, the median [IQR] synovitis GSUS was 4 (3.75) with range between 1 and 8. The median [IQR] synovitis PDUS was 1 (1.75) with range between 0 and 3. The median [IQR] tenosynovitis GSUS was 1 (1) with range between 0 and 2. The median [IQR] tenosynovitis PDUS 1 (1) with range between 0 and 1. The median [IQR] erosions score was 1 (1) with range between 0 and 3.

As demonstrated in Table (3), a statistically-significant positive association existed between serum level of PTX3 and synovitis GSUS score ($p < 0.001$), synovitis PDUS score ($p = .042$), tenosynovitis GSUS score ($p = .038$), tenosynovitis PDUS score ($p = .009$) and, there was no significant correlation with erosions score ($p = 0.114$).

Table (3): Correlation between the PTX3 and the US findings.

	<i>r</i>	<i>p</i>
Synovitis GSUS	0.534	<0.001
Synovitis PDUS	0.323	0.042
Tenosynovitis GSUS	0.329	0.038
Tenosynovitis PDUS	0.410	0.009
Erosions	0.2544	0.114

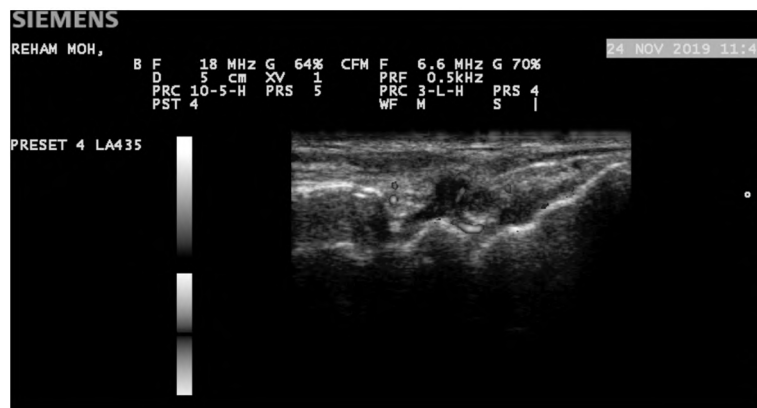


Fig. (4): Longitudinal dorsal scan of the wrist demonstrating synovitis with power Doppler.

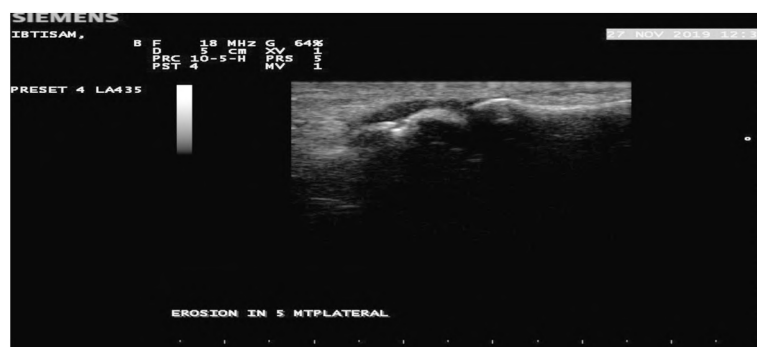


Fig. (5): Longitudinal lateral scan of 2nd metatarsophalangeal (MTP) joint demonstrating erosions and synovitis by gray scale US.

Discussion

Rheumatoid arthritis (RA) is a common systemic inflammatory disease characterized by the presence of destructive polyarthritis which affects the small joints of the hands and feet (though the disease process can virtually affect any synovial joint [43]. There is neither exact definition nor a pathognomonic test of RA. The diagnosis of RA, therefore, rests on a composite of clinical and laboratory observations [44].

Although not specific, CRP and ESR are widely used as clinical markers of inflammation and of acute phase response for identification of rheumatological diseases and for follow-up [45]. Due to the poor efficacy of these conventional markers, there is a need for a novel acute phase reactant which could effectively reflect the disease activity in clinical practice in patients of RA.

Since PTX3 is primarily produced and released by vascular wall cells, it may be used as a sensitive and independent inflammatory marker. PTX3 behaves as an acute phase response protein and the basal blood levels observed in normal condition (<2ng/ml in human) rapidly increase during the course of pathological conditions, can reach up to

100-1,000ng/ml in humans, depending on the severity [46]. PTX3 is thought to more accurately present the actual inflammatory status than CRP [47] and its response is faster than the CRP.

The aim of our study was to determine the serum concentration of Pentraxin3 in RA patients, and to study its association with disease activity evaluated by clinical examination and by musculoskeletal ultrasound.

The current study demonstrated that PTX3 serum level was significantly increased in RA cases in comparison with controls. This finding is consistent with (Balbaloglu and Ozcan, 2020b; Jafari-Nakhjavani et al., 2019; Ekin et al., 2021a ; Sharma et al., 2018a; Tekeoglu et al., 2016; Klimek et al., 2014;) [17-22] and disagree with the results of (Huang et al., 2016; Kahlow et al., 2016) [23,24] that demonstrated that serum levels of PTX3 in RA cases were comparable to control group.

In our study, a ROC curve of serum PTX3 levels was carried out to discriminate between RA and control group. The sensitivity of the PTX3 to discriminate between RA and control group was 65%, and its specificity was 72.5%. The present study demonstrated no significant differences in

PTX3 levels according to age of RA patients. Our results agree with Ekin et al., [19]. The current study demonstrated no significant association between PTX3 and disease duration, and this agrees with Tekeoğlu et al., [21].

Our study revealed significant correlations between PTX3 level and DAS28, CRP, ESR, SJC, TJC, visual analogue scale (VAS) and morning stiffness duration thus indicating that serum PTX3 levels in RA cases has a positive correlation with the disease activity measures. The current results agree with Boutet et al., [25] who noticed that serum PTX3 has a positive correlation with the following; CRP, ESR, DAS28, TJC, SJC and VAS. Also, we agree with several studies of (Jafari-Nakhjavani et al., 2019; Kahlow et al., 2016; Sharma et al., 2018b) [18,24,26] that found that there was a significant association between serum PTX3 level with disease activity and CRP and disagree with (Klimek et al., 2014; Balbaloglu and Ozcan, 2020a) [22,27] who found no significant difference was detected with regard to PTX3 levels according to disease activity or CRP.

Such discrepancies among the results could be owing to changes in studied subjects, disease duration, basal value of disease activity and PTX3 condition and type, dose and duration of medications. Even though results are inconsistent, the potential role of PTX3 with regard to RA pathogenesis cannot be ignored. It was displayed that PTX3 could be formed by different cell lines as monocytes-macrophages, fibroblasts, and endothelial cells after exposure to inflammatory triggers which include TNF- α and IL-1 [28] and could as a result participate in local inflammatory conditions, throughout which cells of natural immunity have a main role.

With regard to PTX3 correlations, the present study demonstrated that there was no significant association existed between the serum level of PTX3 and RF or anti-CCP levels. In addition, there was no significant correlation between PTX3 serum levels and the existence or absence of Anti-CCP and RF in RA cases This finding confirms the study done by Jafari-Nakhjavani et al. [18] who also found the same result. Also, Balbaloglu and Ozcan [27] found that there was no significant difference in PTX3 concentrations between anti-CCP-positive and anti-CCP-negative cases, on the other hand Weitoft et al., [29] found that Seropositive cases were accompanied by a significant elevation in PTX3 concentrations in Synovial fluid (SF) in comparison with seronegative ones, while there was no difference for serum concentrations.

In the context of the association of PTX3 with management in RA cases, the current study demonstrated no significant difference in serum PTX3 level between the cases who received and who didn't receive different treatment including steroids, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine and biological treatment. Our result agrees with Deyab et al. [30] who found that PTX3 serum levels aren't significantly influenced by different therapeutic modalities in terms of inflammatory arthritis.

EULAR recommendations highlight that the use of MSUS is superior to clinical examination to detect inflammation [31]. Preferably, an overall US scoring system has to be precisely expect isolated risk of erosion development, conducting better than DAS 28 which underestimates radiological progression risk in about twenty percent of cases [32]. DAS28 remission misjudgment develops, given that reminiscent inflamed joint may be missed by physical examination [33]. As US is better than physical examination with regard to joint inflammation assessment [34].

Of note, this is the first study investigating the relation of PTX3 serum concentration with ultrasound findings in RA patients. We have demonstrated that; there was a significant positive association existed between PTX3 and synovitis GSUS score, synovitis PDUS score, tenosynovitis GSUS score, tenosynovitis PDUS score of US score 7 but there was no significant correlation with erosion score. There was a study done by Hassan et al. [35] in which they correlate serum and SF levels of PTX3 in juvenile idiopathic arthritis cases with different clinical and laboratory and musculoskeletal US parameters of disease activity and they found that juvenile idiopathic arthritis cases were associated with a significant increase in serum and SF levels of Pentraxin 3 which has a significant correlation with the disease activity and MSUS parameter of inflammation.

The importance of GSUS is due to its ability in measuring synovial hypertrophy as well as detection of tenosynovitis and erosion but PDUS is more accurate in determining of the degree of inflammation in soft tissues and in the disease flares [36].

PTX 3 has a role in angiogenesis, it is of great importance to observe that PTX3 is formed by poorly-angiogenic lipopolysaccharide stimulated myeloid dendritic cells (mDCs) [37] while mDCs otherwise matured in the existence of the anti-inflammatory molecules calcitriol create the potent

angiogenic polypeptide VEGF [38]. As a result, based on the stimulation condition as well as on the cytokine milieu, PTX3 could participate in the various impact on the VEGF-dependent neovascularization process applied by various populations of DCS as it is identified as essential factor of the endothelial dysfunction [39,40].

PTX3 protein was detected in SF from cases with RA. As it was displayed that, contrasting to different acute-phase reactants (such as CRP and ESR), a main source of PTX3 biosynthesis is extra-hepatic, and the primary source of PTX3 in RA is the synovial pannus rich in monocytes / macrophages, endothelial cells and type A and B synoviocytes which, could be a possible source of the protein in the SF, and RNA-seq analysis established a potent correlation between PTX3 expression in the synovial tissue, disease activity and the existence of cytokines and chemokines driving local inflammation [25].

Although PTX3 has a main role in joint inflammation, its participation in bone remodeling is a matter of debate [41], a novel record emphasized a defensive role of PTX3 via the suppression of FGF-2 accompanying osteoclastogenesis in the collagen-induced arthritis model [42]. In such model, recombinant PTX3 injection decreases the inflammatory scores and bony erosions. Additionally, PTX3 binding to FGF-2 has been associated with a reversion of the suppressive action of such growth factor in terms of osteoblastogenesis [42].

Conclusion:

From this study we concluded that PTX-3 was found in higher levels in the serum of RA cases than in control persons indicating that it could have an essential pathogenic role in RA. Serum PTX3 correlated with clinical activity and MSUS parameter of inflammation in RA, thus it is valuable in evaluating disease activity either alone or accompanying with US assessment. Serum PTX-3 correlates with the inflammatory markers ESR and CRP

Limitations:

There were some limitations in our study. One of these limitations was the small sample size and absence of adequate follow-up to allow us to verify our findings. Also, PTX-3 wasn't evaluated in the SF, that may add appreciated data with regard to the pathogenic role of PTX-3 in RA.

Recommendations:

Additional researches on large number of cases with a wider age group, are needed to verify the current results. Additional researches are required

to evaluate PTX-3 level in the SF in RA patients, aiming to clarify its pathogenic role in RA. Additional researches with long-term follow-up are required to assess PTX-3 in different body tissues in RA patients.

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مستوى بنتراكسين ٣ المصلى ف مرضى التهاب المفاصل الروماتويدي وارتباطه بنشاط المرض

تمهيد : يتميز التهاب المفاصل الروماتويدي بالتهاب الغشاء المفصلي والتليف التدريجي للمفاصل والمضاعفات الجهازية وترتبط شدة هذا المرض بشدة الالتهاب وتلف المفاصل وقد أصبح تحديد نشاط المرض لدى مرضى التهاب المفاصل الروماتويدي جزءاً هاماً لعلاج الالتهاب البنتراكسين ٣ هو بروتين متعدد الوظائف له ادوار تنظيمية معقدة ف تنظيم الالتهاب واعادة تشكيل المثقوفة خارج الخلية ويعتقد أنه يعرض الحالة الالتهابية بدقة أكبر من بروتين سى التفاعلى.

هدف الدراسة : كان الهدف من البحث الحالى هو تقييم أهمية مستوى مصلى البنتراكسين ٣ ف التهاب المفاصل الروماتويدي وعلاقته بخصائص المرض سريريا وعن طريق الموجات الصوتية للجهاز العضلى والحركى.

طرق البحث : أجريت الدراسة الحالية على ٨٠ شخص ٤٠ مريضاً من مرضى التهاب المفاصل الروماتويدي المترددين على العيادات الخارجية والقسم الداخلى للروماتيزم والتأهيل مستشفى جامعة المنصورة و ٤٠ من الأصحاء الذين لهم تقريبا نفس العمر والجنس، تم إجراء الفحوصات المخبرية بما فى ذلك صورة دم كاملة المستوى المصلى لبروتين سى التفاعلى وسرعة ترسيب كريات الدم الحمراء وعامل الروماتويد ومضاد بيتيتيدات السيترولين الدورية ومصلى البنتراكسين ٣ وفقاً لتوصيات الشركة المصنعة كما تم عمل الموجات فوق الصوتية العضلية الهيكلية لليدين والقدمين وفقاً لمقياس جيرمان (German US7).

النتائج : مستوى بنتراكسين ٣ المصلى كانت أعلى بشكل ملحوظ ف مرضى التهاب المفاصل الروماتويدي مقارنة بالأصحاء، وهناك ارتباط مطرد نو دلالة إحصائية بين مستوى بنتراكسين ٣ المصلى لدى مرضى التهاب المفاصل الروماتويدي مع معدل نشاط المرض ٢٨ ومدة تيبس المفاصل الصباحية، مستوى بنتراكسين ٣ المصلى يتناسب طردياً مع نتائج التصوير بالموجات فوق الصوتية للجهاز العضلى والحركى التى ظهرت ف صورة التهاب الغشاء المفصلي والتهاب الاربطة والدوبلر المستخدم على هذه الأنسجة لكن لا يوجد ارتباط مع تآكل المفاصل لدى مرضى التهاب المفاصل الروماتويدي.

الاستنتاج : يوجد البنتراكسين ٣ بمستويات أعلى ف مرضى التهاب المفاصل الروماتويدي بالمقارنة بالمجموعة الضابطة مما يشير أنه قد يلعب دوراً مسبباً للمرض، يرتبط مستوى بنتراكسين ٣ المصلى بالنشاط السريرى ودلالات الالتهاب الخاصة بالموجات فوق الصوتية للجهاز العضلى والحركى ف مرضى التهاب المفاصل الروماتويدي وبالتالي فهو ذو قيمة ف تقييم نشاط المرض، مستوى بنتراكسين ٣ المصلى يتناسب طردياً مع بروتين سى التفاعلى ومعدل سرعة ترسيب كريات الدم الحمراء.