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TNF- α in the serum and synovial fluid of patients with rheumatoid arthritis: correlation with sonographic parameters: a cross-sectional study

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Abstract

Background Rheumatoid arthritis (RA) is a chronic, inflammatory joint condition characterized by overproduction of pro-inflammatory cytokines. We aimed to assess TNF- α levels in both serum and synovial fluid in effusive knees in RA patients and find out if synovial fluid levels correlate with ultrasound (US)-detected local knee inflammatory and/or destructive changes in these patients.

Results This study included 40 patients (20 with RA, 10 with systemic lupus erythematosus (SLE), and 10 with osteoarthritis (OA)) who had knee effusion (unilateral or bilateral) upon clinical examination. The mean age of RA patients was 48.4 years; most of them were females (80%), with a median (min–max) duration of knee effusion of 2 (1.5–3) months. Serum TNF- α was significantly higher in RA vs. non-RA and in OA cases ($p=0.052$, 0.022 , respectively), while in the synovial fluid, the difference was not statistically significant (3.73 ± 0.72 vs. 3.48 ± 0.58 U/ml, $p=0.252$). Serum TNF- α at a cut point of >3.24 U/ml can significantly discriminate RA from OA with 65% sensitivity and 90% specificity (AUC = 0.725, $P=0.018$). There was no statistically significant correlation between synovial TNF- α and US parameters of the knee, either in RA or non-RA patients.

Conclusions RA, OA, and SLE effusive joints share the presence of local articular joint inflammation, while systemic inflammation is more discriminative for RA patients regarding the level of TNF- α . The lack of correlation of TNF- α with ultrasonographic findings reflects the multifactorial complexity of these autoimmune diseases.

Keywords TNF- α , Rheumatoid arthritis, Musculoskeletal ultrasound, Knee effusion

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by a chronic inflammatory process that can affect both joints and extra-articular organs, such as the heart, kidney, lung, digestive system, eye, skin, and nervous system. The incidence of RA is greater in women than in men, and it increases with age [2]. It is still unknown what causes RA; nevertheless, researchers have come to the conclusion that a combination of genetic and environmental variables is likely to be involved [3]. RA is primarily characterized by autoantibodies against immunoglobulin G (also known as

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rheumatoid factor [RF]) and antibodies against anti-citrullinated protein (anti-CCP) [4].

RA is a chronic autoimmune disease affecting the joints and characterized by a progressive symmetric inflammation of affected joints, resulting in cartilage destruction, bone erosion, and disability [5]. It primarily affects small joints, such as the proximal interphalangeal and metacarpophalangeal joints, but it can also affect large joints, such as the ankle, knee, elbow, and shoulder [2]. RA is characterized by synovial hyperplasia, which is the primary factor in the development of an invasive pannus [6].

In the management of individuals who have RA, there is an urgent need for biomarkers that can reliably identify specific diseases, predict disease progression, evaluate response to treatment, and predict medication responsiveness in individual patients. It is possible that the biomarkers found in synovial fluid provide the answer to both the correct diagnosis and effective treatment of knee arthritis. Synovial cells are responsible for the production of synovial fluid, which reflects chondrocyte metabolism and matrix turnover. One of the most important regulators in the development of RA is tumor necrosis factor alpha (TNF- α). Its expression is enhanced in those who suffer from RA, and excessive expression of TNF is what leads to autoimmune arthritis in transgenic mice [7]. TNF- α signaling is involved in multiple ways in the pathogenesis of RA. It activates endothelial cells and recruits proinflammatory cells such as synovial fibroblasts and macrophages, which then secrete proinflammatory cytokines including IL-6, IL-1, and TNF- α [8].

Musculoskeletal ultrasound (MSUS) can detect RA manifestations such as early bone erosions, synovitis, the degree of vascularization (Doppler activity), tendinopathy, and tenosynovitis with high sensitivity [9]. Additionally, it can discriminate between RA and OA [10]. As a result, it is widely utilized in clinical practice as well as research settings for the purpose of RA patient diagnosis, monitoring, and prognosis [11].

Even though TNF- α has been shown to play a significant role in the pathogenesis of RA, a comparison of the local and systemic levels of TNF- α in RA, SLE, and OA knees, as well as their relationship with MSUS findings, has not been investigated yet.

Thus, the aim of this study was to assess the level of TNF- α in serum and synovial fluid of the knee in RA and non-RA patients with knee effusion and to evaluate its correlation with US parameters of the effused knee joint.

Patients and methods

Study design and settings

This cross-sectional study was carried out at our rheumatology and immunology unit (inpatient and outpatient), during the period from 2018 to April 2020. The

sample size was determined to be a convenient sample; all patients who met the inclusion criteria were offered the opportunity to participate in the study, unless they met any of the exclusion criteria or refused to participate.

Ethical consideration

The study was conducted according to the principles outlined in the Helsinki Declaration [8], and we used the STROBE cross-sectional checklist when writing our report [12]. The study was permitted to proceed after obtaining approval from the Institutional Research Board (MFM-IRB) (Approval No. MS.19.12.945). Participation in the study was entirely voluntary and kept confidential throughout. The purpose of the research was made crystal clear, and participants' written consent was obtained before the study was carried out. Participants in the study who lacked the capacity to read and write or, for any other reason, were unable to offer their informed consent had to have their parents or legal guardians give consent before they could take part in the study.

Patient population

The inclusion criteria were the following: (a) patients with a confirmed diagnosis of RA according to ACR/EULAR 2010 rheumatoid arthritis classification criteria [13]; (b) age > 18 years; and (c) unilateral or bilateral knee effusion for more than one month detected by clinical examination and confirmed by MSUS.

Twenty age- and sex-matched non-RA patients with knee effusion were also included: 10 patients with a confirmed diagnosis of systemic lupus erythematosus (SLE) according to SLICC classification criteria for SLE [14] and 10 patients with a confirmed diagnosis of knee osteoarthritis (OA). Patients with a history of knee joint fracture, infection, malignancy, intra-articular administration of steroids for at least 3 months prior to evaluation, or a history of other autoimmune or rheumatic diseases were excluded from the study at the outset. Patients displaying clinical symptoms, ultrasound findings, or elevated serum uric acid levels indicative of gout were also excluded from the study.

Sample size calculation

The sample size was calculated using Power Analysis and Sample Size (PASS) software (version 15, 2017; NCSS, LLC., Kaysville, UT, USA). Based on previous research by Inam Illahi et al. [15], in which a significant correlation of serum TNF- α with DAS28-ESR in RA patients was reported, we hypothesized a statistically significant correlation of serum TNF- α with different grades of sonographic findings of RA with a Spearman's correlation coefficient (rs) of moderate positive correlation (rs=0.6) [16]. A sample size of 20 RA patients achieves 85% power

to detect a Pearson correlation of 0.600 using a one-sided hypothesis test with a significance level of 0.050. These results are based on 5000 Monte-Carlo samples from the bivariate normal distribution under the alternative hypothesis.

Clinical assessment and laboratory testing

Sociodemographic data were collected from all patients, including gender, age, and occupation. For RA, a comprehensive medical and clinical examination was performed to assess the current status of the disease, which included counting the number of swollen and tender joints. The patient's overall health was evaluated using a patient global assessment (PGA) score of 100 mm, with 0 indicating the best possible health and 100 indicating the worst possible health. For each RA patient, the disease activity score 28 (DAS28-ESR) was used to assess current disease activity [17] and the health assessment questionnaire (HAQ) to assess functional capacity [18]. Therapeutic data, including NSAIDs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), were also collected.

We questioned the duration of the knee joint effusion. The visual analogue scale (VAS) was used to measure the intensity of the knee pain, with a score of 0 indicating no pain and a score of 10 indicating the most severe pain.

At the time of the clinical evaluation, a venous blood sample was collected from each RA patient, and relevant laboratory tests were evaluated with the assistance of an automated analyzer. The laboratory tests included rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Serum and synovial fluid sampling and testing for TNF- α

The first thing that we did was make sure that there had been no intraarticular injections administered to the knee joint in the past 3 months. Then, under sterile conditions, venipuncture was used to collect 5 ml of venous blood and 5 ml of knee synovial fluid from each participant. Knee synovial fluid was obtained with the guidance of MSUS. A serum separator tube was used for the collection of the samples. After the formation of a clot, the samples were centrifuged at 2000 g for 10 min in order to extract the serum, which was then frozen at -20°C pending further investigation. TNF- α was analyzed in serum and synovial fluid samples using Biolegend's ELISA MAX™ standard set, which is a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) [19].

Musculoskeletal ultrasound of the knee

The EDAN U2 ultrasound device (Shenzhen, China), equipped with a linear array transducer that ranged in frequency from 8 to 13.4 MHz, was used to conduct a

real-time MSUS scan of the knee joint. The sonographic parameters were adjusted, and the frequency was set at 13 MHz in order to obtain the best US images of the knee structures. All sonographic examinations were performed by a rheumatologist with a minimum of 8 years of experience in the field of MSUS. During the evaluation, the operator was blinded to the clinical status of the patients. Knee joint scanning was performed in accordance with a predetermined protocol of the technical guidelines of the European Society of Musculoskeletal Radiology [20].

The suprapatellar and parapatellar joint recesses were examined for effusion and synovial hypertrophy as part of the knee US protocol. With full knee flexion, the V-shaped trochlea of the femur and the overlying articular cartilage were inspected on the axial planes for any abnormalities. Additionally, the thickness of the medial and lateral femoral condylar cartilage was assessed. Measurements of the thickness of the femoral cartilage were taken, while the individuals were lying supine on the examination bed with their knees bent to their maximum flexion. Using the suprapatellar axial view, US imaging was performed, and measurements were acquired from the midpoints of the medial femoral cartilage and the lateral femoral cartilage [21].

Long- and short-axis planes were used to map the quadriceps and patellar tendons from their cranial origin to their distal insertion. MSUS assessment of both the patellar and quadriceps tendons was conducted on a supine patient with the knee slightly flexed at 20°. Tendinosis was identified by a hypoechoic appearance of the tendon and a disruption of its fibrillar pattern. The quadriceps and patellar entheses were also inspected for structural abnormalities, bursitis, bone erosions, or calcification indicating enthesopathy [22]. In order to determine whether or not a Baker's cyst was present, we checked the region located medially between the semimembranosus tendon and the medial head of the gastrocnemius.

The MSUS images of each patient were collected, and then, using proprietary software, they were reviewed later on. The US findings were analyzed and interpreted using the criteria established by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) US group [23]. Knee effusion, synovial hypertrophy, and power Doppler were scored on a semiquantitative scale (where 0=absence, 1=mild, 2=moderate, and 3=severe) [24].

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (IBM Corp., Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Qualitative data were expressed as absolute frequency (N) and relative frequency (% ,percentage). Quantitative data were initially tested for normality using Shapiro–Wilk’s test, with data being normally distributed if $p > 0.050$. Quantitative data were expressed as mean \pm standard deviation (SD) if normally distributed without significant outliers, or median (25th–75th percentiles) if not normally distributed and/or with significant outliers. Chi-square test was used to test the association between two nominal variables when the expected count in all cells was ≥ 5 . Otherwise, Fisher’s exact test was used. One-way ANOVA (with Tukey’s post-hoc tests for statistically significant results) was used if homogeneity of variances was met with. Welsh ANOVA (with Games-Howell post-hoc tests for statistically significant results) was used if homogeneity of variances was violated. Pearson’s correlation, or Spearman’s correlation, was used as appropriate to assess the strength and direction of the association/relationship between variables. Results were considered statistically significant if the p value was ≤ 0.050 . Receiver operating characteristic (ROC) curve analysis was performed for the serum TNF- α to determine the cutoff point above which RA is likely.

Results

Twenty RA patients (16 females and 4 males), and 20 sex- and age-matched non-RA patients (10 SLE and 10 OA) were successfully recruited to participate in the study. The non-RA group included 5 males and 15 females. The flowchart of the study is illustrated in Figure 1. The mean age of the studied RA patients was 48.4 ± 14.1 years, with a median disease duration of 3 years. The administered DMARDs included

methotrexate (80%), leflunomide (80%), and hydroxy-chloroquine (95%). The median (min–max) duration of knee effusion was 2 (1.5–3) months. The mean of synovial fluid TNF- α was 3.73 ± 0.72 U/ml while in serum was 3.66 ± 0.76 U/ml. Other clinical and laboratory data are illustrated in Table 1.

As shown in Fig. 2, serum TNF- α was statistically significantly different between RA, SLE, and OA patients. Games-Howell post-hoc test revealed a statistically significantly higher serum TNF- α in RA vs. OA ($p = 0.022$) but not in SLE.

On the other hand, there was no statistically significant difference between RA patients, SLE patients, and OA patients in the level of TNF- α in their synovial fluid, as seen in Fig. 3.

Figure 4 demonstrates that a serum TNF- α level of > 3.24 U/ml could significantly differentiate between RA and OA with a sensitivity of 65% and a specificity of 90% (AUC = 0.725, $p = 0.018$).

MSUS findings of the knee in the RA and non-RA groups are summarized in Table 2. In RA patients, knee effusion was moderate in 7 (35%) patients and severe in 13 (65%) patients, while synovial hypertrophy was moderate in 8 (40%) patients and severe in 7 (35%) patients. There was no statistically significant difference between RA and non-RA patients regarding the examined MSUS parameters except for synovial hypertrophy. Severe synovial hypertrophy was significantly higher in RA patients in comparison to non-RA patients (7 (35%) versus 1 (5%), respectively, $p = 0.028$).

As shown in Table 3, there was no statistically significant correlation between TNF- α levels in both serum and synovial fluid and US parameters of the knee joint in RA

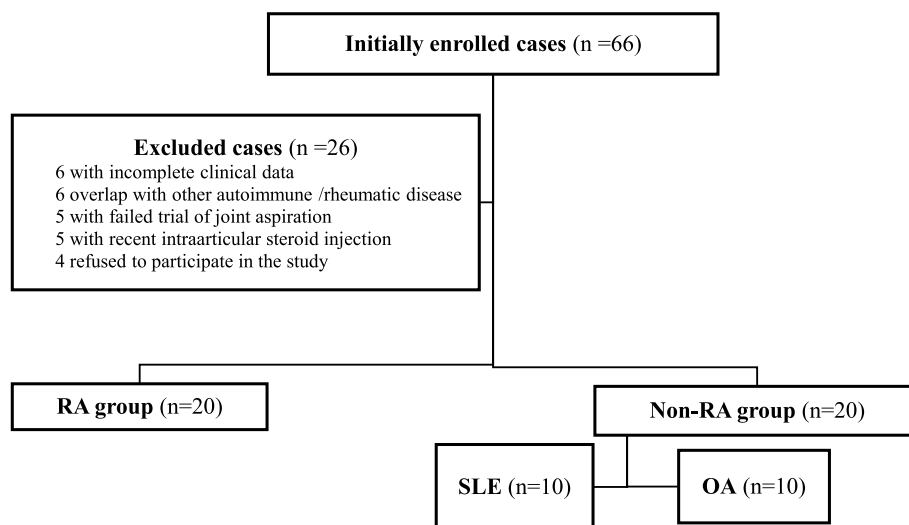


Fig. 1 The study flowchart

Table 1 Sociodemographic characteristics, clinical and therapeutic data of the study RA patients ($n = 20$)

Variable ^a	RA group ($n = 20$)
Gender	
Male	4 (20)
Female	16 (80)
Age, years	48.4 ± 14.1
Occupation	
Unemployed	11 (55)
Employed	
Non-manual	3 (15)
Manual	6 (30)
BMI, kg/m ²	27.7 ± 4
Rheumatoid arthritis clinical data	
Disease duration, years	3 (2–10)
Extra-articular manifestations	10 (50)
Morning stiffness, minutes	15 (10–30)
Swollen joint count (SJC)	8 ± 4
Tender joint count (TJC)	10 ± 5
Patient global assessment (0–100)	73 ± 13.4
Disease activity score 28	6.16 ± 1.9
HAQ score	1.82 ± 0.27
Therapeutic data	
NSAIDs	15 (75)
Systemic corticosteroids	5 (25)
Methotrexate	16 (80)
Leflunomide	16 (80)
Hydroxychloroquine	19 (95)
Knee joint effusion	
Duration, months	2 (1.5–3)
Visual analogue scale, median (min–max)	6.5 (4–9)
Laboratory data	
Rheumatoid factor, IU/ml	30 (20–55)
C-reactive protein, mg/dL	16 (12–24)
Erythrocyte sedimentation rate, mm/hr	52.35 ± 22.1

^a Data are described as n (%), mean ± SD, median (25th–75th percentiles)

BMI Body mass index, HAQ health assessment questionnaire, NSAIDs non-steroidal anti-inflammatory drugs, RA rheumatoid arthritis, TNF- α tumor necrosis factor alpha

patients. Demonstrative MSUS findings of the effused knee joints in RA patients are illustrated in Fig. 5.

Discussion

In this cross-sectional study, we tried to assess the levels of TNF- α in the synovial fluid and serum of RA and non-RA patients who had knee effusion and to determine the extent to which these levels correlated with MSUS findings of the effused knee joint. Even though the serum level of TNF- α in patients with RA was higher than in individuals without RA, the level of TNF- α in synovial

fluid did not differ between the two groups. There was no correlation found between the levels of TNF- α in both serum and synovial fluid and the MSUS parameters of the knee joint. To the best of our knowledge, this is the first study to assess TNF- α in RA synovial fluid and connect it with MSUS characteristics.

In fact, TNF- α is an essential component of a normal immune response. Nevertheless, excessive or improper TNF- α production can be damaging and lead to a disease. It is considered a crucial factor in the pathological development of RA [25]. Patients with RA have abundant TNF- α , which is a key and important cytokine that upsets the normal balance between pro-inflammatory and anti-inflammatory cytokines [26]. TNF- α is known to effectively stimulate the production of other proinflammatory mediators such as IL-1b, chemokines, and proteases [27].

As a result of this, we found that it would be beneficial to investigate this cytokine in patients who have RA and compare their results to those of patients who do not have RA. Considering SLE, which is an inflammatory form of arthritis, and OA, which is a non-inflammatory form of arthritis, it seems like they may be a reasonable candidate for making this comparison.

In this study, we demonstrated that serum TNF- α levels were statistically significantly higher in RA patients versus non-RA patients, and a post-hoc test revealed a statistically significantly higher serum TNF- α level in RA vs. OA but not SLE. This can be explained by the high level of circulating TNF- α in SLE and its association with lupus disease activity [28–30]. However, in OA, TNF- α levels in plasma in RA patients are 10–20 times higher than in OA patients and normal people [31]. TNF- α has shown conflicting outcomes when used as a disease burden marker [32, 33]. TNF- α has demonstrated qualities as an indicator of treatment efficacy in OA patients [34, 35]. Additional research is required to understand its role and determine whether it is effective as a biochemical marker of OA.

Synovial fluid functions primarily as a biological lubricant of the joint, minimizing friction between synovial joint articular cartilage surfaces, but also as a nutrient pool for surrounding tissues and a conduit for cytokine movement [36, 37]. In the current study, there was no statistically significant difference between RA patients, SLE patients, and OA patients when it came to the level of TNF- α in their synovial fluid. In a study conducted by Alaaeddine et al., increased TNF- α receptors were discovered in chondrocytes and synoviocytes produced from OA joints when compared to nonarthritic tissues. When OA chondrocytes were cultured with normal human chondrocytes, TNF- α receptors increased [38, 39]. TNF- α receptors were bound by a 100 μ g (99 m) Tc human anti-TNF- α antibody, and higher levels of

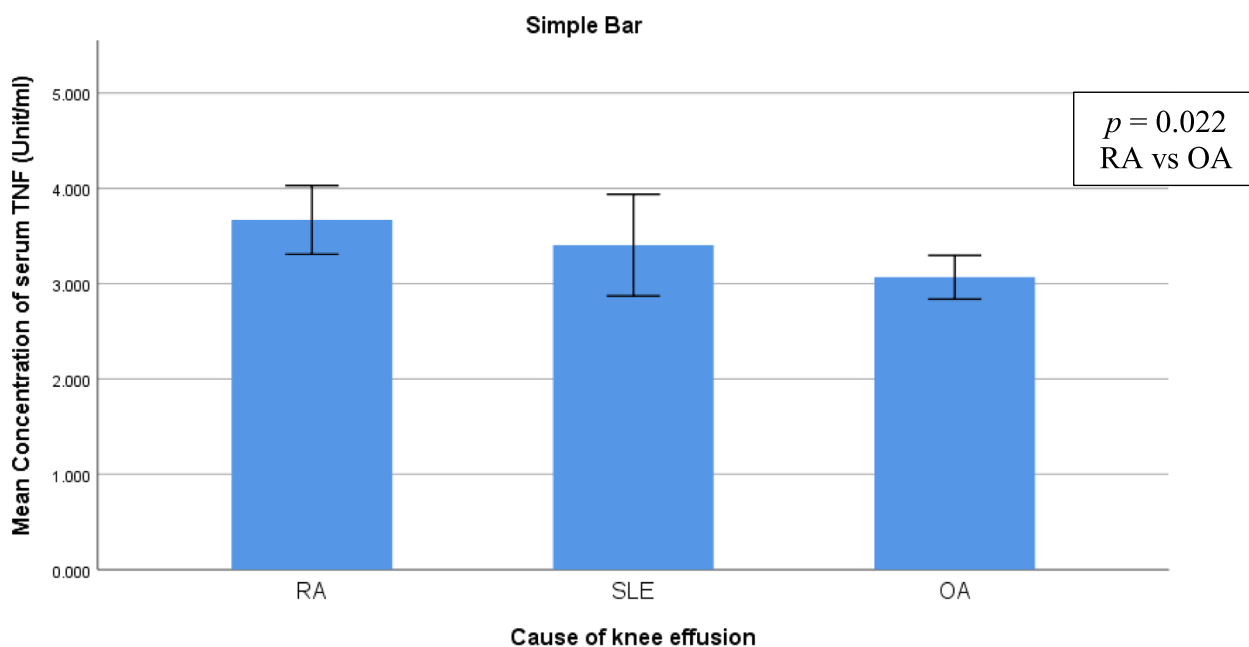


Fig. 2 Serum level of TNF- α in RA patients ($n=20$) and SLE ($n=10$) and osteoarthritis patients ($n=10$)

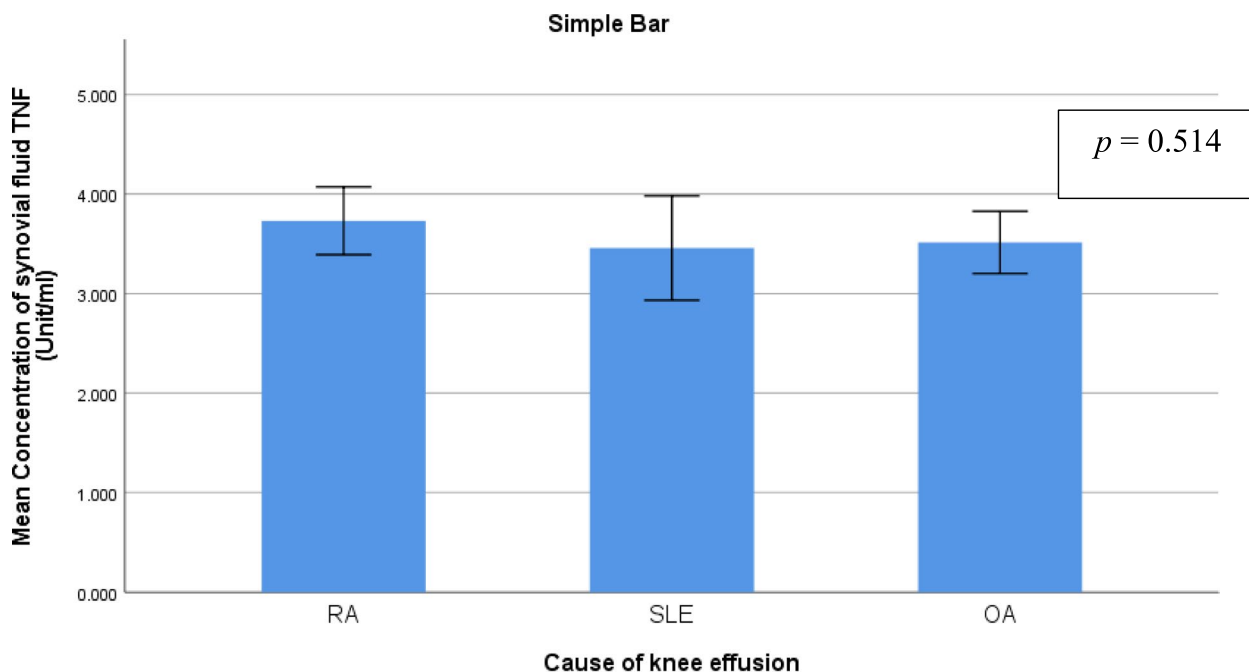


Fig. 3 Synovial fluid level of TNF- α in RA patients ($n=20$) and SLE ($n=10$) and OA patients ($n=10$)

TNF- α were observed in arthritic joints utilizing scintigraphy in OA and RA patients. Tc-infliximab scintigraphy shows a correlation with acute phase reactants, clinical

indicators, and imaging signs of synovitis, suggesting that this approach has the potential to evaluate TNF- α -associated synovitis [40]. Synovial cells cultured from

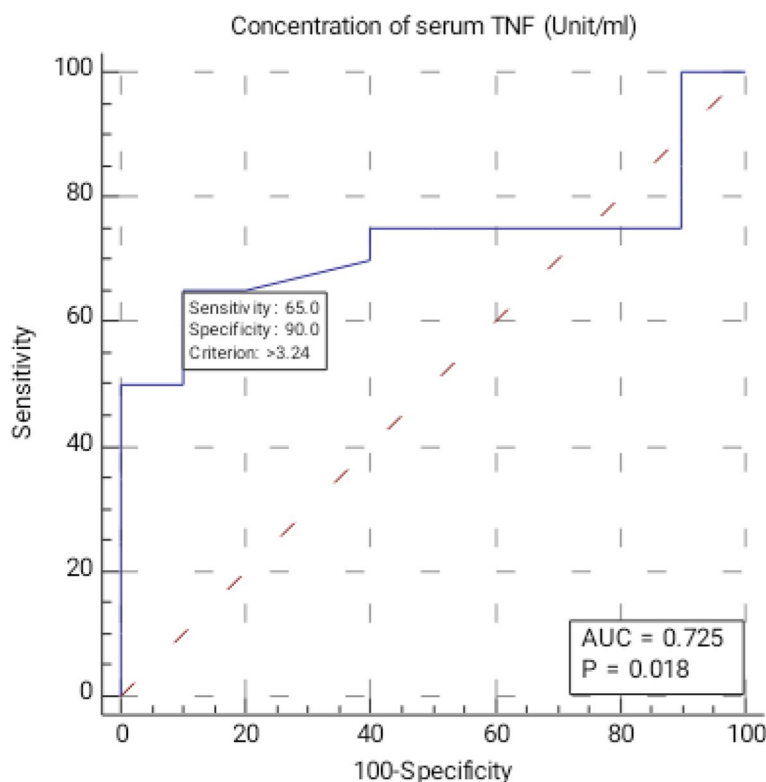


Fig. 4 ROC curve for serum TNF- α as a discriminator of RA ($n=20$) from OA ($n=10$) group

human OA synovium showed that the inflammatory and damaging responses are cytokine-driven by TNF- α [41]. In our study, TNF- α has been identified in the synovial fluid in OA patients and may be linked to the pathophysiological processes involved in OA. It could also help determine the severity of the disease.

The TNF- α concentration in the synovial fluid of RA patients is approximately twice that of OA patients. When immunohistochemistry performed on RA synovium, it revealed that TNF- α was present in the synovial lining cell layer, particularly at the pannus and cartilage junction [42]. In the current study, we found that a serum TNF- α level of > 3.24 U/ml could significantly differentiate between RA and OA with a sensitivity of 65% and a specificity of 90%. Knee involvement is one of the major consequences of RA, which is one of the primary contributors to persistent pain and disabilities [43]. So, serum TNF- α levels may be more useful in patients with knee effusion who do not meet a specific diagnostic criterion, particularly those with serum anti-CCP and/or RF test results. Since early and intensive treatment of undifferentiated arthritis significantly reduces the frequency of progressions to RA and provides an effective strategy for slowing radiologic progression [44], it has been shown that it is possible to delay radiologic progression. As a

result, identifying high-risk patients and initiating therapy sooner would be highly desirable.

In our RA cohort, there was no statistically significant correlation between TNF- α levels in both serum and synovial fluid and US parameters of the knee joint in RA patients. In this regard, power Doppler vascularity was positively linked with the presence of inflammatory cytokines and growth factors in synovial fluid, with larger coefficient values in both untreated and treated individuals with RA. There is also a significant relationship between the findings of the US synovial examination and the levels of serum vascular endothelial growth factor (VEGF) [45], YKL-40 [46], and calprotectin [47] in RA patients.

Regarding the lack of statistical difference in the synovial fluid of effusive joints in OA compared to RA and SLE patients could indicate that the local inflammation in OA knees could be as inflammatory as the RA/SLE joints; however, the systemic inflammation is much more evident by the lower values of OA serum levels compared with the RA patients, which could be discriminative of RA compared with OA.

A possible limitation of this study is that no healthy control group was involved, as it is difficult to attain healthy subjects with knee effusion. In addition, the

Table 2 Musculoskeletal ultrasound findings of the examined knee joints

Variable n (%), median (25th–75th percentiles)	RA group (n = 20)	Non-RA group (n = 20)	p Value
Effusion			0.185
Mild	-	2 (10)	
Moderate	7 (35)	10 (50)	
Severe	13 (65)	8 (40)	
Synovial hypertrophy			0.028*
No	1 (5)	-	
Mild	4 (20)	9 (45)	
Moderate	8 (40)	10 (50)	
Severe	7 (35)	1 (5)	
Doppler US			0.215
0	4 (20)	3 (15)	
1	7 (35)	13 (65)	
2	7 (35)	2 (20)	
3	2 (10)	-	
Abnormal cartilage morphology	9 (45)	12 (60)	0.342
Medial femoral condylar cartilage thickness, mm ^a	1.35 (1.20–1.88)	1.55 (1.20–2.05)	0.565
lateral femoral condylar cartilage thickness, mm ^a	1.40 (1.30–1.70)	1.45 (1.23–1.80)	0.968
Abnormal quadriceps tendon	5 (25)	5 (25)	1.000
Abnormal patellar tendon	5 (25)	5 (25)	1.000
Baker’s cyst	4 (20)	8 (40)	0.168

The numbers between brackets represent the % of patients affected, while it represents the 25th–75th percentiles for the medial/lateral femoral condylar cartilage thickness. Test of significance is Chi-Square test or Fisher’s exact test (FET) for categorical data or

^a Mann–Whitney U-test for quantitative data

* $p \leq 0.05$

RA Rheumatoid arthritis, US ultrasound

Table 3 Correlation between serum and synovial fluid level of TNF-α and disease activity score 28 and ultrasonographic findings in RA patients (n = 20)

Variable ^a	Serum TNF-α		Synovial fluid TNF-α	
	rs Coefficient	p	rs Coefficient	p
Disease activity score 28	-0.377	0.101	-0.193	0.415
Grade of effusion	-0.082	0.731	-0.109	0.647
Synovial thickening	-0.306	0.189	-0.051	0.831
Abnormal cartilage morphology	-0.304	0.192	-0.077	0.748
Medial femoral condylar cartilage thickness, mm	0.250	0.287	-0.001	0.996
lateral femoral condylar cartilage thickness, mm	0.141	0.554	0.140	0.557
Abnormal quadriceps tendon	-0.065	0.787	0.108	0.649
Abnormal patellar tendon	0.038	0.875	0.048	0.841
Baker’s cyst	0.047	0.843	-0.200	0.398

^a Test of significance is Spearman’s correlation test

RA Rheumatoid arthritis, TNF-α Tumor necrosis factor alpha

number of patients is relatively small because of the high expense of testing for TNF-α, which is not carried out on a routine basis. It would be better to exclude patients on steroids, as it might affect the results of TNF-α. Finally, comparing cartilage thickness between

RA patients and both SLE and OA patients would be more appropriate, as it is expected to be lower in OA patients compared with SLE. To our knowledge, there are no reports that correlate TNF-α in both serum and synovial fluid to MSUS parameters in RA patients. The

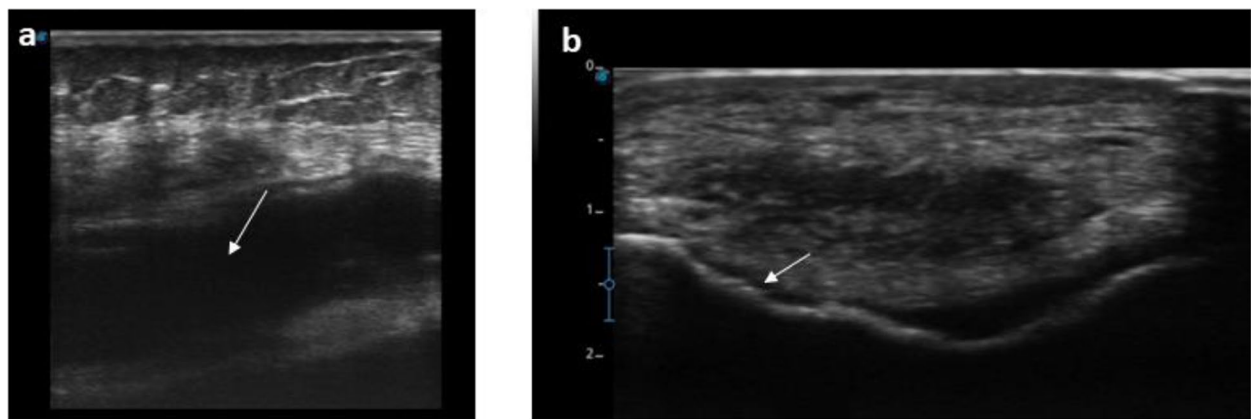


Fig. 5 Musculoskeletal ultrasound findings of the knee joint in RA group. **a** Sagittal scan of the suprapatellar recess shows a well-defined anechoic collection with no internal color flow Doppler signal suggestive of severe knee effusion in a 45-year-old female patient with RA (synovial fluid TNF- α = 3.52 U/ml, serum TNF- α = 3.32). **b** Transverse scan at the end of the femur shows decreased thickness of the cartilage at the medial condyle in a 40-year-old female patient with RA (synovial fluid TNF- α = 2.53, serum TNF- α = 2.65)

expression of serum TNF- α may play a role in the intensification of inflammatory activity in RA, screening for this cytokine in RA patients in order to monitor the disease activity could prove to be beneficial for patients who are undergoing anti-TNF therapy. Furthermore, its high value in knee effusion may be indicative of a better response to intraarticular administration of anti-TNF agents. Further prospective studies are required to ascertain the diagnostic and prognostic value of serum and synovial fluid TNF- α in RA.

RA, OA, and SLE effusive joints share the presence of local articular joint inflammation, while systemic inflammation is more discriminative for RA patients regarding the level of TNF- α . The lack of correlation of TNF- α with ultrasonographic findings reflects the multifactorial complexity of these autoimmune diseases.

Abbreviations

Anti-CCP	Anti-citrullinated protein
CRP	C-reactive protein
DAS28	Disease activity score 28
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
HAQ	Health assessment questionnaire
MSUS	Musculoskeletal ultrasound
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PGA	Patient global assessment
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SLE	Systemic lupus erythematosus
TNF- α	Tumor necrosis factor- α
US	Ultrasound
VAS	Visual analogue scale

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Authors' contributions

Conceptualization: AE, ST. Investigation: all authors. Data curation, formal analysis: MM, AE. Writing—original draft: ST. Writing—review and editing: all authors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the principles outlined in the Helsinki Declaration. The study was permitted to proceed after obtaining approval from the Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB) (Approval No. MS.19.12.945.).

Consent for publication

Not applicable.

Competing interests

All authors have no conflicts of interest to declare.

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