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HIGH RESOLUTION ULTRASONOGRAPHY AND POWER DOPPLER IN EVALUATION OF DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION OR LOW DISEASE ACTIVITY

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ABSTRAct
Background: Chronic Achieving remission or at least low disease activity is the ultimate goal of rheumatoid arthritis patients' treatment nowadays. Defining remission using indices based on clinical and laboratory biomarkers was proved to be lacking sensitivity to detect low levels of inflammation. Musculoskeletal ultrasound (MSUS) has been able to detect and quantify subclinical synovitis, with more specificity and reliability.
Aim: To detect the persistence of GS and PD signals in RA patients in clinical remission or LDA as assessed by DAS28-ESR.
Patients and methods:: Fifty consecutive RA patients in clinical remission or LDA were included. Patients were subjected to routine laboratory work up, RF and Anti-CCP measurement. Disease activity was determined by DAS28-ESR. US7 score was used to assess synovitis and vascularization with GSUS and PDUS respectively.
Results: All patients in LDA showed activity by GSUS or PDSUS. 13 (38.2%) patients of those in clinical remission showed subclinical GSUS or PDUS activity, while 21 (61.2%) were in clinical and US remission. Female patients showed more tenosynovitis PDUS signals than males (*P*=0.039). There was no statistically significant difference between patients on cDMARDs and bDMARDs regarding the US7 score. Anti-CCP showed statistically significant difference between patients in true remission and patients with subclinical US activity (*P*=0.006). A strong correlation was found between Anti-CCP and S-PDUS in patients with subclinical US activity (*P*=0.001), and T-GSUS in same group of patients (*P*=0.023).
Conclusion: Subclinical synovitis is a frequent finding in the joints of RA patients in clinical remission or LDA and occurs independently from the treatment. This may reclassify patients with either LDA or clinical remission. Female patients show more frequent subclinical PDUS activity. Anti-CCP levels of RA patients in clinical remission with subclinical synovitis correlated with PD signals and tenosynovitis GS.

Keywords: *Rheumatoid arthritis, remission, low disease activity, musculoskeletal ultrasound.*

INTRODUCTION

Considered as the most common inflammatory arthritis, rheumatoid arthritis (RA) has a prevalence of 0.5 to 1 % in western countries, and 0.3 to 0.5 % in countries of low or middle income [(1)]. Egyptian patients tend to have higher severity index scores and a liability to suffer from comorbidities [(2)]. The hallmark of RA is the inflammatory synovial proliferation and autoantibodies production that invariably end in cartilage and bone destruction. [(3)]

After the approval of biologic disease modifying antirheumatic drugs (bDMARDs), the Treat-to-Target recommendations have been set aiming at remission or at least low disease activity as the ultimate goal of therapy. Using the composite disease activity measures that include joint counts, regular therapy modifications can be made in order to reach treatment targets within a designated period of time. [(4,5)] The currently used indices in clinical practice include disease activity score (DAS28), with either erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) as acute phase reactants, the simplified disease activity index (SDAI) and clinical disease activity index (CDAI) [(6)]. However, defining remission using indices based on clinical and laboratory biomarkers was proved to be lacking sensitivity to detect low levels of inflammation in many studies. [(7-9)]

Recently, musculoskeletal ultrasound (MSUS) has been able to detect and quantify subclinical synovitis, with more specificity and reliability, in patients classified as being in

remission according to many clinical indices. In addition, power doppler (PD) signals detected in the synovium of patients in remission predict further relapses, joint destruction and deterioration of functional status. [10-13].

The aim of our study was to detect and score the subclinical synovitis using gray scale (GS) and PD in RA joints classified as "in remission or low disease activity" by the DAS28-ESR, and to compare the scored results among the studied groups.

PATIENTS AND METHODS

This study included 50 patients [37 (74%) females and 13 (26%) males) with RA, diagnosed according the ACR/EULAR 2010 criteria for diagnosis of RA [14], and fulfilled the cut-off values of clinical remission or low disease activity (LDA) according to DAS28-ESR score [15,6]. The patients were recruited from those attending the Outpatient Clinic of Physical Medicine, Rheumatology and Rehabilitation Department and the Rheumatology and Immunology unit, Internal Medicine department, Faculty of Medicine, Alexandria University, Patients with osteoarthritis, any systemic disease with inflammatory arthropathies and HCV arthritis were excluded. An informed consent was given by each patient and the study was approved by the ethics committee of the Faculty of

MEDICINE.

Clinical assessment
All patients were subjected to full history taking, including: disease duration, duration of clinical remission or low disease activity and full drug history. The patient's general health was evaluated using a Visual Analog Scale (VAS) of 100 mm, in addition to complete physical examination including 28- tender joint count (28-TJC) and 28 swollen joint count (28-SJC). Disease activity was then assessed using DAS28-ESR score [15,16].

Clinical remission was defined as a DAS28-ESR score of <2.6, while LDA as a DAS28-ESR score of ≥2.6 and ≤3.2[16]. Patients were classified into two groups: those with LDA and those in clinical remission.

Laboratory investigations
All patients underwent routine laboratory workup; ESR, C-reactive protein (CRP) measurement, Rheumatoid Factor (RF) titre in IU/ml by nephelometry [17], Anti-cyclic citrullinated peptide (Anti-CCP) titre in U/ml measured by automated ELISA technique [18].

Musculoskeletal ultrasonographic examination
The Gray Scale (GS) and Power Doppler (PD) ultrasonography (US) examination was performed using high frequency broadband linear array transducer at 10-18 MHz. PD settings were optimized to enhance the sensitivity for detecting synovial vessels without or with minimal artifact [19].

The US examination was performed in two perpendicular planes, according to EULAR guidelines [20]. We followed the OMERACT standardized definitions of US pathological findings [21].

The following joints were examined: the wrist, the 2nd and 3rd MCP, the 2nd and 3rd proximal interphalyngeal joints (PIP), the 2nd and 5thmetatarsophalyngeal joint (MTP), all of the side with no -or least-signs and symptoms.

The examined joints were scored according to US7 score[22], including the sum of synovitis scores in the gray scale ultrasound (GSUS) (0–27) and power Doppler ultrasound (PDUS) (0–39) modes, tenosynovitis/ paratenonitis in the GSUS (0–7) and PDUS (0–21) modes, and erosions (0–14) in the GSUS mode. The US remission was defined as on a GS ≤ 1 and PD = 0 [23,24]. While those patients with GSUS >1 and/or PDUS ≥1 were considered to have ultrasonography activity.

STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp**)** [25] Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were: The Kolmogorov-Smirnov test (KS); was used to verify the normality of distribution of quantitative data, Chi-square test (χ^2); for categorical variables, to compare between different groups, Student t-test (t); for normally distributed quantitative variables, to compare between two studied groups, Pearson coefficient (□); to correlate between two normally distributed quantitative variables, Mann Whitney test (U); for abnormally distributed quantitative variables, to compare between two studied groups. Spearman coefficient (r_s); to correlate between two abnormally distributed quantitative variables.

RESULTS

Patients characteristics

As shown in table 1, our cohort included 50 RA patients of whom 34 (68%) were in clinical remission and 16 (32%) were in low disease activity according to cutoff values of DAS28-ESR score, the score ranged from 1.70 – 3.17, with a mean of 2.52± 0.39. There were 7 RF negative patients (14%) and 43 RF positive patients (86%). RF value ranged from 10.6 – 678 IU/ml, with a median of 45.95 IU/ml. The Anti-CCP of the studied patients ranged from 2.8 – 2940 U/ml, with a median of 36.5 U/ml. There were 21 (42%) Anti-CCP negative patients, and 29 (58%)Anti-CCP positive patients. Patients on biological disease modifying drugs (bDMARDs) were 17 (34%) and 33 patients were on conventional synthetic disease modifying drugs (cDMARDs) (66%). Twenty-three patients (46%) used glucocorticoids with a low dose (≤5mg/ day) as a part of

tapering regimen or during bridging to bDMARDS. Twenty-seven patients (54%) did not use any glucocorticoids

The descriptive analysis of the studied patients according to the US7 score is shown in table 2. The number of patients in ultrasonographic remission according to US7 score was 21 (42%), while 29 patients (58 %) were found to have subclinical ultrasonographic activity. All patients in LDA showed subclinical US activity, while 61.8% (21) of patients in clinical remission were in ultrasonographic remission (true remission), and 38.2% (13) of patients in clinical remission had a degree of subclinical ultrasonographic activity (figure1,2).

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Table (1): Demographic, clinical and laboratory characteristics of patients with rheumatoid arthritis:
TJC; TJC; TJC;tender joint count, SJC; swollen joint count, DAS; disease activity score, LDA; low disease activity, ESR; erythrocyte sedimentation rate, CRP; C reactive protein, RF; rheumatoid factor, Anti-CCP; anti-cyclic citrullinated peptide, bDMARD; biologic disease-modifying antirheumatic drugs, cDMARDS; conventional disease-modifying antirheumatic drugs.

	Patients (n=50)
Age(years)	
Range	27 – 65
Mean±SD	49.58 ± 9.14
Gender	
Male [n (%)]	13 (26)
Female [n (%)]	37 (74)
Disease duration (years)	
Range	1.5 – 17
Mean±SD	6.75 ±3.82
TJC	
Range	0 – 3
Mean±SD	1.26 ±0.83
SJC	
Range	0– 2
Mean±SD	0.14 ±0.4
DAS28-ESR	
Range	1.7 – 3.17
Mean±SD	2.52 ± 0.39
Patients in clinical remission [n (%)]	34 (68)
Patients in LDA [n (%)]	16 (32)
ESR (mm/hour)	
Range	5 – 26
Mean ± SD	12.48 ± 4.15
CRP (mg/dl)	
Range	0.7 – 7.3
Mean ± SD	2.65 ± 1.46
RF (IU/ml)	
Range	10.6 – 678
Median	45.95
Negative (≤15.9) [n (%)]	7 (14)
Positive (>15.9) [n (%)]	43 (86)
Anti-CCP (U/ml)	
Range	2.8 – 2940
Median	36.5
Negative (<20) [n (%)]	21 (42)
Positive (≥20) [n (%)]	29 (58)
bDMARDs [n (%)]	17 (34)
cDMARDs [n (%)]	33 (66)
Glucocorticoids [n (%)]	23 (46)

MSUS assessment with US7 score

Table (2): Values of the US7 score among studied patients (n=50):

	Min-Max	Mean ± SD.
Synovitis score by GSUS (max 27)	0-5	1.98 ± 1.29
Synovitis score by PDUS (max 39)	0-3	0.66 ± 0.82
Tenosynovitis/paratenonitis score by GSUS (max 7)	0-3	0.9 ± 0.84
Tenosynovitis/paratenonitis score by PDUS (max 21)	0-2	0.3 ± 0.65
Erosions score (max 14)	0-3	0.42 ± 0.73

US7: ultrasound 7 score; GSUS: gray-scale US; PDUS: power Doppler US

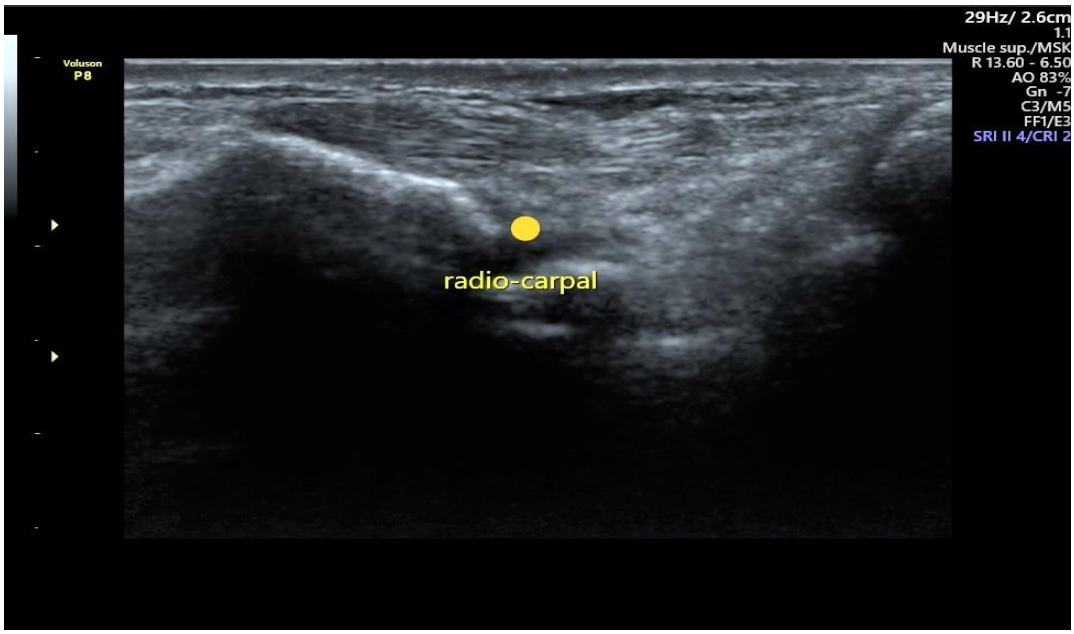

Figure (1): GDUS dorsal longitudinal scan of radiocarpal joint of a patient in clinical remission on bDMARD showing grade 1 synovitis (yellow dot).

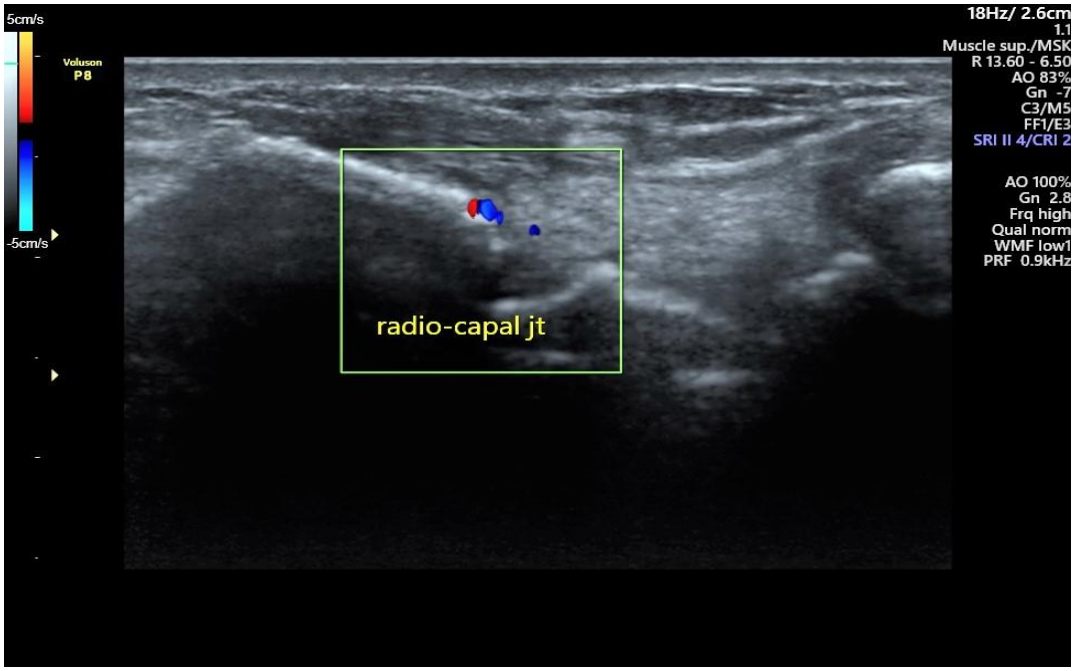

Figure (2): PDUS dorsal scan of radiocarpal joint of the same patient showing grade 1 signal .

There was a significant difference between patients in clinical remission and those with low disease activity regarding ultrasonographic remission (Mann Whitney test; p<0.001). Detailed comparison between the two groups revealed a significant difference regarding synovitis GSUS(p<0.001), synovitis PD (p<0.001), tenosynovitis PD (p<0.006), and erosions score (p<0.001), yet there was no significant difference between the compared groups regarding tenosynovitis GSUS score (p=0.083) (table 3).

There was a significant correlation between disease duration and synovitis score by GSUS (Spearman coefficient; r_s=0.331, P=0.019), while there was no significant correlation between disease duration and other components of US7 score (table 4)

Table (3): Comparison between patients in clinical remission and those with low disease activity according to components of US7 score (n=50)

	DAS28 score		Test of Sig.	p
	Remission (<2.6) (n = 34)	LDA (≥2.6≤3.2) (n = 16)		
S-GSUS				
Min. – Max.	0 – 4	1.0 – 5	U=94.5*	<0.001*
Mean ± SD.	1.5 ±0.9	3 ±1.41		
S-PDUS				
Min. – Max.	0 – 2	0 – 2	U=79.50*	<0.001*
Mean ± SD.	±0.59	1.38 ±0.81		
T-GSUS				
Min. – Max.	0 – 3	0– 3	U=194	0.083
Mean ± SD.	0.76 ±0.82	1.19 ±0.83		
T-PDUS				
Min. – Max. Mean ± SD.	0 – 2	0 – 2	U= 179.50*	0.006*
	0.15 ±0.50	0.63 ±0.81		
Erosions				
Min. – Max.	0 – 2	0 – 3	U=136.50*	<0.001*
Mean ± SD.	0.18 ±0.46	0.94 ±0.93		

S-GSUS; synovitis-gray scale ultrasound, S-PDUS; synovitis-power doppler ultrasound,
T-GSUS; tenosynovitis-gray scale ultrasound, T-PDUS; tenosynovitis-power doppler ultrasound
,U: Mann Whitney test, p: p value for comparing between the two categories.
*: Statistically significant at $p \leq 0.05$

Table (4): Correlation between disease duration and US7score components (n = 50)

	Disease duration (years)	
	r_s	P
Synovitis score by GSUS (max 27)	0.331*	0.019*
Synovitis score by PDUS (max 39)	0.076	0.598
Tenosynovitis/paratenonitis score by GSUS (max 7)	0.208	0.147
Tenosynovitis/paratenonitis score by PDUS (max 21)	0.110	0.447
Erosions score (max 14)	0.152	0.292

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$

Female patients seemed to have higher tenosynovitis PD score than males (Mann Wintey test; p=0.039). Other components of US7 score did not show significant difference between genders (table 5).

There was a significant difference between the number of patients in clinical remission and those with low disease activity regarding the type of treatment used-whether bDMARDs or cDMARDs (Chi square test; p=0.028), the difference was in favor of the group of patients on clinical remission on cDMARDS. There was no significant difference between the number of patients in clinical remission and those with low disease activity regarding glucocorticoids intake (p=0.318) (table 6).

Table (5): Comparison between males and females regarding US7 score (n=50)

US7 score	Gender		U	p
	Male (n=13)	Female (n=37)		
Synovitis score by GSUS (max 27)				
Min. – Max.	1 – 3	0 – 5		
Mean ± SD.	1.77 ± 0.83	2.05 ± 1.41	232.5	0.851
Median	2	2		
Synovitis score by PDUS (max 39)				
Min. – Max.	0– 2	0 – 3		
Mean ± SD.	0.77 ± 0.73	0.62 ± 0.86	202.5	0.353
Median	1	0		
Tenosynovitis/paratenonitis score by GSUS (max 7)				
Min. – Max.	0 – 2	0 – 3		
Mean ± SD.	0.85 ± 0.69	0.92 ± 0.89	238	0.953
Median	1	1		
Tenosynovitis/paratenonitis score by PDUS (max 21)				
Min. – Max.	0	0 – 2.		
Mean ± SD.	0	0.41 ± 0.72	175.50*	0.039*
Median	0	0		
Erosions score (max 14)				
Min. – Max.	0 – 1	0 – 3		
Mean ± SD.	0.31 ± 0.48	0.46 ± 0.8	233	0.837
Median	0	0		

U: Mann Whitney test
p: p value for comparing between the two categories
*: Statistically significant at $p \leq 0.05$

Table (6): Comparison between patients in clinical remission and those with low disease activity according to type of DMARD therapy and glucocorticoids intake

	DAS28 score				χ^2	p
	Remission (<2.6) (n = 34)		LDA (≥2.6≤3.2) (n = 16)			
	No.	%	No.	%		
Type of treatment						
bDMARDS	15	44.1	2	12.5	4.847	0.028*
cDMARDS	19	55.9	14	87.5		
Glucocorticoids use						
No	20	58.8	7	43.8	0.995	0.318
Yes	14	41.2	9	56.3		

χ^2: Chi square test
p: p value for comparing between the two categories *: Statistically significant at $p \leq 0.05$

On the other hand, there was no difference between patients in ultrasonographic remission and those with subclinical activity regarding the type of treatment. Similarly, no significant difference was found between the number of patients in ultrasonographic remission and those with subclinical activity regarding the glucocorticoids use (table 7).

Patients with subclinical synovitis had significantly higher levels of Anti-CCP (Mann Whitney test; p=0.006) than those in combined ultrasonographic and clinical remission (true remission). While RF did not differ between both groups (table 8).

In patients with subclinical synovitis, a strong correlation was found between Anti-CCP and both synovitis PD (Spearman coefficient; r_s=0.553, p=0.001) and tenosynovitis GS (rs=0.389, p=0.023) (table 9).

Table (7): Comparison between patients with ultrasound remission and those with activity according to type of DMARD therapy and glucocorticoids use

	US7 score				χ^2	p
	Remission (n = 21)		Activity (n = 29)			
	No.	%	No.	%		
Type of treatment						
bDMARDS	9	42.9	8	27.6	1.266	0.261
cDMARDS	12	57.1	21	72.4		
Glucocorticoids use						
No	11	52.4	16	55.2	0.038	0.845
Yes	10	47.6	13	44.8		

χ^2: Chi square test

Table (8):Comparison between patients in true remission and those with subclinical US activity according to autoantibodies [Anti-CCP & RF] (n =34 remission cases)

	DAS28 &US7 scores		Test of Sig.	p
	True Remission (n = 21)	Subclinical Activity (n = 13)		
Anti-CCP				
Min. – Max.	2.8 – 278	6.50 – 2940	U= 59*	0.006*
Mean ± SD.	65.57 ±92.81	1151.48 ± 1288.9		
Median	17.5	89.2		
RF				
Min. – Max.	11.5 – 112	10.6 - 678	U= 88	0.086
Mean ± SD.	36.88 ±25.63	150.82 ± 233.87		
Median	23.4	59.3		

U: Mann Whitney test

p: p value for comparing between the two categories

*: Statistically significant at $p \leq 0.05$

Table (9): Correlation between different components of US7 score and Anti-CCP in patients in true remission and patients with subclinical US activity (n = 34)

US7 score components	Anti-CCP			
	True remission (n = 21)		Subclinical Activity (n = 13)	
	r_s	P	r_s	P
Synovitis score by GSUS (max 27)	-0.225	0.461	0.330	0.057
Synovitis score by PDUS (max 39)	0.550	0.051	0.553*	0.001*
Tenosynovitis/paratenonitis score by GSUS (max 7)	-0.200	0.513	0.389*	0.023*
Tenosynovitis/paratenonitis score by PDUS (max 21)	-0.345	0.236	-0.043	0.808
Erosions score (max 14)	-0.153	0.618	0.176	0.319

r_s: Spearman coefficient

DISCUSSION

The present European and American guidelines for RA treatment advocate regimens that aim at prompt and stringent suppression of inflammation and maximal control of synovitis in order to minimize joint destruction [26,27].

Disease remission, being the ultimate goal of RA treatment strategies, is currently defined using index-based criteria that could not define the absence of synovitis, and consequently absence of disease [28]. Therefore, the persistence of subclinical joint inflammation can only be detected through sensitive imaging techniques such as MSUS [29].

In the current study, MSUS examination using US7 score revealed that 58% of our cohort had ultrasonographic activity- whether synovitis detected in GS or PD examination- while 42% showed ultrasonographic remission. For all patients, synovitis detected with GS and PD had the highest scores, ranging from 0-5 for GS and 0-3 for PD. While tenosynovitis and paratenonitis had lower scores ranging from 0-3 for tenosynovitis detected by GS and 0-2 for PD signals in tenosynovitis. In addition, the erosion score ranged from 0-3. This was in agreement with Ramirez et al., 2014 [30] who conducted their study on 55 RA patients in clinical remission by DAS28-ESR, found that 89% of their patients had synovial hypertrophy (SH) on GSUS and 64% had PDUS signals mainly in the wrist and second MCP.

Upon comparing the results of US examination between patients in remission and those with LDA a statistically significant difference was found between the two groups; where all patients (100%) with LDA showed ultrasonographic activity. Patients in LDA had a higher degree synovitis as measured by S-GSUS and higher PD signals for synovitis and to a lesser extent tenosynovitis, in addition to a higher erosion score. This was consistent with the results of Naredo et al., 2013[31], who found that 100% RA patients with LDA included in their study had symovial hypertrophy (SH) using B mode US, and 61.5% of them showed PD signals. Furthermore, Geng et al., 2014 [32] stated that PD signals were significantly higher in the non-remission group of their study. On the other hand, among patients in clinical remission, 38.2 % had subclinical ultrasonographic activity – whether in GS alone or with added PD signals, and that only 61.8% were in true combined clinical and ultrasonographic remission. In congruence with this finding, Nguyen et al., 2014 [33] mentioned, in their meta-analysis that included 19 studies and 1369 patients in remission, that the prevalence of GS and PD signals was 44%. This percentage was comparable in all clinical remission definitions they used for RA patients' assessment, this included: DAS44, DAS28, SDAI, ACR 1981 and ACR/EULAR 2010 criteria. Consistently, Picchianti Damanti et al., 2018 [34] found that 50% of their RA patients in remission had US activity in at least 1 joint.

These aforementioned results reveal the imprecision of the DAS28 in accurately describing remission in our patients. It is also obvious that it falls short of appropriate evaluation of joint activity in patients with LDA. The progression of joint damage and the increased incidence of flare, in patients with subclinical synovitis, has been proved by many studies [35,36].

In our study, we found a statistically significant difference between the number of patients in clinical remission and those with LDA regarding treatment with DMARDs that was in favor of patients in remission on cDMARDS. However, we found no significant difference between patients in US remission and those in US activity regarding DMARDs use. Glucocorticoids use did not show any difference between any of these groups neither. Similarly, Cruces et al., 2017 [37] found no difference in subclinical synovitis, detected by US, between patients on cDMARDs and those on bDMARDs. They stated that once clinical remission is attained, subclinical synovitis becomes independent of the type of treatment. This finding was confirmed later by Sapundzhieva et al., 2018 [38] in their prospective study to test the US findings as a biomarker for remission. They reached a conclusion that there was GS evidence of synovitis regardless the type of treatment-whether bDMARDs or cDMARDs.

Supplementary analysis revealed that PD signals of tenosynovitis was higher in females, reflecting a subclinical inflammatory process. Hammer et al., 2017 [39] found similar subclinical tenosynovitis in their cohort with female majority. Filippou et al., 2018 [40] discovered that the presence of subclinical tenosynovitis can predict the occurrence of disease flares in RA patients in clinical remission. Therefore, it is more likely that female RA patients in remission suffer from disease activity.

Upon further analysis, we compared the RF and Anti-CCP levels between patients in combined clinical and US remission, and those with subclinical activity. Only Anti-CCP levels were significantly higher in those with sonographic subclinical activity. In addition, there was a strong positive correlation between the Anti-CCP levels and PD synovitis score. The Anti-CCP levels also showed positive correlation GS for tenosynovitis. We found a controversy throughout literature about these results, where the association of Anti-CCP was confirmed in some studies and denied in others: Spinella et al., 2011 [41], Ohrndorf *et al.*, 2013[42] and Geng et al., 2014 [31] found no correlation between Anti-CCP and subclinical US activity detected in their patients. Conversely, Filippi *et al.*,2015 [43] studied 103 RA patients to determine the predictors of PD signal persistence and confirmed the association of Anti-CCP and PD signals among patients in clinical remission. Elkhouly et al., 2016 [44] stated that the higher Anti-CCP positivity of their RA patients influenced the occurrence of subclinical synovitis. In the same context, Koga et al.,2017 [45] reported that ACPA positivity was associated with radiographic progression in RA patients in remission or LDA.

The cross-sectional nature of our study constitutes its limitations, that did not enable us to thoroughly study the US changes throughout the duration of remission or to assess the relationship between Anti-CCP and subclinical synovitis over time.

In conclusion, subclinical synovitis is a frequent finding in the joints of RA patients in clinical remission or LDA, and occurs independently from the treatment used to achieve clinical remission. Female RA patients suffer from active subclinical tenosynovitis more than males. Anti-CCP levels of RA patients in remission with subclinical synovitis correlated with PD signals and tenosynovitis GS.

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Conflicts of interest

There are no conflicts of interest.

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