Efficacy of Therapeutic Ultrasound and Resistance Exercises in Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease affecting multiple joints (mainly the wrists and small joints of the hand) with a prevalence of about 0.5–1.0%. We aimed to compare the effectiveness of US therapy in patients with RA combined with resistance exercise in RA patients compared with healthy control subjects.

Methods: This randomized controlled, blinded, parallel group trial was conducted on 76 patients aged 18-75 years, suffered from RA and fulfilling the 2010 American College of Rheumatology classification criteria at the Physiotherapy Department. Cases were randomly divided equally into two groups; group A where patients received ultrasound associated with exercises and group B (control group). All patients were subjected to the clinical examination, laboratory investigations and RA-related characteristics including the presence of rheumatoid factor and anti-cyclic citrullinated protein antibody, disease activity was measured by 28 disease activity, erythrocyte sedimentation C reactive protein, and medications. All patients followed the same training program.

Results: Regarding the radiographic joint damage, erosion score and joint space narrowing score after 3 months were significantly lower in group A compared to group B (P<0.001, 0.010). After 3 months, ultrasound total score and van der Heijde modified Sharp score were significantly lower in group A compared to group B (<0.001, 0.011).

Conclusions: Our study highlights the importance of conducting randomized controlled trials to evaluate not only drugs but also new technologies or new treatment strategies. Ultrasound may have an important role in the diagnosis of rheumatoid arthritis and in procedures such as intra-articular injections.

Keywords: Therapeutic; Ultrasound; Resistance; Exercises; Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease affecting multiple joints (mainly the wrists and small joints of the hand) with a prevalence of about 0.5–1.0% [1]. RA is most common in middle-aged people. Without adequate treatment and care, RA may lead to joint damage and disability. A decrease in the ability to make a closed fist and hand grip strength can occur in the hands; subluxation and limitation of flexion and extension may develop into the wrists [2]. Non-pharmacological treatment options such as physical therapy along with chemical and biological disease modifying anti-rheumatic drugs (DMARDs) can be used to preserve physical function and improve quality of life in addition to reducing pain and inflammation [3, 4].

Despite the remarkable impact of pharmaceutical interventions, physical therapy and exercise training remain an important part of RA management [5, 6]. Moreover, given that cardiovascular events are an important issue in RA outcomes, improving cardiovascular risk through aerobic exercise seems to be the most relevant ancillary therapy in RA management[7, 8]. Indeed, aerobic exercises have been shown to improve cardiovascular fitness and the quality of life of patients, while reducing RA associated disability and pain. However, the useof resistance exercise therapy for RA patients is still controversial because its effects on cardiovascular risk are still a concern [9].

Although some studies have shown a statistically significant effect on RA disability [10, 11], other studies have suggested that this improvement is not statistically significant or clinically relevant [12, 13]. Similarly, discrepancies were observed between studies reporting a positive effect of exercise on functional capacity versus others that did not find such a positive effect [14, 15]. These disparities are likely due to sample size variations and the fact that most of the studies on resistance exercises only addressed changes in muscle strength. In fact, few studies have addressed the efficacy of resistance exercise-based `therapy for RA patients with respect to pain, disease activity, functional capacity, quality of life, and structural damage; thus, the effects of this therapy remain unclear [8].

Therefore, the management of rheumatoid arthritis has improved greatly over the past decade with the introduction of biologic agents, tight control strategies, and early disease modifying anti-rheumatic drug treatment [16]. With the improvement in RA care, remission has become an achievable goal for a large proportion of patients [17, 18], but studies have shown that clinical remission does not necessarily exclude progression of joint damage [19, 20].

An increasing number of rheumatologists use ultrasound in the management of rheumatic diseases. Ultrasound can assess two aspects of synovitis the morphology and quantity by grey scale and synovial vascularity by power Doppler and it has been a promising tool for monitoring of disease activity in rheumatoid arthritis. Ultrasound therapy has been used for medical purposes for more than 70 years. Its biological effects are still not exactly known [21]. Ultrasound has been shown to be more sensitive than clinical examination in detecting joint inflammation and to improve the certainty of a diagnosis of RA, and it may also be helpful in procedures such as aspiration of joint fluid and intra-articular corticosteroid injections [22, 23].

We aimed to compare the effectiveness of US therapy in patients with RA combined with resistance exercise in RA patients compared with healthy control subjects.

Patients and Methods

This randomized controlled, blinded, parallel group trial was conducted on 76 patients suffered from RA at the Physiotherapy Department. An informed written consent was obtained from the patients. The study was done after approval of ethical committee

We included patients aged 18-75 years, patients with RA fulfilling the 2010 AmericanCollege of Rheumatology (ACR) classification criteria who have not been actively exercisingwithin the last 3 months and were on a stable dose of disease-modifying ant rheumatic drugs (DMARDs), non-steroidal Anti-inflammatory Drugs (NSAIDs), steroids) given for at least 2 months prior to screening [24], and ACR functional class I to III were enrolled [25].

The exclusion criteria included patient refusal, age < 18, patients diagnosed with new chronic diseases such as diabetes mellitus or cancers within the last 3 months, diagnosed with unstable angina or myocardial infarction within the past 1 month, or had difficulty with rehabilitation exercise program due to unstable cardiovascular disease or severe disease, in particular, systolic blood pressure more than 180 mmHg or diastolic blood pressure more than 100 mmHg, or heart rate more than 120 at rest, underwent hip or knee joint replacement,and ineligible for rehabilitation exercise based on medical judgment and conditions contraindicating US therapy (infection; fever; osteomyelitis). This manuscript adheres to the CONSORT guidelines.

Randomization and blindness:

Cases were randomly divided equally into two groups by sealed opaque envelopes and a computer-generated sequence. Group A (n=38): patients received ultrasound associated with exercises and group B (n=38): control group.

The ultrasound assessments were performed with Siemens Antares or GE Logiq E9 ultrasound machines with linear probes (11.4/13.0 MHz). Power Doppler parameters were adjusted according to the device used (pulse repetition frequency 391/600 Hz; Doppler frequency 7.3/10.0 MHz) [26]. No changes in ultrasound settings were made during the study, and no software was upgraded. In the ultrasound strategy arm, the sonographer was also the treating physician, and patients were informed of the ultrasound results. All the sonographers participating in the study were experienced and underwent extensive training with both static and dynamic hands-on exercises to calibrate readers before the inclusion of the first patient and an ultrasound workshop to ensure that calibration was repeated annually during data collection. and the control group was composed of patients with RA who received advice only on the benefits of exercise in RA and received sham treatment (the US device was not turned on) during the 10 sessions for 7 min per session.

All patients followed the same training program. The intervention was divided into three phases; phase 1, phase 2 and phase 3; the total duration of the intervention was eight weeks, and there were three sessions per week. Each session lasted 45 minutes; 10 minutes for a warm-up (treadmill, ergometer bike or rowing machine), 30 minutes for two to three sets of P-1, P-2 or P-3 exercises and 5 minutes for stretching exercises (hamstrings, quadriceps, adductors and gastrocnemius).

All patients were subjected to the following included the demographic data (age, height, weight, BMI, clinical examination including heart rate (HR), and blood pressure (BP) and laboratory investigations through complete blood count (CBC), C-reactive protein (CRP), Kidney function test (serum urea and creatinine). RA-related characteristics including disease duration, the presence of rheumatoid factor and anti-cyclic citrullinated protein (anti-CCP) antibody, disease activity was measured by 28 disease activity (measured using Disease Activity Score in 28 Joints [DAS28] [27]), erythrocyte sedimentation C reactive protein (CRP), and medications such as conventional DMARDs and biologics.

Outcome measures

Pain was assessed using the visual analogue scale with a 10-cm ruler (without numbers). VAS which ranges from 0–10, with 0 representing no pain and 10 representing unbearable pain [28]. We included the rheumatoid arthritis impact of disease score, a patient derived weighted score to assess seven domains of the impact of rheumatoid arthritis (range 0-10, where higher values indicate worse status) [29].

Radiographs of hands, wrists, and feet were obtained at 0, 3, months. Two trained readers, blinded for clinical data and treatment strategy, scored radiographs independently in chronological order according to the van der Heijde modified Sharp score (subscores for erosions (0-280) and joint space narrowing (0-168), total range 0-448, higher scores indicating more joint damage). We used the average of the two readings for all analyses [30]. The flexion range of motion of the knees was measured with a universal goniometer (AESCULAP) according to the methods described by Marques [31]. Quality of life (measured using Health Assessment Questionnaire [HAQ]). All these measurements were recorded at baseline, and at 3 months [32].

Statistical analysis

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by unpaired student t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analysed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analysed using the Chi-square test or Fisher's exact test when appropriate. Paired sample t-test is a statistical technique that is used to compare two population means in the case of two samples that are correlated. A two-tailed P value < 0.05 was considered statistically significant.

Results

In this study, 103 patients were assessed for eligibility, 19 patients did not meet the criteria and 8 patients refused to participate in the study. The remaining 76 patients were randomly allocated into two groups (38 patients in each). All allocated patients followed-up and analysed statistically. **Figure 1**

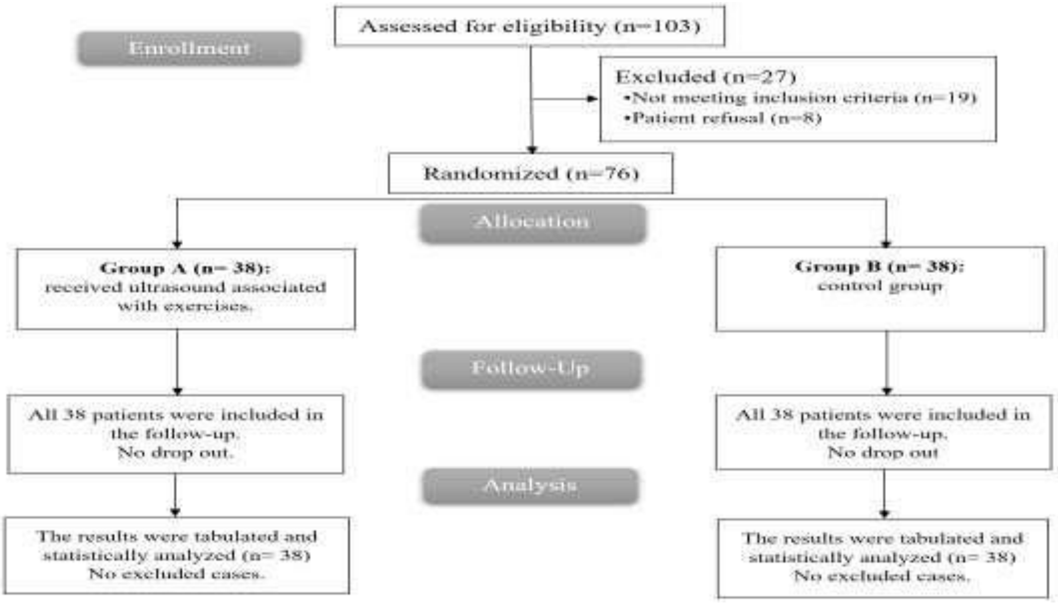

Figure 1: CONSORT flowchart of the enrolled patients

Table 1 shows that there was an insignificant difference between the studied groups regarding the demographic data (age, sex, weight, height, and BMI), RA classification and duration of the disease.

Table 1:Baseline characteristics of the studied groups

		Group A (n=38)	Group B (n=38)	P value
Age (years)		41.39 ± 12.42	43.87 ± 13.92	0.416
Sex	**Male**	18 (47.4%)	16 (42.1%)	0.817
	Female	20 (52.6%)	22 (57.9%)	
Weight (Kg)		70.26 ± 8.33	69.76 ± 8.4	0.795
Height (m)		1.66 ± 0.06	1.66 ± 0.06	0.782
BMI (Kg/m^2)		25.71 ± 3.39	25.52 ± 4.18	0.827
RA classification	**I**	14 (36.8%)	13 (34.2%)	0.811
	II	24 (63.2%)	25 (65.8%)	
Duration of disease (years)		6.55 ± 2.73	6.16 ± 2.32	0.499

Data presented as mean ± SD or frequency (%), BMI: body mass index, RA: rheumatoid arthritis

Regarding the clinical data of RA, number of swollen joints, morning stiffness and tender joint count (Ritchie articular index) were significantly reduced after 3 months in both groups compared to baseline (P<0.05). Range of motion was significantly increased after 3 months in both groups compared to baseline (P<0.001).

When comparing between both groups, number of swollen joints and morning stiffness after 3 months were significantly lower in group A compared to group B (P<0.05), while range of motion and tender joint count (Ritchie articular index) were insignificantly different between both groups. Additionally, baseline number of swollen joints, morning stiffness, range of motion and tender joint count (Ritchie articular index) were insignificantly different between both groups. **Table 2**

Table 2: Clinical data of RA of the studied groups

		Group A (n=38)	Group B (n=38)	P value
Number of swollen joints	**Baseline**	4.84 ± 1.44	4.89 ± 1.37	0.871
	At 3 months	2.95 ± 0.87	3.89 ± 1.37	**0.001***
	P value within group	**<0.001***	**0.003***	
Morning stiffness (min)	**Baseline**	32.08 ± 9.27	30.58 ± 8.64	0.468
	At 3 months	18.32 ± 3.74	27.03 ± 4.71	**<0.001***
	P value within group	**<0.001***	**0.028***	
Range of motion	**Baseline**	67.58 ± 7.13	68.74 ± 8.92	0.534
	At 3 months	85.26 ± 7.16	83.89 ± 5.61	0.357
	P value within group	**<0.001***	**<0.001***	
Tender joint count (Ritchie articular index)	**Baseline**	11.08 ± 1.71	10.63 ± 1.78	0.268
	At 3 months	6.71 ± 2.09	6.68 ± 1.68	0.952
	P value within group	**<0.001***	**<0.001***	

Data presented as mean ± SD, *: statistically significant as P value <0.05.

Regarding the laboratory investigations, number of patients had anti-citrullinated peptide antibody positive, number of patients had rheumatoid factor positive and CRP level after 3 months were significantly lower in both groups compared to baseline (P<0.05). ESR level was significantly lower only in group A compared to baseline (P=0.011) and was insignificantly different after 3 months in group B.

When comparing between both groups, number of patients had anti-citrullinated peptide antibody positive, ESR level and CRP level after 3 months were significantly lower in group A compared to group B (P<0.05), while number of patients had rheumatoid factor positive was insignificantly different between both groups. Additionally, baseline laboratory investigations (number of patients had anti-citrullinated peptide antibody positive, number of patients had rheumatoid factor positive and ESR level) were insignificantly different betweenboth groups except baseline CRP level was significantly higher in group A compared to group B (P=0.002). **Table 3**

Table 3: Laboratory investigations of the studied groups

		Group A (n=38)	Group B (n=38)	P value
No (%) anti-citrullinated peptide antibody positive	Baseline	27 (71.1%)	30 (78.9%)	0.596
	At 3 months	10 (26.3%)	20 (52.6%)	**0.035***
	P value within group	**<0.001***	**0.029***	
No (%) rheumatoid factor positive	Baseline	25 (65.8%)	28 (73.3%)	0.617
	At 3 months	9 (23.7%)	16 (42.1%)	0.143
	P value within group	**<0.001***	**0.011***	
ESR (mm/hr.)	Baseline	27.21 ± 4.94	26.58 ± 4.28	0.553
	At 3 months	24.13 ± 6.01	26.39 ± 3.33	**0.046***
	P value within group	**0.011***	0.833	
CRP (mg/L)	Baseline	18.58 ± 4.39	15.76 ± 3.04	**0.002***
	At 3 months	11.39 ± 1.55	12.29 ± 1.54	**0.014***
	P value within group	**<0.001***	**<0.001***	

Data presented as mean ± SD or frequency (%), ESR: erythrocyte sedimentation rate, CRP: C reactive protein, *: statistically significant as P value <0.05

Table 4 shows that visual analogue scale and DAS28 after 3 months were significantly lower in both groups compared to baseline (P<0.05). When comparing between both groups, visual analogue scale and DAS28 after 3 months were significantly lower in group A compared to group B (P<0.001, 0.004 respectively). Baseline visual analogue scale and DAS28 were insignificantly different between both groups. **Figure 2-Figure 3**

Table 4: Visual analogue scale and DAS28 of the studied groups

		Group A (n=38)	Group B (n=38)	P value
VAS	Baseline	6 (5-7)	6 (5-7)	0.515
	At 3 months	3 (2-4)	4 (3.25-5.75)	**<0.001***
	P value within group	**<0.001***	**<0.001***	
DAS28	Baseline	5 (4-6)	5 (4-7)	0.642
	At 3 months	2 (1-3)	3 (2-4)	**0.004***
	P value within group	**<0.001***	**<0.001***	

Data presented as median (IQR), VAS: visual analogue scale, DAS28: disease activity score in 28 joints, *: statistically significant as P value <0.05

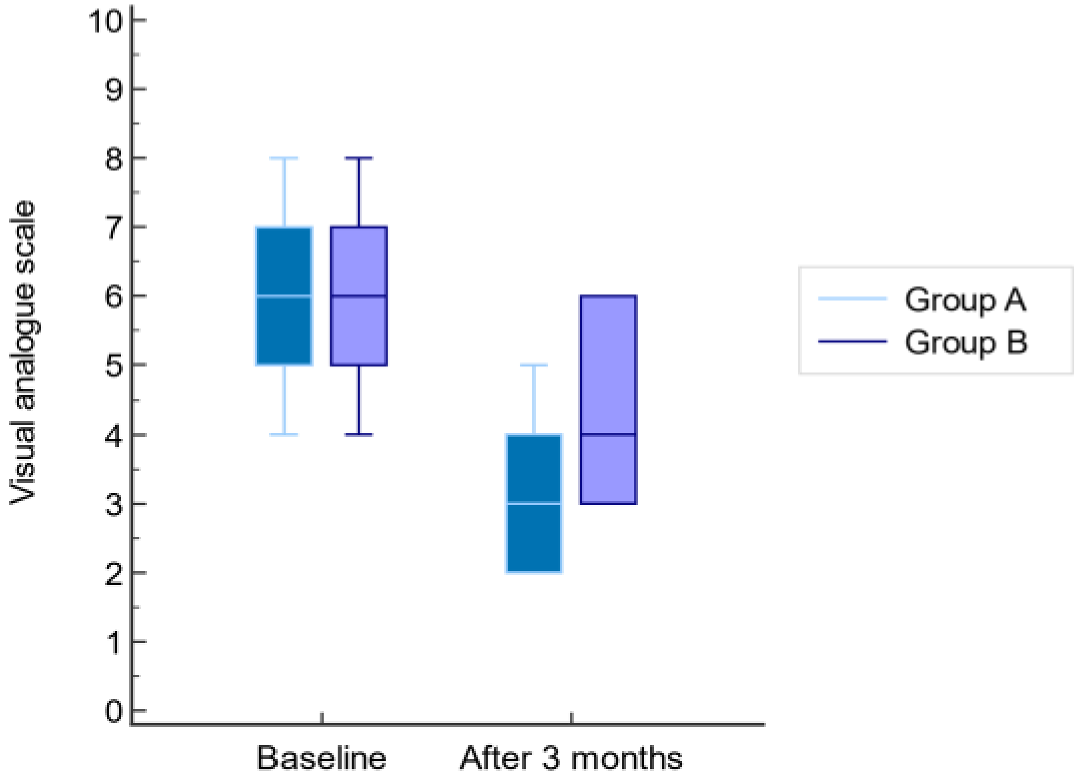

Figure 2: Visual analogue scale of the studied groups

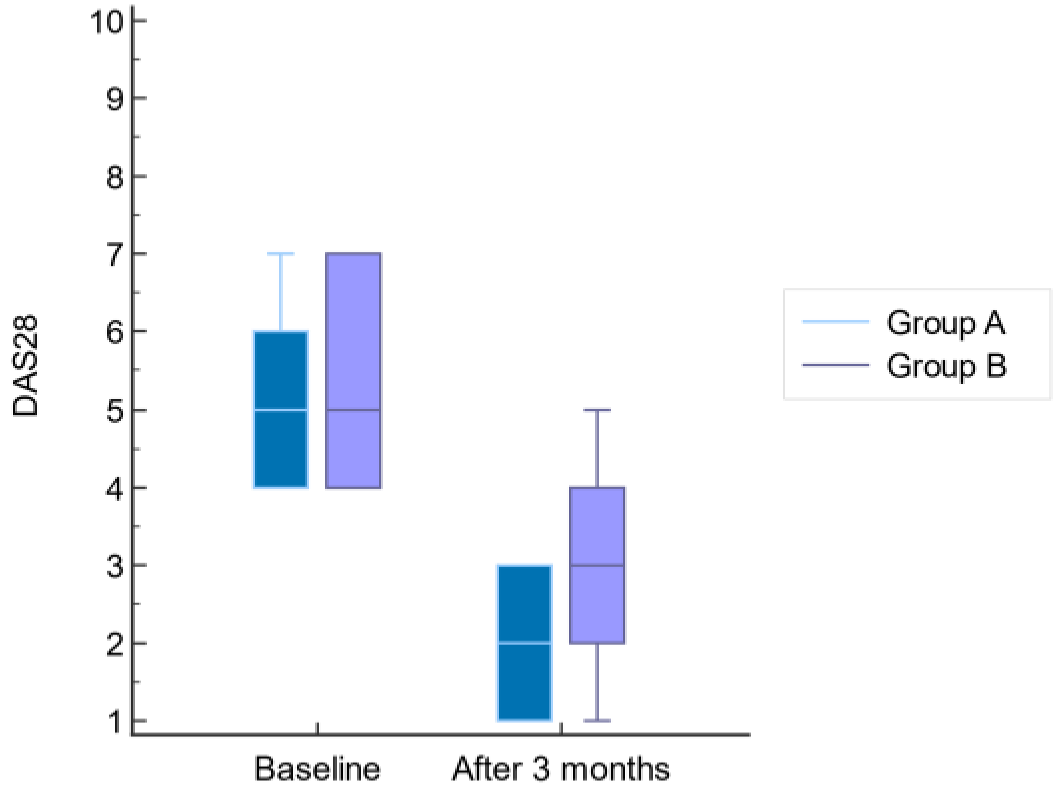

Figure 3: DAS28 of the studied groups

Regarding the radiographic joint damage, erosion score after 3 months in group A only was significantly lower in both groups compared to baseline (P<0.001) while was insignificantly different in group B. Joint space narrowing score after 3 months was significantly lower in both groups compared to baseline (P<0.001, 0.008 respectively).

When comparing between both groups, erosion score and joint space narrowing score after 3 months were significantly lower in group A compared to group B (P<0.001, 0.010 respectively). Baseline erosion score and joint space narrowing score were insignificantly different between both groups. **Table 5; Figure 5- Figure 6**

Table 5: Radiographic joint damage of the studied groups

		Group A (n=38)	Group B (n=38)	P value
Erosion score	**Baseline**	7 (4.25- 8)	6 (4-8)	0.389
	At 3 months	3 (2-4)	6 (4-7)	**<0.001***
	P value within group	**<0.001***	0.341	
Joint space narrowing score	**Baseline**	3 (2-4)	3 (2-4)	0.867
	At 3 months	1 (0-2)	2 (1-4)	**0.010***
	P value within group	**<0.001***	**0.008***	

Data presented as median (IQR), *: statistically significant as P value <0.05

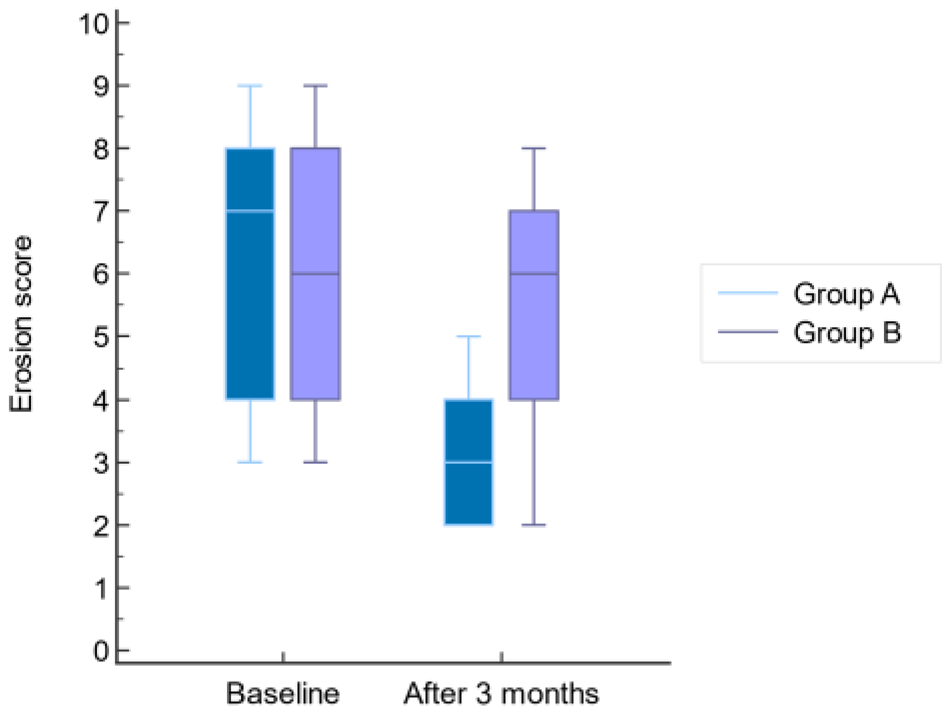

Figure 4: Erosion score of the studied groups

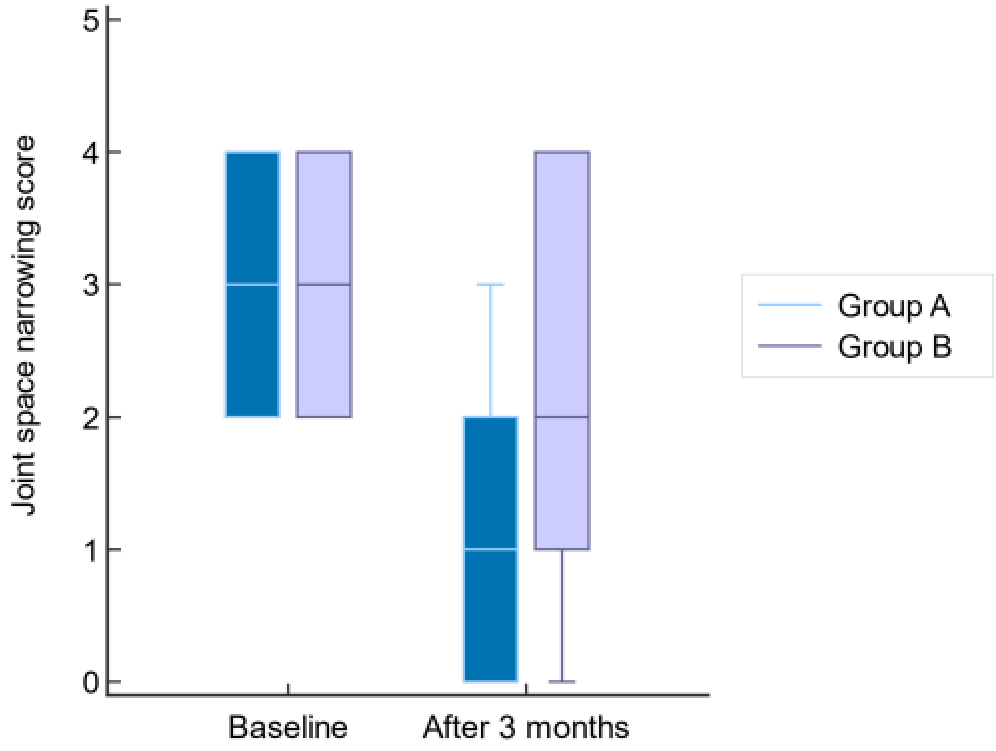

Figure 5: Joint space narrowing score of the studied groups

After 3 months, ultrasound total score and van der Heijde modified Sharp score were significantly lower in group A compared to group B (<0.001, 0.011 respectively). There was an insignificant difference between the studied groups regarding HAQ. **Table 6**

Table 6: Outcome at 3 months of the studied groups

	Group A (n=38)	Group B (n=38)	P value
Ultrasound total score	27.11 ± 7.08	35.76 ± 11.03	**<0.001***
van der Heijde modified Sharp score	5.3 (3.57-6.47)	6.45 (4.8-8.42)	**0.011***
HAQ	2.26 ± 0.45	2.29 ± 0.45	0.703

Data presented as mean ± SD, median (IQR), HAQ: health assessment questionnaire, *: statistically significant as P value <0.05

Discussion

RA is a chronic inflammatory disease in which articular and extra-articular tissue can be damaged. Uncontrolled inflammatory burden in RA results in loss of muscle mass, known as rheumatoid cachexia [33]. Physical inactivity due to pain or deformity also accelerates muscle atrophy and muscle strength. Control of systemic inflammation with antirheumatic drugs is key for the management of RA but also non-pharmacologic management such as exercise increases the beneficial effects of antirheumatic drugs [34].

Exercise has numerous benefits in RA. Based on previous reports, exercise improves disease-related outcomes such as fatigue, functional disability, and disease activity, but also reduces the risk of cardiovascular disease [35, 36]. Exercise also improves body composition or muscle strength and ameliorates the complications of rheumatoid cachexia. Especially, exercise is known to have anti-inflammatory effects on chronic inflammatory diseases such as RA [37, 38]. Joint inflammation visualised by ultrasound is present in most rheumatoid arthritis patients in clinical remission, and several studies have shown that power Doppler activity is associated with radiographic progression and disease flare in these patients [39, 40]. The potential importance of ultrasound in the definition of rheumatoid arthritis remission and the monitoring of disease activity has led to interest in the concept of imaging remission that is, abrogation of inflammation assessed by sensitive imaging techniques [41, 42].

Previous research results have already confirmed the effects of US therapy on pain and function in a range of musculoskeletal disorders [43, 44]. For example Mehmet et al. [45]observed benefits in patients with temporomandibular joint disorder. Similarly, Boyaci et al. [46] found positive results in patients with knee osteoarthritis by using ultrasound therapy. Unlike pain and physical function, there has not been any evidence that ultrasound treatment can alter inflammation.

Our results showed that regarding disease activity score, DAS28 after 3 months was significantly lower in both groups compared to baseline (P<0.05). When comparing between both groups, DAS28 after 3 months was significantly lower in group A compared to group B (P= 0.004 respectively). CRP level after 3 months was significantly lower in both groups compared to baseline (P<0.05). ESR level was significantly lower only in group A compared to baseline (P=0.011) and was insignificantly different after 3 months in group B. When comparing between both groups, ESR level and CRP level after 3 months were significantly lower in group A compared to group B (P<0.05). Additionally, baseline CRP level was significantly higher in group A compared to group B (P=0.002). Morning stiffness was significantly reduced after 3 months in both groups compared to baseline (P<0.05). When comparing between both groups, morning stiffness after 3 months was significantly lower in group A compared to group B (P<0.05).

Regarding resistance exercise, in previous similar studies, Baillet et al. [47] found that resistance exercises significantly improved isokinetic strength, isometric strength, grip strength, and HAQ. Wang et al. [48] include 13 studies and found that functional exercises could delay the development of the disease activity of RA patients (MD= –0.76; 95% CI: – 1.13, –0.38), improve the joint function (MD=0.36; 95% CI: –0.47, –0.24), alleviate the pain of joints (MD= –1.75; 95% CI: –1.98, –1.53), and reduce the duration of morning stiffness (MD= –17.65; 95% CI: –22.09, –13.21). Sieczkowska et al. [49] included 29 studies, indicated that resistance training improves the general health-related quality of life.

Wen et al. [8] performed a meta-analysis included 512 patients in the resistance exercise group and 498 patients in the control group and showed that resistance exercise showed reducing DAS-28 score, ESR score, and the time of 50ft. walking in RA patients compared with the control group.

Regarding US, A previous study found that, the decrease of CRP in the control group could have been due to the normal tissue repair, which was enhanced by the therapy in theultrasound group [32]. Based on the meta-analysis of Robertson and Baker [50] in 2001, the randomized controlled trials evaluating US therapy are heterogenous in terms of the investigated parameters and the dosage of US. In the majority of the studies, no significant differences were found in outcomes between humans treated with ultrasound or placebo US.

The progressive loss of function starts to develop early in RA; inflammation disturbs body functions, which leads to restrictions in daily activities [51]. Tumour necrosis factor-α plays a central role in the pathogenesis of accelerated muscle loss in patients with RA and induces hepatic production of CRP [52]. Elevated serum CRP level has been extensively reported as an independent predictor of CVD [53].

Currently, there is increasing evidence to suggest that CRP might play a role as a direct contributor to the atherosclerotic process. As such, one of the core aims of therapy for RA is the delay of disability and the prevention of CVD [54]. In a previous study, CRP decreased with CT (53%), possibly indicating reduced active inflammation in the trained state [55]. These results are in line with a very recent systematic review by de Salles et al. [56], which demonstrated a significant reduction in serum CRP levels after ST intervention. It is speculated that the anti-inflammatory effect of ST on CRP may be mediated by the modulation of cytokine production from other sites, besides adipose tissue, such as skeletal muscle and mononuclear cells [57].

However, Hawkes et al. [58] compared three treatment groups, all including 10 patients: exercises and wax baths, exercises with ultrasound, and exercises with ultrasound and faradic hand baths. The 3MHz continuous ultrasound with an intensity of 0.250W/cm^2 was applied in water to the palmar aspect of the hand for 3 minutes, five times a week, for 3 weeks. These authors did not find significant differences between the three groups with regard to pain, grip strength, proximal interphalangeal joint circumference, articular index, range of motion or level of activity [58].

In the study by Konrád. [59], the effects of underwater US therapy were compared to placebo treatment in 50 RA patients. US was applied to the dorsal and palmar aspects of the hand, at 0.5W/cm^2 continuously, for ten minutes on alternate days for 3 weeks. Significant improvement in the number of tender and swollen joints, joint stiffness, and dorsiflexion of wrists were reported in patients receiving ultrasound therapy, as compared to sham treatment [59].

Regarding VAS, we found that visual analogue scale after 3 months was significantly lower in both groups compared to baseline (P<0.05). When comparing between both groups, visual analogue scale after 3 months was significantly lower in group A compared to group B (P<0.001).

Six studies with 159 patients in the resistance exercise group and 159 patients in the control group reported changes in VAS scores. Based on the Chi-squared test P-value of= 0.000 value=92.1%>50%, Wen et al. [8] chose the random effects model to analyse changes in VAS scores. The pooled results showed no significant difference in VAS scores after the intervention between the 2 groups (SMD: –0.61, 95% CI: –1.49–0.27. Haavardsholm et al. [60] enrolled 122 patients were randomised to an ultrasound tight control strategy targeting clinical and imaging remission, and 116 patients were randomised to a conventional tight control strategy targeting clinical remission. They found that (disease activity, physical function, and VAS) were similar between the two groups.

We found that regarding pain and HAQ, there was a significant reduction in VAS after 3 months in both groups and was significantly lower in group A compared to group B

($P<0.001$) while an insignificant difference between the studied groups was found regarding the HAQ.

Király et al. [32] in their study randomly assigned to the ultrasound group (n=25) received underwater continuous ultrasound therapy to both wrists and hands for 7min per session with an intensity of $0.7W/cm^2$ for 10 sessions and control group. They reported that both the primary endpoint parameters (i.e., pain and inflammation) and the secondary endpoint parameters (HAQ and hand function) showed significant improvement in the short term in patients with RA treated with ultrasound.

Cruz et al. [61] found that 1MHz continuous ($0.4W/cm^2$ SATA), or pulsed (20% duty cycle, $0.08W/cm^2$ SATA) ultrasound therapy improved endothelial function in humans, which has an anti-inflammatory vascular effect. They postulated that a mechanical effect, which stimulated nitrogen-monoxide production resulting in vasodilation. According to Watson [62], the overall influence of US in the inflamed tissue was pro-inflammatory, which enabled tissue repair.4 This could explain the results of Hashish et al. [63] testing the value of US for reducing postoperative inflammation. They described a placebo-mediated mechanism with maximum anti-inflammatory effect in the placebo group.

To the best of our knowledge, there is a paucity of studies that evaluate the effect of US and resistance exercise in RA.

However, Haavardsholm et al. [60] showed that no additional effect of an ultrasound tight control strategy compared with a conventional tight control strategy for the primary outcome of the study or for other measures of disease activity, joint damage, and physical function. Trial designed to assess the value of ultrasound in rheumatoid arthritis. The clinical target of that study was low disease activity and not remission, which is the preferred target in current treatment recommendations [64, 65]. Results from this trial indicate similar clinical and radiographic outcomes in both study arms [66].

Other studies were investigated both together in Osteoarthritis and found that application of continuous and pulsed ultrasound combined with exercises had beneficial effects. Yildiz et al. [67] found that the application of continuous and pulsed ultrasound combined with exercises resulted in significant recovery in terms of pain, functionality and activity in patients with knee osteoarthritis; however, these results are different from those of Alfredo et al. [68] study, which did not demonstrate an obvious difference between the continuous and pulsed ultrasound groups. Alfredo et al. [68] study employed the same ultrasound frequencies and intensities as the study by Yildiz et al. [67], but the previous study used an application time of 10 minutes, which was twice as long as that used in Alfredo et al. [68] study. The extended application time could have contributed to the more significant thermal effects that led to larger improvements in the continuous ultrasound group than in the pulsed ultrasound group. In addition, Alfredo et al. [68] trial employed ultrasound application during the entire treatment period, which could have resulted in a synergistic effect associated with the exercises. In contrast, the study by Yildiz et al. [67] employed ultrasound application only during the first two weeks of an eight-week protocol.

Similar to the Alfredo et al. [68] study, Ozgonenel et al. [69] and Yegin et al. [70] found pain reduction and improvements in the activity and functionality of patients with knee osteoarthritis who received applications of continuous ultrasound compared to patients who received applications of pulsed ultrasound and the placebo group; however, the authors also did not combine the ultrasound applications with exercises. Zeng et al. [71] and Loyola- Sánchez et al. [72], in their systematic reviews, noted the effectiveness of pulsed ultrasound in patients with knee osteoarthritis. They found that this mode was more effective in both pain relief and functional improvement, while continuous ultrasound could only be considered a pain relief treatment in the management of knee osteoarthritis. However, none of the authors evaluated the combination of ultrasound modalities with exercises.

Our study had some limitation, it is single centre study was relatively small sample size.

Conclusions: We found that after 3 months, number of swollen joints, morning stiffness were significantly lower in group A compared to group B, number of patients had anti-citrullinated peptide antibody positive, ESR level and CRP level were significantly lower in group A compared to group B, visual analogue scale and DAS28 were significantly lower in group A compared to group B, erosion score and joint space narrowing score were significantly lower in group A compared to group B, ultrasound total score and van der Heijde modified Sharp score were significantly lower in group A compared to group B. Our study highlights the importance of conducting randomised controlled trials to evaluate not only drugs but also new technologies or new treatment strategies. Ultrasound may have an important role in the diagnosis of rheumatoid arthritis and in procedures such as intra-articular injections. Future studies should focus on the potential benefit of ultrasound in these areas, as well as the possible role of ultrasound in evaluating disease activity and tailoring treatment in patients with established rheumatoid arthritis.

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Conflict of Interest: Nil

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