The utility of Doppler and greyscale ultrasound in the assessment of treatment response in patients with rheumatoid arthritis of the wrist and hand

Noorany AMK[1], Oyoo GO[2], Onyambu CK[1]

[1]*Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, Kenya*
[2]*Department of Diagnostic Imaging and Radiation Medicine, College of Health Sciences,University of Nairobi, Kenya*

Corresponding author:
Dr. Aisha M.K. Noorany, Department of Diagnostic Imaging and Radiation Medicine, University of Nairobi, Kenya
Email: amknoorany@gmail.com

Abstract

Background: Rheumatoid Arthritis (RA), a chronic autoimmune disease primarily affecting the synovial lining is characterised by flares alternating with remissions with subsequent accrual of joint damage that progresses into functional disability with considerable morbidity and mortality. Currently treatment with Disease Modifying Anti Rheumatic Drugs (DMARDs) has been demonstrated to retard the progression of disease and improve clinical outcomes. The Disease Activity Score for 28 joints (DAS28) score is one of the commonly used disease activity measures that combines clinical and serological data to evaluate the disease severity status of a patient. Musculoskeletal ultrasound (MSUS) with its greater anatomic resolution for soft tissues via high frequency transducers, coupled with Doppler imaging can provide a better insight into the amount of inflammation within a particular joint. Tenosynovitis, synovitis even erosions can be delineated in detail by musculoskeletal ultrasound, and can also be quantified by scoring systems. This makes musculoskeletal ultrasound sensitive to change in the disease status of the patient over a period of time and thus enable clinicians to gauge the efficacy of a particular treatment regimen.

Objective: The purpose of this study was to investigate the efficacy of musculoskeletal ultrasound (which includes greyscale plus Doppler ultrasound) in assessing the change in disease activity of rheumatoid arthritis patients within the wrist and hand joints, from the initiation of therapy to 3 months after, by comparing it to the DAS28 scores calculated during these times.

Design: This was a prospective analytical correlative study.

Setting: Patients were recruited from the Kenyatta National Hospital rheumatology outpatient clinic and were examined in the ultrasound room at the Department of Diagnostic Imaging and Radiation Medicine, University of Nairobi. The study was carried out over a period of 6 months from October 2019 to March 2020 including the initial musculoskeletal ultrasound scan followed up after a period of 3 months by a repeat exam.

Methods: The study involved patients diagnosed with rheumatoid arthritis, either newly initiated on treatment or subject to a change of regimen. These patients were evaluated at baseline and again after 3 months using the DAS28 structured questionnaire and musculoskeletal ultrasound parameters. The hand most affected by disease was examined and a total of 9 joints as well as extensor and flexor tendons of the wrist and hand were evaluated via ultrasound. MSUS parameters scored included greyscale synovitis, Doppler synovitis, Doppler tenosynovitis/ paratenonitis each scored for severity from 0-3, as well as erosions and tenosynovitis/paratenonitis which were scored for presence from 0-1. The means of all the scores were calculated for each interval period and statistically significant difference calculated. A comparison was made between the DAS 28 scores and musculoskeletal ultrasound parameters and the strength and direction of association assessed. Data was analysed using Scientific Package for Social Sciences (SPSS) version 22.0.

Results: The study found that there were statistically significant differences between the scores of DAS28 as well as MSUS parameters over the interval period with the exception of greyscale tenosynovitis/paratenonitis. A significant and positive association between DAS 28 and MSUS parameters was elicited with the exception of erosions. A strong association was measured between

greyscale synovitis and DAS28 (r=0.818) with a moderate association established between Doppler synovitis (r=0.422), greyscale and Doppler tenosynovitis/ paratenonitis (r=0.38), (r=0.339) respectively and DAS 28 scores.

Conclusion: This shows that MSUS is a reliable and accurate tool for the measurement and follow up of disease activity within the wrist and hands of rheumatoid arthritis patients over a period of time.

Key words: Doppler and greyscale ultrasound, Rheumatoid arthritis

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterised by joint inflammation which leads to joint destruction and consequently functional disability. The inflammation targets primarily the synovial lining within tendons and joints causing intrinsic damage. The cause of onset is largely unknown and attributed to a multifactorial aetiology of genetic, infective and environmental factors[1].

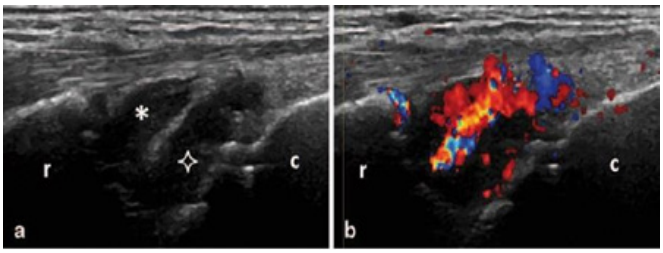
Response to treatment is evaluated clinically using various scoring systems, the commonest of which is the DAS28 score. The DAS28 score is the Disease Activity Index which is a composite of tender and swollen joints (28), a global patient health score on a 10 centimetre line graded from very good to very bad and a measure of inflammation i.e ESR. A score of more than 5.1 implies active disease below 3.2 denotes mild disease and below 2.6 is remission.

Radiography was, and in some instances still is, the main imaging modality used for assessment in patients with rheumatoid arthritis. Early radiographic findings generally include soft tissue swellings which are nonspecific[2]. Evidence of structural damage is obtained later in the disease process.

Musculoskeletal ultrasound with high frequency transducers enables direct visualization of the intra-articular and peri-articular pathology enabling detection of the early inflammatory changes including synovitis, erosions and tenosynovitis[3].

For example, Greyscale MSUS showing synovial hypertrophy as thickened intraarticular hypoechoic tissue can be used to quantify the amount of proliferation and hypertrophy. Doppler ultrasound indicates the amount of neo- vascularity in the synovium and provides a reliable estimate of the amount of active inflammation present in a particular joint[4].

Figure 1: Dorsum of the wrist, longitudinal view a) greyscale b) colour Doppler showing synovitis. Asterix; radiocarpal joint, star: midcarpal joint. r radius c capitate (Adapted from El Meidany Y, musculoskeletal ultrasonography in rheumatic diseases)[5]



Tenosynovitis on ultrasound is denoted by hypertrophied hypoechoic peri-tendinous synovial tissue, observed in orthogonal planes, which may also exhibit Doppler flows[6].

Bony erosions are seen as disruptions of the bony margin within the joint visualised in orthogonal planes[6]. These erosions are mostly within the metacarpal heads at the ulnar and radial aspects, commonly within the 2nd and 5th metacarpophalangeal (MCP) joints[7].

MSUS has thus been reported to be superior to conventional radiography and equal to MRI (Magnetic Resonance Imaging) in the detection of bone erosions[3]. Various scoring systems have been proposed in the west using a number of joints commonly involved and scoring the MSUS parameters delineated above. Among these is the German Us7 score by Bakhaus *et al*[8] who combined the parameters of synovitis, tenosynovitis and erosions into a scoring system which included the wrist and hand joints and compared them to the DAS28 score. They reported a significant association of MSUS parameters and the DAS28 score, excluding erosions[8].

Hence the use of MSUS in the monitoring of inflammatory activity is advocated in RA patients. It can also be used to assess subclinical cases of arthritis. It is also noninvasive, accessible, free of ionizing radiation and cost effective. In summary it is reliable, accurate and sensitive to changes (to progression of inflammation) in assessing intra articular and peri-articular structures of joints involved[5].

The commonly used assessments locally are the clinical disease activity measures, whereas in the west MSUS is becoming the standard of care, and a tool to aid in the initiation and monitoring of treatment. Thus there is a crevice in our setting for the development and implementation of strategies like MSUS in treatment monitoring that will help bring an improvement in the management of rheumatoid arthritis patients.

Materials and methods

This was a prospective analytical correlative study aimed to determine the efficacy of MSUS in monitoring disease activity in the wrist and hand joints of Rheumatoid Arthritis (RA) patients post therapy. Patients were sourced from Kenyatta National Hospital Rheumatology Outpatient Clinic. The study was carried out in the ultrasound room at the Department of Diagnostic Imaging and Radiation Medicine, University of Nairobi.

The study population included adult patients aged 18 years and above with a confirmed diagnosis of RA according to American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria, having involvement of the wrist and hand joints who had not been initiated on therapy or confirmed RA patients whose disease status had not shown a response to initial therapy thus were subject to a change of regimen. Only those patients who were willing to come for follow up exam after 3 months were included in the study. A total of 52 patients were recruited out of whom 41 returned for follow up. All patients gave informed consent to participate in the study.

Data collection

Data collection was initiated after receipt of approval from the Kenyatta National Hospital/ University of Nairobi Ethics Review Committee. Data was collected through interviewing patients, physical examination and musculoskeletal ultrasound examination. Patients recruited into the study were also asked to provide their recent ESR results during the examination.

The DAS28 structured questionnaire was utilised to assess the disease severity of the patient, by the principal investigator. This involved the recording of biodata, ESR values, a count of joints which were swollen and those that were tender plus an analogue score of the patient's personal reflection of disease activity state.

The wrist and hand musculoskeletal ultrasound was thereafter conducted by the principal investigator, and validated by the supervisor. This included greyscale and Doppler ultrasound evaluation and was carried out according to the standard EULAR and ESSR protocol as detailed below. The ultrasound was performed on the hand affected most by disease. Nine joints were examined in total and graded for synovitis, Doppler synovitis, Doppler tenosynovitis for severity from 0-3, whereas tenosynovitis and erosions were graded for presence from 0-1. Exact scores are detailed further below.

The Ultrasound machine used was a General Electric Logic 7. A linear transducer was used with a frequency of 9-15MHz.

These patients were followed up after a period of three months and a second questionnaire containing details of clinical and repeat ESR evaluation as per the DAS28 score was filled in. A follow up MSUS was carried out as delineated below.

Ultrasound examination

(i) The wrist was first placed prone, the transducer placed transverse for initial identification of the 6 compartments of the extensor tendons, each of the 6 compartments was then examined individually in a longitudinal plane and the tendons assessed for tenosynovitis.

(ii) The dorsal radioulnar joint was examined with the palm facing down, the probe transverse and cranial to the joint line, where the capsule has a greater compliance to distension to check for synovitis, in greyscale and power Doppler.

(iii) The radiocarpal joints were examined in a longitudinal plane at the joint line with the hand in the same position as above and assessed for synovitis via greyscale and power Doppler US.

(iv) The carpal tunnel was assessed proximally and distally within the volar aspect of the wrist to assess for flexor tenosynovitis as well as carpal tunnel syndrome.

(v) In the hand the 2nd to 5th MCP and Proximal Interphalangeal (PIP) joints were examined in longitudinal and transverse planes at the dorsal and palmar aspects. The index and little fingers were also examined on their radial and ulnar sides respectively.

Scoring systems used for MSUS

Synovitis
Graded 0 with no thickening of the synovium
Graded 1 with a small hypoechoic line of thickened synovium.
Graded 2 with moderately thickened synovium with distention of capsule parallel tojoint line.
Grade 3 is markedly thickened synovium and distention of capsule beyond the joint

Doppler synovitis
Graded 0 with absence of vascularity.
Graded 1 with either 3 vascular spots or 1 continuous vascular and upto 2 unit signals or 2 continuous vascular signals.
Graded 2 with vascularity demonstrated in below half of the synovial area
Graded 3 with greater than half of the synovial area demonstrating vascularity

Doppler tenosynovitis.
Graded 0 with no vascularity demonstrated within tendon sheath
Graded 1 with low level of vascular signal.
Graded 2 with vascular signals of moderate level.
Graded 3 with marked pathological vascularity demonstrated within the synovium surrounding the tendon.

Tenosynovitis
Graded as 0 if absent and 1 if present.

Erosions
Graded as 0 if absent and 1 if present.

Data analysis

Statistical analysis was performed with SPSS statistical software, version 22.0. The mean and range was used for quantitative parameters such as the number and age of patients. For the other quantitative parameters such as gender, the percentages of the total population were indicated. The DAS28 scores were tabulated for each patient at baseline and at 3 months. The means were calculated for each interval.

The different parameters e.g. synovitis, tenosynovitis, erosions, etc. of the MSUS exam were graded as detailed above and a total joint score for each parameter in every patient was obtainedat baseline and thereafter 3 months. The mean of every score at each interval was calculated.

Significant changes (from baseline to 3 months) for DAS28 scores and MSUS scores were calculated by the 2 sided Wilcoxon's test.

Correlation and strength and direction of association between changes in the DAS28 scores and musculoskeletal ultrasound scores were measured using the two sided Spearman correlation coefficients.

As part of the analysis the sum total of severity of synovitis and frequency of tenosynovitis and erosions was also calculated with regards to each joint and tendon.

Results

A total of 52 patients were enrolled into the study, out of which 41 patients returned for a follow up visit after 3 months, between the months of October 2019 and March 2019. There were 48 women (92.3%) and 4 men (7.7%), aged 20-87 years and mean age of 52.4 years. All the patients recruited were either initiated or substituted treatment with conventional synthetic DMARDs including methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. Most of the patients were also using corticosteroids as adjunctive therapy. The mean scores of DAS28 and MSUS parameters at baseline and 3 months are presented in Table 1.

Table 1: Mean scores of DAS 28 and MSUS parameters from baseline to 3 months

	Baseline	After 3 months	P-value
DAS28	3.95±1.51	3.51±1.49	0.026
Synovitis	14.90±5.1	13.05±5.00	0.007
Doppler synovitis	5.00±3.54	2.73±3.29	<0.01
Erosions	5.71±2.67	6.44±2.60	0.003
Tenosynovitis	3.49±2.73	2.85±2.67	0.163
Doppler tenosynovitis	3.71±4.09	1.98±3.30	0.002

There were 41 patients with complete records. There were statistically significant differences between the DAS28 scores as well as the scores for synovitis, Doppler synovitis, erosions and Doppler tenosynovitis. Greyscale tenosynovitis did not show a statistically significant difference between the interval period. To elaborate further mean DAS28 scores showed a reduction with a difference of 0.44 (p = 0.026). Greyscale synovitis showed an improvement of 12% between the mean scores (p = 0.007). Doppler synovitis indicated marked improvement of 45% (p = <0.01). Erosions however increased during the interval by 13% (p = 0.003). Doppler tenosynovitis showed an improvement of 47% between its mean scores during the interval (p = 0.002).

Correlation between DAS28 and MSUS parameters

The correlation and strength of association between DAS28 and the individual MSUS parameters is as shown in Table 3.

Table 3: Correlation between DAS28 and MSUS parameters

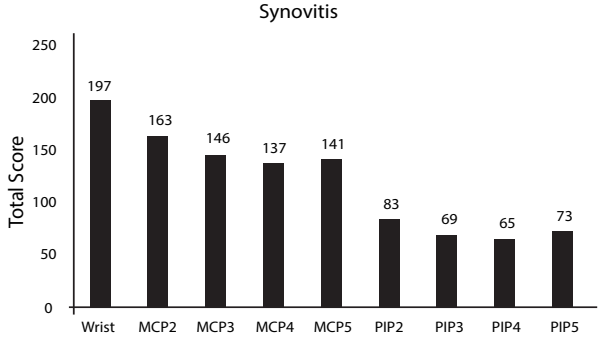
	DAS28	P-value
Synovitis	0.818	<0.01
Doppler synovitis	0.422	0.006
Erosions	0.236	0.138
Tenosynovitis	0.380	0.014
Doppler tenosynovitis	0.339	0.030

Correlations between the differences of the different modalities with DAS28 at baseline and at 3 months were evaluated by 2-sided exact Spearman's correlation coefficients. All parameters showed a positive and statistically significant correlation with DAS28, only the correlation between erosion and DAS28 was not significant (p=0.138). The correlation between synovitis and DAS28 was very strong (r=0.818), while that of Doppler synovitis (r=0.422), tenosynovitis (r=0.380), and Doppler tenosynovitis (0.339) revealed a moderate association.

Frequency of synovitis within individual joints

The severity of synovitis within each joint examined within the wrist and hand is delineated here. It thus presents the extent and frequency of involvement detailing the joints most involved to those least affected (Figure 1).

Figure 1: Severity of synovitis within individual joints

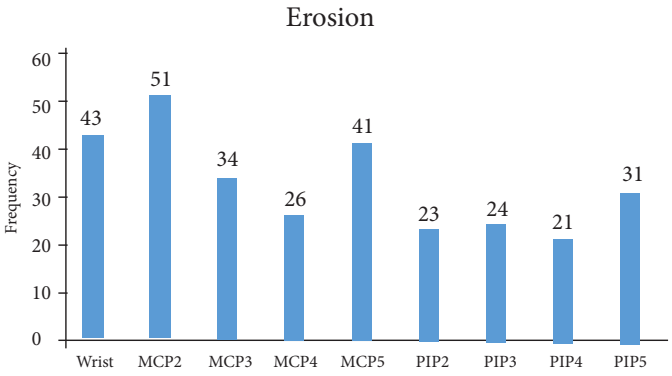


The individual scores of severity of synovitis within each joint were totalled up to reflect the extent of involvement of each joint. According to Figure 1 the wrist is the most frequently involved followed by the metacarpopahalangeal joints of which the 2nd MCP joint is most affected. The PIP joints are next in frequency showing little variation in between them.

Frequency of erosions

The results of the frequency of erosions in the bones examined within the wrist and hand are presented. Specifically, these are the ulnar styloid, the heads of second to fifth metacarpals and heads of the second to fifth proximal phalanges (Figure 2).

Figure 2: Frequency of erosions within individual bones



The results indicate that the highest number of erosions were detected within the head of the second metacarpal, followed by the ulnar styloid within the wrist, there after the 5th metacarpal head. The 4th metacarpal head and the 3rd, 2nd and 4th proximal phalangeal heads were least affected in that order.

Frequency of tenosynovitis /paratenonitis

Data detailing the extent of involvement of individual tendons within the wrist as well as the extensor and flexor tendon slips of the hand is presented.

Figure 3: Frequency of involvement of the extensor tendons of the wrist

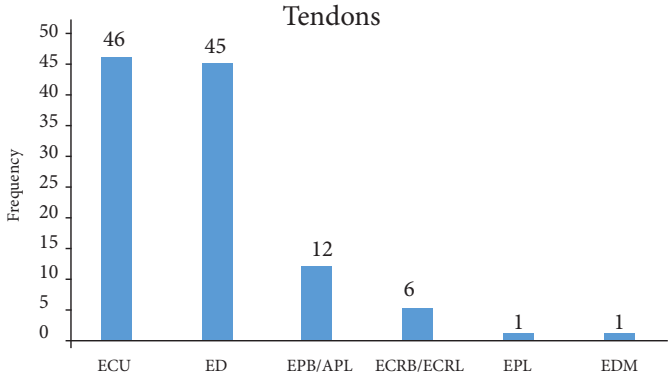
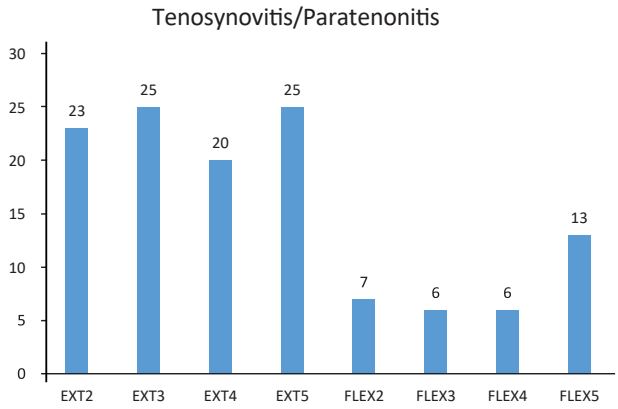


Figure 4 indicates that the extensor carpi ulnaris is the most frequently involved followed closely by the extensor digitorum. The rest of the tendons were infrequently involved. No involvement of the flexor tendons of the wrist was detected within all the patients examined.

Figure 4: Frequency of involvement of extensor and flexor tendon slips of the hand



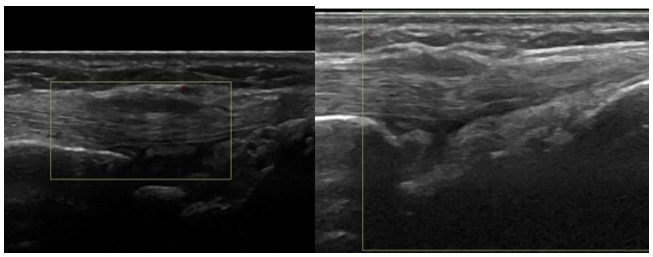
The results indicate higher frequency of involvement of the extensor tendon slips as compared to the flexor tendons.

Representative images of the study

A 50 year old female intolerant to current regimen

At baseline: grade 2 GS synovitis, Grade 0 PD synovitis of radiocarpal joint, GS and grade 1 PD tenosynovitis of the extensor digitorum. After 3 months: grade 1 GS synovitis of radiocarpal joint, GS tenosynovitis of extensor digitorum still present however no PD signal observed.

Figure 5: Radiocarpal joint, baseline b: after 3 months



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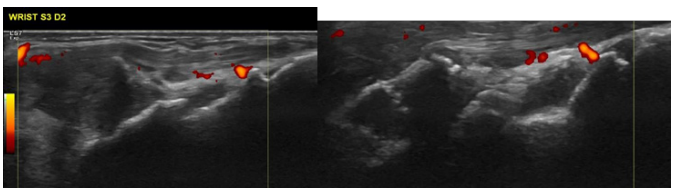
A 75 year old female not responding to therapy, radiocarpal joint at baseline shows grade 3 GS synovitis and grade 2 PD synovitis, after 3 months of change in regimen, GS synovitis down to grade 2, PD down to grade 1. (ED grade 2 PD tenosynovitis was also present, unchanged over 3 months).

Figure 6: Radiocarpal joint, ED tendon baseline b: after 3 months



Discussion

In this study we have assessed the utility of MSUS as an aid in the monitoring of response to therapy in RA. The hand wrist complex was chosen for its high frequency of involvement and for correlation with clinical activity

we used the DAS28 scoring system with an interval of 3 months between assessments. Our patient population was by and large representative of the rheumatoid population in this region[9]. Female patients were predominant at 92.3% while males were few at 7.7%.

The results show that synovitis was most severe within the wrist joint at 63% followed closely by the 2nd MCP joint at 52% with other MCP joints not far behind. The PIP joints were less affected with little variation between individual joints.

Scheel *et al*[10] found similar degrees of synovitis of the 2nd to 5th MCP and PIP joints to ours but a higher frequency of PIP involvement and Bakhaus *et al* [8] found the wrist, MCP 2 and 3, PIP 2 and 3 to be the most affected joints. This difference could be due to racial diversity or lifestyle and occupational differences of the local communities as opposed to the western population.

Tenosynovitis was most frequent in the Extensor Carpi Ulnaris (ECU) at 88% followed closely by the Extensor Digitorum (ED) at 86%. The rest of the extensor tendons of the wrist were less frequently involved. This is in agreement with the study by Filipuccci *et al*[11] who reported most frequent involvement of the ECU. Nieuwenhuis *et al*[12] found the commonest tendons affected were the ECU, ED and the flexor digitorum.

The extensor tendon slips followed next in frequency after ECU and ED. This shows the presence of paratenonitis within RA patients as stated by Bakhaus *et al*[8] who examined the extensor tendons at the MCP joints and graded them as part of the German Us7 score.

Ramrattan *et al*[13] examined the dorsal extensor tendons of the hand and found inflammatory changes including peritendinous fluid and power Doppler signals, and also an association with severe disease within the respective MCP joints.

Wakefield *et al*[14] also state that the dorsal extensor tendons are not uncommonly involved in RA despite not having a synovial sheath.

In our study the flexor tendon slips were less frequently involved compared to the extensor tendons, in agreement with an Egyptian study by Fawzy[15] but in contrast to Filipucci *et al*[11] and Nieuwenhuis *et al*[12] who reported the flexor tendons as one of the most commonly involved. Again these differences could be attributed to geographical and racial variations in disease presentation.

Erosions were most frequent within the second metacarpal head followed by the ulnar styloid and the 5th metacarpal head. The head of the 4th metacarpal as well as heads of the 2nd, 3rd and 4th proximal phalanges were least frequently involved. According to Wakefield *et al*[7] the most frequent site for erosions in RA patients in the hand are the 2nd MCP and 5th MCP joints while the fewest erosions are detected at 4th MCP joint[7].This is in concordance with the results obtained in our study.

The DAS28 and MSUS parameters were assessed for significant changes over the 3-month period using the Wilcoxon Signed Ranked test whereby a p-value of less than 0.05 was considered statistically significant. The results showed that there were significant changes in DAS28 as well as all MSUS parameters apart from greyscale tenosynovitis. This corresponds with data from Scheel *et al*[16] who reported that no matter the number of joints evaluated, a decrease of B Mode and Doppler variables was seen in patients treated with biologic DMARDs or synthetic DMARDs.

Hammer *et al*[17] observed the sensitivity to change of US-detected tenosynovitis in RA patients initiating adalimumab treatment. They evaluated the extensor and flexor tendon of bilateral wrists and ankles and noted a significant decrease of tenosynovitis after twelve months for all studied tendons. This might explain the lack of significant change observed with our greyscale tenosynovitis/paratenonitis observations, implying that a longer period of follow up would be needed to record significant changes.

Correlation between DAS28 and MSUS parameters was measured using the 2 sided Spearman's correlation coefficients. A positive and significant correlation between DAS 28 and the MSUS parameters was elicited apart from erosions. A strong association was elicited between DAS28 and greyscale synovitis. Moderate association was found between DAS28 and Doppler synovitis as well as greyscale and Doppler tenosynovitis/ paratenonitis. This correlates with the study by Bakhaus *et al*[8] who elicited a significant association between both greyscale and Doppler synovitis and DAS28 over a three-month period. They also reported no significant association between erosions and DAS28 over 3 or 6 months. However, the correlation between DAS28 and tenosynovitis (B mode and Doppler) was not significant at 3 months, although at 6 months they did report a significant association. This can be due to the difference in number of joints or tendons included within the two studies. Whereas they included only the extensor and flexor tendons of the wrist plus the extensor and flexor tendons to the 2nd and 3rd digits, our study included those mentioned as well as the extensor and flexor tendons to the 4th and 5th digits as well. The other significant difference is the severity of tenosynovitis at baseline. Bakhaus *et al*[8] reported means of both greyscale and PD tenosynovitis at baseline that were much lower than the values obtained in our setup. Thus allowing greater room for improvement and correlation within our study.

Conclusion

The results thus showed that a significant difference was elicited in between the MSUS parameters during the interval period thereby reflecting the change in patients' disease activity over the 3 month period after initiation/ change in therapy which proves that MSUS is sensitive to change in the progression or regression of disease activity.

Moreover, results obtained prove that a significant association exists between DAS28 scores and B mode and Doppler synovitis and tenosynovitis measured during the interval period demonstrating the reliability of MSUS as a tool for monitoring disease activity in RA patients.

We thus conclude that MSUS is a reliable tool to measure the treatment response in RA patients within

the wrist and hand and can be used as a supplement to clinical disease activity measures.

Recommendations

Further to this study it would be helpful to follow up the patients over a longer period of time from 6 months to 1 year, and assess the relationship between the MSUS parameters and DAS28, with respect to different therapeutic regimens.

A 12-month period would also be ideal to assess for significant changes in tenosynovitis.

A larger cohort of patients could also be recruited to further elaborate on the findings of MSUS within the wrist and hand within the Kenyan population.

In order to assess the progression of erosions, further MSUS assessment of synovitis could be undertaken to elicit if active synovitis serves as a predictor for the development of new erosions.

Dedicated footprint probes for MSUS would also be ideal for future examinations and studies.

Limitations

One of the disadvantages of ultrasound is that it is operator dependent. This was countered by following the ESSR 2010 guidelines on the methodology of performing a wrist and hand ultrasound and with supervision and validation from my supervisors (OGO and OC).

Given that the study involves the follow up of patients from the initiation of treatment to three months after, some patients were lost during the process of follow up and did not present three months later. This was countered by increasing the number of patients examined to keep a margin above the stated sample size. The contacts of the patients were also taken for this purpose.

It would have been more appropriate if the DAS28 score and the MSUS were performed by different investigators and both blinded to the results of the other in order to reduce bias within the study.

Acknowledgment

The authors are grateful to all the patients who agreed to participate in this study.

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