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ORIGINAL ARTICLE

Ultrasonographic assessment of rheumatoid arthritis: A systematic review.

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ABSTRACT… Objective: To evaluate the reliability of ultrasound for the detection of rheumatoid arthritis (RA). **Study Design:** Systematic Review. **Setting:** The University of Lahore. **Period:** 2001 to 2021. **Material & Methods:** A systematic exploration of the literature was achieved by collecting articles related to our topic. Articles reporting the reliability result for the assessment of rheumatoid arthritis by ultrasonography were included in this study. Exclusion criteria were articles reporting large joints including shoulder and knees as well as that articles which were not reporting sufficient information of sensitivity and specificity of US regarding RA. These articles were provided by an online source of PubMed, google scholar, research gate, Embase, Wiley online library, BMJ Journal, AJR, Springer, and Elesvier link. **Results:** Results shows that the specificity and sensitivity of gray-scale US for synovitis assessment ranged from 50% to 90.9% and 47.4% to 100% respectively, specificity and sensitivity of Power Doppler ultrasonography for the evaluation of synovitis hypervascularity ranged from 60% to 98% and 21% to 92% respectively, and specificity and sensitivity of ultrasonography to assess the bone erosion in rheumatoid arthritis patients ranged from 69% to 98.7% and 35.9% to 83% respectively. **Conclusion:** This systematic review concluded that ultrasound is a vital diagnostic tool as compared to X-ray, CT, MRI, clinical and laboratory examination for the evaluation of bone erosion, synovitis, and synovial hypervascularity.

Key words: Bone Erosion, GSUS, PDUS, Rheumatoid Arthritis, Sensitivity, Specificity, Ultrasound.

INTRODUCTION

Rheumatoid arthritis defines as an autoimmune and provocative illness that can cause swelling in the joints. The immune system attacks healthy cells, usually, many at once which leads to inflammation throughout the body's tissues causing pain when walking or moving around. Synovitis primes to structural demolition like cartilage destruction, bone erosion, and joint deformity, which leads to joint pain, stiffness, loss of function, and fatigue.[1] The small joints of the hand, such as proximal interphalangeal (PIP) and metacarpophalangeal (MCP) zones can be involved in rheumatoid arthritis. Early diagnosis is necessary for early treatment because missing damage may result in more severe symptoms down the line which will ultimately require surgery or an indirect approach to healing instead.[2]

MRI is a widely used imaging technique for the diagnosis of early bone erosions, synovitis, and joint effusion. However, musculoskeletal ultrasound (MSUS) is also powerful in this area, as it is more preferred to use musculoskeletal ultrasound instead given how much easier it can be on patients' nerves since there is no need for injection or sedation during procedures.[3] MRI has been the gold standard for scanning humans since its inception. However, there are some drawbacks to this technology as it is not easily accessible as well as expensive in certain environments due to all wiring needs. While the US is readily available at a local hospital or clinic without any need for advanced infrastructure; and does not have any bio effects because they are never actually inside someone.[4]

The US is a highly specific and sensitive technique

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for the assessment of rheumatoid arthritis. Studies done on people with early stages showed that this method can detect them at an earlier stage than clinical exams, blood tests, or x-rays.[5] The use of gray-scale US (GSUS) has shown to be an effective method for characterizing synovitis in patients with rheumatoid arthritis. Grey-scale ultrasonic imaging creates images of different body parts using high-frequency sound waves. It is safe, non-invasive, and does not use radiation for clarity as it creates pictures on an x-ray film-like system that retains contrast between tissues but reduces colorization so that organ structures can be seen better. It is often used, as an initial screening tool to help identify destructive activity in patients with RA.[6] Power Doppler US (PDUS) is useful for evaluating joint inflammation in rheumatoid arthritis patients. PDUS is also used to detect the blood flow to the Synovial membrane, which helps doctors identify areas with increased risk of complications or damage due to their proximity to inflamed tissue in these joints.[7] Color Doppler Ultrasound (CDUS) is a frequently used imaging modality for the assessment of rheumatoid arthritis patients. It involves sending high-frequency sound waves into organs and mapping their function using color flow images. It does not use radiation and is relatively inexpensive. It is used to examine blood vessels and measure the flow of blood. One of the benefits of using a CDUS machine is that it can help identify potential health problems before they become serious.[8]

Early bone erosions are seen at the initial phases of rheumatoid arthritis. However, they also can occur due to other diseases. Conventional radiography (CR) may not detect these changes and more advanced imaging techniques such as the US can identify them earlier than expected because it detects their fragile nature from an outside perspective before damage has been done to healthy tissue around them.[9] Hence, this systematic review is aimed to explain the "ultrasonographic assessment of rheumatoid arthritis".

MATERIAL & METHODS

This Systematic Review was conducted by systematic exploration of the literature, which was achieved by collecting articles related to our topic from 2001 to 2021.

Inclusion Criteria

Articles reporting the reliability result for the assessment of rheumatoid arthritis by ultrasonography were included in this study.

Exclusion Criteria

Exclusion criteria were articles reporting large joints including shoulder and knees[10-13] as well as that articles were not reporting sufficient information of sensitivity and specificity of US regarding RA.[14-18]

These articles were provided by an online source of PubMed, google scholar, research gate, Embase, Wiley online library, BMJ Journal, AJR, Springer, and Elesvier link. Ten articles assessed the specificity and sensitivity of ultrasound for the assessment of bone erosion, synovitis, and synovial hypervascularity in which 388 patients with RA were examined.[19-26,28,29] This review comprises of various types of studies including Comparative study, prospective study, cohort study, Cross-sectional study, and case study.

Statistical analysis (Standard Deviation) was also performed and data analysis elaborated graphic and descriptive clarification of reliability and its factors.

SYNOVITIS

Proliferative synovitis is the initial pathologic change perceived in rheumatoid arthritis that can be detected by clinical examination, X-ray, CT, US, and MRI but the use of ultrasonography seems superior to other assessments in detecting the presence of synovitis. GSUS is useful for rolling out the signs of synovitis, as the following four studies described the US sensitivity and specificity for rolling out the synovitis by comparing with others tools such as MRI, CR, clinical assessment, and laboratory tests (Table-I).[19-22] A study was performed by Horikoshi et al. in 2010 which see the ability of MRI and US to roll out the joint inflammation in those patients that were affected with rheumatoid arthritis (RA). They have

included 6 female patients who were studied on US and low-field 0.3-Tesla MRI. 22 joints in every patient (total of 132 joints) including intercarpal, radioulnar, 2nd to 5th proximal interphalangeal, and 1st to 5th metacarpophalangeal joints were examined by MRI to rule out joint inflammation. The first 24 radiocarpal and interphalangeal joints and the overhead 132 joints (total of 156 joints) were examined on grayscale US (GS-US) and power Doppler US (PD-US) for the detection of joint inflammation by experienced sonographers. They examine joint inflammations on MRI and GS-US/PD-US by reporting sensitivity and specificity of GS-US were 71% and 50%, respectively, while using MRI as a reference.[19]

One more Case-control study was conducted by Szkudlarek *et al*. in 2006 to explore whether ultrasonography can provide useful information on signs of destruction and inflammation in RA of the finger joints that are not detected on x-ray and clinical examination, and compared with the results provided by magnetic resonance imaging (MRI). This study examined 158 2nd to 5th metacarpophalangeal (MCP) and 140 2nd to 5th proximal interphalangeal (PIP) joints of 40 patients that were affected with rheumatoid arthritis (RA). MRI sequences (T1-weighted images) use as the reference, they show specificity, sensitivity and accuracy of GS-US were 70%, 78%, and 76%, respectively.[20] one more prospective study was performed by Ivanac et al. in 2015 to see the importance of gray-scale US and color Doppler ultrasound (CDUS) to roll out the hand joints changes and notice the recovery results of those patients that suffering of rheumatoid arthritis (RA) by US parameters with clinical examination and laboratory results. In this study, they examined the hand joints names as Ulnocarpal, metacarpophalangeal, and proximal interphalangeal (PIP) joints that use GS-US and CD-US before treatment and after treatment of 6 months those patients that were affected with RA. They compare CD-US findings (synovial, resistance index, velocities, effusion, vascularization) with clinical signs of disease development including disease activity score (DAS 28), rheumatoid factor, ESR, Health Assessment Questionnaire, and C reactive protein. They reported that the grayscale ultrasonography for the detection of synovitis has a specificity of 100% and sensitivity of 87%.[21] A Cross-sectional study was performed by Freeston *et al*. in 2010 to assess the role of power Doppler ultrasound (PDUS) in collaboration with general treatment in patients with early inflammatory arthritis (IA). They add those patients with a mean age of 51 years are examined using Power Doppler US, conventional hand, x-ray, and laboratory tests. US sensitivity was increased with the use of power Doppler-US and can detect the synovial hypervascularity in joints, as they reported the sensitivity 47.4% and specificity 90.9% of PD-US for the detection of hypervascularity in inflammatory arthritis (IA) respectively.[22]

US sensitivity increase with Power Doppler US and find the hypervascularity in joints, as following five studies described the US sensitivity and specificity for the role out of synovitis by comparing with x-ray, clinical examination, and MRI (Table 2).[19,23-26] One more study was performing by Horikoshi et al. in 2010 reported the PD-US sensitivity 21% and specificity98%, respectively while using MRI as a reference.[19]

Another study was conducted by Wiell et al. in 2007 to see the role of ultrasound (US) in inflammatory and devastating changes in hand joints, tendons, and entheses in patients with PsA by comparison with MRI, x-ray, and clinical findings. They included 25 patients who were examined on different modalities like US, x-ray, MRI, and clinical assessment to role out bone erosions, bone proliferation, and synovitis. It was found that x-ray and clinical examination are less sensitive as compared to US and MRI for the role out of inflammatory and devastating changes. US results show that specificity is 88% and sensitivity 70% to rule out synovial hypervascularity in MCP joints.[23] One more study was performed by Terslev et al. in 2008 *to* study the specificity and sensitivity of Doppler ultrasound for the detection of arthritis in the small upper limb joints and to describe a cutoff level for our ultrasound measures for color fraction, inflammation, and resistive index (RI). 88 patients included in which RA was active and 27 healthy were included in

control group for examination. A total of 419 wrist and hand joints were examined by using Doppler US. Receiver-operator characteristic (ROC) curves of US measurements including synovial vascularization determined by spectral Doppler US (SD-US) and color Doppler US to estimate the color fraction and RI in the wrist and hand joints. They reported a sensitivity of 92% and specificity of 73% of Doppler ultrasound (DUS) for the role out of synovial hypervascularity of small joints in the upper limb.[24] one more study was performed by Harman et al. in 2015 to see the effectiveness of musculoskeletal ultrasound US (MS-US) in the evaluation of provocative and devastating fluctuations in wrist and hand joints and rheumatoid arthritis (RA) patients tendons and compared with MRI. They included only those patients which were recently diagnosed with rheumatoid arthritis and 279 wrist and hand joints were examined by experienced rheumatology clinicians and MRI was performed by an experienced person. The sensitivity was 73% and specificity 76% of US in detecting PD synovitis in hand joints.[25] Another study was conducted by Melchiorre et al. in 2003 which described the sensitivity of ultrasound compared with MRI to rule out the temporomandibular joint involvement in arthritis. They performed US and MRI of all patients in which some patients were affected with RA and some patients affected with psoriatic arthritis (PsA) to measure the condyle and disc alterations of the condyle. It was reported that US rules out different pathological variations of the TMJ and may be measured a significant investigative tool for clinical estimation of the TMJ in PsA and RA as the sensitivity and specificity was 72.2% and 60% in the valuation of pathological fluctuations of the TMJ while specificity and sensitivity in the taxation of amendments of the disc was 30.0% and 69.6% respectively, and sensitivity and specificity in the valuation of joint effusion was 70.6% and 75.0% respectively. However, significant concordance in the valuation of condylar amendments was not observed.[26]

BONE EROSION

Erosions are common findings in rheumatoid arthritis and are present in up to 97% of patients with the condition.[27] Following studies described the US sensitivity and specificity to rule out early bone erosions by comparing to other modalities like CT Scan, x-ray, clinical examination, and MRI (Table-III).[28,25,29,23,20] A cohort study was performed by Piga et al. in 2016 to see the sensitivity of US for roll out the bone erosion in the hand and wrist joints of patients using CT Scan as the gold-standard reference method. They examined 26 female patients (9 with lupus syndrome, 10 with Jaccoud's arthropathy (JA), and 7 with non-deforming non-erosive (NDNE) arthritis) for the existence of bone erosion by US and CT. It was reported that the US had temperate sensitivity and brilliant specificity for recognition and semi-quantitative valuation of bone erosions in SLE as the overall specificity was 98.7 % and sensitivity was 35.9 % for the finding of bone erosions in SLE patients.[28]

One more study was performed by Harman et al. in 2015 reported that the sensitivity and specificity of PDUS were 75%, and 69% for the detection of bone erosion in rheumatoid arthritis in wrist, and hand joints.[25] Another study was conducted by Melchiorre et al. in 2003 to see the diagnostic importance of US and compare it with magnetic resonance imaging (MRI) in patients who were affected with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). They examine a total of 33 patients on MRI and US of which 22 were RA patients and 11 were psoriatic arthritis (PsA). They calculated the US sensitivity and specificity by comparing the MRI. Results show that US is useful to detect the pathological changes in TMJ of RA patients as well PsA patients as the sensitivity was 72.2% and specificity 60% for diagnosing the pathological changes of the TMJ while sensitivity was 69.6% and specificity 30.0% to rule out the alterations of the disc. To detect the joint effusion the sensitivity and specificity were 70.6% and 75.0% respectively. However, significant concordance to rule out condylar alterations was not observed.[29] A study conducted by Wiell et al. in 2007 showed that specificity was 93% and sensitivity 56% for the detection of bone erosion in rheumatoid arthritis in MCP joints.[23] *A* Case-control study was directed by Szkudlarek *et al*. in 2006 reported the sensitivity of 59%, specificity 98%, and accuracy of ultrasonography rule

the bone erosions in the hand joints was 96%, respectively.[20]

REVIEW RESULTS

The sensitivity and specificity of grayscale ultrasound for synovitis assessment ranged from 47.4% to 100% and 50% to 90.9% respectively (Table-I and Figure-1). Conversely, we have omitted the sensitivity 47.4% because it reduced the mean sensitivity.[22] All the overhead studies were approved with pooled specificity and sensitivity of ultrasound for the evaluation of synovitis.

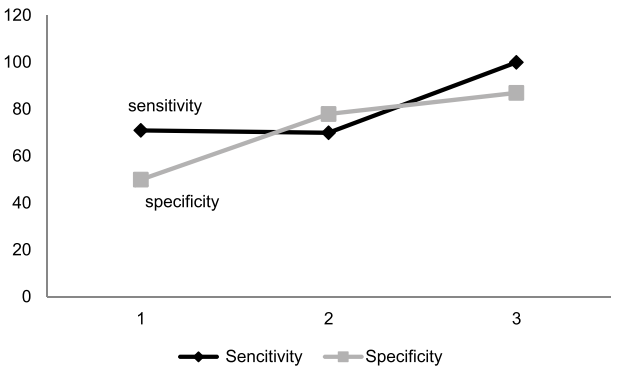


Figure-1. Specificity and sensitivity of grayscale ultrasound for synovitis assessment

Radiography	Sample Size	Study Design	Joints	Specificity (%)	Sensitivity (%)	References
MRI, US	6	Comparative	Metacarpophalangeal joints, proximal interphalangeal joints	50	71	Horikoshi et al., 2010 [19]
MRI, CR	60	Case control	PIP and MCP	78	70	Szkudlarek *et al*., 2006 [20]
US	30	Prospective study	MCP, UC joints	87	100	Ivanac et al., 2015 [21]
PDUS, CR	50	Cross sectional	Wrist and hand	90.9	47.4	Freeston *et al*., 2010 [22]

Table-I. Specificity and sensitivity of grayscale US for the assessment of synovitis in small joints

Radiography	Sample Size	Study Design	Joints	Specificity (%)	Sensitivity (%)	References
US, MRI	6	Comparative	Metacarpophalangeal joints joints, proximal interphalangeal joints	98	21	Horikoshi et al., 2010 [19]
US, x-ray, MRI	25	Comparative	Metacarpophalangeal joints	88	70	Wiell et al., 2007 [23]
US	88	Controlled Clinical Trial	Wrist and hands	73	92	Terslev et al, 2008 [24]
MRI	31	Case-control	Finger and wrist	76	73	Harman et al., 2015 [25]
US, MR	33	Comparative	Temporomandibular joint	60	72.2	Melchiorre et al., 2003 [26]

Table-II. Specificity and sensitivity of Power Doppler US for synovial hypervascularity assessment

Radiography	Sample Size	Study Design	Joints	Specificity (%)	Sensitivity (%)	References
US, CT	26	cohort	Hand joints	98.7	35.9	Piga et al., 2016 [28]
MRI	31	Case control	Wrist and finger	69	75	Harman et al., 2015 [25]
MRI	39	Cohort	MCP and PIP	95	83	Wang *et al*., 2016 [29]
US, MRI, x-ray	25	Comparative	MCP	93	56	Wiell et al., 2007 [23]
CR, MRI	60	Case-control	Finger joint	98	59	Szkudlarek *et al*., 2006 [20]

Table-III. Specificity and sensitivity of ultrasound for bone erosion assessment

The specificity and sensitivity of power doppler ultrasound for the assessment of synovitis hypervascularity ranged from 60% to 98% and 21% to 92% respectively (Table-II and Figure-2). Conversely, we have let off the sensitivity 21% as it lessened the mean sensitivity.[19]

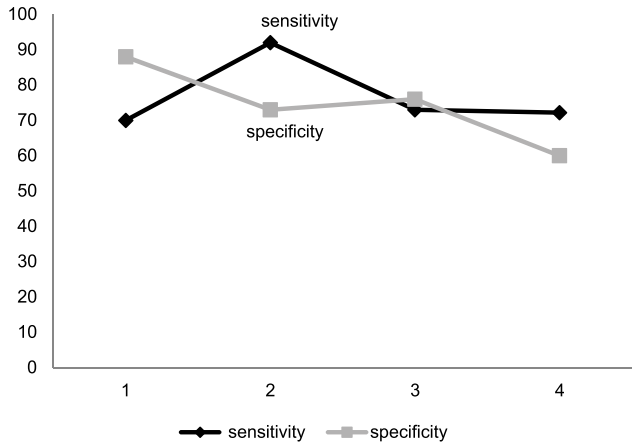


Figure-2. Specificity and sensitivity of Power Doppler ultrasound for synovial hypervascularity assessment

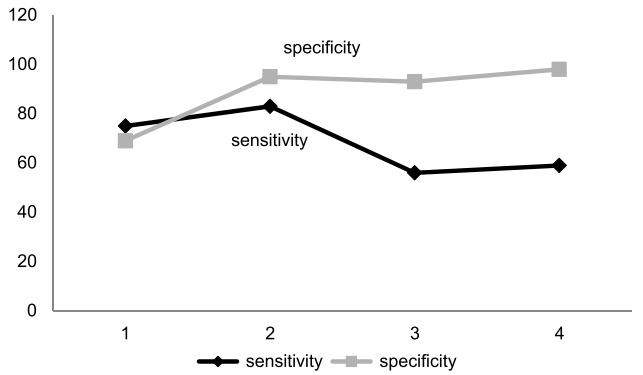


Figure-3. Specificity and sensitivity of ultrasound to assess the bone erosion

The specificity and sensitivity of ultrasound to evaluate bone erosion in rheumatoid arthritis patients ranged from 69% to 98.7% and 35.9% to 83% respectively (Table-II Figure-3). A cohort study performed by Piga et al. in 2016 was excluded because it reduced the mean sensitivity.[28]

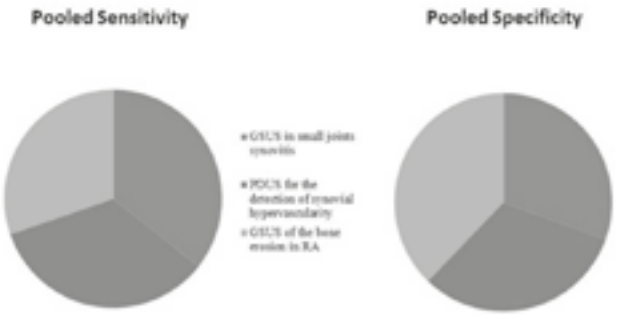
DISCUSSION

US proved as an inexpensive and reliable implement for the analysis of rheumatoid arthritis (RA). According to the previous ten studies the pooled specificity and sensitivity of grayscale ultrasound to assess the synovitis is 71.666% and 80.333%[19-21], the pooled sensitivity of US is 76.8% and specificity 74.25% to assess synovial hypervascularity[23-26], and the pooled sensitivity of US is 68.25% and pooled specificity is 88.75% respectively[25,29,23,20] for the evaluation of bone erosion (Table 4) that is less than a study reported by Hassan et al. the pooled specificity and sensitivity of grayscale US for synovitis assessment in small joints is 79.8% and 83.5%, the pooled specificity and sensitivity of PDUS to examine synovial hypervascularity is 85.233% and 77.633%, and the pooled specificity and sensitivity of US is 93.85% and 58.385% respectively for the assessment of bone erosion.[30]

Ten articles assessed the specificity and sensitivity of ultrasound for the assessment of rheumatoid arthritus in which 388 patients (122 male and 266 female) were examined.[19-26,28,29]

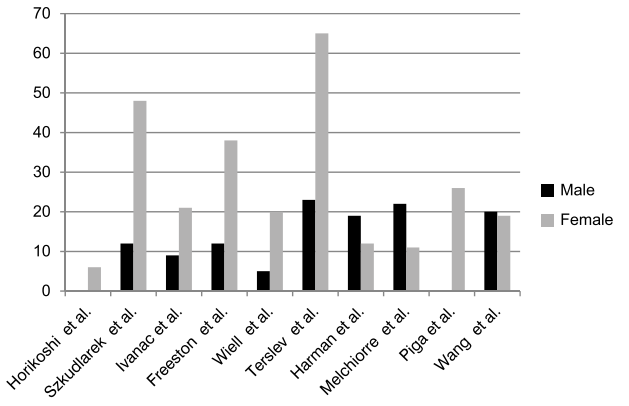
Ultrasonography	No. of Studies	Minimum	Maximum	Mean	Standard Deviation
Grayscale US of the synovitis					
Specificity	3	50.00	87.00	71.6666	19.29594
Sensitivity	3	70.00	100.00	80.3333	17.03917
Power Doppler US of synovial hypervascularity					
Specificity	4	60.00	88.00	74.2500	11.5
Sensitivity	4	70.00	92.00	76.8000	10.21241
GSUS of the bone erosion in RA					
Specificity	4	69.00	98.00	88.7500	13.32603
Sensitivity	4	59.00	83.00	68.2500	12.89379

Table-IV. Pooled specificity and sensitivity of ultrasound



Pie chart for Pooled sensitivity and specificity

Authors	Total	Male	Female
Horikoshi et al.	6	0	6
Szkudlarek *et al*.	60	12	48
Ivanac et al.	30	9	21
Freeston *et al*.	50	12	38
Wiell et al.	25	5	20
Terslev et al.	88	23	65
Harman et al.	31	19	12
Melchiorre et al.	33	22	11
Piga et al.	26	0	26
Wang *et al*.	39	20	19



Graph for Males and Females

Ultrasound is becoming a useful tool for assessing synovitis in rheumatoid arthritis (RA). It has now satisfied the OMERACT filter's requirements, including the ability to identify the issues of face and content.[31] Requirements for reliability vary depending on the application. Some of these include the development of concord guidelines and improving machine value.[32]

In studies where observers did not have full knowledge of US, its reliability was improved by training and standardization. Despite its increasing availability, there are still no quality validation studies.[33] The OMERACT group has proposed the use of terms such as synovial hypertrophy and SF to describe the different phases of joint inflammation. It has also provided various approaches for assessing this condition.[34] The various systems used for assessing synovitis include the greyscale and Doppler US. The evaluation of the condition includes a variety of physical examinations and scores on various components of the disease.[35]

Conventional imaging methods such as radiograms and MRI are well-established support tools for assessing the status of joint inflammation. However, they can't diagnose joint damage and are not very sensitive. High-quality musculoskeletal ultrasound (MSUS) is becoming more prevalent in rheumatological practice. Although it can detect synovial proliferation, it can also recognize neoangiogenic and active inflammation. Both parameters are good candidates for follow-up in patients with RA. MSUS can also be used to evaluate the bone erosions, as well as for the prediction of disease and structural progression.[36]
Musculoskeletal ultrasound has been used to monitor and measure the status of RA diseases, such as rheumatoid arthritis. Its reliability, reproducibility, and sensitivity to change make it an integral part of the rheumatology routine. GS images are commonly used to evaluate the anatomic structures and Doppler shows the blood flow of patients with arthritis. They can also provide an accurate depiction of the bony and soft tissue changes during the disease.[37]

This systematic review has some limitations. Our systematic review concentrated on wrist and finger joints instead of large joints. As renowned above, only four studies are representing the capability of US and MRI to identify synovitis for large joints including knee and shoulder. On the other hand, the small joints in the feet and hands including MCP, PIP, and UC joints play a fundamental role in the analysis of RA.

CONCLUSION

In conclusion, US is a vital diagnostic too alongwith X-ray, CT, MRI, clinical and laboratory inspection for the assessment of bone erosion, synovitis, and synovial hypervascularity. GSUS and PDUS have good pooled sensitivity and specificity and can detect changes on small joints in rheumatoid arthritis patients so, it has become useful in the diagnosis and treatment of RA.

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