ROLE OF ULTRASONOGRAPHY IN EVALUATION OF ANKLE JOINT PATHOLOGIES IN PATIENTS WITH RHEUMATOID ARTHRITIS - A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY

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Sir/Madam,

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LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
USE	Ultrasonography
RA	Rheumatoid Arthritis
TA	Tibialis Anterior
FDL	Flexor Digitorum Longus
FHL	Flexor Hallucis Longus
EDL	Extensor Digitorum Longus
EHL	Extensor Hallucis Longus
TP	Tibialis Posterior
PL	Peroneus Longus
PB	Peroneus Brevis

ABSTRACT

Background and objectives:

Rheumatoid arthritis is one of the common type of inflammatory arthritis especially important among various musculoskeletal disorders. It affects the individuals between 20 to 40 years of age in their more productive years and leads to chronic disability due to pain and deformity. The prevalence is highly variable ranging between 0.3% to 1%. It is more prevalent among females and those living in developed countries.

The term ‘rheumatoid arthritis’ was first introduced by Garrod more than 150 years ago in order to differentiate this condition from other disease conditions with similar manifestations such as gout and acute rheumatic arthritis. Rheumatoid arthritis is characterized as a chronic inflammatory condition where the etiology is not known. The peripheral joints are more commonly involved and the polyarthritis is symmetric

The importance of early diagnosis of rheumatoid arthritis is paramount. Rheumatoid arthritis not only affects the joints, but also has systemic involvement. Diagnosis of rheumatoid arthritis is based on clinical and laboratory findings. Pain, boggy swelling of the small joints with morning stiffness are most commonly reported in rheumatoid arthritis. Rheumatoid factor is positive among those with rheumatoid arthritis, though it may not be specific. Anti-citrulinated protein antibody is more specific for RA.

One of the more recently explored modalities for diagnosis of rheumatoid arthritis is ultrasound of the ankle. Patients presenting with ankle pain during the early stages are more likely to have isolated tenosynovitis of ankle joint. This feature of

rheumatoid arthritis can be found even before the onset of deformities in the advanced stages of the disease. Although MRI is the gold standard for evaluating the ankle changes, it is more expensive and hence not applicable in wider settings. Ultrasound on the other hand, is cost-effective and can be used to screen patients presenting with ankle pain in the outpatient department.

The objective of this study is to evaluate the role of Ultrasonography of Ankle Joint in confirmed cases of Rheumatoid Arthritis presenting with either clinical or subclinical ankle involvement.

Materials and methods

One year prospective cross sectional study was done in Department of Radio-diagnosis at the KLE'S Dr. Prabhakar Kore hospital & MRC, Belagavi.

30 patents were included in the study. These patients are subjected to sonourethrography of bilateral ankle joints.

In this study, tibio talar joint synovits was considered as primary outcome variable and demographic parameters like age, gender etc were considered as primary explanatory variables.

Results

The most common muscle involved in the medial compartment was tibialis posterior. 33.3% of the subjects in the right ankle group had tenosynovitis of tibialis posterior compared to 26.67% in the left ankle group. The vascularity of tibialis posterior was abnormal in 30% of subjects in the right ankle group compared to 26.67% in the left group.

The most common muscle involved in the lateral compartment was penoneus longus. In the lateral compartment, 30% had tenosynovitis of peroneus longus in the right ankle group compared to 23.33% in the left ankle group.

The most common muscle involved in the anterior compartment was tibialis anterior. In the anterior compartment, 30 % had tenosynovitis of tibialis anterior in the right side group and 20% in the left group.

Thickening of the synovium of talocalcaneal joint and increased vascularity were other parameters evaluated affecting 23.3% in the right side group compared to 13.33% in the left side group and 20% of subjects in the right side group and 10% in the left side group respectively.

16.67% had bulky and hypoechoic tendoachilles at insertion (Enthesitis) in the right sided group compared to 10% in the left sided group.

Interpretation and conclusion

Rheumatoid arthritis is a chronic inflammatory condition with systemic involvement. In our study majority (73.3%) of the study population were females and majority aged between 30 to 39 years. 80% of subjects were positive for RA factor. The most common muscle involved in the medial, lateral and anterior compartments were tibialis posterior, peroneus longus and tibialis anterior respectively. The common findings observed were tenosynovitis and increased vascularity in the tendons involved, presence of increased joint fluid, joint erosions and synovium thickening of talocalcaneal joint and retrocalcaneal region. In the medial compartment, 33.3% of the subjects in the right ankle group had tenosynovitis of tibialis posterior compared to 26.67% in the left ankle group. In the medial

compartment, 20% had tenoynovitis of flexor digitorum longus in the right ankle group compared to 16.67% in the left ankle group. In the lateral compartment, 30% had tenosynovitis of peroneus longus in the right ankle group compared to 23.33% in the left ankle group. In the anterior compartment, 30% had tenosynovitis of tibialis anterior in the right side group and 20% in the left group. In Talocalcaneal joint, 23.3% had thickened synovium in the right side group compared to 13.33% in the left side group.

Ultrasound of the ankle is a very efficient, simple, reliable and easily accessible modality distinguishing rheumatological pathologies of the ankle such as tenosynovitis, synovitis, and erosions. USG gives a wide range of information that can be used as complementary data to the clinical assessment. Early diagnosis of rheumatoid arthritis by USG will aid in early initiation of treatment and better quality of life.

Keywords: Rheumatoid arthritis, Ultrasonography, Tenosynovitis.

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INTRODUCTION

According to the World Health Organization, the broad category of musculoskeletal conditions consist of more than 150 diseases. In general, they are all progressive and characterized by chronic pain. Globally, musculoskeletal disorders are the major cause of disability and long-term morbidity. This in turn, results in reduced productivity, decreased quality of life and increased health expenses. Rheumatoid arthritis is especially important among the various musculoskeletal disorders. It affects the individuals between 20 to 40 years of age in their more productive years and leads to chronic disability due to pain and deformity. The prevalence is highly variable ranging between 0.3% to 1%. It is more prevalent among females and those living in developed countries. Almost 50% of those affected by rheumatoid arthritis cannot work in a full-time occupation in less than 10 years of disease onset[1].

The term 'rheumatoid arthritis' was first introduced by Garrod more than 150 years ago in order to differentiate this condition from other disease conditions with similar manifestations such as gout and acute rheumatic arthritis[2]. Many decades later, rheumatoid arthritis was further subclassified based on criteria such as presence of autoantibodies. Clinically divergent phenotypes are prevalent due to factors such as various gene involvement, environmental factors influencing the disease process and the patient response to treatment[3].

Rheumatoid arthritis is characterized as a chronic inflammatory condition where the etiology is not known. The peripheral joints are more commonly involved and the polyarthritis is symmetric. It is one of the most widespread auto-immune conditions all over the world. The joint involvement and resultant inflammation leads

to damage to the joints, deformities and disabilities. Rheumatoid arthritis not only affects the joints, but also has systemic involvement. The systemic involvement is characterized by symptoms such as pulmonary involvement, fatigue, peripheral neuropathy and abnormalities in the hematologic parameters[4].

Rheumatoid arthritis is characterized by a plethora of symptoms such as joint ache, stiffness in joints and swelling of joints. The involvement in rheumatoid arthritis is symmetric, distinguishing it from other forms of arthritis. In addition, non-specific constitutional symptoms such as loss of weight, lethargy and fever may also be present[5].

The presence of certain factors is associated with increased propensity for rheumatoid arthritis. The risk of RA increases with advancing age. Moreover, females are at 2 to 3 times increased risk of acquiring RA when compared to men. Hispanic ethnicity, low socio-economic status, smoking and obesity are known to be additional risk factors for acquiring RA and its increased severity. Breastfeeding is a protective factor for decreasing the risk of RA[6].

The importance of early diagnosis of rheumatoid arthritis is paramount. Rheumatoid arthritis is associated with multiple consequences which can lead to disability, morbidity and impaired quality of life. Those with RA are at an increased risk for developing cardiac complications, diabetes, hypertension and dyslipidemia. The individuals with co-existing obesity have a lesser response to therapy. In addition, loss of employment can occur due to pain and resultant disability. This is significant since RA and cardiovascular co-morbidities increase with advancing age. Due to the aging population globally, the burden of rheumatoid arthritis is expected to increase, resulting in increased debility.

Diagnosis of rheumatoid arthritis is based on clinical and laboratory findings. Pain, boggy swelling of the small joints with morning stiffness are most commonly reported in rheumatoid arthritis. Rheumatoid factor is positive among those with rheumatoid arthritis, though it may not be specific. Anti-citrulinated protein antibody is more specific for RA. During the active phase of the disease, C-reactive protein and erythrocyte sedimentation rate are also elevated[7].

One of the more recently explored modalities for diagnosis of rheumatoid arthritis is ultrasound of the ankle. Patients presenting with ankle pain during the early stages are more likely to have isolated tenosynovitis of ankle joint. This feature of rheumatoid arthritis can be found even before the onset of deformities in the advanced stages of the disease. Although MRI is the gold standard for evaluating the ankle changes, it is more expensive and hence not applicable in wider settings. Ultrasound on the other hand, is cost-effective and can be used to screen patients presenting with ankle pain in the outpatient department[8].

Early diagnosis of rheumatoid arthritis will aid in early initiation of treatment. This in turn, will impede the onset of deformities, thus improving the patients' quality of life.

Need for the study:

Rheumatoid arthritis is a highly prevalent autoimmune condition. It significantly impairs the quality of life. The burden is increasing with aging population and in developing countries it leads to a significant loss of productivity. Early diagnosis is of paramount importance in early initiation of treatment for improving the quality of life and preventing deformities. Ultrasonography of the ankle is one of the recently explored modalities to aid in the early diagnosis and evaluation of rheumatoid arthritis among patients presenting with ankle pain. Early diagnosis of RA and evaluation of ankle pathologies using ankle ultrasound is thus expected to aid in early initiation of therapeutic modalities. There is a lack of studies regarding this in developing countries such as India. Hence, this study seeks to explore the diagnostic utility of ankle ultrasound in rheumatoid arthritis.

AIMS AND OBJECTIVES

- To evaluate the role of Ultrasonography of Ankle Joint in cases of Rheumatoid Arthritis presenting with either clinical or subclinical ankle involvement.

REVIEW OF LITERATURE

Rheumatoid arthritis – basics:

Rheumatoid arthritis has been mentioned to be the most frequently prevalent autoimmune conditions affecting the joints. Approximately, 0.5% to 1% of the global population have been estimated to be suffering from rheumatoid arthritis[9]. The etiology of rheumatoid arthritis has not been fully known. However, so far, the involvement of type 17 helper T cells along with the dendritic cells have been known to be the key in the inflammatory processes involved in rheumatoid arthritis.

Rheumatoid arthritis affects the small joints more commonly. The joint inflammation results in destruction of joints along with disintegration. This disintegration of joints results in deformities classical of rheumatoid arthritis such as swan neck deformity and boutonniere deformity. The prognosis of the condition is variable. It is mostly dependent on the response of the individuals to the various treatment methods. Inadequate treatment causes progression of the condition and the resultant decline in the quality of life[10].

Rheumatoid arthritis – burden (Global):

The study by Symmons et al[11] (2002) aimed to estimated the burden of rheumatoid arthritis in the United Kingdom. They enrolled 7050 individuals for the study. On analysis, it was found that the overall prevalence of RA in the United Kingdom was 1.16% among females and 0.44% among males. The authors mention that the true prevalence may even be higher since this study might have under-reported the cases which were on remission after management as well as those cases which had significant disability.

Vanhoof et al[12] (2002) conducted a study to assess the burden of rheumatological diseases in Belgium. Among those who were included in the study, 69% were women. Joint involvement was diagnosed among 42% of all the patients who reported rheumatologic symptoms. Among those who returned with similar complaints to the out patient department, 28% had rheumatoid arthritis. The authors conclude that degenerative diseases of the joint and spine were common rheumatological conditions reporting in the outpatient department. Among patients who report recurrent complaints, inflammatory rheumatic diseases were more common.

Silman et al[13] (2002) conducted a study on the burden of RA. They mention that some ethnicities such as the Native American Pima Indians and the Chippewa Indians have the highest prevalence of rheumatoid arthritis, where the prevalence ranges between 5% to 6%. Countries such as China and Japan report a lower prevalence. This indicates the role of genetics in the risk of RA. Rheumatoid arthritis commonly occurs in populations where the HLA DRB1 allele, in particular HLA DRB1*0404, is common. Other factors known to increase the risk are TNF genes, estrogen synthase, and environmental factors. Furthermore, viral infections such as Epstein Barr virus and parvovirus have also been implicated in etiology of RA.

Gibofsky et al[14] (2012) performed a study on the epidemiology of rheumatoid arthritis. They mentioned that the global prevalence of rheumatoid arthritis varies between 0.5% to 1% but it may be decreasing in America. From 1995 to 2005, there were 1.29 million cases of RA in America which had decreased from 2.1 million earlier.

Dowman et al[15] (2012) conducted a systematic review on the burden of rheumatoid arthritis in Africa. They included a total of 335 studies which included 10 population-based studies and 11 hospital-based studies. According to their study, the prevalence of RA in Africa was 0.36%. The prevalence was projected to increase to 0.42%. This reflects a total of 2.3 million cases of rheumatoid arthritis which was projected to increase to 4.3 million in the next decade. The prevalence was under-reported among hospital-based studies compared to population-based studies.

Humphreys et al[16] (2013) conducted an analysis of the Norfolk register for estimating the incidence of Rheumatoid arthritis. They report that the overall incidence rate for RA was 40 per 100,000 in the general population. The incidence rate was higher among women at 54 per 100,000 compared to men (25 per 100,000).

Handa et al[17] (2016) conducted a literature review on the epidemiology of rheumatoid arthritis in the Indian subcontinent. They reported that the prevalence of RA in the Indian population ranged from 0.28% to 0.7%. Among various studies, 62% of the clinically diagnosed cases were positive for rheumatoid factor. But all of the cases were positive for anti-CCP antibody. Among those with prior rheumatic musculo-skeletal diseases, the prevalence of RA was higher at 3.5%. The authors emphasize the need for longitudinal studies for studying the trend of RA in India.

Iltchev et al[18] (2016) conducted a study on the trends of RA in Poland from 2008 to 2012. During their study, the number of cases of RA had increased to 2.3 lakhs from the previous 1.73 lakhs. Those hailing from rural areas comprised of one-third of the total number of cases. The morbidity rate among urban areas increased from 5.08 to 8.14. The concurrent increase among rural areas was from 3.74 in 2008 to 3.98 in 2012. The risk of RA was 3.5 times higher among females. Decreased

access to health care was found to be associated with increasing morbidity. The authors concluded that with the increase in aging population, the prevalence of RA continues to rise.

Jin S et al[19] (2017) conducted an analysis of those enrolled in the Chinese registry for RA. They included 13,210 patients. Among them, 80.6% were women. The average age was 52.9 years. The patients had RA since an average of 4 years duration. The overall prevalence of co-morbidities was 4.2%. Among the various co-morbidities, cardiovascular disease had a prevalence of 2.2% and 1.7% had fragility fractures. Women who had a long duration of RA had an increased risk for fragility fractures. Methotrexate was found to be protective from various co-morbidities.

Rheumatoid arthritis – burden (India):

One of the earliest studies on the burden of rheumatoid arthritis in India was conducted by Malaviya et al[20] (1993). They conducted a house to community-based study in a rural population in the vicinity of Delhi. Around 44,551 individuals above the age of 16 were included. On analysis, it was found that the overall prevalence of rheumatoid arthritis in the study population was 0.75%. The authors report that this would translate to 7 million cases of rheumatoid arthritis in India. The prevalence of RA is higher than the prevalence reported in countries such as Africa, Indonesia and China. This was postulated to be due to the genetic similarity of North Indians with Caucasians.

Mijiyawa et al[21] (1995) conducted a study on the epidemiology of RA among developing countries. In their study, the prevalence of RA in India was reported to be 0.75% which was similar to the Western countries. On contrast, countries such as China and Philippines report a relatively lower prevalence of 0.4% irrespective of

urban or rural locality. In Africa, the prevalence is highly variable. It is quite rare in the rural regions while in Jamaica, the prevalence was as high as 2%. In Latin America, among those who reported to the clinics with musculoskeletal symptoms, as many as 22% had rheumatoid arthritis. The HLA DR4 antigen was more common among South African population.

Chopra et al[22] (2012) conducted a nationwide survey on the burden of rheumatoid arthritis in India. They mentioned that 198 patients in their survey were found to have clinical rheumatoid arthritis. Among them 83% were females. The overall crude prevalence of RA was 0.38% ranging between 0.30% to 0.44%. The adjusted prevalence was 0.34%. RA was 5 times more common among women when compared to men. Among various age groups, highest prevalence was reported among 25 to 44 years with 42% prevalence. Among those who had RA, 40% were between 45 and 64 years of age. Extremes of age had a comparatively lesser prevalence. Only 16% of RA cases were more than 65 years old and only 2% were between 15 and 24 years of age. In India, Rajasthan had a high prevalence of 0.8%. But due to the high population density of India, even a prevalence as low as 0.34% translates to a total of 5 million cases of rheumatoid arthritis. The authors emphasize that despite a low prevalence, due to the increased number of cases overall, rheumatoid arthritis needs to be focused at the national level.

Chopra et al[23] (2015) conducted a study on the burden of RA in India. They report that the overall prevalence of rheumatoid arthritis across India was 0.34% ranging between 0.08% to 0.79%. In regions such as Gwahati, Kolkata and Trivandrum the prevalence was 0.4%. A higher prevalence of 0.8% was reported in Bikaner. The incidence of RA among young women in India was higher compared to

global reports. Regions with increased tobacco use also reported higher prevalence of rheumatoid arthritis.

Rudan et al[24] (2015) conducted a meta-analysis on the burden of RA among low and middle income countries. The authors report that the prevalence of RA among the South East Asian countries and Mediterranean countries was 0.4% and 0.37% respectively. Among the low- and middle-income countries, the prevalence among females was 0.75% and among males it was 0.16%. There were no significant differences in the prevalence between urban and rural areas. According to their study, 3.16 million men and 14.87 million women living in the low- and middle-income countries were estimated to be suffering from RA.

Kumar et al[25] (2018) conducted a study on the burden of rheumatic diseases among the rural and urban regions of Lucknow in India. They mentioned that in their community-based study, among those who report musculoskeletal pain, 35% had osteoarthritis, 32.1% had fibromyalgia, 28.4% had backache and only 1.2% had rheumatoid arthritis. In urban areas, the prevalence of RA was 1.6%. The projected overall prevalence of RA among the rural and urban populations were 1.56% and 4.74% respectively.

Yadav et al[26] (2019) conducted a study on the epidemiology of various rheumatic diseases in a tertiary care hospital. They included 1000 patients in the study. Their average age was 44.78 years. The mean BMI was 25 kg/m^2. The study population had rheumatic diseases for an average of 3.62 years. Among the study participants, the most common rheumatic disease was rheumatoid arthritis prevalent among 49.3%. Other conditions such as SLE and spondylo-arthritis were prevalent among 9.1% and 16.5% respectively. The age group between 40 to 60 years had the

highest incidence of RA. Obesity was significantly associated with increased risk of rheumatoid arthritis.

Pathophysiology of rheumatoid arthritis:

Rheumatoid arthritis involves the inflammation of the synovial tissue and also the cartilage and bony structures. In RA, there is inflammation of the synovium, proliferation and bony erosion. There is thinning of cartilage in the articular surface due to the chronic inflammatory process. Long standing inflammation causes hyperplasia of the synovium. Fibroblast like cells in the synovium along with fibrovascular tissue proliferate and produces pannus and this extends into the cartilage and bone beneath the synovium. New blood vessels are formed in the underlining of synovium due to the growth factors which are produced by the fibroblasts[14, 27].

Near the edge of the articular cartilage and along the insertions of tendons and ligaments, osteoclasts appear. These are responsible for the damage to the bone and cartilage occurring in rheumatoid arthritis. During the inflammatory process, osteopenia also occurs in the periarticular region. The third cause for bone loss is the diffuse osteopenia all over the body in the trabecular bones. All these factors contribute to the osteopenia among those who have RA.

Cartilage damage also occurs together with bone damage. Initially it is limited near the regions of synovial pannus. In the superficial regions where the cartilage is near the synovial fluid, there is a decreased level of proteoglycans. Later on, the cartilage loss extends to the peri-chondrocytic and sub-chondral bones as well[28, 29].

The multiple pathologic mechanisms which result in inflammatory process of RA is due to genetic and environmental factors which interact with immunologic

responses. This results in loss of self-tolerance and leads to auto-immunity. The exact triggering factors for the pathogenesis in RA are yet to be understood in entirety[30].

Pre-clinical stage:

Even before the occurrence of overt disease, the pre-clinical stage occurs which is characterized by the presence of rheumatoid factor and anti-CCP antibodies in the blood. However, the exact role of such antibodies during the pre-clinical phase is unknown. Anti-CCP antibodies act against proteins such as fibrinogen, keratin and vimentin which are found in the synovial fluid at high levels. This explains why smoking is a risk factor for RA since, smoking increases the levels of citrullination of such proteins leading to the formation of immune complexes and inflammation[31].

Another explored etiology of RA is infectious etiology. The presence of toll-like receptors in the body is responsible for identification of microbial proteins, double-stranded RNA viruses and bacterial DNA. There are 10 types of toll-like receptors. Among these, types 2,3 and 4 are expressed in large quantities by the fibroblasts in the synovial membrane during the initial stages of RA. Binding of microbial products to such receptors results in release of cytokines which cause inflammation. Some of the microbes implicated so far include Epstein Barr virus, mycoplasma, Proteus mirabilis, Salmonella and Enterobacterium[32, 33].

In the thymus, immature T cells undergo the process of selection. T cells which react to body's own antigens are not selected and hence auto immunity is prevented. Defects in this mechanism of T cell selection occurring in the thymus or dysregulation of signaling mechanisms decrease the level at which the T cells drive inflammation. Additional mechanisms postulated include pre-mature aging of T cells and decrease in production of new T lymphocytes from the thymus[34-36].

There is also a significant involvement of CD4 + T helper cells in the inflammation occurring in RA. In animal studies, CD4 + T cells play a significant role in the pathogenesis of arthritis. Binding of the co-receptor in CD4 cells to MHC class II antigens result in production of complexes during the activation of T lymphocytes. The shared epitope present in the class II MHC molecules acts as a risk factor for rheumatoid arthritis. This implies that activation of CD4 + T cells might be involved in the pathological process in RA[37, 38]. Among patients who have RA, the memory T cells are primed with the synovial tissue, thus implying an additional mechanism. Moreover, therapies which are directed at the T cell mediated immune response have been shown to be effective in rheumatoid arthritis. Pathogenesis in RA might also be influenced by other cells such as B cells, natural killer cells and CD 8+ T cells[39].

Among those with RA, due to the release of soluble mediators and through direct cell-cell contact, stimulation of fibroblast like cells in the synovium and macrophages occurs. This in turn, causes the release of cytokines which results in the inflammatory process and subsequently results in damage to cartilage and bone. Activation of CD4 + T cells can occur in two pathways, by binding to either the peptide-MHC or the CD 80/86 present in the surface of the antigen presenting cells[40]. A recently discovered subset of T lymphocytes are Th17 cells. When the T cells are exposed to interleukin-1, IL-6 and IL-23, they differentiate into Th17 cells. These subset of T cells produce cytokines such as IL-6, IL-17, Tumor Necrosis Factor-alpha and Granulocyte-Macrophage-Colony stimulating factor. These cytokines cause joint damage and inflammation[41-43].

In order to prevent the inflammatory processes from being activated, there are regulatory mechanisms in the form of regulatory T cells. In the periphery they

suppress the inflammatory responses due to triggers and thus prevent auto-immunity. The regulatory T cells are identified by the expression of CD-25 on their surface and they secrete factors such as IL-10, TGF-β, which serve as inhibitory cytokines. There are various subclasses of T regulatory cells. Each subset suppresses a different class of T cell namely T helper 1, T helper 2 and T helper 17 types of immune mediated response. However, the mechanisms which affect the regulatory T cells in RA are not yet clearly understood[44, 45].

Once the inflammatory process is initiated, it is amplified due to the cascade of cytokines, antibodies and other chemokines. This is of use in targeted therapy for RA when such inflammatory loops are blocked by the drugs that bind to inflammatory mediators. Some key target molecules include Janus kinase (JAK), nuclear factor- κB and spleen tyrosine kinase[46, 47].

In addition to T cell mediated immune mechanisms, B cells also play a significant role in RA. When B cells are activated, they produce antibody secreting plasma cells. These antibodies include autoantibodies such as rheumatoid factor and anti-CCP antibodies. The formation of immune complexes inside the joint space occurs which activates the complement pathway and releases inflammatory cytokines. This further accentuates the local inflammatory process[48, 49].

The major type of cells in addition to T cells and B cells are the macrophages. The macrophages present in the synovium release the cytokines responsible for joint inflammation. TNF-α, a key cytokine in the pathogenesis of RA is secreted by both the macrophages as well as the synovial fibroblasts. This cytokine is responsible for the infiltration of leukocytes into the synovium. It also promotes angiogenesis and

production of osteoclasts. The synovial fibroblasts promote the degeneration of articular cartilage by the secretion of matrix metalloproteinases[50, 51].

The bony erosion occurring in RA is due to activation of osteoclasts. The T cells, stromal cells and the fibroblasts present in synovium express the ligand for nuclear factor-κB. The osteoclast progenitors are usually present as the monocytic cells of synovial membrane. When this ligand binds with the corresponding receptor present in the progenitors of osteoclasts, the osteoclast progenitors are induced to differentiate into osteoclasts and thus result in bone resorption. This process is further aggravated by the release of inflammatory cytokines such as IL-6, IL-17 in the synovial microenvironment. Osteoclasts contribute to bone damage by the release of a protease called cathepsin K[52, 53].

Bone resorption and bone remodelling usually occurs in a regulated manner, but in case of patients with RA, the bone formation process is suppressed because of the inflammation. In particular, the TNF-α increases the genetic expression of DKK-1. The translational product of this DKK-1 gene inhibits the Wnt pathway which stimulates bone formation. The proteins of the Wnt pathway also increase the expression of osteoprotegerin, which in turn inhibits the action of osteoclasts[54].

Ankle involvement in rheumatoid arthritis:

Pain in the feet region especially ankle region is a significant presenting complaint in rheumatoid arthritis[55]. It is also a challenge in managing the various aspects of RA. In one of the earliest studies by Minaker et al[56], among 50 patients with rheumatoid arthritis, 28% had a history of painful feet as an early presenting symptom. Among the patients, almost 90% had a complaint of foot pain at any point

during the disease course. Almost all of them had radiological signs suggestive of feet involvement as well.

Michelson et al[57] (1994) assessed the prevalence of ankle involvement among those with RA. Their study population included a total of 99 patients who had RA. Among them, 93.94% had pain in the feet or ankle at any point since they were diagnosed with RA. The prevalence of ankle problems was significant among 42%, pain in forefoot was reported among 28% and 14% had pain in both forefoot and ankle. Although there was a positive correlation of ankle pain with illness duration, more than half of the study population reported a history of feet or ankle pain at any point during the disease.

Abdo et al[58] (1994) studied the involvement of feet and ankle in rheumatoid arthritis. They mention that RA affecting the ankle or foot is debilitating. The most common findings included the involvement of forefoot with hallux valgus deformity, subluxation and dislocation of the smaller metatarsophalangeal joints. Excisional arthroplasty of the lesser MTP joint and arthrodesis of first MTP joint are the common surgical reconstruction methods. Involvement of hindfoot commonly resulst in pes planovalgus deformity. Ankle joint has a lesser predilection for RA, though when conservative measures are not adequate in pain management, arthrodesis may be required. A combination of various measures is needed for improving the functional capability of patients with RA.

Jaakkola et al[59] (2004) mentioned that rheumatoid arthritis has a predilection for the feet, especially the ankle. Around 20% of the cases with RA initially present with ankle pain in the absence of other symptoms. A majority of the patients with RA eventually develop inflammatory changes in the ankle in the course of the disease.

Management of ankle and feet symptoms is essential for reducing the morbidity and disability.

According to Clair et al[60] (2004), ankle involvement in rheumatoid arthritis can be subclinical during the initial stages but is prone for rapid progression. The subtalar joint and talonavicular joints are most commonly affected by synovitis. The tibialis posterior and peroneus tendons near the ankle joint are more commonly affected. On clinical examination, pain response is elicited by tendon palpation. Severe deformities of the hindfoot can result due to inadequate treatment of the tenosynovitis of tibialis posterior. They concluded that the ankle joint can be spared until the advanced stages of the disease in case of hindfoot involvement. But valgus of hindfoot can result due to the affected subtalar or talonavicular joints. Forefoot involvement is more frequently prevalent.

Grondal et al[61] (2008) studied the disability due to foot involvement among those with RA. They included 1000 patients with rheumatoid arthritis and enquired regarding foot symptoms. Among 45% of the study population, there was involvement of the forefoot at the earlier stages of the disease. Among 17%, ankle involvement was present at the initial stages. Almost half of the study participants (52%) reported having pain in the ankle in the present. Forefoot pain was reported among 86% of the study population. Foot pain was mentioned as the cause for walking difficulty among 71% patients. Among 41%, foot involvement was only one of the major factors and among 32%, foot involvement was the sole factor for walking disability. The authors conclude that foot involvement results in significant disability among those with RA.

Otter et al[62] (2010) conducted a study on the involvement of feet and ankle in RA. They included 1040 individuals with rheumatoid arthritis and enquired regarding their foot symptoms. In their study, the prevalence of pain in feet and ankle was 93.5% and among them, 35.4% had foot pain currently. Persistent presence of moderate to severe pain in the ankle and feet was reported by 35.4%. Overweight/obesity and longer duration of disease was significantly associated with pain in ankle or feet. The authors conclude that despite the various advances in treatment of RA, ankle and feet pain are commonly prevalent and often under diagnosed.

Borman et al[63] (2012) conducted a study on foot problems among those with rheumatoid arthritis. They included 100 participants for the study and evaluated them for foot symptoms. Among the study participants, the female to male ratio was 9:1. Their average age was 52.5 years. Around 36% of the patients had ankle pain. The prevalence of forefoot pain was 30%. Hindfoot and midfoot pain was present among 17% and 7% respectively. Among the study participants, 66.7% of the females and 50% males had a past history of ankle pain. There was a significant correlation of ankle pain with the disease duration and BMI.

Rao et al[64] (2013) investigated the recent advances in foot function among those with RA. They mentioned that debilitating pain in the feet and foot deformities are present among many individuals who have rheumatoid arthritis. Foot symptoms are a major contributor to the functional disability in RA. A history of moderate to severe pain in foot is present among almost 70% patients with RA. Hence this poses a challenge to the clinicians. Deformity prevention and management of pain are of paramount importance in management of RA. Lack of clinical consensus in assessing

foot function and reduced access to foot care are the lacunae in the management of foot symptoms in RA.

Carter et al[65] (2016) conducted a study on the epidemiology of foot problems among those who had autoimmune arthritis in Singapore. The study population comprised of 50% women. The study participants had a mean age of 52 years. Rheumatoid arthritis was the most common inflammatory arthritis among the study population. A history of current foot pain was present among 48% of the participants. A prior history of pain in the foot was reported among 81% of the study population. Despite the high prevalence, only 21% had access to foot care. Hence the authors recommend increased focus on foot care among those with inflammatory arthritis such as rheumatoid arthritis.

Jeong et al[66] (2017) conducted a study on the functional disability in RA due to the involvement of ankle and foot. A total of 120 individuals were included in the study. Among them, 61.7% had involvement of either the foot or the ankle. Among the study population, 62.2% had involvement of the hindfoot and 5.4% had involvement of the ankle. The forefoot and midfoot were affected among 43.2% and 32.4% respectively. The individuals who had involvement of foot or ankle had more functional disability, a lesser quality of life and increased disease activity compared to those without foot or ankle involvement. In particular, involvement of the hindfoot or ankle was associated with increased functional disability.

Wilson et al[67] (2017) conducted a study in United Kingdom on foot problems among those who had rheumatoid arthritis. Among the 413 individuals included in the survey, 92.1% had a history of foot pain. Among those, 73.8% had pain in the joints of feet such as the ankle joints. Among those who reported a history of pain, 63.7%

mentioned having the pain currently while 82.8% reported a history of pain at any time during the course of RA. The participants had RA for an average duration of 10 years. The authors mentioned reduced access to foot care as a main reason for increased disability. Hence regular foot examination for those with RA was recommended by the authors for improving the functional ability.

Harman et al[68] (2017) studied the ankle pathology among those with inflammatory rheumatic arthritis. Among the study population, 98.6% had tender joints. Tenosynovitis of the tibialis posterior tendon was the most significantly prevalent finding among those with rheumatoid arthritis. Among the patients in the early stages of the disease, synovitis of the subtalar joint and the talonavicular joints were more common. For those with disease duration of more than 1 year, synovitis of the tibiotalar joint was prevalent. Foot function was significantly correlated with the presence of synovitis of subtalar joint and tenosynovitis of tendons of tibialis posterior and peroneus tendons. The authors conclude that tibialis posterior tenosynovitis is a specific finding for rheumatoid arthritis. With the longer disease onset, there is greater involvement of tibiotalar joint.

Yano et al[69] (2018) conducted a study in Japan on the profile of patients with rheumatoid arthritis who have ankle joint involvement as the initial clinical feature. Among the 5,637 patients included in the study, 43.8% had involvement of the feet or ankle as the earliest symptom of rheumatoid arthritis. The proportion of females was greater among those who had early foot involvement (87.7%) compared to those who did not have initial foot involvement (84.8%). Those who had early ankle involvement had a greater degree of disability, more severe disease activity, more seropositivity and increased dosage requirements for anti-inflammatory drugs. Hence

the authors recommend increased focus on ankle and foot symptoms among those in whom RA is suspected.

Role of ultrasound in rheumatoid arthritis- overall:

Koski et al[70] (1998) conducted a study on the ultrasound changes among those with rheumatoid arthritis. They performed clinical examination, X-ray and ultrasound examination among 30 healthy individuals and compared them to those with RA in early stages of the disease. It was found that on clinical examination, only 8 cases of plantar bursitis were identified. However, out of 25 patients with RA that were assessed, ultrasound diagnosed 14 cases of plantar bursitis. Hence the authors recommend that ultrasound examination is a more objective diagnostic tool in assessment of patients with RA.

Musculoskeletal sonography is being increasingly used all over the world. The gray scale ultrasound can be used to identify proliferation of the synovium. The Power Doppler ultrasound is useful in identifying active inflammation and neovascularization. Both can be of use in the diagnosis and follow up among those with rheumatoid arthritis[71, 72].

Delle Sedie et al[73] (2008) assessed the various perspectives and role of the Ultrasonography in the management of rheumatic diseases. They mentioned that sonography of musculoskeletal structures has been emerging as a significant tool for assessing and managing rheumatoid arthritis. Ultrasound enables imaging of the soft tissue structures and hence aids in early identification of synovitis, cortical erosion and damage to cartilage structures during the initial stages of the disease. Furthermore, the imaging is done in real time and hence it can also be used in aiding interventional procedures. Musculoskeletal sonography, together with imaging using

power doppler is of great utility for evaluating patients of rheumatoid arthritis regarding disease activity and progression. In addition, for monitoring of therapy using DMARDs and steroids, ultrasound can be used since it can measure vascular changes in the synovium. The authors recommended widespread use of ultrasound imaging in RA and also development of standardized protocols.

Chan et al[74] (2013) studied the natural history of foot involvement in rheumatoid arthritis. They mention that patients with RA experience foot-related symptoms in less than 10 years of disease onset. In the early stages, the symptoms are not obvious. Most patients only report a history of vague ankle pain. Additional symptoms include the presence of swelling posterior to the malleoli or the dorsum of the foot. Despite the presence of pain, localization may not be possible. In the initial 2 years, almost 90% of the patients with RA experience foot pain.

The European League against Rheumatism developed a set of recommendations for the use of ultrasound in rheumatoid arthritis. They performed a systematic review comprising of 199 studies. According to their findings, performing ultrasound or MRI can be used for confirming the diagnosis of RA in addition to the clinical criteria. Inflammation present during ultrasound evaluation can be utilized in predicting the risk of progression from non-specific arthritis to clinical rheumatoid arthritis. The risk increases with the number of joints involved. For assessing inflammation of joints, ultrasound has better sensitivity compared to clinical examination alone. Presence of synovitis and tenosynovitis in ultrasound is indicative of the risk of joint damage and bony erosion. Monitoring response to therapy and disease activity can be better assessed using ultrasound. Residual inflammation and

the risk of further joint damage can be predicted using ultrasound even when the patient is on clinical remission[75].

Iwamoto et al[76] (2015) conducted a study on the use of ultrasound in predicting relapse among those with rheumatoid arthritis. Patients with RA on either TNF-alpha blocker or tocilizumab were included in the study. When scoring was performed using gray scale or power doppler ultrasound, patients who had high scores during treatment discontinuation had an increased risk of relapse compared to those who had lower scores. The gray scale ultrasound had a positive predictive value of 80% and negative predictive value of 73.3%. Performing ultrasonographic assessment identifies the presence of residual inflammation of synovium among those who were on biological agents. The residual inflammation indicates a high risk of relapse on treatment discontinuation thus indicating the utility of ultrasound in therapy monitoring.

Zayat et al[72] (2015) conducted a study on the specificity of bony erosions in RA diagnosed using ultrasound. A total of 315 subjects were included for the study. Overall, the bony erosions detected using ultrasound commonly occurred in RA though the findings were not specific. The sensitivity was high at 91.4% but the specificity was only 32.9%. But when only 4 target joints were included, namely second and fifth metacarpophalangeal joints, 5^{th} metatarsophalangeal joints along with distal ulna, it increased the specificity to 97.9%. In particular, the presence of erosions in the 5^{th} metatarsophalangeal joint irrespective of size had a high sensitivity (68.6%) and high specificity (97.9%) for RA. There was also a positive correlation between the size of bony erosions and the likelihood of RA.

According to Ohrndorf et al[77] (2015), musculoskeletal ultrasound has a wide range of capabilities both as a diagnostic tool in rheumatoid arthritis, correlating with disease activity as well as monitoring response to therapy. Compared with clinical examination, musculoskeletal ultrasound using both gray scale as well as power doppler are more effective and reliable. In individuals with non-specific arthritis symptoms, ultrasound can aid in a conclusive diagnosis compared to performing clinical examination alone. Other roles include, monitoring response to therapy, diagnosing disease remission and ultrasound guided therapeutic interventional procedures.

Do Prado et al[78] (2018) studied the utility of ultrasound in rheumatoid arthritis. They mentioned that musculoskeletal ultrasonography can be a useful adjunct in the clinical assessment of RA. There is a significant correlation of ultrasound with the disease activity. In some instances, ultrasound can even be superior since it can identify even subclinical synovitis. The diagnostic utility of ultrasound is better for bony erosion when compared with synovitis. However, the authors conclude that there is still an unmet need for developing scoring systems for performing ultrasound in rheumatoid arthritis.

Role of ultrasound in ankle rheumatoid arthritis- specific:

Lehtinen et al[79] (1996) assessed the soft tissue changes in the ankles among those who have rheumatoid arthritis. Patients with RA in whom there were no X-ray changes were included in the study. Both ultrasound and MRI was used to assess the ankles of RA patients. It was found that ultrasound and MRI together diagnosed 76% of those with RA. Among the study population, 53% were positive by MRI findings alone and 59% had positive findings using ultrasound. Among the involved joints,

41% had involvement of talocrural joint and 41% had subtalar joint involvement. Synovitis was the most commonly reported finding in the joints. Among the tendons involved, 23% had involvement of peroneus tendon and tenosynovitis was the most common finding. There was a significantly high degree of concordance between MRI and ultrasound imaging of ankle joints in rheumatoid arthritis. But there was a poor correlation between clinical findings and ultrasound imaging. Hence the authors recommend ultrasonographic imaging of ankle joints due to the diagnosis of even subclinical changes, its wide availability and cost-effectiveness.

Micu et al[80] (2012) conducted a study on the ultrasound evaluation of the ankle and feet among rheumatoid arthritis patients. They recommend a systematic assessment for evaluating all the components such as the anatomical structures at ankle and foot level. The anterior, posterior, medial and lateral compartments are evaluated. In the assessment of joints, bony cortical erosions are typically found in rheumatoid arthritis. Compared to X-ray imaging, Ultrasound is superior for detection of erosions and synovitis. Tenosynovitis of the tibialis posterior tendon and tendon rupture at the level of insertion of navicular bone are also characteristic of RA. Early stages of RA also manifest as flexor hallucis longus tendon tenosynovitis. These findings are also recommended as a result of the "Outcome Measures in Rheumatoid Arthritis Clinical Trials"[81]. Hence the authors recommend sonography of ankle as a part of routine clinical assessment in rheumatology.

Suzuki et al[8] (2013) performed a clinical study on the ankle joint assessment among RA patients by ultrasound. They included 74 patients for the study. Among them the average age was 63.3 years and 70.2% were women. The average duration of RA was 4.2 months. Among the 100 ankle joints assessed, 56 had findings

consistent with synovitis of the talar joints. Ankle teno-synovitis was found among the medial recess, lateral recess or ankle recess. Thirty-nine individuals also had involvement of the Achilles tendon manifesting as enthesitis or paratendinitis. Presence of tenosynovitis in ankle joint was associated with a shorter duration of disease. Hence the authors recommend that ankle assessment in early stages of RA is beneficial and more feasible compared to MRI imaging.

Bowen et al (2013) reviewed the use of ultrasound for foot imaging in cases of rheumatoid arthritis. They mention that ultrasound of foot has advantages over MRI due to its imaging done in real-time, decreased cost, ability to be performed in bed-side and ability to image both bone and soft tissue simultaneously. In addition, the sensitivity and specificity of ultrasound is comparable to that of MRI. Clinical examination often leads to underestimation of the disease pathology in case of ankle RA. This drawback is overcome using ultrasound. Joint effusion and synovitis are 10 times more likely to be detected using ultrasound compared to clinical examination. The authors underline the need for specific protocols for ultrasound of foot in rheumatoid arthritis.

Alsuwaidi et al (2015) performed a sonographic comparison of the asymptomatic and symptomatic ankle joints among those who had rheumatoid arthritis. They included 80 patients and examined a total of 160 ankle joints. Among the study population, ankle pain was present in 97 ankles and 63 were symptomatic ankles. Tibiotalar joint arthritis or talonavicular joint arthritis was present among 77% of the ankles. The second most common pathology was the tenosynovitis of the tendons in the medial compartment among 28% ankles. Isolated arthritis in tibiotalar joint was diagnosed among 59% of the symptomatic ankles and 35% of asymptomatic

ankle. Around 35% symptomatic ankles and 18% of the asymptomatic ankles had synovitis of the talonavicular joint. The authors mentioned that ultrasound findings of ankle pathologies are more common among those with ankle symptoms.

Gutierrez et al[82] (2016) studied the ankle involvement in those with rheumatoid arthritis. In each ankle joint, evaluation was done regarding findings such as tendon rupture, tenosynovitis, synovitis and enthesopathy. The laboratory parameters such as ESR and C-reactive protein levels were assessed. The ankle findings were compared to those among healthy controls. It was reported that ankle abnormalities were present among 87% of those with RA compared to only 28.5% among the healthy individuals. The most common findings were tenosynovitis of the tibialis posterior tendon (31.9%), and peroneus longus tendon (26.9%). Synovitis of the tibio-talar joint was present among 25% and tenosynovitis of peroneus brevis was reported among 23.6%. In the Achilles tendon, 19% had enthesopathy and 10.2% had bursitis. The authors mention that subclinical involvement of ankle joint is more common among patients with rheumatoid arthritis.

Enache et al[83] (2017) conducted a study on ankle involvement among those with rheumatoid arthritis. They included 76 patients for the study and evaluated the ankle using power doppler and gray scale ultrasonography. In the ankle joint, the various components such as the achilles tendon, tibialis anterior tendon, tibialis posterior tendon, extensor hallux tendon, flexor hallux tendon, extensor and flexor digitorum tendons, peroneus longus and brevis tendons, the joints such as the tibio-talar joint, talo-navicular joints. The average age of the study population was 57.2 years. Among them 88% were females. Ankle abnormalities were detected among 81.6% using sonography. The various abnormalities diagnosed using USG included

synovitis of talo-navicular joint (38.2%), tibialis posterior tenosynovitis (30.3%), subtalar joint synovitis (56.6%) and tenosynovitis of the peroneus longus tendon. Among the patients who did not have ankle symptoms only 66.7% had ankle abnormalities while among those who were symptomatic, almost 93% had ankle abnormalities in USG. There was a significant correlation between ankle involvement with the ultrasound findings and the disease activity.

Elsaman et al[84] (2017) conducted a study on sonographic evaluation of ankle joints among those with rheumatoid arthritis. They evaluated 63 patients with active rheumatoid arthritis and assessed 126 ankle joints. They examined the tibio-talar and talo-navicular joints of those with active RA. The average age of the study population was 35.1 years. Females were twice at risk of RA compared to males. The study population had RA for an average of 22.7 months. DAS 28-ESR score on an average was 3.05. Among 30.2% of the patients, there was 'teno-synovitis of the flexor, extensor and peroneal tendons.' Other common sonographic findings were ankle joint synovitis (18.3%), joint erosion (8.7%) and tendinosis (4%). Hence, the authors emphasized the significance of performing sonographic assessment of ankle joints among RA patients. In the ankle joint, the most common areas of involvement are the tendons of tibialis anterior, posterior, the tibio-talar and talo-navicular joints. The onset of tenosynovitis is before the onset of synovitis. Tenosynovitis and synovitis correlated with the disease activity. Ankle joint erosion was found among those with longer duration of disease. Those who were positive for rheumatoid factor had more sonographic findings in the ankle joint.

Ultrasound of the ankle has been demonstrated to aid in the therapeutic aspects of rheumatoid arthritis as well. Wang et al (2017) assessed the efficacy of ultrasound

guided injection of hyaluronic acid on the outcomes among those who had RA of ankle joint. The authors reported US-guided injection resulted in significant improvement in functional capability and reduction of pain.

Toyota et al[85] (2017) evaluated the ankle symptoms in rheumatoid arthritis using ultrasound. They included patients with RA irrespective of ankle symptoms. Ankle examination was done by clinical examination, visual analog scale for pain and ultrasound. Gray scale ultrasound as well as power doppler were used for assessing synovitis or tenosynovitis of tibiotalar joint. Among the 120 ankles evaluated, 35% had positive findings in ultrasonography. There was a moderate degree of concordance between clinical examination and ultrasound. Among those who were negative for ankle symptoms in clinical examination, 10.2% had positive findings using USG. The presence of findings in USG correlated with disease activity and presence of pain. Hence the authors recommend that ultrasound of ankle can be of great utility among patients who have ankle pain but lack findings on clinical examination.

Hernandez- Diaz et al[86] (2019) compared the clinical and ultrasound findings in rheumatoid arthritis patients who had ankle pain. They assessed a total of 112 patients among whom 89.3% were females and 10.7% were males. Their average age was 51 years. Among the study population, 56.2% had a history of ankle pain. On sonography, pathological findings in the tendon or joint were reported among 65.2% of the patients. On grayscale ultrasound, 37.5% had joint involvement while only 22.3% had tendon involvement. The presence of clinical findings significantly correlated with the presence of tenosynovitis of peroneus tendon or synovitis of tibiotalar joint.

Management of ankle rheumatoid arthritis:

Treatment of the disease ideally begins with the education of the patient regarding the condition and the risks of complications such as joint damage and functional loss. Counselling about the risks and benefits of available treatment modalities is essential. A multi-disciplinary approach is beneficial. Consultations with physical therapists, social workers, occupational therapists, patient educators etcetera will be useful. A podiatrist should also be part of the team[87].

Pharmacotherapy:

Pharmacological management is the mainstay of treatment for all RA patients. Pharmacotherapy typically includes a non-steroidal anti-inflammatory drug (NSAID) for pain control, along with discriminatory use of low-dose oral or intra-articular steroids (glucocorticoids). Initiation of a Disease-Modifying Anti-Rheumatic Drug (DMARD) is usually done[59].

Previously the drug treatment of Rheumatoid Arthritis followed a pyramid approach - initially symptomatic treatment was started on diagnosing the condition and changes in doses with use of additional drugs was considered only if the symptoms aggravated. This approach has relatively fallen out of favour in recent times[88]. Now a "reverse pyramid" plan is preferred. In this approach, the DMARDs are started as soon as possible to retard the progression of the disease processes[89]. The change from a pyramid plan to a "reverse pyramid" approach was the culmination of several research conclusions - joint damage is an early process in the disease[90], DMARDs have important advantages when started early, the uses of DMARDs could be potentiated when combinations are used[91-93] and newer DMARDs have demonstrated good beneficial effects[94].

The DMARDs, which are frequently used include hydroxychloroquine, methotraxate, penicillamine, gold and sulfasalazine. Anakinra (an Interleukin-1 agonist), leflunomide (a pyrimidine synthesis inhibitor), etanercept, adalimumab and infliximab (which are tumour necrosis factor or TNF antagonists) and rituximab (B-cell depleting agent) are some of the newer DMARDs[95, 96].

The DMARDs only control the disease and do not cure it. So, the treatment of RA with DMARDs is a continuous process. The patients should be regularly re-examined for signs of disease progression and also for toxicities related to the regimens used for treatment. Changes in the treatment plan using DMARDs are necessitated by repeated flares, significant disease activity typified by continuing disease processes even after 3 months of maximal treatment or increasing joint disruptions[87].

Nonsurgical Management:

The impairment caused by RA of ankle to the functioning and ambulation of the patient may be alleviated by several rehabilitative interventions. They include prescription footwear, custom and remoulded ankle-foot orthoses, modified shoes and physiotherapeutic exercises[97]. Prescription footwear can minimise pain by relieving vertical pressure and decreasing shear and shock. This is especially important in RA as the patients usually lose fatty tissue and have a hypersensitive skin and inflamed joints. Similarly, a custom-made-orthoses made of either soft (cross-linked polyethylene foam), semiflexible (cork or leather) or rigid (thermoplastic polymers) materials, have been proved to reduce pain and disability[98, 99.]

Operative Treatment:

Surgical management is required for all patients with pain or deformity which is persistent even after nonoperative management. Rheumatoid arthritis of the ankle joint is usually treated with arthrodesis or arthroplasty.

Arthrodesis of the ankle has demonstrated reasonably good results, with high union and patient satisfaction rates. Tibiotalar arthrodesis has been the standard procedure for several decades[100]. Commonly used methods are internal rotation, external rotation or both internal and external rotation[101, 102]. There is some evidence for preferring internal rotation due to relatively high frequency of pin track infections and non-unions associated with external rotation. A neutrally dorsiflexed ankle, with 0-5 degrees of valgus and rotation to match the contralateral side is the ideal position of arthrodesis. Severe ankle deformity or bilateral ankle involvement may require a tibiotalocalcaneal, tibiocalcaneal, or pantalar arthrodesis[59].

Ankle arthroplasty is a valid alternative to arthrodesis in cases of advanced ankle RA or in the elderly or debilitated patients[95, 103, 104]. Earlier generations of ankle arthroplasties employed a two-part mechanism with a metal talar cup and a plastic tibial part such as a Mayo ankle or multidirectional two-part systems such as Newton arthroplasties. Newer versions of ankle prostheses contain a meniscal unrestrained plastic component which can be stabilised without cement[100].

Recent research has demonstrated that arthroscopic synovectomy may be used in cases where the disease process is in the early stage and there is no sign of degradation of the cartilage. In the study by Choi et al[105] (2013), arthroscopic synovectomy was performed among 18 patients who had rheumatoid arthritis. They were followed up at the end of 6 months and 12 months and then annually. It was

found that the pain score and absence of synovitis had a significant improvement at the end of 60 months. The rate of improvement was the greatest during the initial 12 months. Clinical success without the need for further interventions was reported among 77.8% of the patients. Earlier identification of ankle changes and performing surgery was associated with better response to surgery. Hence the authors recommend early identification of ankle involvement in RA and performing surgery for the eligible patients for better outcomes.

Lacunae in literature:

In summary, rheumatoid arthritis is a highly prevalent autoimmune disease across the world. The burden has been increasing with the aging population. It causes significant disability and impairment of quality of life. The impact of the disease is worse among developing countries where there is lack of access to speciality care.

Among the various joints involved in rheumatoid arthritis, there is a significant underestimation of the ankle joint involvement. This is often underdiagnosed even though most patients report a history of ankle pain in the early course of the disease. Pathological changes in the ankle joint might commence even in the absence of clinical symptoms. Hence, additional diagnostics are necessitated for identification of ankle pathologies in rheumatoid arthritis even in the subclinical stages.

Musculoskeletal ultrasound imaging has been gaining momentum in the recent years for identification of bone and soft tissue involvement in rheumatoid arthritis. Compared to magnetic resonance imaging, ultrasound is more feasible, cost-effective, has real time imaging and also can be used to guide therapy. Ultrasound imaging of tendons and bones can identify subtle pathologies of the ankle in rheumatoid arthritis

even in the absence of findings by clinical examination. Early identification of ankle pathologies will aid in earlier initiation of treatment, thus impeding the onset of pain and disability.

So far, there is a lack of studies on the ankle evaluation for rheumatoid arthritis using ultrasound among developed countries such as India. If ultrasound imaging is found to be of use in evaluating the ankles of patients with rheumatoid arthritis, it can be expected to be implemented on a wider scale in the evaluation of patients. This in turn, will aid in reducing disability and improving the quality of life. This study seeks to assess the utility of ultrasound imaging of ankle in rheumatoid arthritis and thus fill the gaps in existing knowledge.

MATERIALS AND METHODS

Study site: This study was conducted in the Department of Radiodiagnosis at KLE Hospital , Belgaum.

Study population: All the cases who have confirmed rheumatoid arthritis during the course of study were considered as study population.

Study design: The current study was a cross sectional study.

Sample size: 30

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection for the study was done between January 2018 to December 2018 for a period of 1 year.

Inclusion Criteria:

- Patients of all age groups, who are confirmed cases of rheumatoid arthritis.

Exclusion criteria:

- Trauma involving the ankle joint.
- Previous surgery involving the ankle Joint.
- Corticosteroid injections (in the last 6 months) taken in the structures being examined.
- Other concomitant chronic inflammatory diseases i.e. Spondylarthritis, crystal-related arthropathies or connective tissue disorders

Ethical considerations: Study was approved by institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology: Informed written consent was taken from the patient or patient's relatives. A pre-structured proforma was used for collection of baseline data. A detailed history and wherever necessary, an ankle radiograph were taken. Study was done using Philips Ultrasonography machine (HD 11 XE) with a high frequency linear probe (5 – 7.5 MHz) and GE LogiQ P9 Ultrasound Machine with a high frequency hockey-stick probe (6.7 – 18 MHz).

Statistical Methods: Tibio talar joint synovits was considered as primary outcome variable. Demographic parameters like age, gender etc. were considered as primary explanatory variables.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots.

RESULTS

Result:

A total of 30 (60 ankles) patients were included in the final analysis.

Table 1: Descriptive analysis of side in the study population (N=30)

Side	Frequency	Percentages
Right	30	50.0%
Left	30	50.0%

Among the study population, 30 (50%) were right side ankle and 30 (50%) were left side ankle. (Table 1 & Figure 1)

Table 2: Descriptive analysis of age group in the study population (N=30)

Age Group	Frequency	Percentages
Less than 30 Years	2	6.7%
30 to 39 Years	15	50.0%
40 to 49 Years	12	40.0%
Above 50 Years	1	3.3%

Among the study population, 2 (6.7%) were aged less than 30, 15 (50%) were aged 30 to 39 years, 12 (40%) were aged 40 to 49 years and 1 (3.3%) was aged above 50 years. (Table 3 & Figure 2)

Table 3: Descriptive analysis of gender in the study population (N=30)

Gender	Frequency	Percentages
Male	8	26.7%
Female	22	73.3%

Among the study population, 8 (26.7%) were male and 22 (73.3%) were female. (Table 4 & Figure 3)

Table 4: Comparison of ankle pain & swelling (N=30)

Ankle Pain & Swelling	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
Yes	16 (53.33%)	12 (40%)	1.071	0.301
No	14 (46.67%)	18 (60%)		

Among the right side ankle, 16 (53.33%) had ankle pain and swelling. Among the left side ankle, 12 (40%) had ankle pain and swelling. The difference in the proportion of ankle pain and swelling between both sides was statistically not significant. (P value 0.301). (Table 5 & Figure 4)

Figure 1: Cluster bar chart of comparison of ankle pain & swelling (N=30)

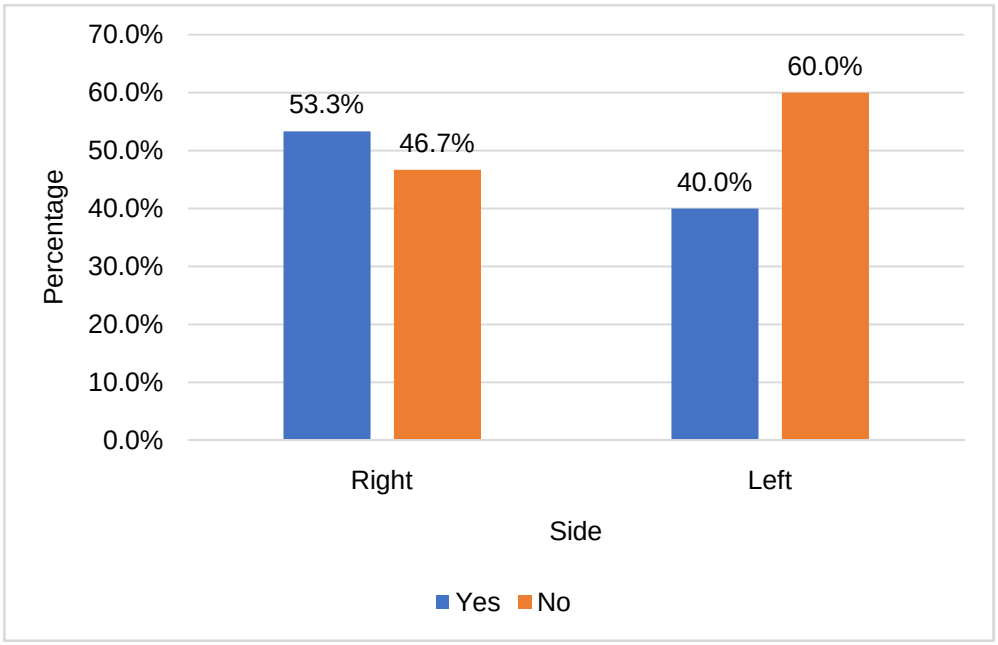

Table 5: Descriptive analysis of RA factor +ve in the study population (N=30)

RA Factor +ve	Frequency	Percentages
Yes	24	80.0%
No	6	20.0%

Among the study population, 24 (80%) had RA factor positive. (Table 6 & Figure 5)

Figure 2: Pie chart of RA factor +ve in the study population (N=30)

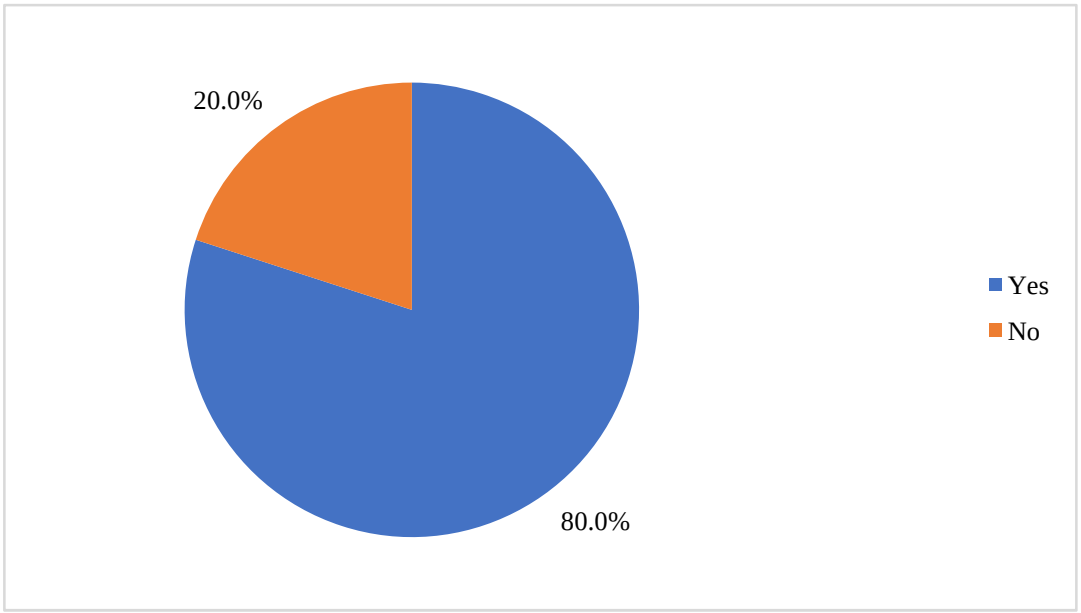

Table 6: Comparison of tendon evaluation of medial compartment (N=30)

Tendon Evaluation of medial Compartment	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
Tibialis Posterior -Bulky and Hypoechoic				
Present	10 (33.33%)	8 (26.67%)	0.317	0.573
Absent	20 (66.67%)	22 (73.33%)		
Tibialis Posterior -Vascularity				
Normal	21 (70%)	22 (73.33%)	0.082	0.774
Abnormal	9 (30%)	8 (26.67%)		
Flexor Digitorum longus bulky and Hypoechoic				
Present	6 (20%)	5 (16.67%)	0.111	0.739
Absent	24 (80%)	25 (83.33%)		
Flexor Digitorum longus-Vascularity				
Normal	24 (80%)	25 (83.33%)	0.111	0.739
Abnormal	6 (20%)	5 (16.67%)		
Flexor Hallucis longus-Bulky and Hypoechoic				
Present	1 (3.33%)	0 (0%)	*	**
Absent	29 (96.67%)	30 (100%)		
Flexor Hallucis longus-Vascularity				
Normal	29 (96.67%)	30 (100%)	*	**
Abnormal	1 (3.33%)	0 (0%)		

Among the right side ankle, 10 (33.33%) had bulky and hypoechoic tibialis posterior. Among the left side ankle, 8 (26.67%) had bulky and hypoechoic tibialis posterior. The difference in the proportion of tenosynovitis between two sides was statistically not significant (P value 0.573). Among the right side ankle, 21 (70%) had normal vascularity in tibialis posterior and 9 (30%) had abnormal vascularity. Among the left side ankle, 22 (73.33%) had normal vascularity in tibialis posterior and 8 (26.67%) had abnormal vascularity. The difference in the proportion of vascularity in tibialis posterior between both sides was statistically not significant (P value 0.774). Among the right side ankle, 6 (20%) had bulky and hypoechoic flexor digitorum longus. Among the left side ankle, 5 (16.67%) had bulky and hypoechoic flexor digitorum longus. The difference in the proportion of tenosynovitis of flexor digitorum longus between two sides was statistically not significant (P value 0.739). Among the right side ankle, 24 (80%) had normal vascularity in flexor digitorum longus and 6 (20%) had abnormal vascularity. Among the left side ankle, 25 (83.33%) had normal vascularity in flexor digitorum longus and 5 (16.67%) had abnormal vascularity. The difference in the proportion of vascularity of flexor digitorum longus between both sides was statistically not significant (P value 0.739). Among the right side ankle, 1 (3.33%) had bulky and hypoechoic flexor hallucis longus. Among the right side ankle, 29 (96.67%) had normal vascularity in flexor hallucis longus and 1 (3.33%) had abnormal vascularity. Among the left side ankle, 30 (100%) had normal vascularity in flexor hallucis longus. (Table 7)

Table 7: Comparison of tendon evaluation in lateral compartment (N=30)

Tendon Evaluation Lateral Compartment	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
Peroneus Longus-Bulky & Hypoechoic				
Present	9 (30%)	7 (23.33%)	0.341	0.559
Absent	21 (70%)	23 (76.67%)		
Peroneus Longus-Vascularity				
Normal	22 (73.33%)	24 (80%)	0.373	0.542
Abnormal	8 (26.67%)	6 (20%)		
Peroneus Brevis-Bulky & Hypoechoic				
Present	6 (20%)	5 (16.67%)	0.111	0.739
Absent	24 (80%)	25 (83.33%)		
Peroneus Brevis-Vascularity				
Normal	25 (83.33%)	25 (83.33%)	0.000	1.000
Abnormal	5 (16.67%)	5 (16.67%)		

Among the right side ankle, 9 (30%) had bulky and hypoechoic peroneus longus. Among the left side ankle, 7 (23.33%) had bulky and hypoechoic peroneus longus. The difference in the proportion of tenosynovitis of peroneus longus between both sides was statistically not significant (P value 0.559). Among the right side ankle, 22 (73.33%) had normal vascularity of peroneus longus and 8 (26.67%) had abnormal vascularity. Among the left side ankle, 24 (80%) had normal vascularity of peroneus longus and 6 (20%) had abnormal vascularity. The difference in the proportion of vascularity of peroneus longus between both sides was statistically not significant (P value 0.542). Among the right side ankle, 6 (20%) had bulky and hypoechoic peroneus brevis. Among the left side ankle, 5 (16.67%) had bulky and hypoechoic peroneus brevis. The difference in the proportion of peroneus brevis tenosynovitis between both sides was statistically not significant (P value 0.739). Among the right side ankle, 25 (83.33%) had normal vascularity of peroneus brevis and 5 (16.67%) had abnormal vascularity. Among the left side ankle, 25 (83.33%) had normal peroneus brevis vascularity and 5 (16.67%) had abnormal vascularity. The difference in the proportion of peroneus brevis vascularity between side was statistically not significant (P value 1.000). (Table 8)

Table 8: Comparison of tendon evaluation in anterior compartment between both sides (N=30)

Tendon Evaluation Anterior Compartment	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
Tibialis Anterior-Bulky & Hypoechoic				
Present	9 (30%)	6 (20%)	0.800	0.371
Absent	21 (70%)	24 (80%)		
Tibialis Anterior-Vascularity				
Normal	22 (73.33%)	25 (83.33%)	0.884	0.347
Abnormal	8 (26.67%)	5 (16.67%)		
Extensor hallucis longus-Bulky & Hypoechoic				
Present	5 (16.67%)	3 (10%)	0.577	0.706
Absent	25 (83.33%)	27 (90%)		
Extensor hallucis longus-Vascularity				
Normal	25 (83.33%)	27 (90%)	0.577	0.706
Abnormal	5 (16.67%)	3 (10%)		
Extensor digitorum longus-Bulky & Hypoechoic				
Present	5 (16.67%)	6 (20%)	0.111	0.739
Absent	25 (83.33%)	24 (80%)		
Extensor digitorum longus-Vascularity				
Normal	26 (86.67%)	28 (93.33%)	0.741	0.671
Abnormal	4 (13.33%)	2 (6.67%)		

Among the right side ankle, 9 (30%) had bulky and hypoechoic tibialis anterior. Among the left side ankle, 6 (20%) had bulky and hypoechoic tibialis

anterior. The difference in the proportion of tenosynovitis in tibialis anterior between both sides was statistically not significant (P value 0.371). Among the right side ankle, 22 (73.33%) had normal vascularity in tibialis anterior and 8 (26.67%) had abnormal vascularity. Among the left side ankle, 25 (83.33%) had normal vascularity in tibialis anterior and 5 (16.67%) had abnormal vascularity. The difference in the proportion of vascularity of tibialis anterior between both sides was statistically not significant (P value 0.347). Among the right side ankle, 5 (16.67%) had bulky and hypoechoic extensor hallucis longus. Among the left side ankle, 3 (10%) had bulky and hypoechoic extensor hallucis longus. The difference in the proportion of extensor hallucis longus tenosynovitis between both sides was statistically not significant (P value 0.706). Among the right side ankle, 25 (83.33%) had normal vascularity in extensor hallucis longus and 5 (16.67%) had abnormal vascularity. Among the left side ankle, 27 (90%) had normal vascularity in extensor hallucis longus and 3 (10%) had abnormal vascularity in extensor hallucis longus. The difference in the proportion of extensor hallucis longus vascularity between both sides was statistically not significant (P value 0.706). Among the right side ankle, 5 (16.67%) had bulky and hypoechoic extensor digitorum longus. Among the left side ankle, 6 (20%) had bulky and hypoechoic extensor digitorum longus. The difference in the proportion of tenosynovitis in extensor digitorum longus between both sides was statistically not significant (P value 0.739). Among the right side ankle, 26 (86.67%) had normal vascularity in extensor digitorum longus and 4 (13.33%) had abnormal vascularity. Among the left side ankle, 28 (93.33%) had normal vascularity in extensor digitorum longus and 2 (6.67%) had abnormal vascularity. The difference in the proportion of vascularity in extensor digitorum longus between both sides was statistically not significant (P value 0.671). (Table 7)

Table 9: Comparison of synovitis talocalcaneal joint (N=30)

Synovitis of Talocalcaneal Joint	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
Synovial Thickening				
Present	7 (23.33%)	4 (13.33%)	1.002	0.317
Absent	23 (76.67%)	26 (86.67%)		
Vascularity				
Abnormal	6 (20%)	3 (10%)	1.176	0.472
Normal	24 (80%)	27 (90%)		
Joint fluid				
Present	5 (16.67%)	3 (10%)	0.577	0.706
Absent	25 (83.33%)	27 (90%)		

Among the right side ankle, 7 (23.33%) had synovial thickening in the talocalcaneal joint. Among the left side ankle, 4 (13.33%) had synovial thickening. The difference in the proportion of synovial thickening between both sides was statistically not significant (P value 0.317). Among the right side ankle, 6 (20%) had increased vascularity. Among the left side ankle, 3 (10%) had increased vascularity. The difference in the proportion of increased vascularity between both sides was statistically not significant (P value 0.472). Among the right side ankle, 5 (16.67%) had fluid in talocalcaneal joint. Among the left side ankle, 3 (10%) had joint fluid. The difference in the proportion of joint effusion in talocalcaneal joint was statistically not significant (P value 0.706). (Table 10)

Table 10: Comparison of synovitis of tibio talar joint (N=30)

Synovitis-Tibio talar Joint	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
Synovial Thickening				
Present	6 (20%)	4 (13.33%)	0.480	0.488
Absent	24 (80%)	26 (86.67%)		
Vascularity				
Abnormal	5 (16.67%)	3 (10%)	0.577	0.706
Normal	25 (83.33%)	27 (90%)		
Joint fluid				
Present	5 (16.67%)	4 (13.33%)	0.131	1.000
Absent	25 (83.33%)	26 (86.67%)		

Among the right side ankle, 6 (20%) had synovial thickening. Among the left side ankle, 4 (13.33%) had synovial thickening. The difference in the proportion of synovial thickening between both sides was statistically not significant (P value 0.488). Among the right side ankle, 5 (16.67%) had increased vascularity. Among the left side ankle, 3 (10%) had increased vascularity. The difference in the proportion of vascularity between both sides was statistically not significant (P value 0.706). Among the right side ankle, 5 (16.67%) had joint effusion. Among the left side ankle, 4 (13.33%) had joint effusion. The difference in the proportion of joint effusion between both sides was statistically not significant (P value 1.00). (Table 11)

Table 11: Comparison of enthesitis of tendoachilles (N=30)

Tendoachilles - Bulky And Hypoechoic at Insertion (Enthesitis)	Side		Chi square	Fisher exact P value
	Right (N=30)	Left (N=30)		
Present	5 (16.67%)	3 (10%)	0.577	0.706
Absent	25 (83.33%)	27 (90%)		

Among the right side ankle, 5 (16.67%) had bulky and hypoechoic tendoachilles at insertion (enthesitis). Among the left side ankle, 3 (10%) had bulky and hypoechoic tendoachilles - at insertion (enthesitis). The difference in the proportion of enthesitis between both sides was statistically not significant (P value 706). (Table 12)

Table 12: Comparison of Retro Calcaneal Synovial Thickening (N=30)

Retro calcaneal Synovial Thickening	Side		Chi square	Fisher exact P value
	Right (N=30)	Left (N=30)		
Present	5 (16.67%)	3 (10%)	0.577	0.706
Absent	25 (83.33%)	27 (90%)		

Among the right side ankle, 5 (16.67%) had retro calcaneal synovial thickening. Among the left side ankle, 3 (10%) had retro calcaneal synovial thickening. The difference in the proportion of retro calcaneal synovial thickening between both sides was statistically not significant (P value 0.706). (Table 13)

Table 13: Comparison of metatarsal erosions (N=30)

Parameters	Side		Chi square	P value
	Right (N=30)	Left (N=30)		
1st Metatarsal				
Present	6 (20%)	4 (13.33%)	0.480	0.488
Absent	24 (80%)	26 (86.67%)		
2nd Metatarsal				
Present	3 (10%)	1 (3.33%)	1.071	0.612
Absent	27 (90%)	29 (96.67%)		
3rd Metatarsal				
Present	5 (16.67%)	3 (10%)	0.577	0.706
Absent	25 (83.33%)	27 (90%)		
4th Metatarsal				
Present	4 (13.33%)	3 (10%)	0.162	1.000
Absent	26 (86.67%)	27 (90%)		
5th Metatarsal				
Present	4 (13.33%)	2 (6.67%)	0.741	0.671
Absent	26 (86.67%)	28 (93.33%)		

Among the right side ankle, 6 (20%) patients had erosions in 1st metatarsal bone. Among the left side ankle, 4 (13.33%) patients had erosions in 1st metatarsal. The difference in the proportion of patients having erosions in 1st metatarsal bone between both sides was statistically not significant (P value 0.488). Among the right side ankle, 3 (10%) patients had erosions in 2nd metatarsal bone. Among the left side ankle, 1 (3.33%) patient had erosions in 2nd metatarsal bone. The difference in the proportion between erosions involving 2nd metatarsal bone between both sides was statistically not significant (P value 0.612). Among the right side ankle, 5 (16.67%) patients had erosions in 3rd metatarsal. Among the left side ankle, 3 (10%) patients had erosions in 3rd metatarsal. The difference in the proportion of erosions in 3rd metatarsal between both sides was statistically not significant (P value 0.706). Among the right side ankle, 4 (13.33%) patients had erosions in 4th metatarsal. Among the left side ankle, 3 (10%) patients had erosions in 4th metatarsal. The difference in the proportion of erosions in 4th metatarsal between both sides was statistically not significant (P value 0.1000). Among the right side ankle, 4 (13.33%) patients had erosions in 5th metatarsal. Among the left side ankle, 2 (6.67%) patients had erosions in 5th metatarsal. The difference in the proportion erosions in 5th metatarsal between both sides was statistically not significant (P value 0.1000). (Table 14)

DISCUSSION

Rheumatoid arthritis is a chronic inflammatory condition with systemic involvement. The risk of Rheumatoid arthritis increases with increase in age. Diagnosis of rheumatoid arthritis is based on clinical and laboratory findings. Pain, boggy swelling of the small joints with morning stiffness are most commonly reported in rheumatoid arthritis. One of the more recently explored modalities for diagnosis of rheumatoid arthritis is ultrasound of the ankle. Patients presenting with ankle pain during the early stages are more likely to have isolated tenosynovitis of ankle joint. This feature of rheumatoid arthritis is found even before the onset of deformities in the advanced stages of the disease. Although MRI is the gold standard for evaluating the ankle changes, it is more expensive and hence not applicable in the wider settings. Ultrasound on the other hand, is cost-effective and can be used to screen patients presenting with ankle pain in the outpatient department[8]. Early diagnosis of rheumatoid arthritis will aid in early initiation of treatment. This in turn, will impede the onset of deformities, thus improving the patients' quality of life. Hence we carried out this study to explore the diagnostic utility of ankle ultrasound in rheumatoid arthritis.

BASELINE SOCIODEMOGRAPHIC VARIABLES:

A Cross sectional study was conducted on 30 subjects with rheumatoid arthritis in the Department of Radiodiagnosis In KLE hospital, Belagum between January 2018 to December 2018. The diagnostic utility of ankle ultrasound in rheumatoid arthritis was evaluated. Majority (73.3%) of the study population were females in this study. Similarly Rudan et al[24] (2015) in their meta-analysis also observed that prevalence of RA among females was higher compared to males. Many

females enrolled in our study compared to males. Chopra et al[23] (2015) also observed that the incidence of RA among young women in India was higher compared to global reports. In our study, in 50% of subjects, right side was involved while in the rest (50%), left side was involved. Chopra et al[22] (2012) observed that prevalence of RA was 5 times more common among women when compared to men. The majority (50%) of our study subjects were aged between 30 to 39 years, while 40% were aged between 40 to 49 years. Chopra et al[22] (2012) also observed that highest prevalence was reported among 25 to 44 years with 42% prevalence. In their study also, 40% of subjects with RA were between 45 and 64 years of age.

BASELINE CLINICAL VARIABLES:

Rheumatoid arthritis is characterized by a plethora of symptoms such as joint ache, stiffness in joints, swelling of joints. The involvement in rheumatoid arthritis is symmetric, distinguishing it from other forms of arthritis. In addition, non-specific constitutional symptoms such as loss of weight, lethargy and fever may also be present[5]. Pain in the feet, especially ankles is a significant presenting complaint in rheumatoid arthritis.[55] It is also a challenge in managing among the various aspects of RA. At presentation, 53.3% of our study subjects had ankle pain and swelling. Similar to our study, Hernandez- Diaz et al[86] (2019) in their study observed that 56.2% of RA subjects had a history of ankle pain. Yano et al[69] (2018) in their study in japan observed that 43.8% had involvement of the feet or ankle as the earliest symptom of rheumatoid arthritis. Wilson et al[67] (2017) in their study in UK observed that 73.8% had pain in the joints of feet such as the ankle joints.Borman et al[63] (2012) in their study observed that there was a significant correlation of ankle pain with the disease duration.

DIAGNOSIS AND IMPORTANCE OF ULTRASOUND:

The importance of early diagnosis of rheumatoid arthritis is paramount. Yano et al[69] (2018) in their study observed that those who had early ankle involvement had a greater degree of disability, more severe disease activity and more seropositivity. In our study, 80% of subjects were positive for Rh factor. Rheumatoid arthritis is associated with multiple consequences which can lead to disability, morbidity and impaired quality of life. Those with RA are at an increased risk for developing cardiac complications and diabetes. The individuals with co-existing obesity have a lesser response to therapy. In addition, they are at an increased risk for hypertension and dyslipidemia. In addition, loss of employment can occur due to pain and resultant disability. One of the more recently explored modalities for diagnosis of rheumatoid arthritis is ultrasound of the ankle. Patients presenting with ankle pain during the early stages are more likely to have isolated tenosynovitis of ankle joint. This feature of rheumatoid arthritis is found even before the onset of deformities in the advanced stages of the disease. Although MRI is the gold standard for evaluating the ankle changes, it is more expensive and hence not applicable in the wider settings. Ultrasound on the other hand, is cost-effective and can be used to screen patients presenting with ankle pain in the outpatient department[8].

ULTRASOUND OF MEDIAL COMPARTMENT:

There is a significant correlation of ultrasound with the disease activity. In some instances, ultrasound can even be superior since it can identify even subclinical synovitis. The diagnostic utility of ultrasound is better for bony erosion when compared with synovitis.[78] In our study 30% of patients had tenosynovitis of tibialis posterior. The vascularity of tibialis posterior was abnormal in 28.3% of subjects.

Harman et al[68] (2017) in their study observed that tibialis posterior tenosynovitis is a specific finding for rheumatoid arthritis. In our study, 18.3% had tenosynovitis of flexor digitorum longus while only 1.7% had tenosynovitis of flexor hallucis longus and the vascularity of flexor digitorum longus was abnormal in 18.3% of subjects while the vascularity of flexor hallucis longus was abnormal in 10% of subjects.

ULTRASOUND OF LATERAL COMPARTMENT:

Hernandez- Diaz et al[86] (2019) in their study observed that the presence of clinical findings significantly correlated with the presence of tenosynovitis of peroneus tendon or synovitis of tibiotalar joint. In our study, 26.7% had tenosynovitis of peroneus longus while 18.3% had tenosynovitis of peroneus brevis. The vascularity of peroneus longus was abnormal in 23.3% of subjects while in peroneus brevis, it was abnormal in 16.7% of subjects.

ULTRASOUND OF ANTERIOR COMPARTMENT:

In the study by Elsaman AM et al [106] (2017), the most common tendon affected by tenosynovitis was the tibialis anterior (22.2%), followed by the tibialis posterior (20.6%). In our study, on USG, 30 % had tenosynovitis of tibialis anterior while the vascularity of tibialis anterior was abnormal in 26.7% of subjects. In our study, 13.3 % had tenosynovitis of exterior hallucis longus while the vascularity of exterior hallucis longus was abnormal in 20% of subjects. On USG in our study, 16.7 % had bulky/hypoechoic exterior digitorum longus while the vascularity of exterior digitorum longus was abnormal in 20% of subjects.

ULTRASOUND OF JOINTS:

Harman et al[68] (2017) in their study observed that with the longer disease onset, there is greater involvement of tibiotalar joint. They also observed that among the patients in the early stages of the disease, synovitis of the subtalar joint and the talonavicular joints were more common. For those with disease duration of more than 1 year, synovitis of the tibiotalar joint was prevalent. In our study, in Talocalcaneal joint, 23.3% had thickened synovium. The vascularity was absent in colour Doppler in 76.7% of subjects while the synovial fluid was absent in 90% of subjects In Tibiotalar joint, 20 % had thickened synovium. The vascularity was absent in colour doppler in 90% of subjects while the synovial fluid was absent in 63.3% of subjects. With regards to joint erosion 16.7% had 1st metatarsal and 6.7% had 2nd metatarsal joint erosion. 13.3% had 3rd metatarsal joint erosion while 11.7% had 4th and 10% had 5th metatarsal joint erosion.13.3%of our study subjects also had retrocalcaneal synovial thickening. Zayat et al[72] (2015) in their study observed that the presence of erosions in the 5th metatarsophalangeal joint irrespective of size had a high sensitivity (68.6%) and high specificity (97.9%) for RA. There was also a positive correlation between the size of bony erosions and the likelihood of RA. In our study, 13.3% had bulky and hypoechoic tendoachilles at insertion (Enthesitis). Harman et al[68] (2017) in their study observed that among the patients in the early stages of the disease, synovitis of the subtalar joint and the talonavicular joints were more common.Elsaman AM et al [106] (2017) in their study observed that the most frequent pathologies detected were tenosynovitis (30.2%), followed by synovitis (18.3%), erosion (8.7%) and tendinosis (4%). The earliest sonographic signs were tenosynovitis, followed by synovitis, erosion and tendinosis. Toyota et al[85] (2017) in their study observed that 35% of subjects had positive findings in ultrasonography.

There was a moderate degree of concordance between clinical examination and ultrasound. Hernandez- Diaz et al[86] (2019) in their study similar to our study observed that the presence of clinical findings significantly correlated with the presence of tenosynovitis of peroneus tendon or synovitis of tibiotalar joint.

CONCLUSIONS

1. According to ACR/EULAR classification criteria, 30 patients with rheumatoid arthritis were enrolled for the study out of which 80 % were RA factor positive.
2. Majority (73.3%) of the study population were females with majority (50%) of our study subjects aged between 30 to 39 years, while 40% were aged between 40 to 49 years.
3. At presentation, out of the 30 right sided ankles, 53.3% had ankle pain and swelling while only 40% had ankle pain and swelling in the evaluation of left sided ankles.
4. In the medial compartment, the most common tendon with findings of tenosynovitis was tibialis anterior (28%).
5. In the lateral compartment, the most common tendon with findings of tenosynovitis was peroneus longus (26.6%).
6. In the anterior compartment, the most common tendon with findings of tenosynovitis was tibialis anterior (25.0%).
7. In Talocalcaneal joint, 18.3% had synovitis while the synovial fluid was present in 13.3 % of subjects.
8. In Talonavicular joint, 16.6% had synovitis while the synovial fluid was present in 13.3 % of subjects.
9. With regards to joint erosion, all metatarsal bones had joint erosions, though erosions were present more commonly in 1^{st} and 3^{rd} metatarsals.
10. 13.3% of our study subjects had retrocalcaneal synovial thickening.
11. Findings of enthesitis of tendoachilles although more common in patients with psoriatic arthritis were present in our patients in 13.3%.

12. Sonography of ankle joint is therefore an efficient, reliable, cost effective and easily accessible modality for patients with rheumatoid arthritis. It is very useful for detecting tenosynovitis, joint synovitis and bone erosions and can help in early detection and initiation of treatment and better quality of life in patients.

SUMMARY

- The study was a cross sectional study.
- Patients presenting to the department of radiology with rheumatoid arthritis with or without symptoms of ankle pain and swelling.
- 30 cases were included in the study after observing the inclusion and exclusion criteria.
- All patients first underwent sonography of both ankle joints.
- Findings of tenosynovitis of anterior, middle and lateral compartments, synovitis of talocalcaneal joint and talonavicular joint, retrocalcaneal bursitis, enthesitis of tendoachilles and erosions involving metatarsal bones were evaluated.
- Sonography is very sensitive in detecting the above mentioned pathologies involving ankle joints in patients with rheumatoid arthritis especially in developing countries as it is affordable, easily accessible and will help in early detection and treatment of patients having subclinical presentation.

LIMITATIONS AND RECOMMENDATIONS

This study has a few limitations. Conclusive interpretation of causality is questionable as it is only a cross sectional study with a small sample size. The limitation with USG lies in the fact that artefact characteristic for tendons may appear falsely hypoechoic when the USG beam is not perpendicular to tendon fibers; it should not be confounded with tendon pathology like tenosynovitis or tendon tear. Ultrasound of the ankle is a very efficient, simple, reliable and easily accessible modality distinguishing rheumatological pathologies of the ankle such as tendinitis, synovitis, bursitis. USG gives a wide range of information that can be used as complementary data to the clinical assessment. Early diagnosis of rheumatoid arthritis by USG will aid in early initiation of treatment and better quality of life.

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ANNEXURE I-CONSENT FORM

INFORMED CONSENT

TITLE OF THE STUDY: ROLE OF ULTRASONOGRAPHY IN EVALUATION OF ANKLE JOINT PATHOLOGIES IN PATIENTS WITH RHEUMATOID ARTHRITIS - A ONE YEAR HOSPITAL BASED STUDY"

PRINCIPAL INVESTIGATOR: DR. _____

INTRODUCTION AND PURPOSE:

Rheumatoid arthritis is especially important among the various musculoskeletal disorders. It affects the individuals between 20 to 40 years of age in their more productive years and leads to chronic disability due to pain and deformity. The prevalence is highly variable ranging between 0.3% to 1%. It is more prevalent among females and those living in developed countries. The importance of early diagnosis of rheumatoid arthritis is paramount. Rheumatoid arthritis not only affects the joints, but also has systemic involvement.

One of the more recently explored modalities for diagnosis of rheumatoid arthritis is ultrasound of the ankle. Patients presenting with ankle pain during the early stages are more likely to have isolated tenosynovitis of ankle joint. This feature of rheumatoid arthritis can be found even before the onset of deformities in the advanced stages of the disease. Although MRI is the gold standard for evaluating the ankle changes, it is more expensive and hence not applicable in wider settings.

Ultrasound on the other hand, is cost-effective and can be used to screen patients presenting with ankle pain in the outpatient department.

The objective of this study is to evaluate the role of Ultrasonography of Ankle Joint in confirmed cases of Rheumatoid Arthritis presenting with either clinical or subclinical ankle involvement and to begin or modify treatment if necessary based on ankle involvement.

PROCEDURE:

I request you to kindly participate in the study titled **" ROLE OF ULTRASONOGRAPHY IN EVALUATION OF ANKLE JOINT PATHOLOGIES IN PATIENTS WITH RHEUMATOID ARTHRITIS - A ONE YEAR HOSPITAL BASED STUDY"** at Dr. Prabhakar Kore hospital and Medical Research Centre, Belagavi" being conducted by Dr. _____ post graduate in Radiodiagnosis at J. N. Medical College Belagavi.

We request you to participate in this study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you will be required to answer to the best of your knowledge.

If you agree to participate in the study please furnish the details pertaining to the study.

BENEFITS:

1. Accurate diagnosis.
2. Non invasive.
3. Short duration of study.
4. Cost effective.

RISKS:

1. No risk to the patient has been documented from sonography of ankle joint.

ALTERNATIVES: If patient is not willing to take part in the study, his / her treatment or any other further investigations the patient wants to undergo, in future, in KLE will not be affected by his / her decision

VOLUNTARY PARTICIPATION/WITHDRAWAL: Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other services that I receive. The study doctor or the sponsor may stop my participation in this study. I will tell if any important new findings that may change my willingness to continue to take part. If I choose not to take part in the study I will receive the standard treatment for patients with my condition.

COSTS: NIL (The study is to be conducted on the participants who are advised ultrasonography of ankle by the referring consultant and the participants will bear the charges for it.)

PAYMENT FOR PARTICIPATION: No incentive will be paid to you for participating in this study.

COMPENSATION: In the event that I become injured as a result of taking part in this study, treatment whatever available at KLE hospital, Belagavi, will be offered to me. No reimbursement, compensation or free medical care is given.

CONFIDENTIALITY: All information collected about me during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify me in this research record. Information from this study may be published but my identity will be confidential in any publication.

If any enquiries in the future or in case of research related injury illness, you may contact following person.

Dr. Roopa Bellad
Professor Of Paediatrics Chairperson, J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Belagavi
Ph. 0831-2471525 Ext- 4032

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. I understand that I am participating in the study, which includes retrograde urethrogram and sonorethrogram.

2. I confirm that I have read and understood the information in the patient information sheet. Procedure is explained to me in detail along with information about the advantages and disadvantages of taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions and hereby consent to participation in the trial outlined above.

3. I understand that the decision to take part in this study is completely voluntary and I am aware that I can choose to withdraw from the study at any point of time.

4. I consent to the photographing or recording of the procedure to be performed including portions of my body, for medical, scientific or educational purposes provided my identity is not revealed in the pictures or by the descriptive texts accompanying them.

5. I understand that there is no significant risk involved in the test that would be done in this study.

6. No guarantee or assurance has given by anyone as to the results that may be obtained.

7. My signature on this form signifies that I have willingly decided to participate after understanding the above information.

Participant's / legally authorized representatives name_____

Signature _____

Name and signature of witness _____

Investigators name and Signature : …….

Date:

Place: Belagavi

ANNEXURE II - ETHICAL CLEARANCE LETTER

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http//www.jnmc.edu
E-Mail : domc@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 10 **Date: 22/11/2017**

To,

PG student in Radiodiagnosis,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"ROLE OF ULTRASONOGRAPHY IN EVALUATION OF ANKLE JOINT PATHOLOGIES IN PATIENTS WITH RHEUMATOID ARTHRITIS - A ONE YEAR HOSPITAL BASED STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research.
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE III -PROFORMA

PROFORMA FOR DATA COLLECTION

1. PATIENT PARTICULARS:

NAME		DATE	
AGE		SEX	
IPD/OPD NO		USG NO	
ADDRESS		MOBILE NO	

2. CHIEF COMPLAINTS:

ANKLE JOINT SWELLING	Present/Absent
ANKLE JOINT PAIN	Present/Absent
ANKLE JOINT STIFFNESS	Present/Absent

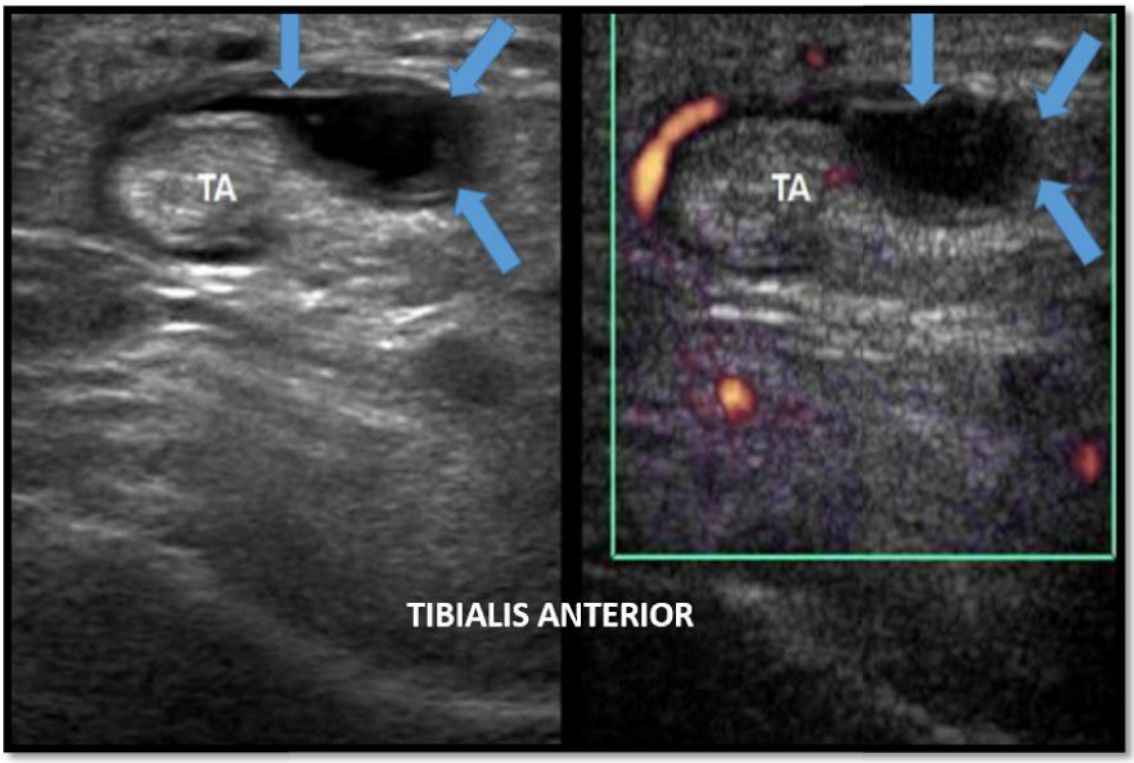
3. PERSONAL HISTORY

SMOKING	Yes/No
ALCHOHOLISM	Yes/No

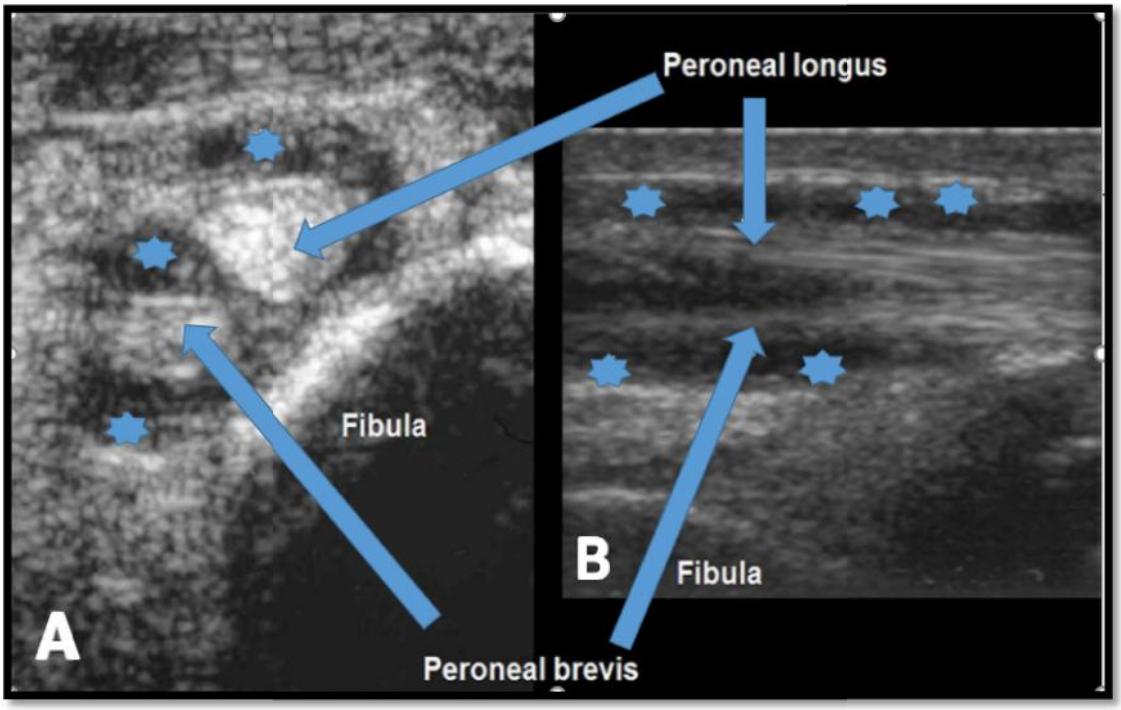
ANTERIOR COMPARTMENT	HYPOECHOIC & BULKY TENDON		INCREASED VASCULARITY
	PRESENT	ABSENT	
TIBIALIS ANTERIOR			
EXTENSOR HALLUCIS LONGUS			
EXTENSOR DIGITORUM LONGUS			
LATERAL COMPARTMENT			
PERONEUS LONGUS			
PERONEUS BREVIS			
MEDIAL COMPARTMENT			
TIBIALIS POSTERIOR			
FLEXOR DIGITORUM LONGUS			
FLEXOR HALLUCIS LONGUS			
POSTERIOR COMPARTMENT	ENTHESITIS – BULKY / HYPOECHOIC AT INSERTION		
ACHILLES TENDON			
	RETROCALCANEAL	BURSITIS	

JOINTS	SYNOVITIS		
TALONAVICULAR JOINT			
TALOCALCANEAL JOINT			
METATARSAL EROSION			
1ST METATARSAL			
2ND METATARSAL			
3RD METATARSAL			
4TH METATARSAL			
5TH METATARSAL			

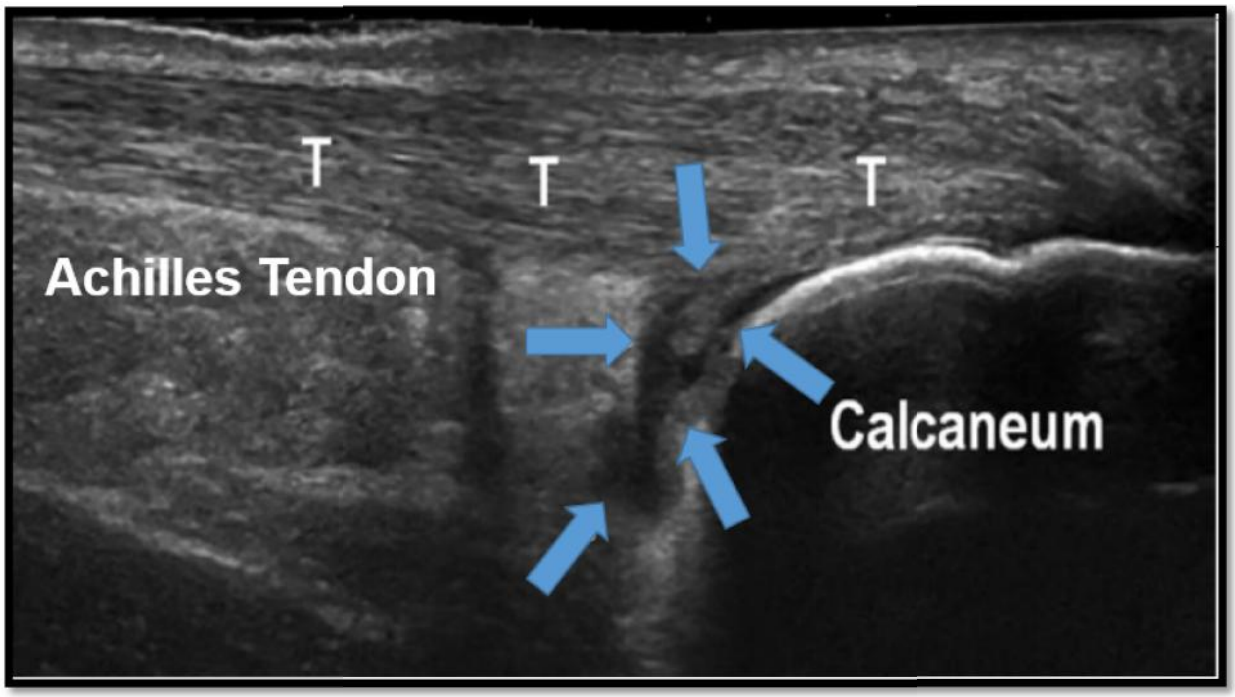
ANNEXURE IV - PHOTOGRAPHS



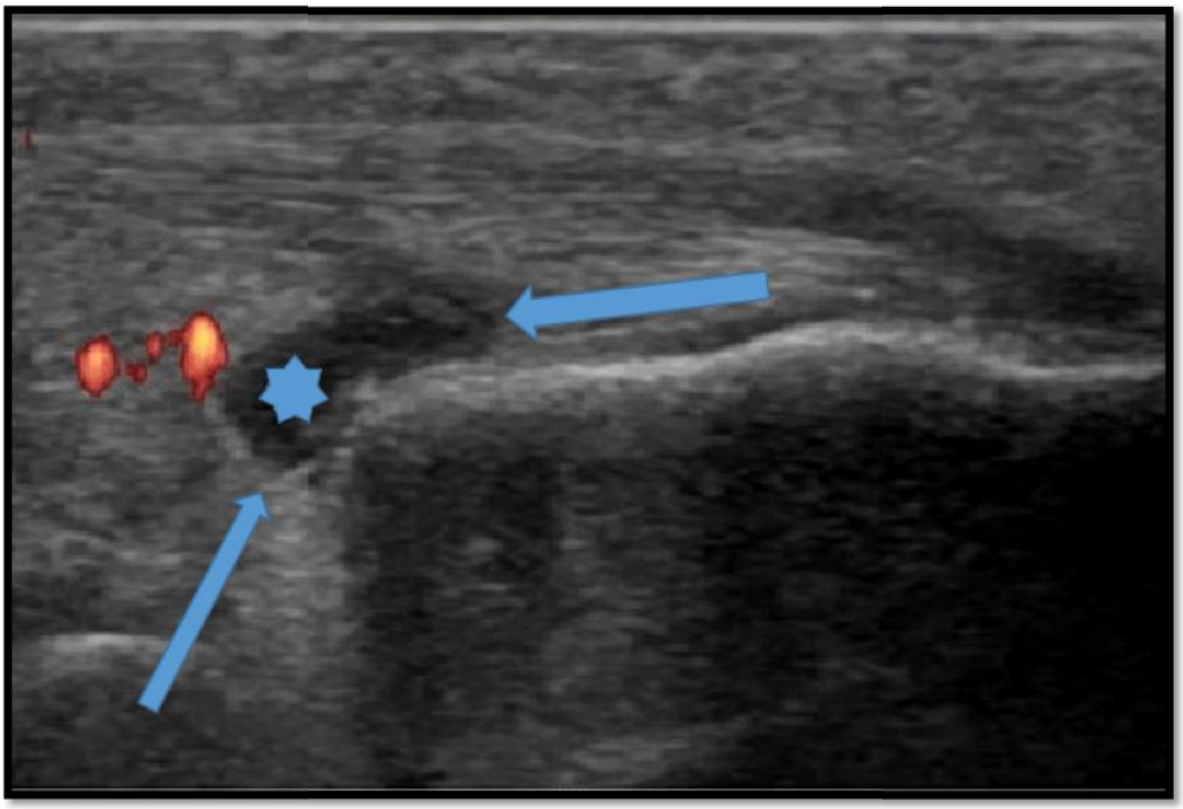
Tibialis anterior tendon - The tendon appears normal (echogenic and homogenous) but the tendon sheath is distended with fluid and there is increased Doppler signal: suggestive of tenosynovitis



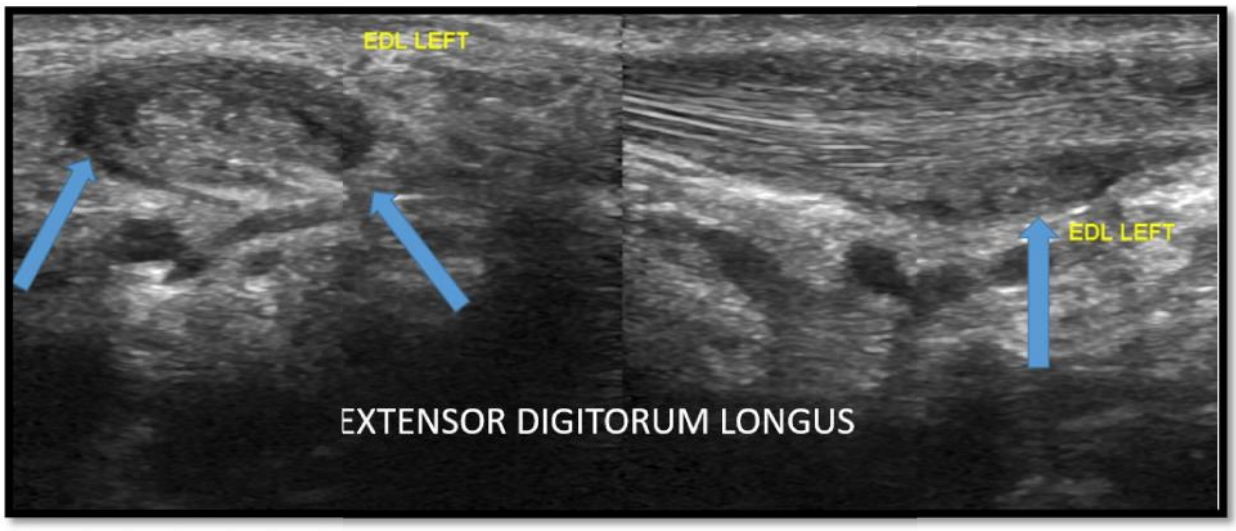
Transverse (A) and longitudinal view (B) through the peroneal tendons. There is expansion of the tendon sheath consistent with a diagnosis of tenosynovitis.



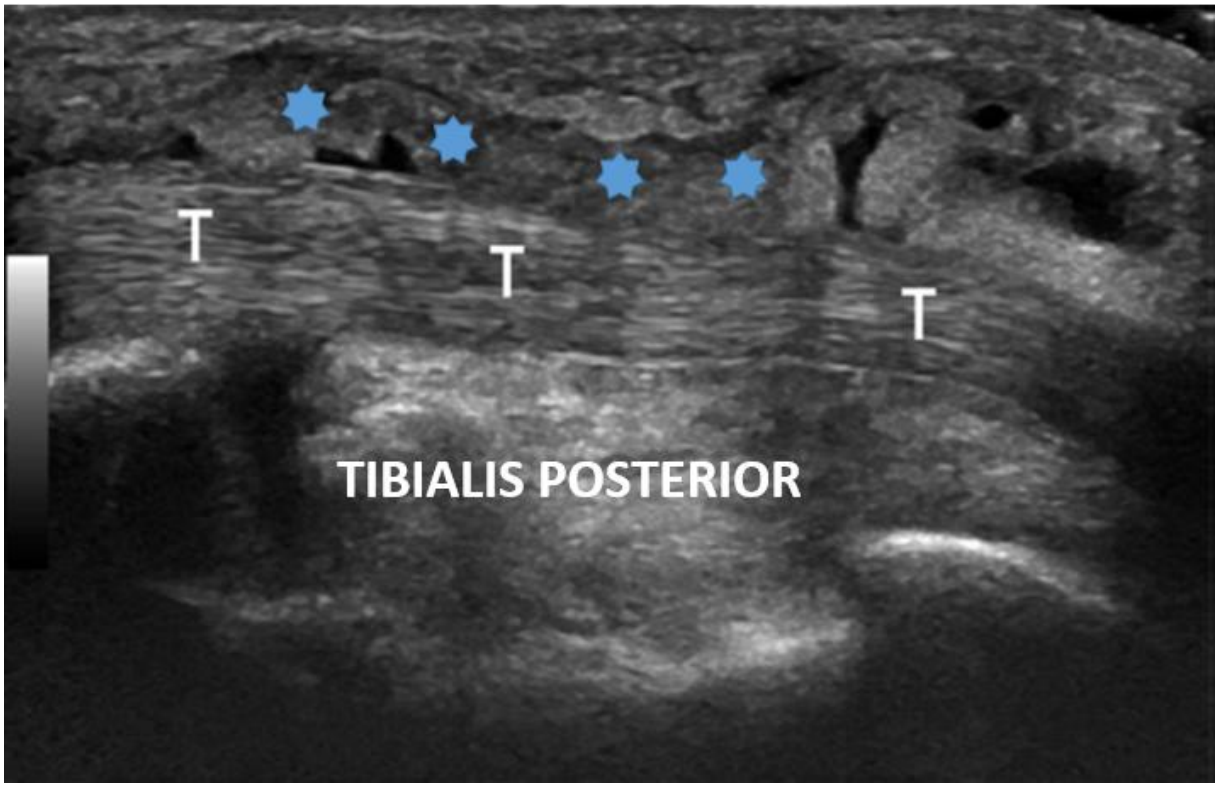
Longitudinal section through the posterior ankle. A large retrocalcaneal bursa is seen (white arrows). Distal tendon thickening is also noted.



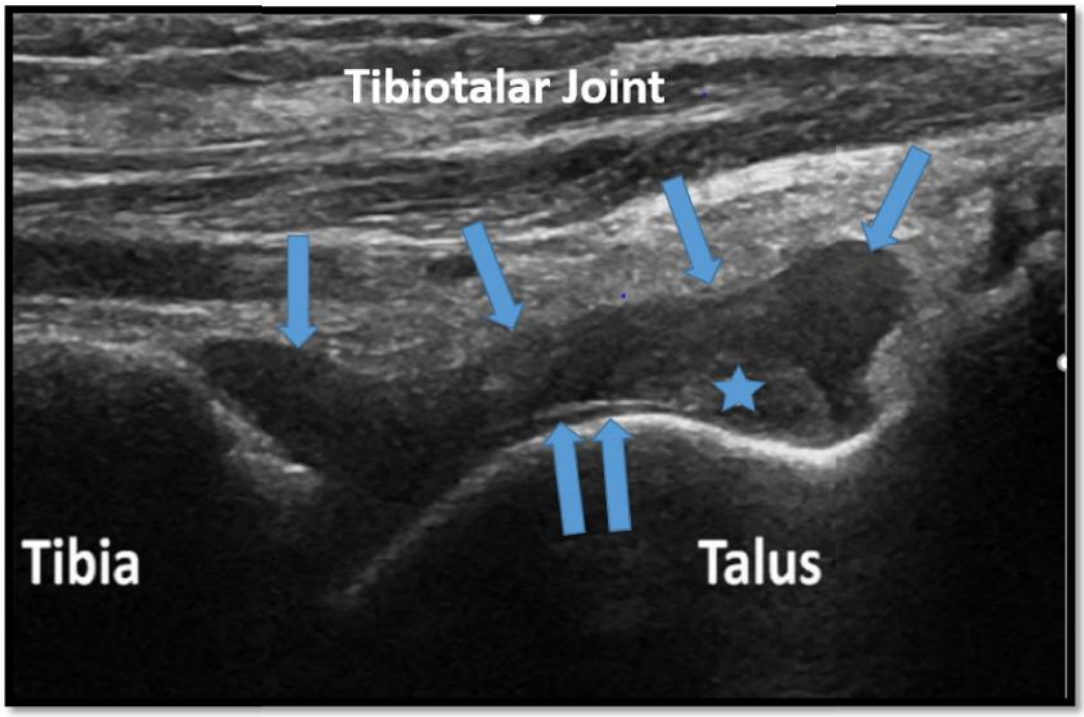
Longitudinal section through posterior ankle shows retrocalcaneal fluid with synovial thickening and increased vascularity on colour doppler, findings which are suggestive of retrocalcaneal bursitis



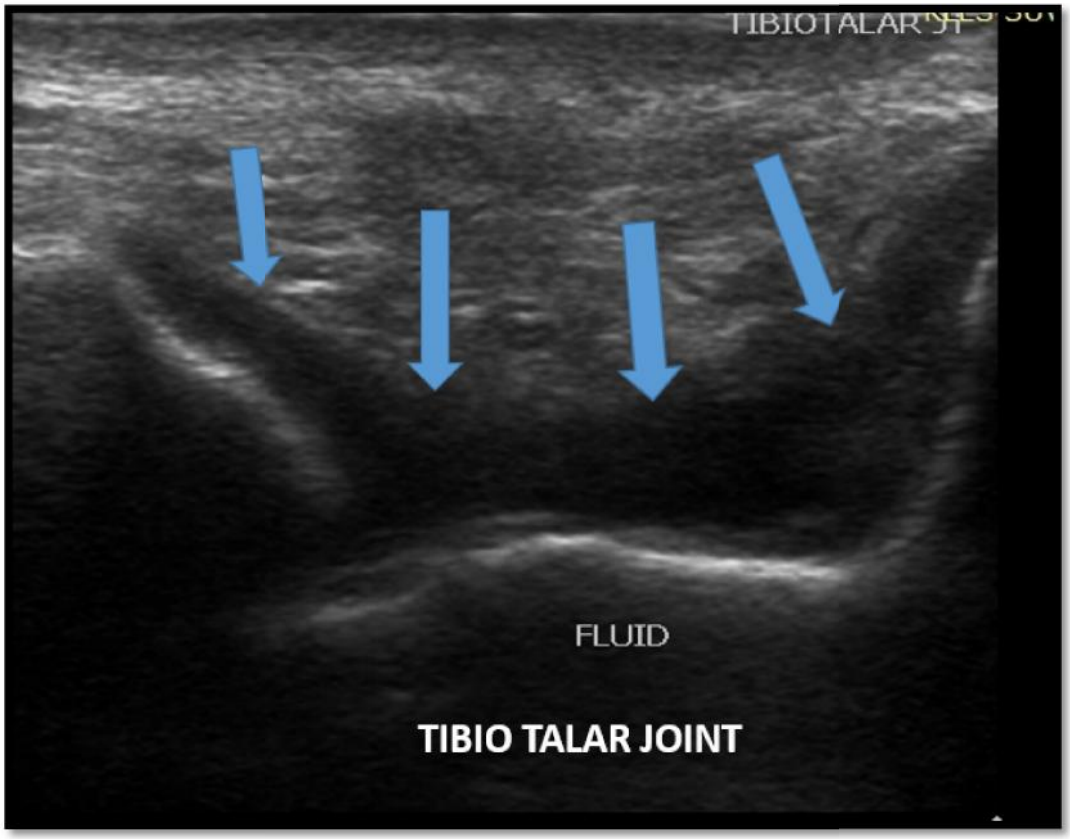
Transverse and longitudinal view of Extensor Digitorum Longus tendon shows synovial hypertrophy surrounding the tendon suggestive of tenosynovitis



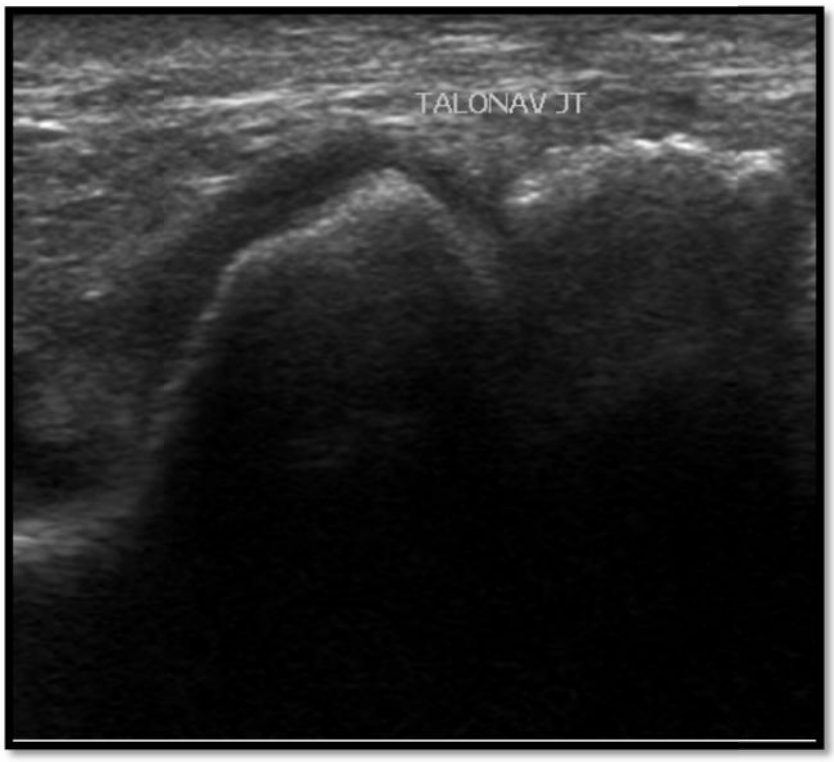
Longitudinal view of the tibialis posterior tendon (T). The tendon appears normal but there is marked synovial hypertrophy within the tendon sheath.



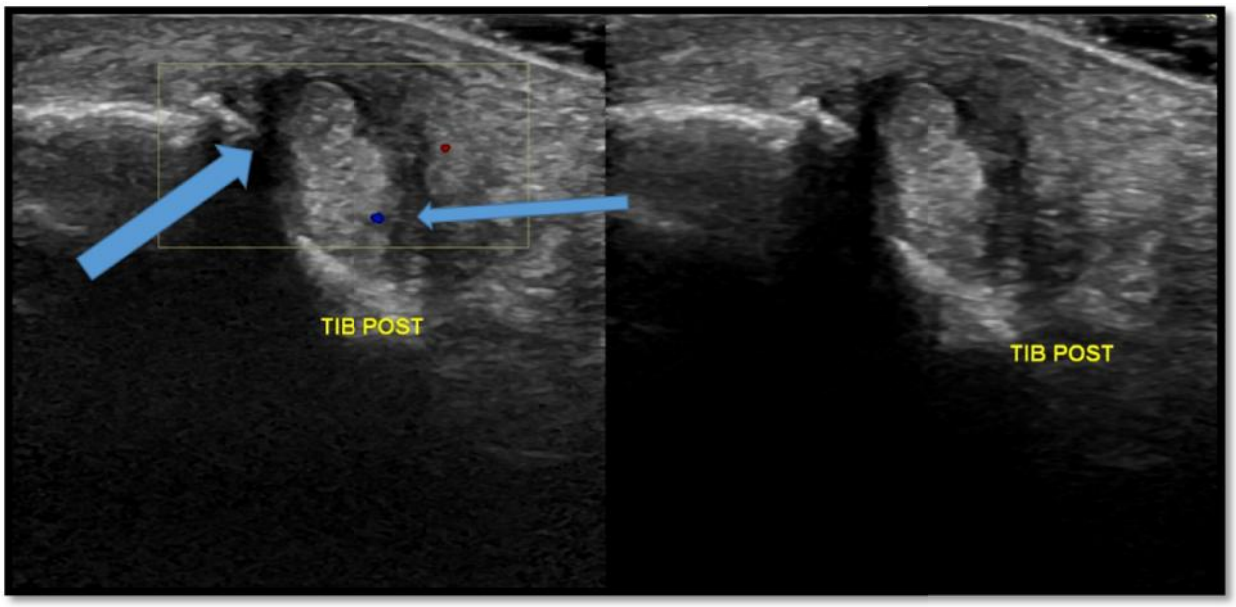
Longitudinal anterior view shows tibio talar joint.
There is a large effusion distending the joint capsule (solid arrows) with synovial hypertrophy (*) located within the joint capsule.



Longitudinal view of Tibiotalar joint showing joint effusion



Transverse view of Talo-navicular joint shows synovial hypertrophy



Transverse view of Tibialis Posterior tendon shows synovial hypertrophy in the tendon sheath and minimal fluid -