“ROLE OF MUSCULOSKELETAL ULTRASOUND IN THE EVALUATION OF JOINT PATHOLOGIES IN PATIENTS WITH HYPERURICEMIA AND GOUT- A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY”

BY

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LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
MTP	Metatarsophalangeal joint
USG	Ultrasonography
DCS/DC	Double contour sign
MSU	Monosodium urate
HUA/ HU	Hyperuricemia
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
SUA	Serum uric acid
NHANES	National Health and Nutrition Study
MSUS	Musculoskeletal ultrasound
HRUS	High resolution ultrasound
US	Ultrasound
GLUT	Glucose Transporter
PIP	Proximal interphalangeal joint
NSAID	Nonsteroidal Anti-inflammatory Drug
NCKDS	National Chronic Kidney Disease Survey
CKD	Chronic kidney disease
BMI	Body Mass Index
ARB	Angiotensin Receptor blockers

ACE	Angiotensin converting Enzyme
CRP	C- reactive protein
DECT	Dual Energy Computed Tomography
HU	Hounsfield unit
kV	Kilo Volt
ACR	American College of Rheumatology
ULT	Urate Lowering Therapy
EULAR	European League Against Rheumatism
MSK	Musculoskeletal

ABSTRACT

Background: Hyperuricemia is defined as raise in serum uric acid levels (monosodium urate). Deposition of monosodium urate in the form of crystals, within the tissues results in an inflammatory response termed as gout. Gouty arthritis is one of the commonest inflammatory joint diseases and appears to be rapidly increasing worldwide. Higher prevalence is seen in men and incidence increases with age. The cartilaginous deposits which are characteristic are not readily demonstrated with conventional diagnostic imaging including roentgenography, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). The sensitivity of simple radiography of the involved joint is found to be low. Though Computed Tomography and Magnetic Resonance Imaging has the advantages of early detection of tophi and bone erosion, the disadvantages include inconvenience to the patients, exposure to the radiation (CT), high cost and lack of specificity (MRI). [2] Demonstration of monosodium urate crystals under polarizing microscope from the joint or tophi aspirate is gold standard for the diagnosis of gout. But it is an invasive procedure and is infrequently done. [2] Ultrasound has emerged as a useful non-invasive tool for the diagnosis of gout. It can also be used to evaluate the involvement of joints in the patients with hyperuricemia which aids in the clinical management and thus alters the disease progression.

Materials and methods: A hospital based cross-sectional study was performed on 50 patients of which 20 had symptomatic gout and 30 patients had asymptomatic hyperuricemia (serum uric acid levels >7gm/dL). All the patients were clinically evaluated and subjected to USG of bilateral 1st MTP joint, knee and ankle joints. The association between the outcome, clinical and demographic characteristics were tested using Chi-square test, test of proportion and Fisher's exact test.

Results: In our study, majority of patients were of age group 50-60 years' age group (38%), followed by 60-70 years age group (26%). Majority were males (70%). 32% patients had diabetes mellitus, 26% patients had IHD and 20% had hypertension. 30 (60%) had asymptomatic HUA while 20 (40%) had gout symptoms. Of 20 symptomatic gout patients, 12 (60%) patients had HUA and 8 (40%) had normal uric acid levels. 10 out of 30 patients with asymptomatic hyperuricemia had joint disease evident on USG. i.e 33% of patients with hyperuricemia has asymptomatic joint disease. Among the study population, Joint erosions and joint effusions were the major findings on USG, followed by snowstorm appearance, Synovitis, Double contour sign and tophus.

Conclusion: In our study of 50 patients, 30 patients were having asymptomatic hyperuricemia among which 10 patients (33%) had significant joint involvement in the form of either joint erosion, effusion, synovitis, Double contour sign or snowstorm appearance. 8 out of 20 symptomatic patients had normal serum uric acid levels. In such patients, USG will help to eliminate the misdiagnosis (infective or other inflammatory diseases) by demonstrating the features of gout in the joints and thus helps in proper management of such patients. Thus, Musculoskeletal USG of joints is a very useful tool for early diagnosis of joint involvement in patients with asymptomatic hyperuricemia. However, to generalise the statement large volume multicentric randomised studies are necessary.

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INTRODUCTION

Hyperuricemia is defined as raise in serum levels of uric acid (monosodium urate). Deposition of monosodium urate in the form of crystals, within the tissues results in an inflammatory response termed as gout. Monosodium urate (MSU) crystals build up in tissues such as cartilage, bone, synovial membranes and skin, which results in illness gout[1]. Gout affects both extra-articular and articular components of the musculoskeletal system, causing arthritis, tendinitis, and bursitis. Hyperuricemia, a condition where serum uric acid levels are above the threshold at which MSU crystals can form, is the situation that leads to this deposition[2,3].

Gout and Hyperuricemia (HUA) prevalence rates have been observed to be much greater in industrialized nations than in underdeveloped nations. According to the 2015–2016 National Health and Nutrition Study (NHANES), 20.1 percent of US adults have HUA, which is comparable to the figure from the 2007–2008 survey. In adults from Australia, it was 16.6%. According to the 2016 Korean NHANES (KNHANES), 11.4 percent of Korean adults have HUA (17.0 percent for males and 5.9 percent for females). Most wealthy nations, including the USA (3.9%), Australia (5.2%), Canada (3.8%), Greece (4.75%), Germany (1.4%), and the UK, have gout prevalence rates higher than 1 percent (2.5 percent). However, Thailand and Bangladesh had HUA prevalence rates of 10.6% and 9.3%, respectively. In underdeveloped nations like Bangladesh, India, and Pakistan, the frequency of gout is essentially less than 0.5 percent. China's geographical areas, economy, and ethnic groupings are diverse, making it the biggest developing nation in the world. The National Chronic Kidney Disease Survey (NCKDS), which encompassed 13 provinces, provided extensive epidemiological data on HUA in Chinese people.

According to that study, the prevalence of HUA was 8.4%. The prevalence rates of HUA and gout in China between 2000 and 2014 were 13.3 percent and 1.1 percent, respectively, according to another meta-analysis.[4]

The deposition of urate crystals is seen to be predominant in the superficial portions of the articular cartilage. Gouty arthritis is one of the commonest inflammatory joint diseases and appears to be rapidly increasing worldwide. Higher prevalence is seen in men and incidence increases with age. The cartilaginous deposits which are characteristic are not readily demonstrated with conventional diagnostic imaging including roentgenography, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).[5,6]

The sensitivity of simple radiography of the involved joint is found to be low. Though Computed Tomography and Magnetic Resonance Imaging has the advantages of early detection of tophi and bone erosion, the disadvantages include inconvenience to the patients, exposure to the radiation (CT), high cost and lack of specificity (MRI). Demonstration of monosodium urate crystals under polarizing microscope from the joint or tophi aspirate is gold standard for the diagnosis of gout. But it is an invasive procedure and is infrequently done.[6]

Ultrasound has emerged as a useful non-invasive tool for the diagnosis of gout. It can also be used to evaluate the involvement of joints in the patients with hyperuricemia which aids in the clinical management and thus alters the disease progression. There is limited published data regarding the usage of musculoskeletal ultrasound in study of Gout. Such study is not done previously in our institution; hence this study is being carried out.

AIM AND OBJECTIVES

- To assess the role of musculoskeletal ultrasonography in the evaluation of structural changes in the joints of the patients with hyperuricemia and gout.

REVIEW OF LITERATURE

History

One of the first recognized disorders, gout was initially described by the Egyptians in 2640 BC as painful ailment affecting great toe. In the fifth century BC, Hippocrates wrote about a "unwalkable condition," which he called podagra (from the Greek pous, means foot, and agra, means prey- "foot-trap"). Hippocrates recognized connection between the gout and unbalanced lifestyle characterized by fatty meals and binge drinking. [7,8] It was thought that gout was caused by an imbalance of the four primary body humors, where one of the humors would collect in joints due to an overindulgent lifestyle. The name "gout" - used in mediaeval era and was derived from “gutta -Latin word, meaning drop.”[9,10]

It wasn't until Karl Scheele[11], a scientist, discovered the molecular identification of uric acid in 1776. As a result, Sir Alfred Garrod identified hyperuricemia (an excessively high serum urate) as the underlying cause of gouty arthritis in 1848. [12] Using polarizing light microscopy for the first time to look for MSU crystals in joint fluid in 1961, McCarty and Hollander also identified the roles of excessive urate synthesis and poor excretion in the pathophysiology of hyperuricemia [12,13,14]. By the end of the 20th century, pharmaceutical treatments combined with dietary and lifestyle modifications that addressed these primary causes of hyperuricemia allowed for the effective management of gouty arthritis.

Uric acid and hyperuricemia

The end result of the metabolic breakdown of purines is uric acid. Since uric acid is a weak acid with an acidic dissociation constant (Pka) of 5.5, it mostly converts to the urate-ionized form at physiological pH 7.4. Since sodium is the most prevalent extracellular ion, monosodium urate makes up the majority of this urate. The kidneys remove two-thirds of the uric acid that is created each day, with the remaining one-third going through various channels such saliva, gastric juice, pancreatic secretions, and bowel movements. Hyperuricemia is mostly brought on by impaired renal excretion of uric acid. Urate crystallizes and precipitates in tissues when its solubility limit is reached (380 mol/l, or 6.8 mg/dL at 37 ^{o}C). [15]

Primates, birds, certain reptiles, and the majority of insects are devoid of the uricase enzyme, which in other species breaks down urate into soluble molecule allantoin.[16,17] The usage of foods high in fructose and purines in western nations has caused uric acid levels to rise to hazardous levels that are linked to morbidity and a higher mortality. [18,19]

According to physiochemical definition, hyperuricemia occurs when the serum urate level exceeds MSU solubility limit, that is 6.8 mg/dL at 37°C. Hyperuricemia is considered when this concentration is higher above the normal range, which is defined as the mean serum urate value plus 2 SD in a sex- and age-matched healthy population. The upper limit in this case is different for males and female. In males it is 7 mg/dL and females, 6 mg/dL. The incidence of gout is 0.1 percent per year for values under 7 mg/dL, 0.5 percent for values between 7 and 8.9 mg/dL, and 4.9 percent for values over 9 mg/dL. As uric acid rise, the risk of developing gouty arthritis increases. With urate levels at 9 mg/dL, the cumulative incidence of gouty arthritis is 22 percent after five years, showing that not everyone with increased urate will experience gout symptoms due to unknown causes. [20]

Epidemiology

Prevalence and incidence of gout and hyperuricemia

The food and way of life that make people more susceptible to gout and hyperuricemia have proliferated in recent decades. The frequency and incidence of gout and hyperuricemia are rising worldwide, especially in America, Europe, Asia, and Australia, according to epidemiological research. According to estimates, one in ten persons will experience hyperuricemia at some point in their lives, and as serum urate levels rise, the likelihood of developing gout rises exponentially. The odds ratio for developing gout in men with serum urate levels between 0.39 and 0.47 mmol/l was found to be 11.2 times higher than that in those with normal levels, and the chance ratio for developing gout in men with hyperuricemia > 0.56 mmol/l was 624.8.[21-24]

Gout prevalence has recently been estimated to be 0.6% worldwide, however there is substantial variation due to factors including age, sex, and geography. In those under 65 years of age, the male to female gout prevalence ratio is around 4:1, and it drops to 3:1 in those over 65. Younger women seldom get gout, but older women are more susceptible due to the kidneys' decreased ability to remove uric acid after menopause-related estrogen depletion. [25,26]

Risk factors

In addition to the demographic risk factors of advancing age and male sex, a number of genetic, behavioral, and pharmacological variables are crucial for maintaining the homeostasis of serum urate. Gout and hyperuricemia are likely caused by a complicated interplay between a number of risk factors.[27]

Genetic factors [28,29,30]

Given that one out of four patients with gout have family history of the ailment, genetic factors play significant position in gout pathogenesis through modulation of homeostasis of serum urate. In several cultures, notably Taiwanese Aborigines, Pacific Islanders, and New Zealand Mori, a high incidence of genetic variations linked to urate regulation contributes to the degree of hyperuricemia and gout. Renal urate transport proteins are mostly encoded by genes associated with gout and hyperuricemia, making renal uric acid regulation highly heritable.

Both fractional excretion of uric acid and renal clearance of uric acid exhibit substantial heritability, according to twin studies. Urate homeostasis can be upset by even a single polymorphism in urate transporter proteins, which changes the protein's structure and function. Genetic studies on gout and hyperuricemia have generated a lot of interest in genes that control urate transport. A genomic-wide association study revealed 28 genetic loci involved in transport of uric acid by the kidney and stomach to be associated with hyperuricemia. GLUT9 (SLC2A9) and ABCG2 are the two most significant urate transporter genes for controlling serum urate and gout incidence.

Dietary factors

Gout has long been linked to dietary considerations, notably the consumption of excessive alcohol and foods rich in purines. On the other hand, a recent study discovered that tomato intake was favorably correlated with serum urate levels. Fructose, included in fruit and beverages with added sugar to sweeten them, has been linked to a higher risk of developing gout. It has been demonstrated that fructose raises serum urate through improving the purine nucleotide metabolism and increasing purine synthesis. [31,32,33]

Perhaps the most well-known factor in the onset of gout is alcohol drinking. While the dehydration and metabolic acidosis brought on by alcohol consumption diminish urine excretion, the ethanol component of alcohol has been found to enhance uric acid synthesis. It has been demonstrated that drinking alcohol considerably raises the likelihood of developing incident gout in both men and women. While modest wine consumption has no impact, beer consumption increases the risk of incident gout more than spirits do. The increased purine content in beer may help to explain this disparity. [34,35,36]

Hypertension and chronic kidney disease[37,38,39]

In several epidemiological studies, hyperuricemia and high blood pressure have been linked. In the 2007–2008 NHANES study, the hypertension prevalence was 24 percent in normouricemic people, 47 percent in hyperuricemic people, and 74 percent in patients with gout. It rose with uric acid levels and peaked at 83.8 percent in those with urate levels over 10 mg/dL. Through the proliferation of vascular smooth muscle cells, inflammation, inhibition of nitric oxide (NO), and activation of the renin-angiotensin system, uric acid causes afferent arteriolopathy in animal models, which results in ischemia in the post glomerular circulation. In the presence of elevated uric acid levels, the emergence of hypertension has been explained using a two-stage paradigm. As uric acid elevates blood pressure by increasing renal renin activity and decreasing circulating plasma nitrates, hypertension in early stages is uric acid dependent. The second stage is characterized by urate-independent but sodium-dependent anatomical changes, such as thickening of wall and proliferation of smooth muscle, that are brought on by uric acid. Allopurinol and probenecid medication is associated with a reduction in blood pressure, indicating that the beneficial effects of urate-lowering therapy are not dependent on the suppression of xanthine oxidase activity. Even yet, there is currently no rationale for urate-lowering medication in individuals with hypertension, despite these results.

Urinary pH, which has been related to gout as acidic urine increases the formation of urate, is the main risk factor for uric acid stone formation. Since uric acid is eliminated through the kidneys, it can be challenging to distinguish whether it or reduced renal clearance is the cause of chronic kidney disease (CKD) and hyperuricemia.

Comorbidities

Obesity, hypertension, and renal disease are among the common comorbidities seen in gout patients. According to reports, the average gout patient has four comorbidities, with the number increasing with the severity of the gout condition. In 62.8 percent of gout sufferers, the metabolic syndrome—the concomitant presence of obesity, hypertension, dyslipidemia, insulin resistance, and hyperglycemia—is present. In actuality, obesity and renal illness have been found to be independent risk factors for gout, as have other elements of the metabolic syndrome. [40,41]

Body mass index (BMI) has been reported to increase the risk of incident gout, with a BMI more than 25 kg/m^2 being associated with a 28 percent incidence of gout. It has also been demonstrated that high blood pressure is a separate risk factor for developing gout.

Those with hypertension has twice as high chance of developing gout as men without hypertension. Renal disease and gout are frequently associated because of the decline in glomerular filtration rate and consequent rise in hyperuricemia. The incidence of incident gout was 2.4 times higher in those with poor glomerular filtration rates compared to those with a normal rate. Numerous studies have demonstrated that the presence of diabetes lowers the incidence of incident gout, despite the metabolic syndrome's co-existence of insulin resistance and hyperglycemia. A case-control study revealed that males with type 2 diabetes had a relative risk for incident gout of 0.67 compared to men without diabetes, independent of other risk factors. Glycosuria, a common complication of diabetes, is thought to play a role in the lower incidence of gout, as does a compromised inflammatory response. [42]

Medications [43]

Gout has been linked to pharmaceutical usage, especially the use of diuretics, which are used for a number of comorbid illnesses include hypertension and renal failure. It has been shown that women with diuretic intake have 2.4 times more chance of getting gout than males, who are estimated to be 3.4 times more probable.

With dose and time spent on diuretics, this risk rises. Except for losartan, other anti-hypertensive medications, such as beta-blockers, ARB's and ACE inhibitors, have similarly been reported to raise the incidence of "incident gout" by 1.5, 1.3, and 1.2 times, respectively. If used within the previous 48 hours, aspirin is proven to increase the incidence acute gout recurrence and has effects on the uric acid processing by the kidney, especially at low dosages.

Clinical staging [44]

Asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout, and chronic gouty arthropathy have historically been regarded as the four progressive phases of hyperuricemia and gout. The MSU crystal deposition demonstration in asymptomatic people with hyperuricemia but without history or clinical signs of gout is not recognised by this method. This staging system defines gout as a condition of recurrent flares interspersed with remissive periods when in reality it is a chronic disease of MSU crystal deposition because it does not acknowledge the continuous deposition of MSU crystals in the asymptomatic intervals between acute gouty arthritis.

Recently, a brand-new staging method was put forward (Figure). The pathogenic stages of gout are recognised by this staging system as a chronic, progressive illness caused by MSU deposition. Stage A comprises 'people with asymptomatic hyperuricemia' who do not exhibit symptoms or proof of MSU crystal deposition, whereas Stage B includes those with asymptomatic hyperuricemia who do, whether by advanced imaging or microscopy. If a person has experienced an episode of acute gouty arthritis in the past or is currently experiencing one, they are classified as having Stage C MSU deposition and symptomatic gout. If they also exhibit features of advanced gout, such as tophaceous disease or chronic arthropathy, they are classified as having Stage D MSU deposition and symptomatic gout. The phases are often progressed in a linear fashion, although those with Stage B (asymptomatic hyperuricemia with MSU crystal deposition) may alternatively proceed straight to Stage D without having acute gouty arthritis.

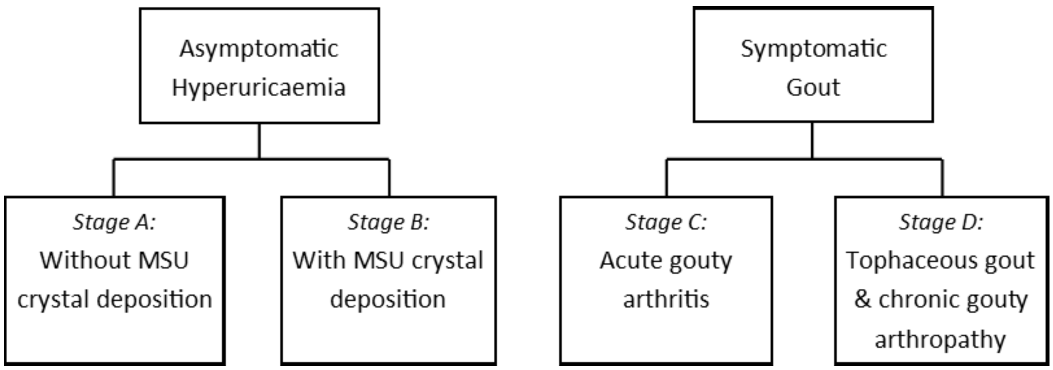


Figure 1 Dalbeth et al staging of gout and hyperuricemia [52]

Clinical features of gout

Acute gouty arthritis [45]

A "flare" or "attack" of acute gouty arthritis is described as a quick onset of excruciating musculoskeletal pain brought on by acute inflammation due to MSU crystal deposition. Acute flares primarily affect the musculoskeletal system's synovial structures, such as the joints, tendon sheaths, and bursa, leading to acute arthritis, tendonitis, and bursitis. The most often affected structures are those in the periphery; 83 percent of flares are said to occur in the lower limbs. The mid-foot, ankle, and knee joints are the next most often affected structures in early flares, followed by the first metatarsophalangeal joint (1^{st} MTP). The most often damaged upper limb structure is the olecranon bursa of the elbow, whereas elderly persons and those with long-standing illness duration frequently experience wrist and finger joint problems. Those with well-established gout may experience acute gouty arthritis in centrally positioned joints, such as the hips, shoulders, and axial skeleton. Even while oligo-articular and poly-articular patterns of joint involvement can happen in older people or people with chronic and poorly managed hyperuricemia, even though 90 percent of first flares are mono-articular.

The moderate pain, discomfort, and functional limitations that precede the severe inflammatory symptoms of acute gouty arthritis are known as the gouty "aura." The incidence of flares is typically sporadic and unpredictable. According to a new meta-analysis looking at seasonal differences in acute gouty arthritic episodes, flares start to happen more frequently in the spring. This may be due to an increase in physical activity, dehydration, and changes in cortisol levels. New large prospective research supported the historical finding that acute flares frequently occur at night or in the early morning hours. The authors found that the frequency of nocturnal flares was 2.4 times more than that of daytime flares, which they related to changes in body temperature, serum cortisol levels, and purine synthesis brought on by sleep apnoea. Due to the frequent night time flares, the patient is frequently awakened by sudden, extreme agony. The joint and peri-articular soft tissue are sensitive and warm, and there is widespread erythema, edema, restricted joint mobility, and warmth associated with the pain, which often peaks in 6 to 24 hours (Figure).

As the result of severe inflammatory response to MSU crystals, systemic symptoms of inflammation, which are less frequent, such as fever, elevated serum CRP levels and leucocytosis may manifest. Acute gouty arthritis is self-limiting and goes away on its own without treatment in one to two weeks.

Figure 2 Acute gouty arthritis of the right 1st MTP showing localised erythema and swelling

Between acute gouty arthritis, there are often asymptomatic episodes that last anywhere from a few months to many years. People with long-term gout and untreated hyperuricemia experience shorter asymptomatic intervals followed by more frequent, protracted, and incapacitating flares. It has also been demonstrated that those who get gout earlier in life (between the ages of 12 and 24 years) experience shorter asymptomatic intervals, due to past flares reoccurring before they have completely subsided. However, the majority of gout sufferers have three to four annual flare-ups and asymptomatic intervals that continue for many months. Studies have shown that low-grade inflammation persisted even though there were no symptoms throughout the asymptomatic period, as well as ongoing MSU crystal formation. [53]

Chronic gouty arthropathy and tophaceous gout [46]

'Chronic gouty arthropathy' is characterised by tophus development, joint dysfunction, and chronic clinical signs of inflammation. The severity and persistence of untreated hyperuricemia are related to the emergence of tophi. Tophi developed in a cohort of patients with untreated gout in 12% of cases within 5 years and in 55% of cases after 20 years.

Subcutaneous tophi, also known as palpable tophi, are often found intradermally, within tendons or bursae, or within the synovial joint capsule. Tophi are often found inside and around the toe and finger joints, especially over osteoarthritic Heberden's or Bouchard's nodes, around the knees, over the olecranon process at the elbow, the Achilles tendon. They are frequently seen in places that experience a lot of pressure or friction. Under tight overlaying skin, intra-dermal tophi show as white or yellowish deposits. Even though it is uncommon, deposition in the median nerve and spinal involvement can cause carpal tunnel syndrome and nerve compression, respectively. Although uncommon, skin overlaying tophi may ulcerate, expel white, chalky debris, and develop an infection.

Tophaceous gout causes noticeable joint degeneration and musculoskeletal impairment, despite the fact that tophi are typically asymptomatic. Joint restriction is a crucial aspect of gouty arthropathy and may result from tophus buildup in the joints themselves or in the ligaments and tendons that surround them, which can impair normal joint biomechanics.[47]

Imaging in gout and asymptomatic hyperuricemia [48]

Recent studies have shown a significant development and advancement in gout-related medical imaging modalities. The usage of increasingly sophisticated imaging methods has overtaken the use of traditional radiography, including musculoskeletal ultrasonography, magnetic resonance imaging (MRI), dual-energy computed tomography (DECT) and conventional computed tomography (CT). When monosodium urate (MSU) crystals cannot be seen under a microscope, these cutting-edge approaches have enhanced accuracy in the early diagnosis of gout. Imaging has been used in gout research to track the progression of the condition and how well treatments are working as well as to promote a better understanding of its pathophysiology. A greater comprehension of the effects of subclinical MSU accumulation in persons with asymptomatic hyperuricemia has also been made possible by advanced imaging techniques, notably DECT and ultrasonography. This chapter will discuss recent research that has evaluated musculoskeletal structures in gout patients using conventional radiography, CT, DECT, MRI, and musculoskeletal ultrasound. The chapter's conclusion will put a special emphasis on the sonographic characteristics of gout as well as the monitoring and diagnostic utility of ultrasound in gout sufferers and patients with asymptomatic HUA.

Conventional radiography

The oldest and most accessible imaging technique is conventional radiography, which uses radiation to create a two-dimensional projected picture of interior body components. The density and makeup of the item being photographed affect how much radiation is absorbed or reflected, and this affects the picture that is produced. With little ionizing radiation exposure, it enables inexpensive, multi-area visualization. As a result, several categorization criteria include the characteristic radiographic symptoms of gout are well-established. However, because the conventional radiographic appearance of acute gouty arthritis is non-specific and frequently normal, aside from soft-tissue swelling, the diagnostic role of conventional radiography is restricted to the detection of advanced gout features, which frequently take up to 10 years to develop after disease onset. Additionally, even while traditional radiography has a high specificity (0.93) when compared to the clinical gold standard in individuals with advanced gout, the diagnostic sensitivity is limited (0.31). This demonstrates that while radiography has a limited power to accurately identify people who do have gout (sensitivity), it has an excellent capacity to identify persons who do not (specificity).

Figure 3: X- ray of bilateral foot AP view- Extensive juxta-articular erosions with dense soft tissue swelling noted at first MTP joints on both sides, first toe interphalangeal joint on right side, PIP of the left foot second toe and PIP of right foot second and third toes.[49]

Conventional radiography can visualize characteristics found in more severe gouty arthropathy, such as tophi, erosions, and new bone formation, but it cannot reveal MSU crystal accumulation or inflammatory alterations in synovial and osseous tissue. Subcutaneous tophi show as vague soft tissue opacities that may or may not be calcified. Gouty erosions can occur intra- or peri-articular as well as intra-osseous, and they often have an overhanging edge and a distinctive punched-outlook. Until the illness progresses, the joint space in gout is often conserved. Sclerosis, osteophyte growth, and bone spurs are common manifestations of new bone production in gout. Subchondral cystic alterations and collapse may happen in gout, despite the absence of peri-articular osteopenia. Clinically obvious tophi and DECT-evident MSU crystal deposition are highly linked with conventional radiographic characteristics of chronic gouty arthropathy. Alterations in gout are most frequently found in the first metatarsophalangeal joint (1st MTP), fifth metatarsophalangeal joint, midfoot, and hand on conventional radiography. [50,51,52]

While conventional radiography has limited ability to diagnose gout, it can be a valuable tool for disease monitoring. Based on the Sharp/van der Heijde approach, a 'conventional radiographic bone erosion scoring system for chronic gouty arthropathy' was created, and it has shown a strong association with musculoskeletal dysfunction and indicators of bone resorption in gout. Furthermore, over a 12-month period, urate lowering therapy has been shown to increase sclerosis, decrease soft tissue masses, and this conventional radiographic score, indicating that it may be sensitive to track changes in bone damage over time using conventional radiographic scoring of bone erosion.[53,54]

Conventional computed tomography [55]

Conventional CT is regarded as the gold standard for identifying bone loss in inflammatory joint disease due to its three-dimensional multi-planar scanning methodology. A cross-sectional image is created by the use of numerous x-ray beams that are aimed at the body from different angles during CT scanning. The expense and radiation exposure are higher than with traditional radiography, nevertheless. Similar to conventional radiography, CT has a low diagnostic sensitivity for early gout changes, because it cannot identify MSU crystal accumulation or inflamed soft tissue.

On a CT scan, tophi may be distinguished from bone and soft tissue because they appear as distinct, dense masses that are around ‘170 Hounsfield units’ in size. Both within and outside of joints, as well as in tendons and subcutaneous tissue, tophi are easily visible. With tophi present in 82 percent of joints with CT-evident bone erosions, CT has also made it possible to show the connection between tophi and bone erosions. This supports the tophus infiltration's role as the primary mechanism causing bone degradation in gout. Additionally, sclerosis, osteophytes, and periosteal new bone development can all be seen on CT scan when a patient has gout.

Figure 4: Coronal multiplanar reformatted CT image of right ankle and foot in a 42-year-old man with right ankle pain showing high-attenuation tophi associated with erosions in distal tibia, fibula, and talus.[56]

Despite CT's limited ability to diagnose gout, it may be helpful in determining the extent of bone destruction and the weight of tophi. For use in gout research, a ‘semi-quantitative CT bone erosion scoring system’ has been created. This entails evaluating seven bones in the midfoot and ankle that are commonly impacted by gout but are difficult to see on standard radiography. This grading system had shown outstanding inter-rater dependability. For the measurement of tophus volume, CT has further demonstrated great inter-rater reliability. The dimensions of Tophus were measured physically and by using CT, it was found that there was a significant link between the two. However, additional research and confirmation of CT in gout monitoring has to be done.

Dual-energy computed tomography [57,58]

DECT is able to identify and distinguish MSU crystals from surrounding material in joints, tendons, ligaments, and soft tissue structures, in contrast to conventional imaging modalities. DECT uses two x-ray sources operating concurrently at ‘80 kV and 140 kV’, providing two data sets with various attenuations. This makes it possible to color-code the materials' chemical makeup. Recently, a criterion for DECT-evident MSU deposition was added to the “2015 ACR/EULAR Classification Criteria for gout”. This criterion is validated against the industry-standard synovial fluid assay. For the detection of MSU crystal deposition, DECT has also demonstrated strong inter-rater reliability. DECT exposes the patient to ionizing radiation & is costly, and is not as widely available as other imaging modalities.

The MSU deposits identified by DECT have sensitivity and specificity that vary from 0.75 to 1.0 and 0.84 to 1.0, respectively. DECT's diagnostic sensitivity is decreased in the absence of tophaceous illness, despite the fact that it has been able to detect MSU deposits in individuals without any clinical symptoms of tophi. Twenty percent of subjects in a DECT trial of people with acute gouty arthritis who had no prior gout history lacked MSU deposition. The link between detectable MSU deposits and illness duration, urate reducing treatment, and serum urate levels might be due to the difficulty to detect tiny MSU deposits. Therefore, early gout may restrict the diagnostic use of DECT.

The '1st MTP, knee joint, and ankle' are the most frequent locations for MSU deposition, but DECT-detectable MSU deposits are less prevalent in joints of the upper limbs. This indicates that the DECT sensitivity in gout depends on anatomical site that is scanned. Furthermore, the imaging software parameters, particularly the parameter ratios, have an impact on the specificity and sensitivity of DECT. For DECT, a standardized diagnostic technique has not yet been created. Previous study techniques have ranged from merely scanning the most symptomatic joint, or the most commonly afflicted region (such as the feet or ankles), to scanning all peripheral joints (such as the feet or ankles, knees, wrists or hands, or elbows). Given the cost of DECT and the exposure to ionizing radiation, fewer sites would be preferred when developing a diagnostic procedure.

Figure 5 3D dual-energy CT with color mapping of foot and ankle in a 70-year-old man shows extensive monosodium urate (MSU) crystal deposition (green) consistent with tophaceous gout of first metatarsophalangeal joint, with additional MSU deposition in ankle and midfoot.[56]

DECT's capacity to quantify tophus volume suggests that it may be helpful in tracking changes in the MSU load in response to therapy. DECT tophus volume measurements have very good repeatability and great inter- and intra-rater reliability. Additionally, DECT is demonstrated to be more repeatable than physical techniques for determining tophus size. However, it has been demonstrated that in gout patients receiving urate-lowering medication, the quantifiable MSU volume is below the lowest detectable change, which may restrict the potential of DECT in monitoring treatment response.

DECT has been used in three trials to far, with varying degrees of success, to measure urate deposition in patients with asymptomatic hyperuricemia. The incidence of urate deposition was evaluated in 27 renal transplant recipients with asymptomatic hyperuricemia by Kimura-Hayama et al.[59]. They only found one MSU deposit, for a frequency of only 0.03 percent, in a quadriceps tendon. Although this might be explained by the definition of “hyperuricemia as > 0.38 mmol/l”. But only 86 percent of 22 asymptomatic people with mild hyperuricemia (mean urate 0.49 mmol/l) had MSU deposits, according to a two-arm cross-sectional study. Both groups had comparable urate distribution patterns, within the distal first toe, 1st MTP, and distal fifth toe being the most frequent. The distribution of MSU deposition in the foot, including joints and tendons, was similarly evaluated by Dalbeth et al.[60]. However, compared to 84 percent of 33 persons with gout, only 24 percent of 25 asymptomatic participants with severe hyperuricemia (defined as > 0.54 mmol/l) had MSU deposition. Despite the fact that people with asymptomatic hyperuricemia had DECT urate deposition in their joints and tendons, the volume of their tophus was significantly smaller than that of the gout group, suggesting that volume may affect the development of symptomatic gout. These three studies serve as a foundation for additional longitudinal investigation into the urate volume and presence-related parameters that influence the development of symptomatic gout in people with hyperuricemia.

Magnetic resonance imaging[61]

MRI uses radio waves and a strong oscillating magnetic field to give good contrast resolution of both soft tissue and osseous structures without exposure to ionizing radiation. Its importance in the regular evaluation of gout is however diminished by its expensive price, limited availability, and low patient tolerability, particularly in patients with aneurysm clips and pacemakers.

Similar to DECT, tiny MSU deposits on cartilage surfaces is not identified by MRI; however, MRI outperforms DECT in terms of tophi identification with high specificity (0.98) and intermediate sensitivity (0.63). On T1-weighted images, tophi appear as discrete masses with low signal strength, whereas on T2-weighted images, tophi have varied signal intensity. When compared to traditional radiography and physical examination, MRI has shown tophi and soft tissue tophi detection to be more sensitive. For the identification of tophi on an MRI, inter- and intra-rater reliability are both quite good.

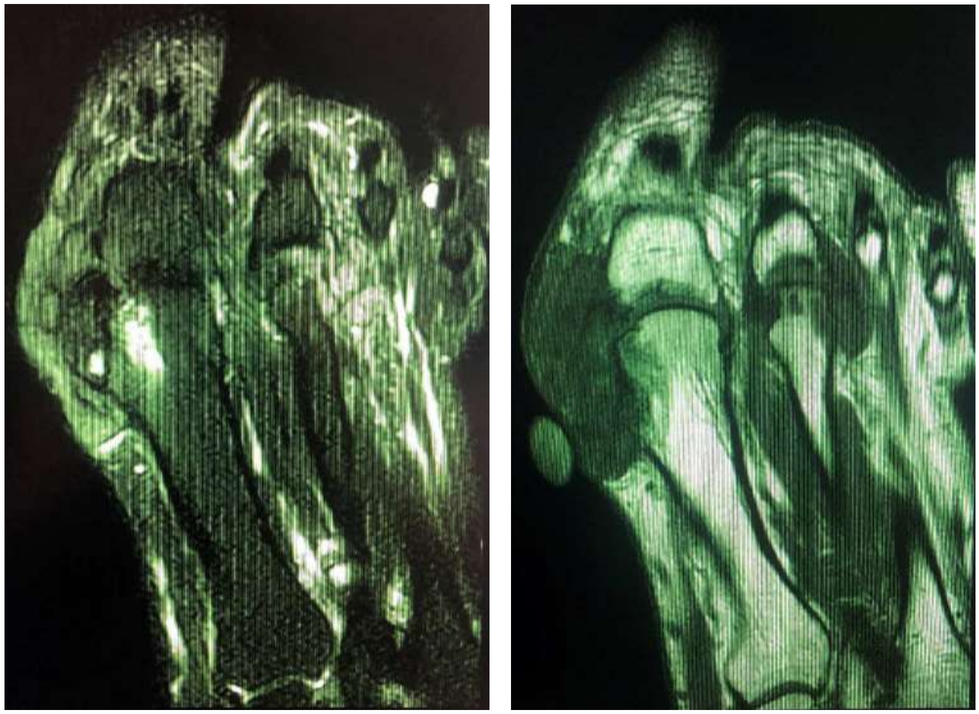


Figure 6: MR Coronal STIR and T1w images of foot showing erosive arthropathic changes of the 1st and 2nd MTP articulations with juxta-articular bony erosions and punched-out/overhanging edges, underlying mild marrow edema and pseudocystic changes, evident at the 1st metatarsal head. Associated surrounding mass-like soft tissue sheets seen causing overlying contour bulge, likely representing tophi. Mild metatarsophalangeal and interphalangeal joints effusion seen [49]

Additionally, less specific gout symptoms such as synovitis, effusions, erosions, cartilage destruction, and bone marrow edema may be consistently seen using MRI. Synovial inflammation was detected by MRI in 87.5 percent of patients with asymptomatic gout, demonstrating the continuation of “subclinical inflammation” despite the lack of acute gouty arthritis.

Participants with gout frequently have erosions on MRI, which exhibits better sensitivity for this characteristic than traditional radiography and ultrasound. In individuals with simple gout, the prevalence of bone marrow edema varies greatly (between 1 and 56 percent), but its appearance to be a defining hallmark in gout worsened by osteomyelitis. An 'MRI cartilage damage scoring system (GOMRICS)' has further shown positive connection with the standard radiographic 'Sharp/van der Heijde score' for persons with gouty joint constriction. According to the scientists, erosions, synovitis, and tophus size were all strongly related to cartilage injury.

Tophus volume assessment using MRI has demonstrated "high inter- and intra-rater reliability, with absolute percentage variances reported as 17.2% and 14.2%, respectively. It has not yet been demonstrated that MRI is useful for assessing treatment response. The time-consuming manual outlining process required for tophus volume assessment using MRI, in contrast to DECT, limits its use in clinical and research contexts.

Ultrasonography [62-65]

In musculoskeletal ultrasonography, high frequency sound waves are transmitted and then bounced off interior tissue surfaces to create a two-dimensional picture. By using this method, ultrasonography produces high resolution pictures of osseous and soft tissue structures. Due to its dynamic, real-time capabilities, which enable the evaluation of moving joints and provide the examiner total control to thoroughly probe the regions of interest, ultrasound has a number of benefits over other sophisticated imaging modalities. Compared to other imaging methods, ultrasound is reasonably inexpensive, relatively quick, and emits no radiation. However, the accuracy of ultrasonography depends largely on the examiner's expertise and necessitates some level of experience in both picture capture and interpretation. When compared to other imaging methods, ultrasound has a limited depth of penetration, but it delivers excellent resolution of tiny peripheral joints, especially those affected by gout.

Image acquisition and interpretation [65]

Normal range of high frequency sound waves for ultrasound imaging is 3 to 15 MHz. The ultrasonic probe, which uses the piezoelectric effect to convert electrical energy to mechanical energy, generates these sound waves. The resolution improves with frequency, but sound waves don't go as far into deeper structures. A two-dimensional greyscale image is created. The term "echogenicity" describes a structure's capacity to return ultrasonic waves to the transducer. In contrast to hypoechoic structures, which are less reflecting and seem grey, hyperechoic structures are reflective and appear whiter. Anechoic structures seem fully reflective-free and dark.

Bone is anechoic on ultrasound, with a hyperechoic ring and an acoustic shadow behind it, and cannot be penetrated by sound waves. Muscle and cartilage, which are more permeable to ultrasound than bone, have a hypoechoic appearance. On grey scale pictures, fat and fluid seem anechoic whereas ligaments, tendons, fascia, and other connective tissues appear hyperechoic due to their higher reflectivity. Power Doppler capabilities are also available with musculoskeletal ultrasonography, allowing for the detection of blood vessel flow rate. While flow away from the probe shows blue, flow toward it appears red. The ‘angle of incidence’ at which sound waves hit a structure's surface has a significant impact on how echogenic the structure is. Because more ultrasonic waves are reflected back to the transducer when the probe is perpendicular, a higher quality image is created. When the angle of incidence is not perpendicular, anisotropy, a misleading hypoechoic appearance, develops and can have a significant impact on how the resultant picture is interpreted. [65]

Sonographic features in gout

Synovial inflammation

In cases with gout, sonographic evaluation will show a wide range of results suggestive of synovial inflammation. Synovial hypertrophy, joint effusion and increased signal on Power Doppler are all signs of synovial inflammation. Even in cases when there is no clinical indication of acute arthritis, these characteristics have been linked to gout. In a longitudinal study (n = 30), the number of clinically active joints reduced when acute arthritis subsided, but sonographic characteristics of synovitis did not go away, demonstrating the enduring nature of subclinical inflammation in gout.

Synovial effusion has been seen in anywhere between 26% and 90% of gout sufferers, according to various reports. Joint effusion is far more likely to be detected sonographically than clinically. In spite of this great sensitivity, joint effusion has also been noted in 13 percent of healthy controls and 64 percent to 73 percent of sick controls. The first MTP and knee joints, which are commonly imaged in sonographic examinations, are vulnerable to joint effusions due to hydrostatic pressure and dynamic joint mobility.

Incidence of synovial hypertrophy which is seen as hypoechoic thickening of the synovial membrane, varies from 8 percent to 97 percent in gout. Synovial hypertrophy has also been noted in 15% to 64% of various inflammatory disorders and in 6% of controls, similar to synovial effusion.

8 percent to 100 percent of gout sufferers have shown evidence of the power Doppler signal, which denotes enhanced vascularization, throughout both episodes of acute arthritis and asymptomatic times. This extremely sensitive characteristic, however, lacks specificity because it occurs in 50% of other arthropathies. Excellent inter-rater reliability for determining the power Doppler signal in gout (fi = 0.96). [65]

Bright stippled foci, also known as intra-articular hyperechoic patches in synovial fluid, with prevalence rates ranging from 12 percent to 93 percent of joints studied are seen in gout. These spots are believed to be MSU crystals that are emitting tiny, brilliant echoes in the synovial fluid. These tiny mobile aggregates give the joint region a "snowstorm appearance" when the ultrasonic transducer applies little pressure. However, it has been noted that up to 25% of controls and 14–35% of various kinds of arthritis exhibit intra-articular hyperechoic areas. These shiny specks might possibly be bubbles or joint debris from joint movement, which are frequently difficult to distinguish from MSU crystal clusters. Therefore, the appearance of hyperechoic patches is not regarded as a distinctive sonographic sign for gout. However, research has shown that bright stippled foci and the snowy appearance have good inter-rate agreement and great intra-rater agreement (fi = 0.73 and 0.88, respectively). The inter-rater reliability for aggregates, however, was reportedly low (fi = 0.21) in a recent research.

Figure 7 Joint effusion and Snow Storm Appearance

Four studies have looked at the frequency of synovial inflammation in people with asymptomatic hyperuricemia. Participants with asymptomatic hyperuricemia reported ‘synovial hypertrophy in 52%, effusion in 15%, and the Power Doppler signal in 23% of cases’. According to a later research, 42 percent of subjects with asymptomatic hyperuricemia had one of these signs of soft tissue inflammation.

Articular cartilage

Sonographically, articular cartilage often appears as two clearly defined hyperechoic edges separating a homogeneous anechoic layer. The superficial margin is improved and appears to be as thick as subchondral bone because to MSU deposition on the cartilage surface. The twofold contour indication refers to this hyperechoic, erratic band above the anechoic hyaline cartilage. The cartilage interface sign, which is visible at a 90 degree insonation angle, may be distinguished from the margin's reflectivity, which is independent of the angle of incidence and can be validated by dynamic evaluation. The dorsal side of the 1st MTP and the femoral condyles are where the double contour sign may be best seen, but osteoarthritis or joints with thin cartilage reduce the sign's appearance.

Figure 8: 1st MTP joint-Joint effusion and Double Contour Sign

In the gout population, the reported prevalence of the double contour sign incidence is quite diverse, ranging from 10% to 92.0% of people scanned. Prevalence varies from 2 to 44 percent in knee joints and from 22 to 92 percent in 1st MTPs, suggesting that it depends on the joint being evaluated. The larger incidence of 92 percent was found in joints with active acute gouty arthritis, whereas the lower prevalence of 22 percent was seen in 1st MTPs with no symptoms. The double contour sign has been seen more frequently in joints with a history of acute gout than in clinically unaffected joints, although it has also been seen in 25% to 48% of people with asymptomatic hyperuricemia.

When measured against the gold standard of MSU crystals under microscopy, the sensitivity of the double contour sign in gout sufferers varies from 44% to 77.6%. Numerous investigations have shown the lack of the double contour sign in both healthy controls and those with various rheumatic illnesses, suggesting that the double contour sign's specificity is larger than its sensitivity. In contrast, Naredo et al.[10] found the double contour sign in 17% of individuals in the control group, of whom 64% also had other rheumatic conditions. Ottaviani et al.68 also noted the double contour sign in 21% of the disease-free controls' knees, but neither the metatarso- nor the metacarpo-phalangeal joints showed the double contour sign. The double contour sign might indicate a crystal-related joint condition, according to a recent retrospective research (n = 225 joints), but it was unable to discriminate between them, with a specificity of just 64% for gout.

The double contour sign's long held strong diagnostic significance has been questioned in light of reliability analyses' contradictory results for both the inter- and intra-rater agreement for this sonographic characteristic. The double contour sign is measured with moderate (fi = 0.47) to good (fi = 0.96) inter-rater reliability. Additionally, there is a moderate to good range in intra-rater reliability (fi = 0.53 to 1.00).

Tophi

On ultrasonography, tophi can be seen in a variety of places, including intra-articularly, inside bursa, tendons, ligaments, and other soft tissues. Tophi have variable degrees of echogenicity according to the MSU crystal compaction's density. Most tophi (between 69 and 80 percent) manifest as amorphous heterogenic masses. On ultrasonography, tophi often seem hyperechoic (75 percent to 96 percent of imaged tophi). Sonolucent tophi are referred to as "soft" tophi, whereas persistent "hard" tophi are made up of more hyperechoic material. Only a small percentage of tophi seen on ultrasonography are hard; the bulk are either soft or mixed. Eighty-three to eighty-nine percent of tophi also have ill-defined margins, and 56 percent have an anechoic halo around the edges that represents inflammatory cells. Only a small percentage (15%) exhibit posterior acoustic shadowing. Since formed tophi do not move with bone or cartilage when the joint moves, they may be separated from urate deposition along cartilage surfaces. The definition of tophi according to sonography varies greatly between research. As a result, 'Outcome Measures in Rheumatology (OMERACT)' has developed a standard description of a confined, inhomogeneous, hyperechoic and/or hypoechoic aggregation as a possible tiny anechoic rim that may or may not cause posterior acoustic shadow. [66]

Gout sufferers had a sensitivity of 19 percent to 100% for intra-articular tophi identified by ultrasound, compared to a sensitivity of 64% for tendon or ligament tophi. The length of the gout illness, the level of serum urate, and the anatomical location being scanned all seem to have an impact on prevalence. The 1st MTP, radiocarpal joint, midcarpal joint, and knees are the most frequent locations for ultrasound-detected tophi, whereas the patellar, triceps, quadriceps, and Achilles tendons are the most frequent sites for tophi in tendons. Tophi have reportedly been found in both asymptomatic joints in individuals with gout and joints with active acute arthritis. Additionally, with an incidence ranging from 16 to 45 percent, intra-articular and tendinous tophi have been discovered in people with asymptomatic hyperuricemia. [67,68]

Tophi identified by ultrasonography can also vary in specificity. Reuss-Borst [67] found that the prevalence of tophi ranged from 7 to 35 percent in people with arthropathies other than gout, whereas it was reported to be 19 percent in healthy control participants. In control subjects, no tophi were found in three investigations. When tophi or the double contour sign are seen, ultrasound's sensitivity and specificity for detecting gout and asymptomatic hyperuricemia rise, with a sensitivity of 100% and a range of 76–88%, respectively.

When compared to the gold standard of microscopic detection of MSU crystals, the criterion validity of tophi discovered by sonography is strong (83 percent to 93 percent). When compared to MRI for the purpose of identifying tophi, ultrasound has good construct validity, with 90% of tophi on MRI being detected by ultrasound. Sonographic evidence of tophi has an inter-rater reliability of fi = 0.63 to 1.0.

Bone

Bone erosion appears sonographically as two perpendicular planes of the hyperechoic bone surface that are uneven or discontinuous. Participants with gout have an erosion prevalence ranging from 24 to 66 percent when diagnosed by ultrasonography. Participants with asymptomatic hyperuricemia ranged from 12 to 23%. Participants with gout tend to have more erosions in their clinically affected joints, and there is a significant correlation between the prevalence of acute arthritis and presence of erosion. However, erosions have also been seen in joints without any clinical discomfort and without ever having experienced acute arthritis. However, there is no correlation between serum urate and erosion occurrence in terms of illness duration. [67,68]

The incidence of erosions has been recorded in up to 43% of joints examined in other inflammatory disorders, hence the specificity of ultrasound-detected erosions is low for gout. Similar to this, erosions are visible in 6 to 19 percent of healthy individuals who do not have any arthritic conditions. By keeping an eye out for nearby tophi or synovial inflammation, it may be possible to boost the specificity of erosions found on ultrasonography in the diagnosis of gout. Bone erosions and the existence of ultrasound-detected tophi have been found to be strongly correlated, and 37 percent of erosions have also been demonstrated to exhibit a power Doppler signal. [69]

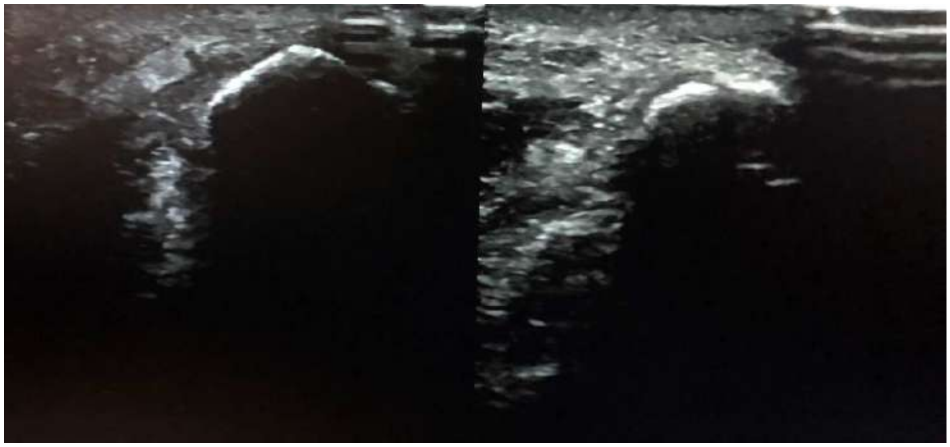


Figure 9: Joint erosions

Ultrasound underestimates the size and quantity of erosions compared to MRI. However, several studies have demonstrated that ultrasonography has a higher sensitivity for detecting erosions than traditional radiography. In patients with gout, ultrasonography revealed considerably (P 0.05) more 1st MTP erosions (66%) than conventional radiography, according to Wright et al [69](28 percent). Small erosions under 2 mm that cannot be detected radiographically can be found with ultrasound, which is particularly helpful in this situation. [67] While the intra-observer reliability has been observed to be great, the inter-rater reliability for identifying erosions in gout is high, ranging from fi = 0.74 to 1.0.

Diagnostic value

There are few studies evaluating the diagnostic effectiveness of ultrasonography. Participants in long-term gout for which a diagnosis has been made are often assessed by ultrasonography. Recent research by Pascal et al.[79] evaluated the effectiveness of ultrasound for diagnosing acute arthritis in participants, many of whom were just beginning to show symptoms. Joints with symptoms and other joints were examined for tophi or the double contour sign (knee, ankle, 1st MTP). Sensitivity for gout was 60 percent and specificity was 92 percent when evaluating symptomatic joints experiencing recent flares. Sensitivity increased to 84 percent when other joints were included. The specificity, however, decreased to 78%. Given that MSU crystals are known to grow over time, the individuals' shorter duration of gout illness may have contributed to the lower sensitivity. This is demonstrated in a recent multi-centre research published by Ogdie et al.[70], which evaluated the diagnostic utility of ultrasonography in the detection of both acute and chronic illness using MSU crystal identification as the gold standard. The existence of the double contour sign and tophus was more sensitively detected in patients with long-standing illness duration (> 2 years) than in those with early disease (63 percent vs. 51 percent), according to the investigators (51 percent vs. 34 percent). Specificity, which ranged from 91 to 95 percent, was continuously high over the course of the illness.

There is presently no agreement on the sonographic characteristics and anatomical locations that should be examined to diagnose gout. For the diagnosis of gout, only a few sonographic evaluation techniques have been suggested. Peiteado et al. [71] demonstrated the precision of a four-joint ultrasound test for the diagnosis of gout using MSU crystal identification as the gold standard. They discovered that in 97 percent of subjects with crystal-proven gout, a straightforward six-minute ultrasound scan of the bilateral knees and 1st MTPs enabled for the diagnosis of either tophi or the double contour sign. Similar to this, Naredo et al. [75] evaluated the diagnostic usefulness of a 12-site ultrasound examination for MSU deposits and the double contour sign. This assessment included bilateral evaluation of one joint, three articular cartilages, and two tendons. For the diagnosis of gout, they reported respectable sensitivity (85%) and specificity (83%) rates. However, it should be noted that participants in these trials had a chronic illness, were asymptomatic at the time of examination, and had a previously confirmed diagnosis of gout.

Lamers-Karnebeek [72], in contrast, suggested a six-joint evaluation in patients with initial presentations of current acute arthritis. When compared to the gold standard identification of MSU under microscopy, the sensitivity of the double contour sign, tophi, or snowstorm appearance was 96 percent. A research by Loffler et al.[73] examined the accuracy of ultrasonography in distinguishing gout from other crystal deposition disorders (namely calcium phosphate deposition disease) by imaging just the afflicted joint. Participants who presented with acutely affected joints were also evaluated. The specificity for gout when evaluating for the double contour sign was comparable to CPPD (64 percent vs 52 percent). The specificity for gout rose to 92 percent when the double contour sign was combined with the power Doppler signal and high serum urate, while the sensitivity dropped to just 42 percent. These findings make it abundantly evident that more testing and validation of the existing recommended diagnostic techniques are necessary to determine ultrasound's capacity to identify gout and distinguish it from other inflammatory diseases.

Monitoring value

Numerous studies have evaluated the use of ultrasonography in assessing therapy response in gout patients. Following seven to 18 months of urate lowering medication, Thiele et al.[77] and Ottaviani et al.[64] found a good association (fi = 0.81 to 1.00) between the reduction or removal of the ‘double contour sign’ and blood uric acid. In those who reached a serum urate goal of 0.36 mmol/l, the double contour sign improved or disappeared in 100% of knee joints and 90% of 1st MTPs.

Participants who met this urate target also showed a disappearance or reduction in tophi in all knee and 1st MTP joints, according to Ottaviani et al.68. Similar to this, Perez-Ruiz [74] reported that after 12 months of urate lowering medication, 53 percent of subjects had a decrease in the maximal diameter and volume of ultrasound detected tophi, while 24 percent saw a full resolution of tophi. The authors came to the conclusion that ultrasonography satisfied the OMERACT filter for an outcome measure satisfactorily and provided measures of tophus diameter and volume with strong inter-rater reliability (ICC 0.71 to 0.83 and 0.95 to 0.98, respectively).

Although less than urate deposition observed sonographically, the power Doppler signal also seems to be responsive to urate reducing treatment (double contour sign and tophi). At baseline, 96 percent of individuals had the power Doppler signal observed by Peiteado et al.[71]; this number fell to 73 percent at the 24-month follow-up. Even when it indicates a reaction to change, the Doppler signal's persistence raises questions about utilizing this ultrasound result to assess the effectiveness of the current pharmaceutical therapy for gout.

In conclusion, ultrasonography provides distinct benefits over other imaging modalities, but its application in clinical practice is constrained by its operator dependence and the high degree of competence needed to acquire and interpret pictures. However, the use of ultrasound in research settings has made it possible to identify a number of characteristics of gout and asymptomatic hyperuricemia, including more specific characteristics of gout, such as MSU deposition on cartilage surfaces and in the form of tophi. These characteristics include generic signs of inflammation and damage seen in synovial inflammation and erosions.

Ultrasonography is demonstrated to be sensitive to alter with urate lowering treatment and to be beneficial as a diagnostic tool as well. But as technology develops and our knowledge of ultrasound interpretation in gout and asymptomatic hyperuricemia expands, it's probable that we'll also get more insight into how useful ultrasonography is at various disease stages, clinical severity levels, and anatomic sites.

A cross-sectional study was done by Ogdie and his colleagues on 824 participants, found that the musculoskeletal ultrasound features of monosodium urate crystal deposition had high specificity for the diagnosis of gout and ultrasound maybe useful adjunct in differential diagnosis of acute gout in patients presenting with acute arthritis. This study concluded that ultrasound may potentially be the most useful in establishing diagnosis of hyperuricemia in individuals with high clinical suspicion of gout and aids in early management, thus preventing the further progression of disease.[70]

A cross-sectional study was done in New Zealand which included 23 participants with gout, 29 participants with asymptomatic hyperuricemia and age & sex matched 34 normouricemic controls. This study showed that in gout patients, urate deposition, inflammation of soft tissues and bone erosions are common at first metatarsophalangeal joint as seen on ultrasound, though the clinical symptoms of acute arthritis are absent. Despite the lack of ultrasound features of structural joint changes and inflammation in asymptomatic hyperuricemia patients, they demonstrated subclinical urate deposition of similar frequency. This study concluded that features other than crystal deposition, synovitis and bony erosion specifically can be useful in differentiating gout from asymptomatic hyperuricemia and that gout is a chronic joint inflammatory disease with presence of monosodium urate crystals in joints with subclinical persistent immune response to it.[75]

A prospective study was done in Germany at University clinic, with 74 patients who presented with musculoskeletal problems and they were assessed for the presence of hyperuricemia and gout. This study contributed some evidence that long standing, untreated hyperuricemia might cause joint damage, even if the patient is asymptomatic. It concluded that ultrasound can be used as a suitable tool for early detection of structural changes in hyperuricemia patients and that it may have impact on further treatment decisions. [67]

A cross-sectional study was done in Spain at La Paz University Hospital with 35 subjects who were found to be hyperuricemic and ultrasonography of knees and ankles was performed in them. This study concluded that identification of tophus-like structures or deposits of monosodium urate in the joints/ tendons of asymptomatic hyperuricemia by ultrasound might modify the diagnostic evaluation of hyperuricemia.[76]

A retrospective study was done in New Brunswick, New jersey, USA with 23 patients and all musculoskeletal ultrasound studies that were performed from November 2003 to December 2004 were reviewed. The results showed that specific diagnostic features of gout included a hyper-echoic band over the superficial margin of articular cartilage which is described as double contour sign. This study concluded that ultrasound can detect monosodium urate crystal deposition on cartilaginous surfaces as well as tophaceous material and typical erosions and that the ultrasound may serve as a non-invasive means to diagnose gout.[77]

Esperanza Naredo carried performed a prospective research with 42 age-matched controls and 91 males who had gout. The results show that US bilateral evaluation of one joint (the radiocarpal), three articular cartilages (the first metatarsal, talar, and second metacarpal or femoral condyle), and two tendons (the patellar tendon and triceps tendon) may be helpful for diagnosing gout.[78]

A study by Das S. et al. found that serial ultrasonographic determination of DCS, tophi, or HES during hypouricemic therapy is a non-invasive, effective method to detect the lowering of urate load in gouty joints among adult gout patients who were examined by serial ultrasonography after initiating ULT with target serum uric acid (SUA) 6 mg/dL.[79]

In a study by Sabra AI et al., [80] 30 patients with gouty arthritis and 20 matched controls received febuxostat 80 mg once day for three months. Results of MSUS in patients' and controls' knee and first metatarsophalangeal "1st MTP" joints were reported before and three months after therapy. Febuxostat is used to treat gout, and ultrasonography can spot changes. When recognising sickness indicators and changes, clinical examination is less sensitive than ultrasonography.

High resolution ultrasound (HRUS) can detect these deposits and the harm they cause, such as hyaline cartilage pathology, joint effusions, synovitis, bone erosions, tendonitis, bursitis, and other soft tissue involvement, according to Daniela Fodor's research. The typical characteristics of these aggregates that may be detected by US can also be used by the physician to make a positive and differential diagnosis.[81]

According to a meta-analysis by Quingu Zhang et al.[82], ultrasonography can be used to diagnose gout. For individual assessments, the blizzard sign, tophi, and the double contour sign on ultrasonography have medium to low sensitivity but excellent specificity in the diagnosis of gout. They went on to say that taking all of these factors into account at once could increase the diagnostic accuracy of ultrasonography for gout. For joint-/location-based assessments, the double contour sign is ineffective in differentiating between gout and non-gout.

According to a research by Pascal Zufferey et al.[83] US is far more beneficial than X-ray imaging. When it comes to puncturing tiny joints, US may be a big aid. It can also be used as a backup plan if joint aspiration is impossible or dangerous. The diagnosis of gout is strongly suggested by the presence of MSU symptoms on the affected joint. However, US shouldn't be restricted to the affected joint alone. The diagnostic sensitivity is higher but the specificity is decreased when using US on numerous joints.

METHODOLOGY

SOURCE OF DATA: Patients who are incidentally detected to be hyperuricemic on routine blood examination from Endocrinology clinic & patients admitted in wards with various ailments and patients presenting with gout to Rheumatology clinic will be referred for ultrasound scan to the Department of Radio-diagnosis at the KLE's Dr Prabhakar Kore Hospital & MRC, Belagavi.

STUDY DESIGN: A one-year hospital based cross-sectional study.

SAMPLE SIZE: The minimum sample size formula based on prevalence rate is

Where P is the percentage of prevalence and d is the percentage likely difference in the prevalence.

$Z\alpha$ is linked with the level of significance. For 5% level of the significance $Z\alpha = 1.96$.

Ref: With P-78.3% and d-15% of P-11 75%, the sample size is 47

This sample size will be raised to 50. Participants will be in the age group of 18-90 years.

SAMPLING METHOD: Universal sampling

STUDY PERIOD: January 2021 to December 2021

INCLUSION CRITERIA

Adult patients (above 18 years and below 90 years of age) who are incidentally detected to be hyperuricemic in their blood investigations and those of confirmed cases of gout referred from Endocrinology and Rheumatology clinic to the Department of Radio-Diagnosis.

(Serum uric acid >7mg/dL is considered as hyperuricemia)

EXCLUSION CRITERIA

- Previous surgery involving the affected joint.
- Intra-articular corticosteroid injections (in the last 3 months) in the structures being examined.
- History of fracture in and around joints.
- Patients below the age of 18 years and above the age of 90 years.

METHODOLOGY

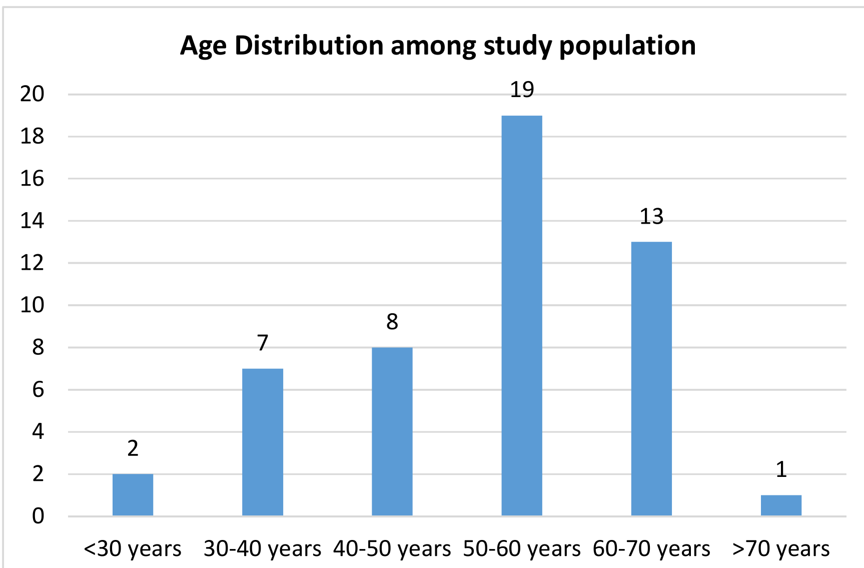
An informed written consent will be obtained from all the study subjects. A pre-structured Performa shall be used for collection of clinical data. A detailed history, associated risk factors (sedentary lifestyle, smoking, alcoholism) will be taken. The above-mentioned study population will be subjected Ultrasonography on GE LOGIQ P9 R2 Machine equipped with 5-9 MHz L8-18i-D linear array hockey stick ultrasound probe transducer and 7.5Mhz-12Mhz high frequency linear array transducer (GE Health care, USA).

Patients will be positioned supine with their legs flexed for examining the knee, ankle and 1^{st} MTP joints on both sides. All studies will be performed in two dimensions by scanning across the joints and moving the probe from medial to lateral and from distal to proximal. Each site will be scanned in Gray scale mode to detect any structural changes and Power Doppler technique to detect abnormal vascularity.

RESULTS

Table 1 Age Distribution among study population

		N	%
Age Distribution	<30 years	2	4.0%
	30-40 years	7	14.0%
	40-50 years	8	16.0%
	50-60 years	19	38.0%
	60-70 years	13	26.0%
	>70 years	1	2.0%

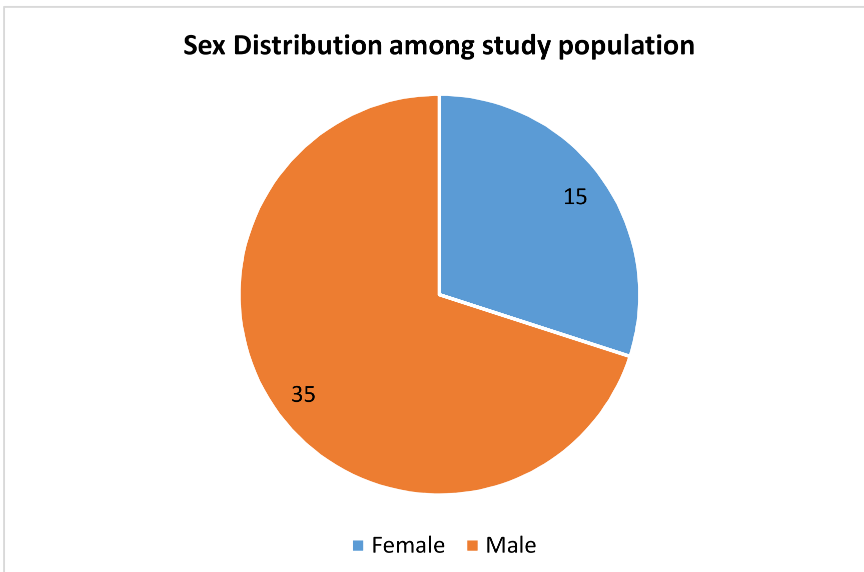


Graph 1 Age Distribution among study population

In our study of 50 patients, 19 patients were in the age group of 50-60 years, followed by 13 patients in 60-70 years' age group. There were 7,8,2 and 1 patients in 30-40, 40-50, <30 years and >70 years' age groups respectively

Table 2 Sex Distribution among study population

		N	%
Sex	Female	15	30.0%
	Male	35	70.0%

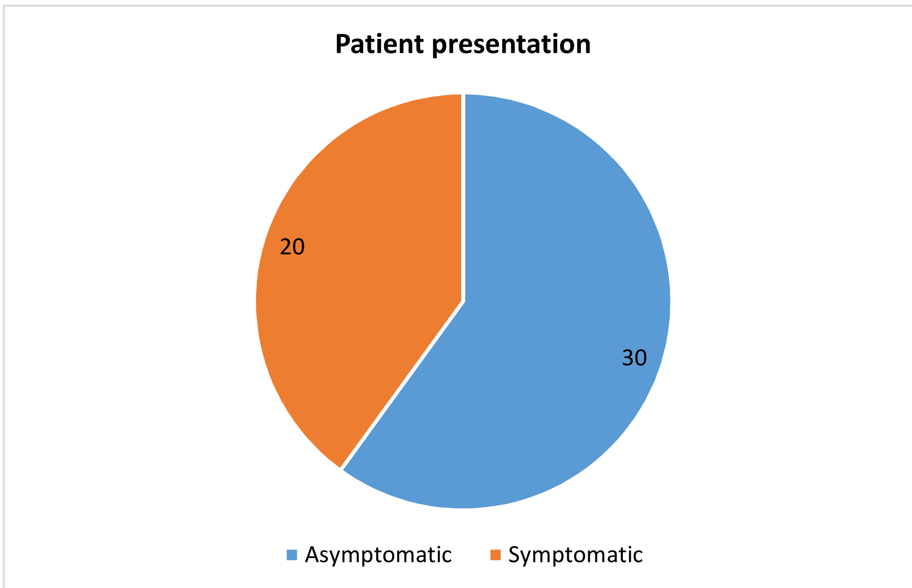


Graph 2 Sex Distribution among study population

In our study of 50 patients, 35 are male and 15 are females with a male predominance in our study.

Table 3 Patient presentation

		N	%
Symptomatology	Asymptomatic	30	60.0%
	Symptomatic	20	40.0%

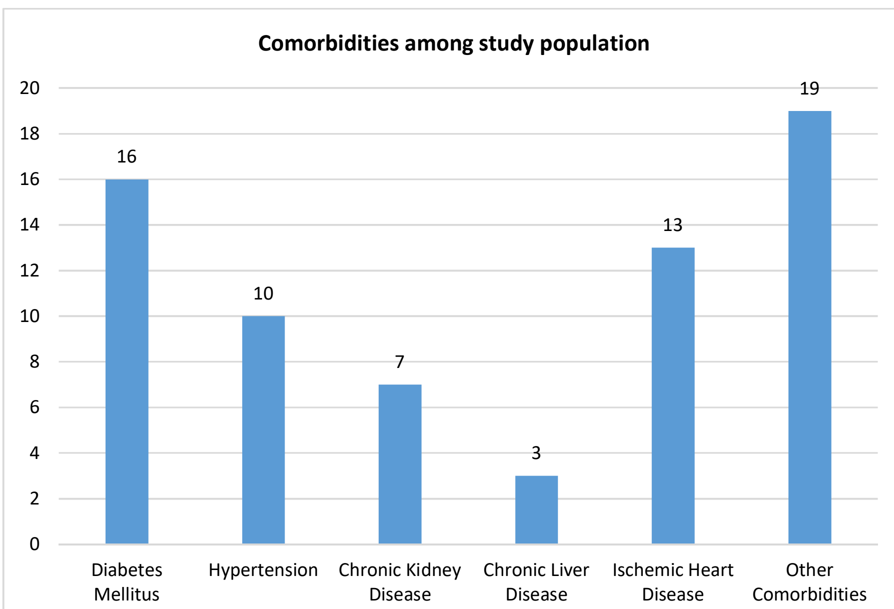


Graph 3 Patient presentation

In our study of 50 patients, 20 patients had symptoms of gout and the rest 30 patients had asymptomatic hyperuricemia.

Table 4 Comorbidities among the study population

	Comorbidities	
	N	%
Diabetes Mellitus	16	32.0%
Hypertension	10	20.0%
Chronic Kidney Disease	7	14.0%
Chronic Liver Disease	3	6.0%
Ischemic Heart Disease	13	26.0%
Other Comorbidities	19	38.0%



Graph 4 Comorbidities among our study population

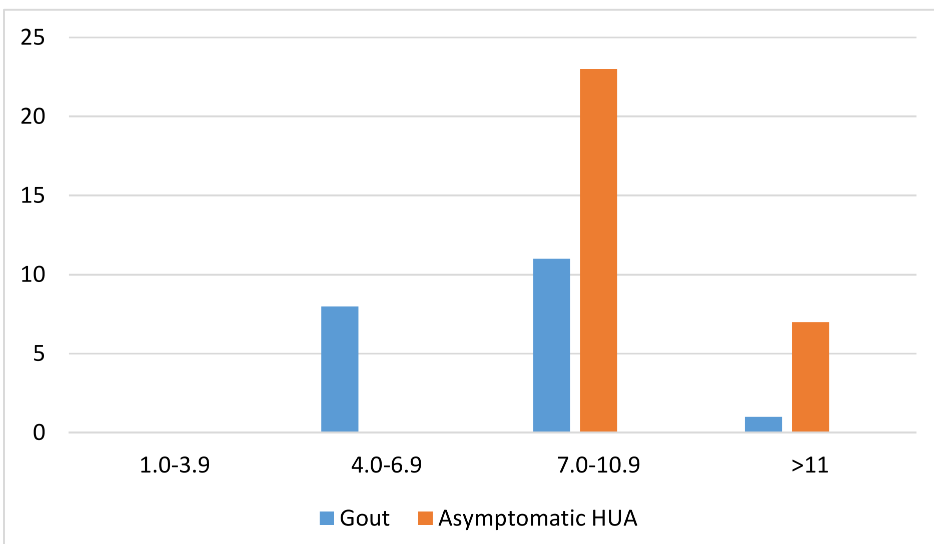
In our study, Diabetes was the major comorbidity which was present in 16 patients, followed by IHD (13) and Hypertension in 10 patients.

Table 5 Distribution of uric acid levels in symptomatic Gout patients

Uric acid levels in mg/dL	N
1.0 – 3.9	-
4.0-6.9	8
7.0-10.9	11
> 11	1

Table 6 Distribution of uric acid levels in asymptomatic hyperuricemia patients

Uric acid levels in mg/dL	N
7.0-10.9	23
> 11	7

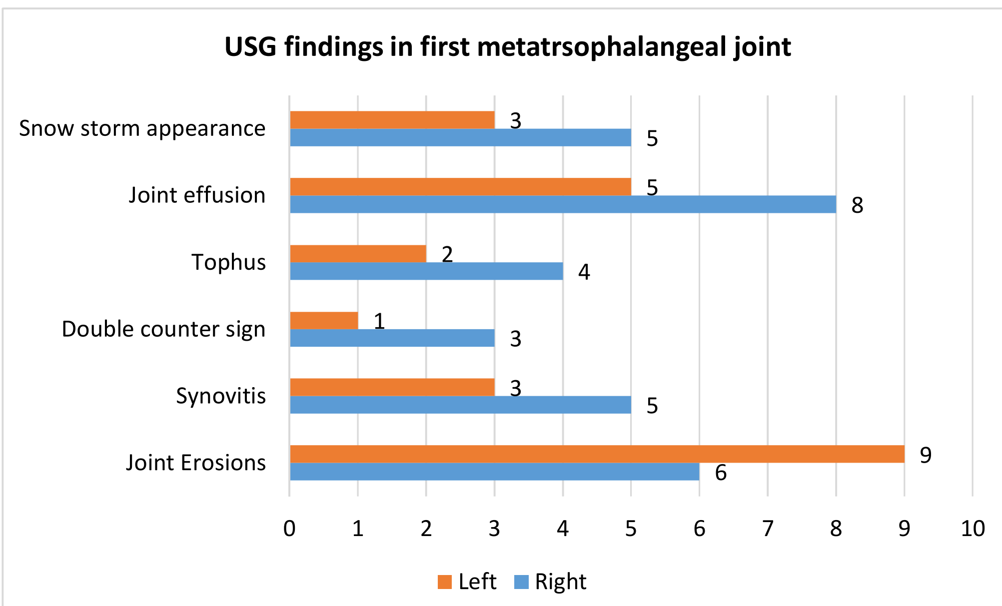


Graph 5- Distribution of uric acid levels in gout and asymptomatic hyperuricemia patients

Of 20 symptomatic gout patients, 12 patients had raised serum uric acid levels >7 mg/dL while 8 patients had normal serum uric acid levels (<7mg/dL).

Table 7 USG findings in first metatarsophalangeal joint

USG findings in 1st metatarsophalangeal joint				
	Right		Left	
	N	%	N	%
Joint Erosions	6	12.0%	9	18.0%
Synovitis	5	10.0%	3	6.0%
Double counter sign	3	6.0%	1	2.0%
Tophus	4	8.0%	2	4.0%
Joint effusion	8	16.0%	5	10.0%
Snow storm appearance	5	10.0%	3	6.0%

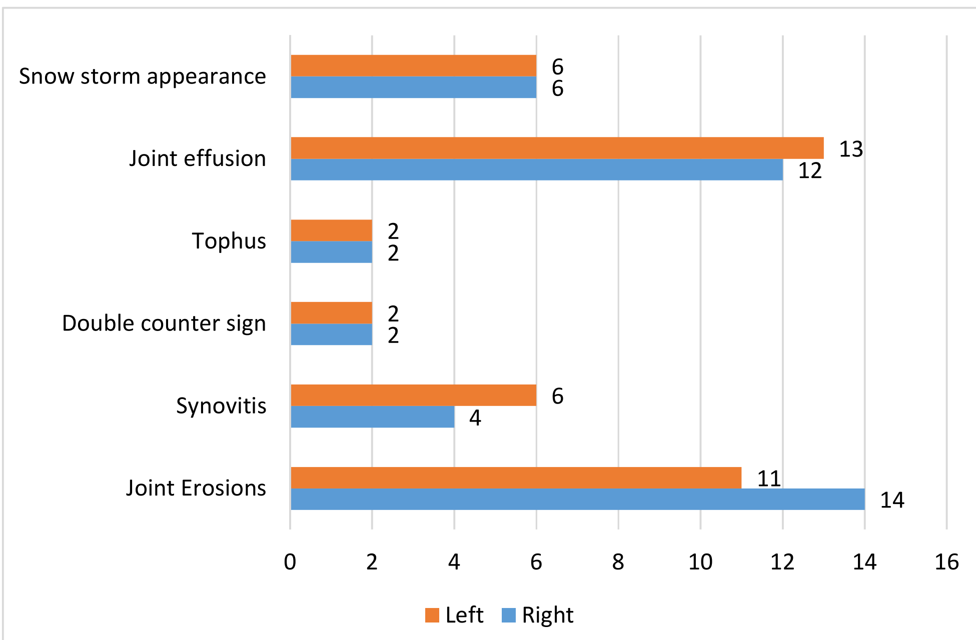


Graph 6 USG findings in first metatarsophalangeal joint

Among the study population, Joint erosions and joint effusions were the major findings on USG of 1st metatarsophalangeal joint. Followed by snowstorm appearance, Synovitis, Double contour sign and tophus.

Table 8 USG findings in Knee joint

USG findings in Knee joint				
	Right		Left	
	N	%	N	%
Joint Erosions	14	28.0%	11	22.0%
Synovitis	4	8.0%	6	12.0%
Double counter sign	2	4.0%	2	4.0%
Tophus	2	4.0%	2	4.0%
Joint effusion	12	24.0%	13	26.0%
Snow storm appearance	6	12.0%	6	12.0%

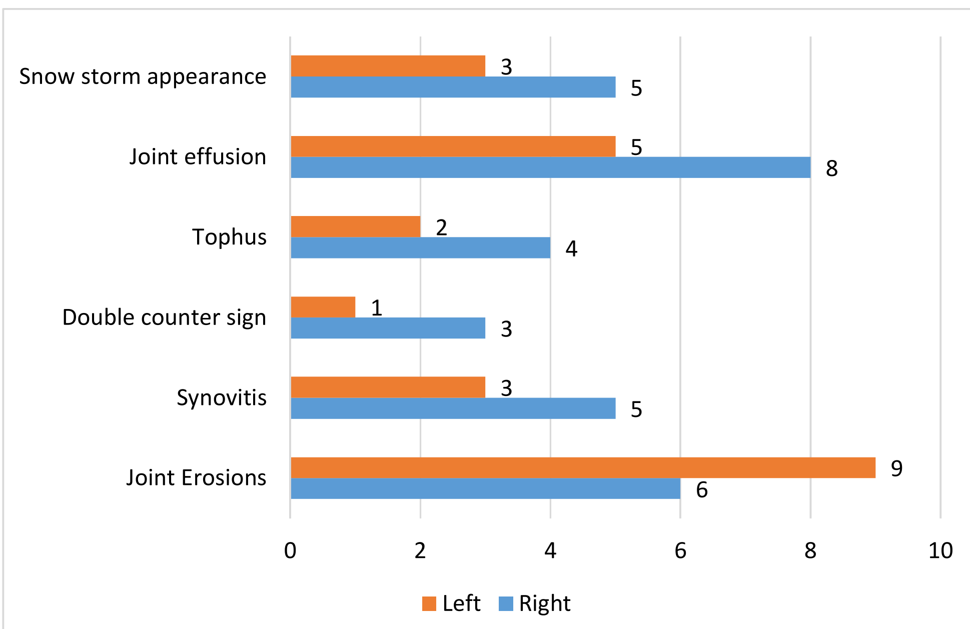


Graph 7 USG findings in Knee joint

Among the study population, Joint erosions and joint effusions were the major findings on USG of Knee joint, followed by snowstorm appearance, Synovitis, Double contour sign and tophus.

Table 9 USG findings in ankle joint

USG findings in Ankle joint				
	Right		Left	
	N	%	N	%
Joint Erosions	4	8.0%	4	8.0%
Synovitis	5	10.0%	4	8.0%
Double counter sign	2	4.0%	0	0.0%
Tophus	2	4.0%	2	4.0%
Joint effusion	8	16.0%	6	12.0%
Snow storm appearance	5	10.0%	2	4.0%

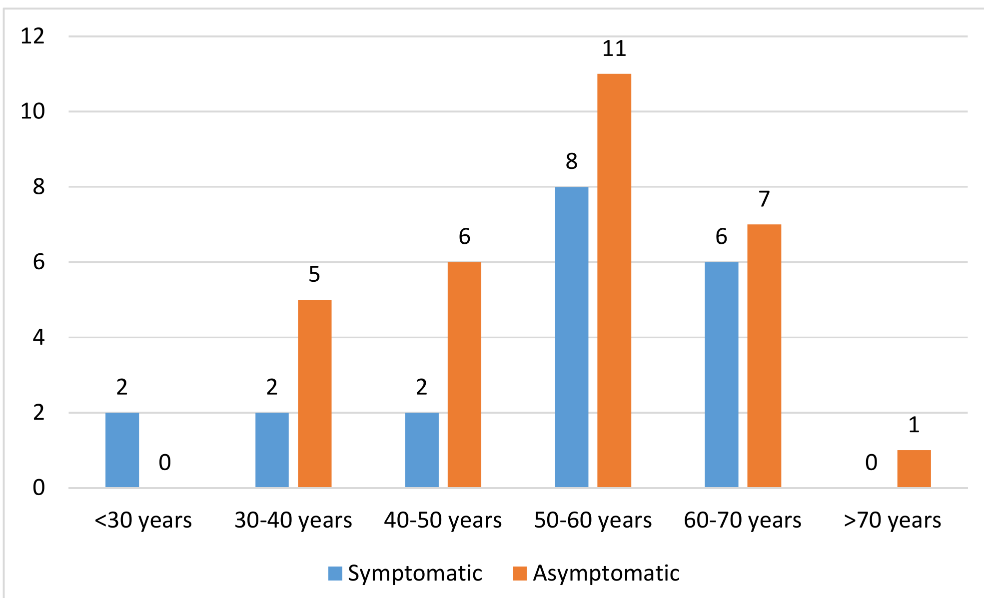


Graph 8 USG findings in Ankle joint

Among the study population, Joint erosions and joint effusions were the major findings on USG of Ankle joint in patients with hyperuricemia. Followed by snowstorm appearance, Synovitis, Double contour sign and tophus.

Table 10 Distribution of Age among patients presenting with Gout and HUA

		Symptomatology					
		Symptomatic		Asymptomatic		Total	
		N	%	N	%	N	%
Age Distribution	<30 years	2	10.0%	0	0.0%	2	4.0%
	30-40 years	2	10.0%	5	16.7%	7	14.0%
	40-50 years	2	10.0%	6	20.0%	8	16.0%
	50-60 years	8	40.0%	11	36.7%	19	38.0%
	60-70 years	6	30.0%	7	23.3%	13	26.0%
	>70 years	0	0.0%	1	3.3%	1	2.0%
	Total	20	100.0%	30	100.0%	50	100.0%

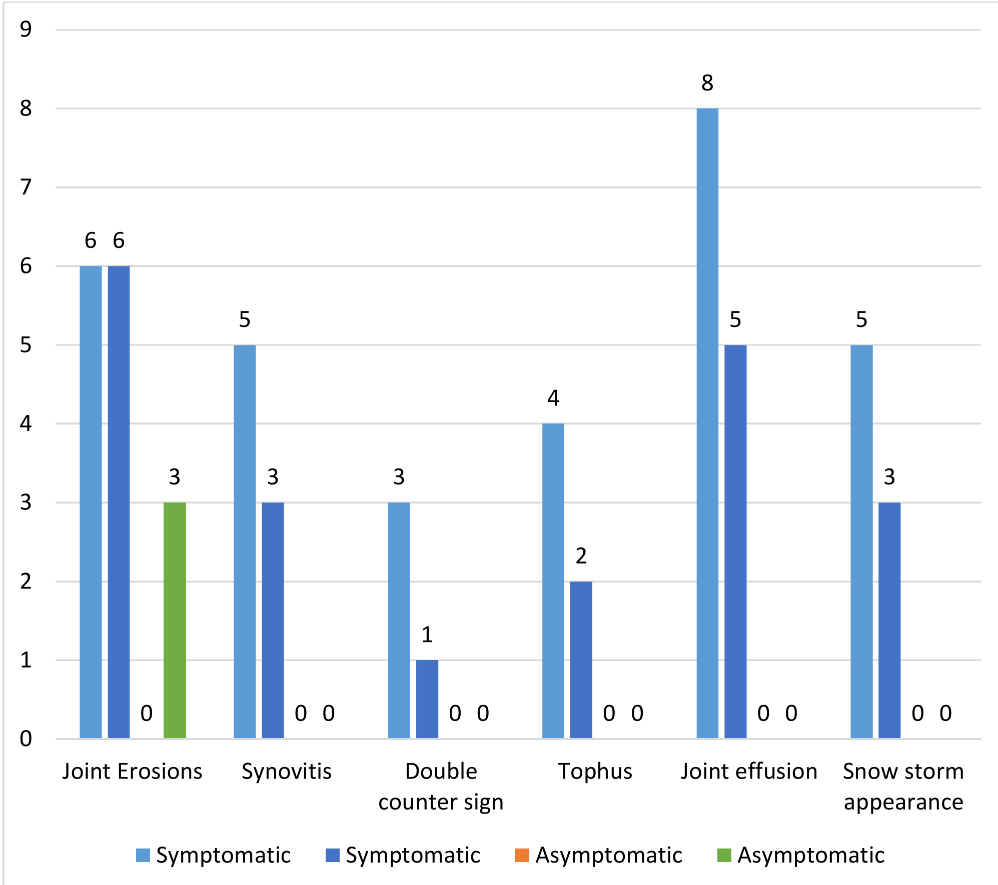


Graph 9 Distribution of Age among patients presenting with Gout and HUA

Asymptomatic hyperuricemia is predominant in patients older than 40 years' age and is seen majorly among 50-60 years' age group in our study. The distribution is statistically insignificant at $p<0.05$.

Table 11 Comparison of USG findings in 1st MTP joints of Gout (symptomatic) and HUA (asymptomatic) patients

First Metatarsophalangeal joint									
		Symptomatic				Asymptomatic			
		Right	%	Left	%	Right	%	Left	%
Joint Erosions	Present	6	30.00%	6	30.00%	0	0.00%	3	10.00%
	Absent	14	70.00%	14	70.00%	30	100.00%	27	90.00%
Synovitis	Present	5	25.00%	3	15.00%	0	0.00%	0	0.00%
	Absent	15	75.00%	17	85.00%	30	100.00%	30	100.00%
Double counter sign	Present	3	15.00%	1	5.00%	0	0.00%	0	0.00%
	Absent	17	85.00%	19	95.00%	30	100.00%	30	100.00%
Tophus	Present	4	20.00%	2	10.00%	0	0.00%	0	0.00%
	Absent	16	80.00%	18	90.00%	30	100.00%	30	100.00%
Joint effusion	Present	8	40.00%	5	25.00%	0	0.00%	0	0.00%
	Absent	12	60.00%	15	75.00%	30	100.00%	30	100.00%
Snow storm appearance	Present	5	25.00%	3	15.00%	0	0.00%	0	0.00%
	Absent	15	75.00%	17	85.00%	30	100.00%	30	100.00%



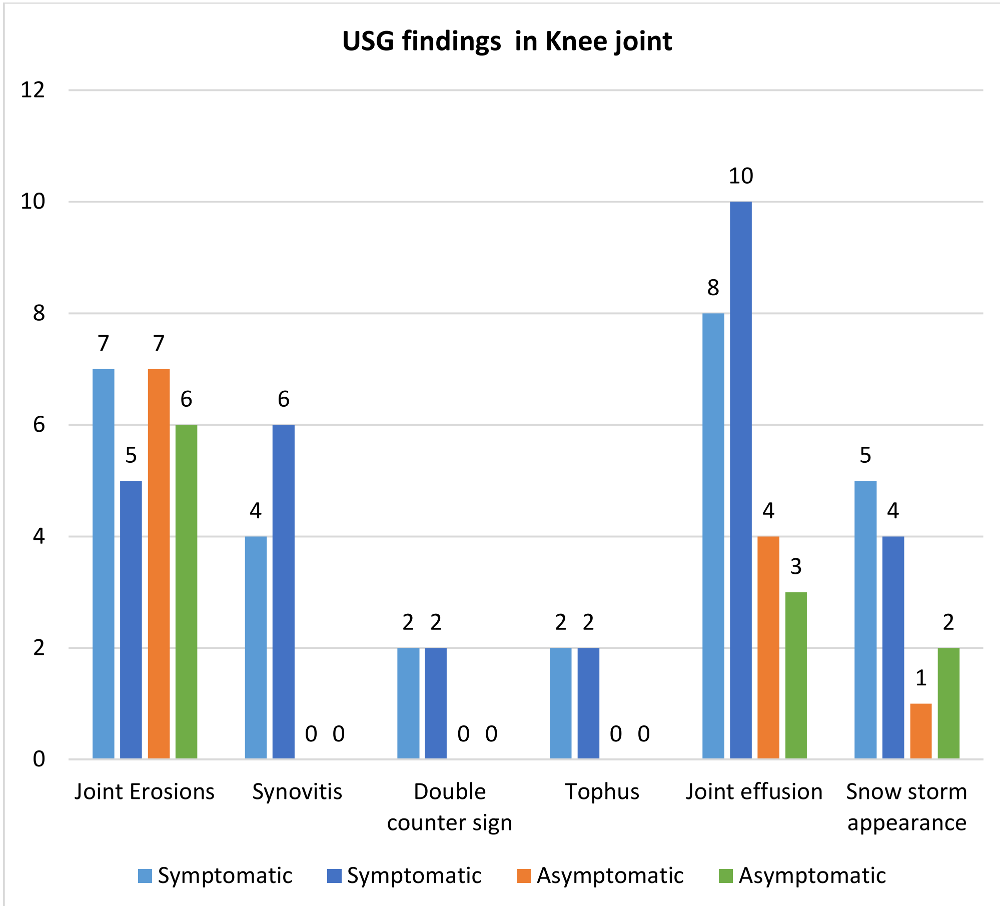
Graph 10 Comparison of USG findings in 1st MTP joints of Gout (symptomatic) and HUA (asymptomatic) patients

There were 3 patients with joint erosions in the asymptomatic hyperuricemia on USG of first metatarsophalangeal joint. There were no other findings of 1st metatarsophalangeal joint on USG in patients with asymptomatic hyperuricemia.

Table 52 Comparison of USG findings in knee joints of Gout (symptomatic) and HUA (asymptomatic) patients

Knee Joint									
		Symptomatic				Asymptomatic			
		Right	%	Left	%	Right	%	Left	%
Joint Erosions	Present	7	35.0%	5	25.0%	7	23.3%	6	20.0%
	Absent	13	65.0%	15	75.0%	23	76.7%	24	80.0%
Synovitis	Present	4	20.0%	6	30.0%	0	0.0%	0	0.0%
	Absent	16	80.0%	14	70.0%	30	100.0%	30	100.0%
Double counter sign	Present	2	10.0%	2	10.0%	0	0.0%	0	0.0%
	Absent	18	90.0%	18	90.0%	30	100.0%	30	100.0%
Tophus	Present	2	10.0%	2	10.0%	0	0.0%	0	0.0%
	Absent	18	90.0%	18	90.0%	30	100.0%	30	100.0%
Joint effusion	Present	8	40.0%	10	50.0%	4	13.3%	3	10.0%
	Absent	12	60.0%	10	50.0%	26	86.7%	27	90.0%
Snowstorm appearance	Present	5	25.0%	4	20.0%	1	3.3%	2	6.7%
	Absent	15	75.0%	16	80.0%	29	96.7%	28	93.3%

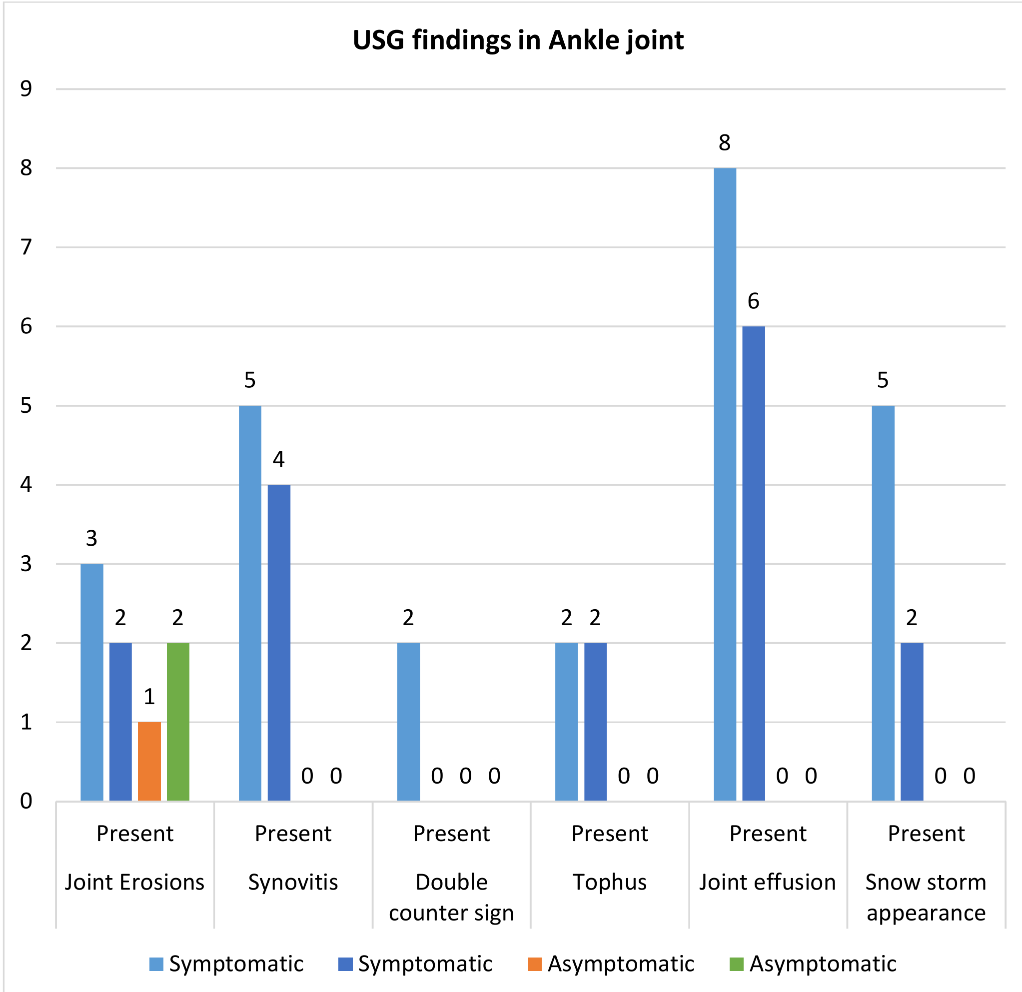
On USG examination of Knee joint revealed Joint erosions in 7 Right knees (23.3%) and 6 left knee joints (20%) of asymptomatic hyperuricemia among study population. There were Joint effusion in 4 right knee (13.33%) and 3 left knee joints (10%). Snow storm appearance was seen in a right knee (3.3%) and 2 left knee joints (6.7%) on USG among asymptomatic hyperuricemia patients.



Graph 11 Comparison of USG findings in 1st knee joints of Gout (symptomatic) and HUA (asymptomatic) patients

Table 13 Comparison of USG findings in ankle joints of Gout (symptomatic) and HUA (asymptomatic) patients

Ankle Joint									
		Symptomatic				Asymptomatic			
		Right	%	Left	%	Right	%	Left	%
Joint Erosions	Present	3	15.00%	2	100.00%	1	3.33%	2	6.66%
	Absent	17	85.00%	18	90.00%	29	96.66.%	28	93.33%
Synovitis	Present	5	25.00%	4	20.00%	0	0.00%	0	0.00%
	Absent	15	75.00%	16	80.00%	30	100%	30	100.00%
Double counter sign	Present	2	10.00%	0	0.00%	0	0.00%	0	0.00%
	Absent	18	90.00%	20	100.00%	30	100.0%	30	100.0%
Tophus	Present	2	10.00%	2	10.00%	0	0.00%	0	0.00%
	Absent	18	90.00%	18	90.00%	30	100.0%	30	100.0%
Joint effusion	Present	8	40.00%	6	30.00%	0	0.00%	0	0.00%
	Absent	12	60.00%	14	70.00%	30	100.0%	30	100.0%
Snow storm appearance	Present	5	25.00%	2	10.00%	0	0.00%	0	0.00%
	Absent	15	75.00%	18	90.00%	30	100.0%	30	100.0%



Graph 52 Comparison of USG findings in ankle joints of Gout (symptomatic) and HUA (asymptomatic) patients

On USG examination of Ankle joints, Joint erosions are seen in 3.33% (1) of examined right ankle joints and 6.66 % (2) of left ankle joints No other findings were seen in ankle joints of patients with asymptomatic hyperuricemia on USG.

Table 64 Comparison of Symptomatology and USG findings

		Symptomatology					
		Symptomatic		Asymptomatic		Total	
		N	%	N	%	N	%
USG findings of gout	Absent	0	0.0%	20	100.0%	20	100.0%
	Present	20	66.7%	10	33.3%	30	100.0%
	Total	20	40.0%	30	60.0%	50	100.0%

On comparing USG finding of patients with hyperuricemia and clinical symptoms it was found that 10 patients out of 30 asymptomatic hyperuricemia patients had one or the other USG finding.

DISCUSSION

Clinical characteristics and sonographic features in participants with gout and participants with asymptomatic hyperuricemia are studied in the present thesis study. Various parameters like Joint Erosions, Synovitis, Double counter sign, Tophus, Joint effusion and Snow storm appearance were studied in lower limb joints and compared among symptomatic and asymptomatic hyperuricemia patients.

In our study, majority of patients were of age group 50-60 years' age group, followed by 60-70 years' age group. This shows that Hyperuricemia is predominant in 6th and 7th decade which is similar to the study by Alexis Ogdie in which the mean age was 60.2 years.[70]

Similarly, J G Puig et al studied 35 patients among which the mean age was 63 years, our study is in line with this study.[76]

A similar study by Sarah sewart et al[80]., reported a mean age of 58 years. Naredo E et al[78] reported a mean age of 54 years in their study. In the study by Elsamann et al[84] the mean age of the study population was 53 years and majority of the patients were of 40-75 years of age.

In the study by S Das et al [79], the mean age was 50 + 11 years. Our study is in concurrence with the above studies.

In our study there were 35 males and 15 females showing a male predominance for hyperuricemia. Our study is in line with other previous studies by Alexis Ogdie et al, Elsamann et al, Pascal Zuffery et al, Sarah stewart et al and J G Puig et al which reported a high male predominance in hyperuricemia and gout.

In our study 32 % of patients had Diabetes Mellitus, 26% of patients had IHD and 20 % of patients had Hypertension accounting for major comorbidities among our study population.

In a study by Sarah stewart et al., Hypertension was the major comorbidity in both symptomatic gout and asymptomatic Hyperuricemia followed by Diabetes and IHD. They also added that there was a significant use of Diuretics and NSAIDs in their study population. The results are similar to our study.

In a study by S Das et al., Hypertension was seen in 30.6% of the patients, Obesity and Diabetes in 13.9% of patients and Dyslipidemia in 13.9% of patients. In this studies 50% of the study population was overweight. Our study had similar results and in line with this study.

In our study, Joint erosions were found in 3 first metatarsophalangeal joints with, 12 Knee joints, and 3 Ankle joints in patients with asymptomatic hyperuricemia. Similarly, Joint effusions were seen in 7 knee joints among patients with asymptomatic hyperuricemia. Snow storm appearance was seen in 3 knee joints with asymptomatic hyperuricemia.

Figure 10: Joint effusion and Tophus in Right 1st MTP

Twelve individuals in the research by J G Puig et al.[76] had tophi found in tendons, synovium, or other soft tissues (34 percent). In 8 cases, Power Doppler ultrasonography found enhanced vascularity within or around the tophi (23 percent). Among the 12 patients, 10 of them had multiple lesions. 22 individuals satisfied three or more of the criteria for the metabolic syndrome. There was no discernible difference in age, gender, serum urate levels, or the presence of the metabolic syndrome between participants with and without tophi. The duration of asymptomatic hyperuricemia was not linked to tophi presence.

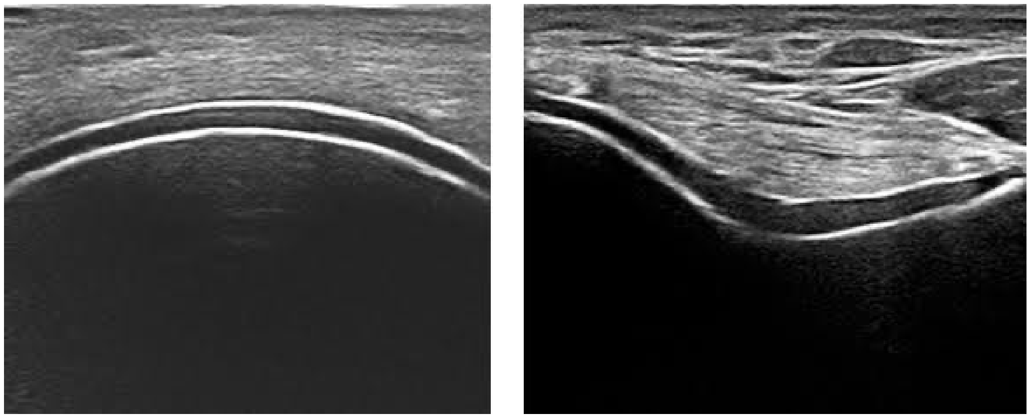


Figure 11: Right knee joint - Double Contour sign

In a research by Monika AR, individuals' 888 joints in total were examined. The DC sign was the pathological finding that was most frequently reported, particularly in 44/324 joints (14%) of gout patients, 29/372 joints (8%) of HU patients, and 2/192 joints (1%), which had normal uric acid levels. Thus, compared to HU patients' joints (2(1) = 6,172, p =.026) and those of normouricemic controls (2(1) = 23,342, p .001), joints of gout patients were considerably more likely to have DC symptoms specified in them. Additionally, HU patients displayed much higher DC symptoms compared to normouricemic controls (2(1) = 11,121, p =.001).

52 of the 372 joints that were examined (14%) in HU individuals without a history of typical gouty arthritis had pathological findings. Only 9 out of 31 patients (29%) with HU had sonography that was deemed to be entirely normal in the joints panel under investigation. Only 17/62 (27%) of the first MTP joints under investigation had the DC indication. The investigator detected echogenic structures and/or double contour sign in the MTP joints in 17/31 patients (55%) and synovitis and erosions in the MTP joints in 5/31 individuals.

Our study is similar to this study with findings on USG in asymptomatic Hyperuricemia.

The double contour sign was the most prevalent ultrasonography evidence of urate deposition in the research by Sarah Stewart et al. It was seen in a comparable proportion of MTP joints in both the gout (n517, 37 percent) and asymptomatic hyperuricemia groups (n521, 36 percent). But in the first MTP joint, only the gout group had tophus (n56, 13 percent). In comparison to the control (n55, 7 percent) and asymptomatic hyperuricemia (n52, 3 percent) groups, synovitis was most prevalent in the gout group (n520, 44 percent). However, compared to the gout group, the asymptomatic hyperuricemia group (n513, 22%) had a higher rate of joint effusion (n54, 9 percent). Only 2–11% of joints had synovial hypertrophy, which was less frequently detected. In the gout group, 15 first MTP joints (33%) had bone degradation, compared to just 2 (3%) and 1 (2%) in the control and asymptomatic hyperuricemia groups, respectively.

A total of 120 first MTP joints and 120 knee joints of gout patients were investigated by US in a research by Ismaiel A. H. et al.[6] First MTPJs with the DCS and tophi were detected in 68 (57.5%) and 50 (41.6%) respectively. A total of 120 knee joints were tested, and only tophi and 31 (25.8% and 2.5%, respectively) of those joints had DCS. Bony erosions in the first MTPJs were seen in 3 (10%) persons in the control group and 26 (43.3%) gout patients (P 0.001). Rheumatoid arthritis was present in every patient in the control group who developed erosions. Additionally, compared to the control group, the low SUA sub-group had substantially greater rates of erosions 9 (42.8%) and tophi 11 (52.3%) in initial MTP Joints.

A case report by Daniel J. McCarty [85], of 88-year-old who presented with pain and swelling in his right foot was clinically evaluated as gout and was kept on NSAID's. Since the patient's serum uric level was normal, hence an alternate diagnosis of osteomyelitis and cellulitis was made and the patient was kept on broad-spectrum antibiotics. Patient's clinical condition did not improve and joint fluid was aspirated for further evaluation which revealed negatively biréfringent needle shaped crystals favoring towards the initial diagnosis, gout. In our study 8 out of 20 patients with symptomatic gout had normal uric acid levels at the time of presentation to the hospital.

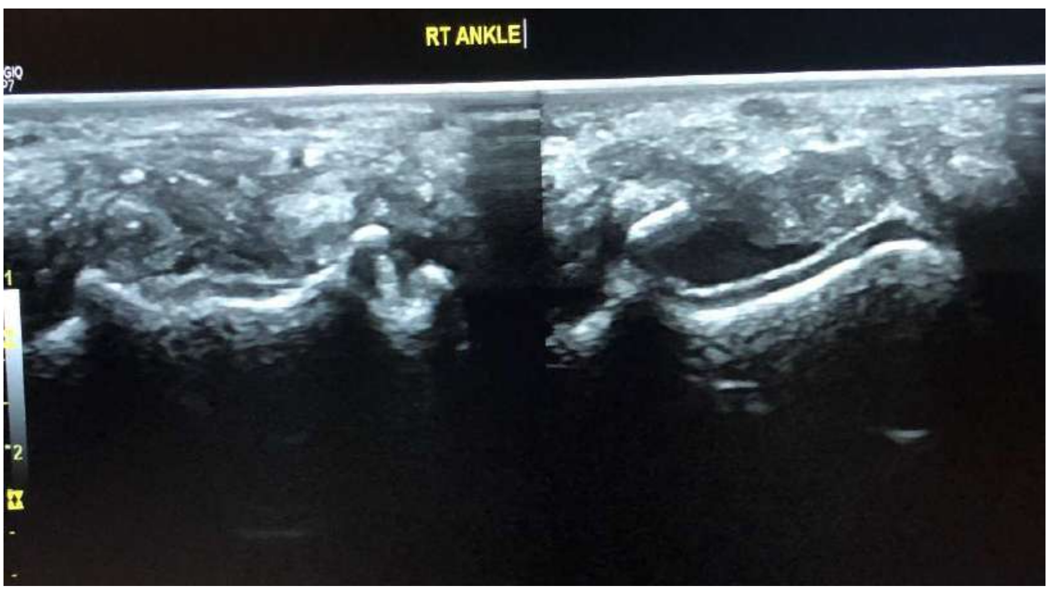


Figure 12: Right Ankle USG showing tophi, Double Contour Sign and joint effusion

Figure 13: Left ankle USG showing , erosions, effusion and tophus

10 out of 30 patients with asymptomatic hyperuricemia had joint disease evident on USG. i.e 33% of patients with hyperuricemia has asymptomatic joint disease. This USG of asymptomatic hyperuricemia patients helps is early screening of about 33% of the patients.

CONCLUSION

In our study of 50 patients, 30 patients were having asymptomatic hyperuricemia among which 10 patients (33%) had significant joint involvement in the form of either joint erosion, effusion, synovitis, Double contour sign or snow storm appearance. 8 out of 20 symptomatic patients had normal serum uric acid levels. In such patients, USG will help to eliminate the misdiagnosis (infective or other inflammatory diseases) by demonstrating the features of gout in the joints and thus helps in proper management of such patients. Thus, Musculoskeletal USG of joints is a very useful tool for early diagnosis of joint involvement in patients with asymptomatic hyperuricemia. However, to generalize the statement large volume multicentric randomized studies are necessary.

SUMMARY

- Gout is one of the most common inflammatory diseases affecting the joints with its prevalence increasing with age. Hyperuricemia is the cause of gout. This study is to aimed to study the involvement of joints in patients with hyperuricemia and gout.
- The pathophysiology of gout includes disturbance in purine metabolism, decreased excretion of uric acid by the kidneys, raise in levels of blood uric acid, and monosodium urate crystal deposition in the soft tissues and joints, thus resulting in inflammatory arthritis.
- Many people having hyperuricemia, though asymptomatic, are found to be having structural changes when examined by ultrasound.
- Ultrasound examination of joints and soft tissues in hyperuricemia patients helps to categorize them into various groups and aids in decision-making whether to start urate-lowering therapy, which alters the disease progression.
- The study was a hospital-based cross-sectional study, conducted from January 2021 – December 2021 in patients referred to the radiology department of KLE'S Dr. Prabhakar Kore Hospital Belagavi for a musculoskeletal ultrasound of suspected joints.
- The sample consisted of 50 patients, of which 20 patients had symptomatic gout and 30 had asymptomatic hyperuricemia.
- Exclusion criteria were patients with a previous history of surgery involving the affected joint, intra-articular corticosteroid injections and fractures.

- After obtaining informed consent baseline data was recorded on a self-designed proforma. MSK USG was performed using GE LOGIQ P9 R2 Machine equipped with 5-9 MHz L8-18i-D linear array hockey stick ultrasound probe transducer and 7.5Mhz-12Mhz high frequency linear array transducer.
- Patients was positioned supine with their legs flexed for examining the knee, ankle and 1st MTP joints on both sides. All studies will be performed in two dimensions by scanning across the joints and moving the probe from medial to lateral and from distal to proximal.
- Each site was scanned in Gray scale mode to detect any structural changes and Power Doppler technique to detect abnormal vascularity.
- It was found that males were affected more as compared to females.
- Maximum numbers of cases were in the age group of 50-60 years, followed by 60-70 yrs
- Majority of the study population had diabetes mellitus as underlying comorbidity followed by ischemic heart disease and hypertension. Few patients had chronic kidney disease and chronic liver disease.
- Of 20 symptomatic gout patients, 8 patients are found to be normouricemic while 12 had hyperuricemia.
- In such patients, USG will help to eliminate the misdiagnosis (infective or other inflammatory diseases) by demonstrating the features of gout in the joints and thus helps in proper management of such patients.
- 10 out of 30 asymptomatic HUA patients had joint involvement in the form of joint effusion, erosions and snowstorm appearance.

- Thus, USG helps to identify the involvement of joints in patients with asymptomatic hyperuricemia and aids in early intervention such as urate lowering therapy which will further stops the progression of disease.
- Ultrasonography is a non-invasive useful tool that can be used to assess the disease response to the treatment

LIMITATIONS OF OUR STUDY.

1. Selection bias – this is an observational study and the selection of the patients is by the investigator on the basis of the presentation of the patient.
2. Blinding: the presentation of the patient could mislead the interpretation into a positive finding. This could have been avoided by double blinding of the study.
3. As this is a single center observational study conducted at our hospital, it cannot be generalized to the population, more randomized control trials are necessary to do the same.
4. The study is not compared with the gold standard for the diagnosis and hence sensitivity in diagnosing patients cannot be established, however a close monitoring and disease modification could be started.

RECOMMENDATIONS

1. Comparative double blinded trial among Hyperuricemia patients to establish the diagnostic accuracy of ultrasound in early screening of asymptomatic hyperuricemia.
2. Large volume multicentre studies should be conducted to generalize the statement.
3. Comparing Musculoskeletal US findings with pathological diagnosis to increase the diagnostic accuracy.

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ANNEXURE – I

INFORMED CONSENT FORM

TITLE OF THE STUDY: "ROLE OF MUSCULOSKELETAL ULTRASOUND IN THE EVALUATION OF JOINT PATHOLOGIES IN PATIENTS WITH HYPERURICEMIA AND GOUT- A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY"

PRINCIPAL INVESTIGATOR:

GUIDE:

CO-GUIDE:

INTRODUCTION AND PURPOSE:

Gout is one of the most common inflammatory diseases affecting the joints. Its prevalence seems to be increasing with age and incidence is more common in men. Hyperuricemia is the cause of gout. The pathophysiology of gout includes disturbance in purine metabolism, decreased excretion of uric acid by the kidneys, raise in levels of blood uric acid, and monosodium urate crystal deposition in the soft tissues and joints, thus resulting in inflammatory arthritis. Many people having hyperuricemia, though asymptomatic, are found to be having structural changes when examined by ultrasound.

Ultrasound examination of joints and soft tissues in hyperuricemia patients helps to categorize them into various groups and aids in decision making whether to start urate-lowering therapy, which alters the disease progression.

Hence this study is aimed at finding the same in our set up.

PROCEDURE:

The purpose of the study will be explained and written informed consent will be obtained from all participants.

The subjects will be selected based on inclusion and exclusion criteria.

Study will be conducted over a period of one year. Once the patient signs the informed consent, history and examination will be recorded as per proforma.

Patient will be asked to change into examination gown and is subjected to Ultrasonography on GE LOGIQ P9 R2 Machine equipped with 5-9 MHz L8-18i-D linear array hockey stick ultrasound probe transducer and 7.5Mhz-12Mhz high frequency linear array transducer (GE Health care, USA). Patient will be positioned supine and gel will be applied over skin surface of interest and with the help of hockey stick and high frequency linear array transducer examination is done. The gel is non allergic, can be easily wiped off and allows the transducer probe to move over the skin surface smoothly and aids for getting proper images.

We request you to kindly participate in the study titled "**ROLE OF MUSCULOSKELETAL ULTRASOUND IN THE EVALUATION OF JOINT PATHOLOGIES IN PATIENTS WITH HYPERURICEMIA AND GOUT- A ONE YEAR HOSPITAL BASED CROSS-SECTIONAL STUDY"** at Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi , being conducted by ______________________, Post graduate in Radio-Diagnosis at J. N. Medical College Belagavi, Karnataka, under the guidance of ______________________, Professor, Department of Radio-Diagnosis, J. N. Medical College, Belagavi 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. You will also be clinically examined as per the protocol drawn.

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

BENEFITS:

Disease progression and treatment assessment can be done in gout patients and assessing structural changes in hyperuricemia patients helps in early intervention and further management.

COMPLICATIONS:

No risk to the patient has been documented from ULTRASONOGRAPHY earlier.

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. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or the sponsor may stop your participation in this study. Even if you choose not to take part in the study you will receive the standard treatment for patients with your condition.

COSTS:

NIL (The study is to be conducted on the participants who are advised USG as an investigation for Gout and Hyperuricemia 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 you become injured as a result of taking part in this study, treatment whatever available at KLE charitable hospital, Belagavi, will be offered to you. No reimbursement or compensation or free medical care will be given.

CONFIDENTIALITY:

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

QUESTION:

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

- **DR HARSHA HEGDE** Chairperson, JNMC, IEC& Scientist D, ICMR, National Institute of Traditional Medicine, Belagavi Ph. No: 0831-2473777, Ext. 1529 Mob No: 9480422500

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. I understand that I am participating in the study, which involves the examination of involved joint in case of gout and joints that are most likely to be affected in case of hyperuricemia by using ultrasound.

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 appropriate 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 Name/ legally authorized representative ___________________

Signature ____________________

Name and signature of witness ___________________

Name and signature of interviewer ___________________

Date:

Place:

ANNEXURE – II

PROFORMA FOR DATA COLLECTION:

DATE	
NAME OF THE PATIENT	
AGE (IN YEARS)/ SEX	
OP/IP NO	
ADDRESS	
USG NUMBER	

CHIEF COMPLAINTS: **DURATION**

1)

2)

3)

SERUM URIC ACID LEVELS:

PAST HISTORY

1)

2)

FAMILY HISTORY

PHYSICAL EXAMINATION:

CVS:

RS:

RENAL:

CLINICAL DIAGNOSIS

ULTRASONOGRAPHY FINDINGS:

ANNEXURE III -IMAGES

GE LOGIQ P9 R2 Machine used for the study

5-9 MHz L8-18i-D Linear array hockey stick ultrasound probe transducer

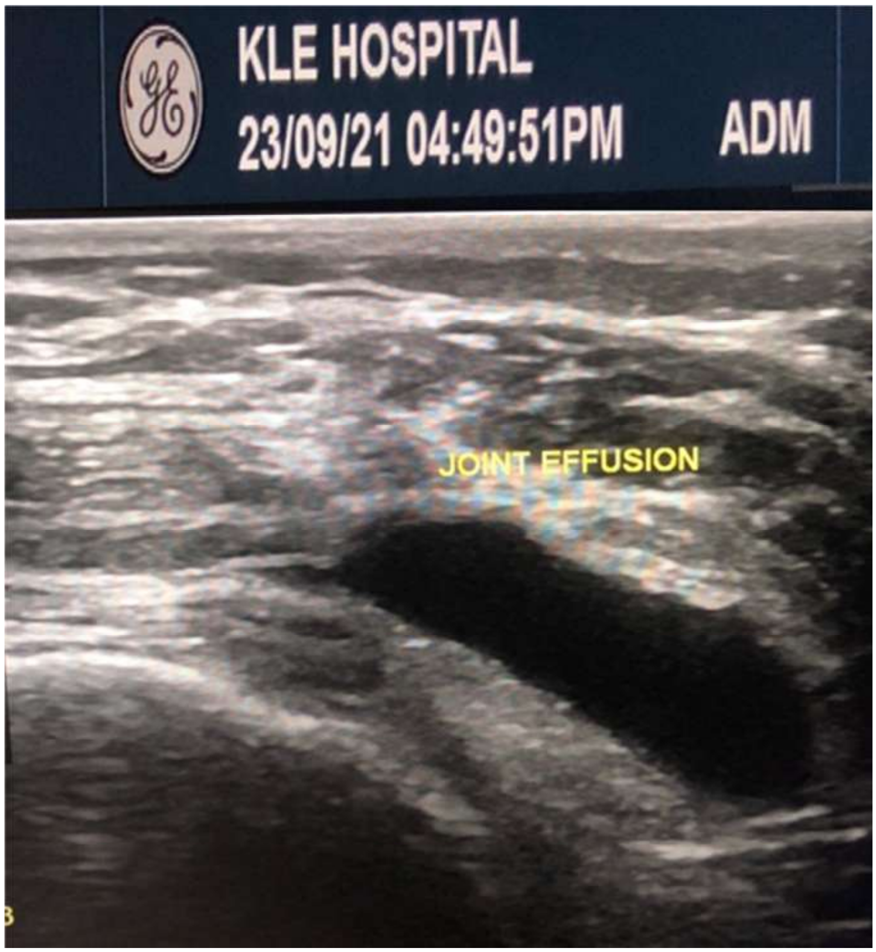
7.5MHz-12MHz High frequency linear array transducer

PHOTOGRAPH OF CASES

CASE 1: A 52-year-old female patient presented with acute history of pain and swelling in the 1st MTP joint and ankle region of right leg since 1.5 months. The patient is known diabetic. Her serum uric acid levels are normal (5.3 mg/dL). A clinical diagnosis of gout was made, and the patient was referred for USG. On USG of 1st MTP joint, minimal joint effusion is seen. Hyperechoic line noted parallel to the subchondral bone along the outer surface of the joint cartilage (Double contour sign)- due to deposition of monosodium urate crystals on the surface of the hyaline articular cartilage-pathognomic of gout.

1st MTP joint-Joint effusion and Double Contour Sign

CASE 2: A 48-year-old male patient came with the complaints of abdominal distension since 4 months. He's a known case of chronic liver disease with portal hypertension. His serum uric acid levels were raised-13 mg/dL. On subjecting the patient to MSK USG, minimal joint effusion noted in the right knee joint. No evidence of erosions/ synovial inflammatory changes noted.



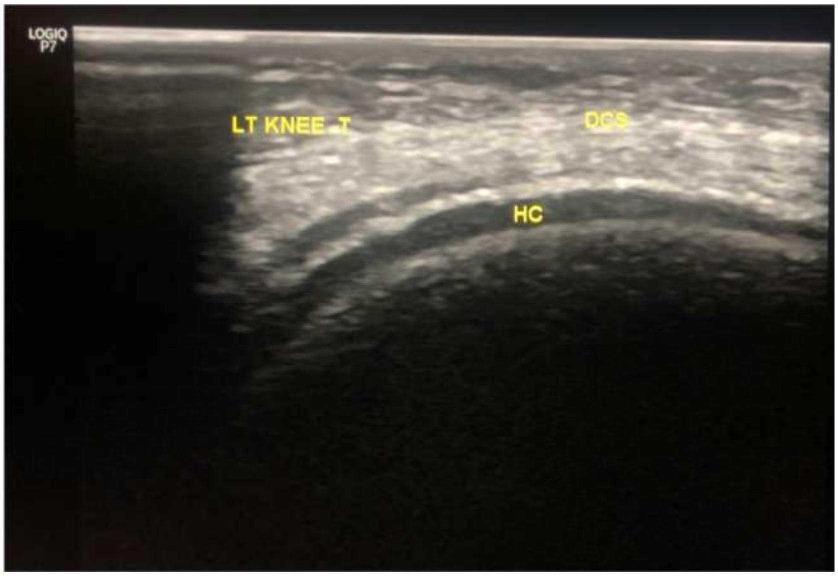
USG right Knee joint- minimal joint effusion

CASE 3: A 57-year-old male patient came with the complaints of painful swelling in the left 1st MTP and left ankle joint since 2 months. History of chronic alcoholism is present. His serum uric acid levels were elevated- 8.8 ml/dL. On USG of left ankle joint, minimal joint effusion with tiny hyperechoic foci (snowstorm appearance) noted with underlying bony erosion. USG of 1st MTP joint revealed mild joint effusion with synovial thickening which showed increased vascularity on color doppler study suggestive of synovitis.

USG left ankle- joint effusion with snowstorm appearance

USG left 1st MTP- Joint effusion and Synovial thickening

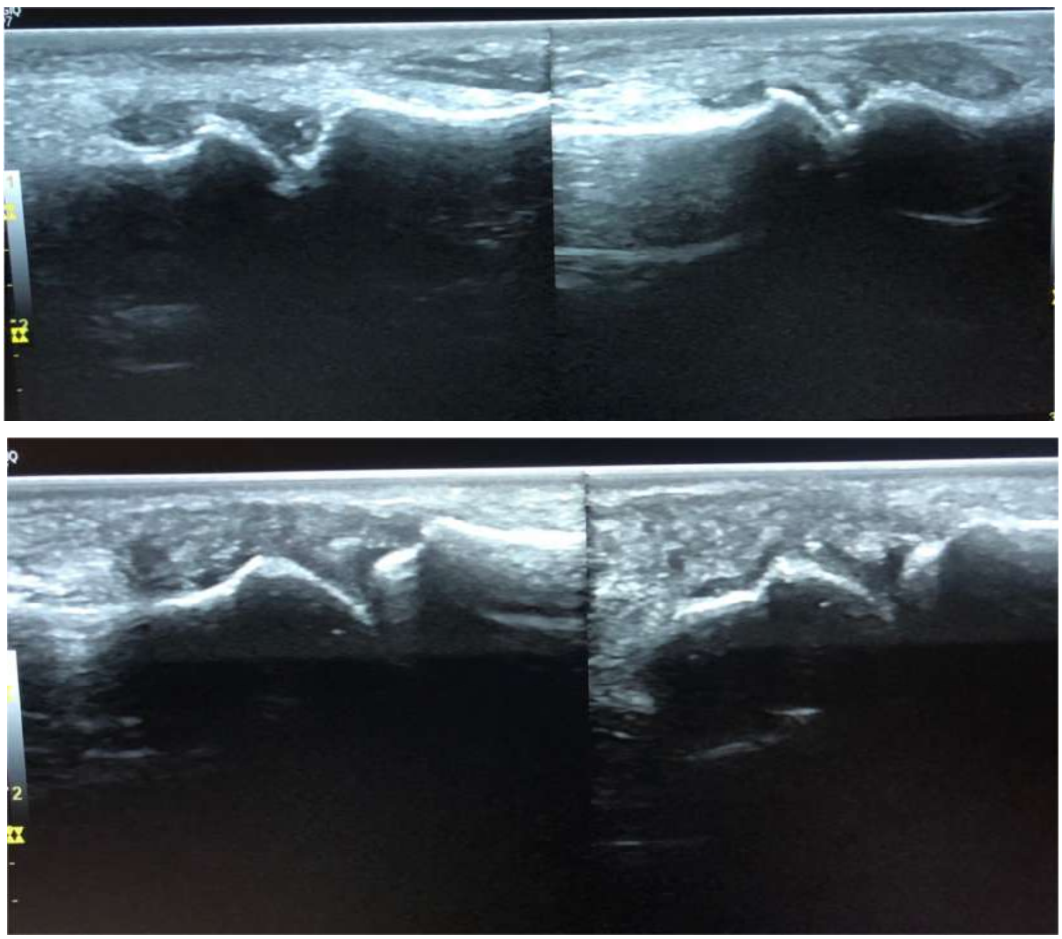
CASE 4: A 57-year-old male patient presented with the complaints of pain and swelling in the bilateral knee joints & erythema over left knee region. He is a known case of chronic kidney disease and hypertensive. His serum uric levels are elevated- 7. 9 mg/dL. On USG of bilateral knee joints, there is linear hyperechoic line over the hypoechoic hyaline cartilage (double contour sign) and minimal joint effusion. Right knee joint appears normal



USG left knee-Double contour sign and minimal joint effusion

USG right knee- normal

CASE 5: A 25-year-old male patient presented with complaints of acute swelling in the right great toe. He is a known alcoholic. His uric acid level is raised – 11.8 mg/dL. USG of right 1st MTP joint showed minimal joint effusion with hyperechoic uric acid crystals (snowstorm appearance) with minimal cortical irregularity and hyperechoic deposits (tophi). USG right ankle joint revealed joint effusion with double contour sign and synovitis on color doppler study. USG left ankle showed minimal joint effusion, cortical irregularity and tophi.



USG right 1st MTP joint- joint effusion, hyperechoic crystals, minimal cortical irregularity, and tophi

USG right ankle- joint effusion, double contour sign and synovitis

USG left ankle- joint irregularity, minimal joint effusion and tophi

ANNEXURE – IV

KEY TO MASTER CHART

J Ero	**Joint Erosions**
SP	**Synovial proliferation**
DCS	**Double contour sign**
J Eff	**Joint effusion**
SSA	**Snowstorm appearance**

HTN	**Hypertension**
DM	**Diabetes mellitus**
IHD	**Ischemic heart disease**
CKD	**Chronic kidney disease**
AKI	**Acute kidney injury**
ILD	**Interstitial lung disease**
MI	**Myocardial infarction**
RHD	**Rheumatic heart disease**
HCC	**Hepatocellular carcinoma**
ICSOL	**Intracranial space occupying lesion**
CVA	**Cerebro-vascular attack**
RCC	**Renal cell carcinoma**
TB	**Tuberculosis**
ALD	**Alcoholic liver disease**

	Present	**Absent**
Joint Erosions	**1**	**2**
Synovitis	**1**	**2**
Tophus	**1**	**2**
Double contour sign	**1**	**2**
Joint effusion	**1**	**2**
Snowstorm appearance	**1**	**2**

Male	**M**
Female	**F**

ANNEXURE – V MASTER CHART

S.NO	USG No	AGE	SEX	SYMPTOMATIC	CHEIF COMPLAINTS	DURATION	UNDERLYING COMORBIDITIES	URIC ACID LEVEL	USG FINDINGS																																			
		(in yrs)		(YES/ NO)		(in months)		(mg/dl)	1st METATARSO-PHALANGEAL JOINT												KNEE JOINT												ANKLE											
									RIGHT						LEFT						RIGHT						LEFT						RIGHT						LEFT					
									J Ero	SY	DCS	TOPHUS	J Eff	SSA	J Ero	SP	DCS	TOPHUS	J Eff	SSA	J Ero	SP	DCS	TOPHUS	J Eff	SSA	J Ero	SP	DCS	TOPHUS	J Eff	SSA	J Ero	SP	DCS	TOPHUS	J Eff	SSA	J Ero	SP	DCS	TOPHUS	J Eff	SSA
1	20156	25	M	YES	Acute swelling in the rt great toe	1	HTN	11.8	1	1	2	1	1	1	1	2	2	2	2	2	1	2	2	2	2	2	1	1	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2
2	21224	62	F	YES	k/c/o gouty arthritis	6	DM	8.5	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3	23586	66	M	YES	swelling in the left knee joint	2	DM, IHD	7.8	2	2	2	2	2	2	1	1	2	2	1	2	1	2	2	2	2	2	1	1	2	2	1	2	1	2	2	2	2	2	1	2	2	2	2	2
4	26789	55	M	NO	generalized weakness, breathlessness	2	CKD, HTN	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
5	29875	48	M	YES	pain& swelling in left 1st toe & rt knee	3	DM	5.6	1	2	2	2	2	2	1	1	2	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	1	1	1	2	2	2	2	2
6	30010	58	F	NO	pain abdomen	0.7	IHD	8.5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
7	30090	53	M	NO	drowsiness	24	ALD	7.4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
8	31569	70	M	NO	pain in right lower limb	2	MI	7.3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
9	34569	55	F	NO	altered sensorium	0.5	AKI ON CKD	7.4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
10	34987	55	M	YES	pain the right ankle & knee joints	6	DM	8.4	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	1	2	2	2	2	2	1	1	2	2	1	2	2	2	2	2	2	2
11	35100	72	F	NO	chest pain	0.7	IHD	7	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
12	35498	56	M	NO	breathlessness, tachycardia	0.5	CKD	13.7	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2
13	35657	48	M	NO	fever, chestpain, generalised weakness	0.5	MI, HTN	10.6	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
14	35769	45	M	NO	abdominal distention	4	CLD WITH PORTAL HYPERTENSION	13	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2
15	35812	70	M	NO	fever, acute glomerulonephritis	0.5	DRUG INDUCED HEPATITIS	12.5	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
16	35989	61	M	YES	pain in the knee, ankle and foot region on right side	1	DM, MI	8	1	2	2	2	1	2	1	2	2	2	2	2	1	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
17	36003	48	F	YES	swelling in the left knee joint	1	DM, HYPOTHYROID	5.3	2	2	2	2	2	2	2	2	2	1	1	1	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
18	36101	55	M	YES	swelling and pain in the b/l ankle joints	0.5	DM, CLD	6.5	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	1	1
19	36368	37	F	NO	pedal edema	0.7	IHD, HTN	11	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
20	36587	62	M	YES	pain and swelling in b/l knee	2.5	SCHIZOPHRENIC	8.3	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2
21	36845	42	M	NO	pain in right hip radiating to lower limb- AVN	18	DM	7.8	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
22	36901	52	F	YES	pain in the right 1st MTP, anke, b/l knee & b/lelbow joints	0.7	DM, HYPOTHYROID	5.3	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2
23	36987	68	F	NO	chest pain & breathlessness	0.25	MI	9.3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
24	37005	46	M	NO	chest pain	0.25	DM, IHD	7.8	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
25	37091	28	F	YES	swelling in the right ankle region	0.5	RHD	6.9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	1	2	1	1	2	2	2	2	2	2
26	37258	57	M	YES	pain and swelling in right 1st MTP and left knee	1	IHD , HTN	4.9	2	1	1	1	1	1	2	2	2	2	1	2	1	1	1	1	1	1	2	1	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2
27	37365	60	M	NO	fever and abdominal distention	2	HCC , CLD	7.9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
28	37399	62	M	NO	breathlessness, pedal edema, abdomianl distention	1	AKI on CKD, on dialysis	7.1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2
29	37401	60	M	NO	chest pain, cough	6	DM, ILD	7.7	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
30	37456	62	M	NO	k/c/o AVN of bilateral femora	6	DM	9.6	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
31	37490	38	M	NO	abdominal distention, pedal edema	1	RHD & CKD	8.6	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2
32	37501	63	F	NO	pain in bilateral knee joints	24	osteoarthritis	7.9	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
33	37526	55	F	YES	pain and swelling in right elbow, left knee and left ankle	3	ALD	7	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	2	2	2	1	2	1	1	2
34	37545	53	M	NO	altered sensorium	0.5	ICSOL	8	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
35	37678	40	M	NO	right UL & LL weakness	0.25	c/o CVA, HTN	7.9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
36	37689	63	M	YES	pain and swelling in the bilateral 1st MTPs, left knee	0.75	DM	9.8	2	1	1	2	1	1	2	1	1	2	1	1	1	2	2	2	2	2	1	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
37	37001	38	M	NO	abdominal pain, hematuria	0.25	c/o RCC	8	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
38	37019	59	M	NO	fever, painful burning micturition	0.5	DM , IHD	7.3	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	1	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2
39	37356	57	M	YES	swelling in bilateral knee joints	1	CKD, HTN	6.8	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	1	2	2	1	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2
40	37392	40	M	YES	pain, swelling the right ankle & knee joints	0.5	MI, HTN	7	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	1	1	2	1	2	1	1	2	2	2	2	2	2	2
41	37425	62	F	NO	abdominal pain, jaundice	6	c/o fibrolamellar HCC	10.3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
42	37475	53	M	NO	hematuria	3	bladder carcinoma	13	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
43	37498	35	F	YES	pain and swelling in elbow joints and right ankle	0.5	HYPOTHYROID	8.4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1	2	2	2	2	1	2
44	37554	53	M	NO	low back pain radiating to right lower limb	12	DM, HTN	11	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
45	37894	40	M	NO	fever, genaralised weakness, cough	6	TB	11.8	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
46	38415	57	M	YES	pain in the knee, ankle and foot region on right side	3	MI	8.4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	1	1	2	2	2	2	1	2
47	38712	45	M	NO	abdominal distention, pedal edema	4	CLD	6.9	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
48	39102	50	F	NO	chest pain & breathlessness, fever	5	LUNG CARCINOMA	9.4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
49	39445	63	F	YES	bilateral lower limb pain with swelling in ankle joints	2	DM, HTN	7.5	2	2	2	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	1	2	1	2	2	1	2
50	40001	54	M	YES	pain and swelling in the right 1st mtp & left ankle joint	2	ALD	5.9	1	1	2	1	1	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	1