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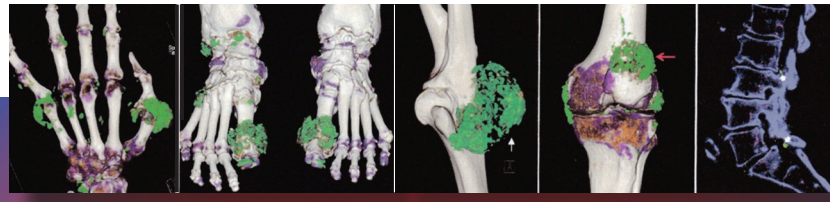

Update on Non-Invasive Diagnosis of Refractory and Chronic Gout

This can be accomplished via various imaging techniques.

BY JOHN COZZARELLI, DEMI TURNER, AND NICHOLAS F. COZZARELLI

Goals and Objectives

To understand the various modalities utilized in imaging gout in all phases of the disease state, either acute or chronic in nature.

To allow the reader to realize that utilizing various imaging modalities for early intervention leads to better management of gout.

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Introduction

Gout is the most common inflammatory arthropathy worldwide and occurs when sodium urate is converted to monosodium uric acid (MSU) and deposits within the joints. Crystallization in the body at normothermia of 98.6 degrees occurs when serum uric acid is 6.8mg/dl or higher.[1] In a national health survey conducted in 2007 and 2008, 4.3 million Americans reported to have a clinical diagnosis of gout.[2] This corresponds to 3.9% of the U.S. adult population. In 2020, the latest study there are 9.4 million people in the United States with gout. The prevalence of gout in the United States is rapidly rising, increasing by 150% in the last decade. Between 2016 and 2017, the number of hospital emissions and emergency visits secondary to uncontrolled gout has doubled.[3]

Gout generally presents as a monoarticular arthritis, though it can be polyarticular and asymmetrical in distribution. The over-saturation of the MSU crystals in the body interacting with specific immune system cells produces a tophus. Tophi are an abrasive by-product of failed purine metabolism in humans, causing inter-articular and extra-articular damage. While early diagnosis is clinically difficult, it is imperative to prevent permanent and long-term sequelae. The diagnosis of gout has improved due to availability of tests, the ability to definitely identify the MSU crystals in the affected joints via arthrocentesis, and direct fluid examination for crystals.

Lifestyle factors, dietary choices,

and socioeconomic parameters have been proposed to explain the more prevalent epidemiological observations. Unhealthy dietary habits and a sedentary lifestyle appear to be major factors for the rise of gout in western countries. Choi, et al. reported a 1.85 relative risk factor for the incidence of gout in males consuming two or more sugar-sweetened soft drinks per day.[4] This is attributed to an increased production of uric acid in the liver, as well as attenuated renal uric acid clearance, both secondary to excessive fructose consumption. Sugar-sweetened soft drinks represent the single largest food source of calories in the U.S. population, and their consumption has consistently increased over the last several decades.[4] This is especially true for fructose and its most popular form HFCS (high fructose corn syrup) that converts to uric acid upon ingestion. Also, this has caused a rise in increased adiposity in the U.S. populace because of the large availability of HFCS in comparison to other forms of fructose. It should be noted that it was thought that purines are the main source for an increase in uric acid production but is has been demonstrated that after consuming a high sugar meal uric acid will be elevated and spike within thirty minutes.

With the rise of these co-morbidities, the result has been an increased incidence of gout. Co-morbid conditions including obesity, hypertension, insulin resistance, type 2 diabetes, and chronic kidney disease. These are all associated with the metabolic syndrome and are well-established independent risk factors for the occurrence of gout. When there is hyperuricemia without the presence of these co-morbidities, it is a good predictor that higher uric acid levels often will precede the comorbidities, which will be worse in presentation. With the advent of bariatric surgery, these patients are also more prone to gout attacks secondary to increased protein intake with dehydration.[5] The rising prevalence may also be secondary to the increased consumption of inexpensive sources of animal protein, and concentrated animal protein supplements. There is a larger number of sweeteners available today that are metabolically difficult for the kidneys

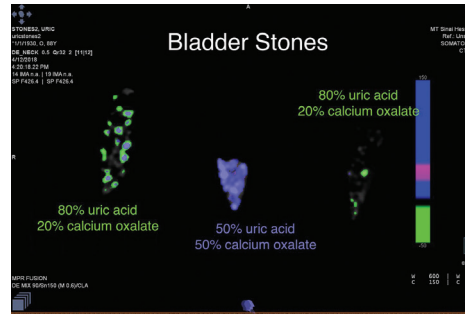


Figure 1A: To confirm the calibration of the DECT scanner, we tested three bladder stone samples whose UA composition ranged from 50-80%; the remainder being calcium oxalate. Scans and analysis confirmed that the scanner is able to pick up MSU (green) and differentiate it from calcium derivatives (purple).

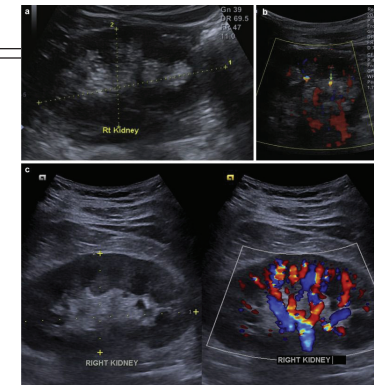


Figure 1B: Diffuse hyperechogenicity of renal medulla on B-mode ultrasonography. (b) Color Doppler ultrasonography showing numerous twinkling artifacts (green arrow). (c) Ultrasonographic image of a normal patient. Note that the renal medulla is hypoechoic as compared to the cortex on B-mode scanning, and there is no twinkling artifact on color Doppler (right).

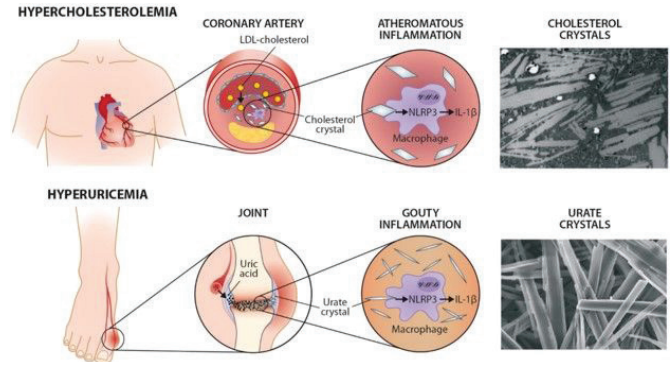
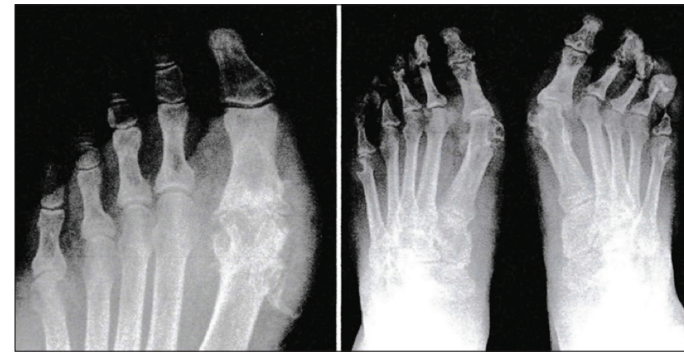
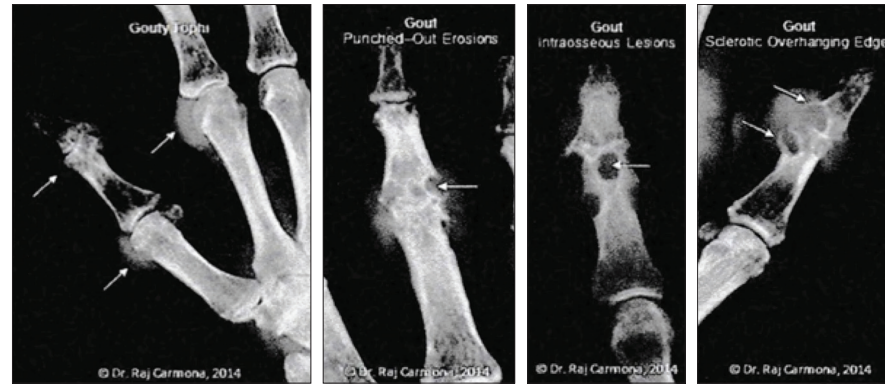


Figure 1C: Atherosclerotic cardiovascular disease and gout through a 'crystal lens'. Clearing demonstrating cholesterol and crystal induced inflammation with the same identical pathway.



Figures 1D and 2: Severe chronic gout demonstrating classic sclerotic edges and tophus in soft tissue and "Martel's sign."



Figures 3, 4, 5, 6: Periarticular, punched out, intra-articular, sclerotic edges.

to efficiently process.[4]

This directly yields to a condition of uric acid under excretion in the kidneys. It is thought to be the most relevant failed metabolic action versus the overproduction of serum urate in the body. A 2009-2010 NHANES sub-analysis reported a prevalence rate >60% for CKD 3 and CKD 4 in patients with gout. Sustained hyperuricemia may cause renal interstitial urate crystal deposition causing gouty nephropathy. Renal inflammation and renal insufficiency often follow. There is a 22% prevalence of nephrolithiasis among patients with primary gout. Further, 10% of patients had kidney stones (urolithiasis) comprised of urate. When kidney stones are formed and are comprised of calcium oxalate, the nidus in these stones is now known to be uric acid. The nidus starts the cascade of calcification (Figure 1A). Therefore, new techniques for early detection and treatment of gout will be necessary in managing this rising epidemic, along with pharmacological and lifestyle changes. With advanced imaging techniques, earlier diagnosis can be made, facilitating prompt treatment and intervention, preventing long-term damage and having the patients achieve clinical remission. Clinical remission is defined as serum uric acid below 4.[7]

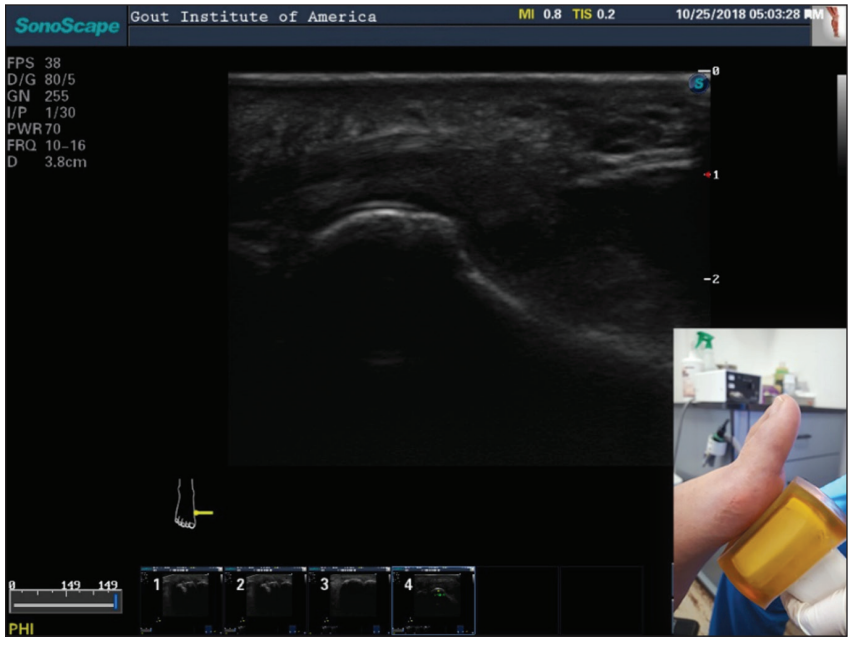


Figure 7: Sonoscape 16 mgHz linear array transducer demonstrating the double contour sign of the first MTPJ in plantar long axis with standoff.

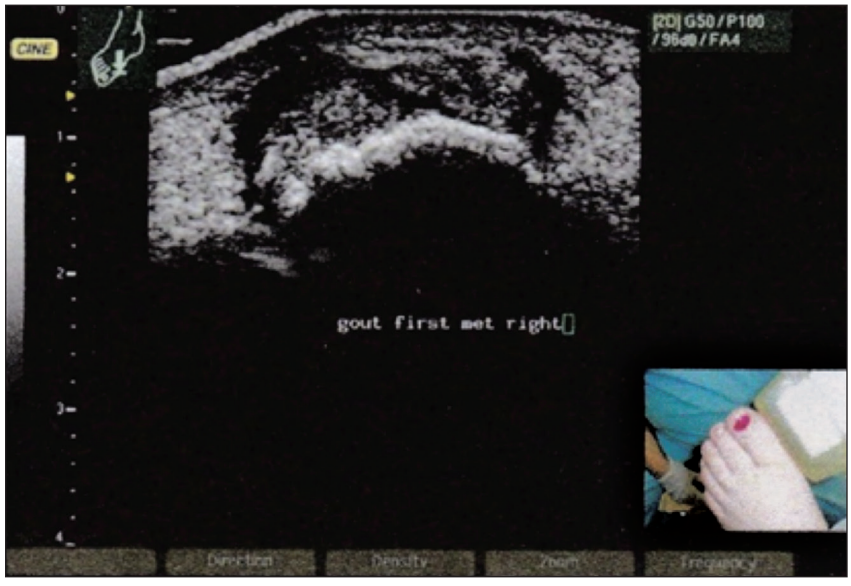


Figure 8: Classic snowstorm effect with standoff in medial long axis position.

Elevated serum uric acid levels are present in 21% of the U.S. population, but only 5-20% of the individuals with hyperuricemia develop gout. Patients with hyperuricemia may not necessarily develop gout; and those with gout may have normal serum uric levels, particularly during acute gout attacks. Higher degrees and longer duration of elevated urate levels can lead to a greater severity of disease of gouty arthritis, which is the impetus for early and aggressive lowering of urate levels in the treatment of gout to sUA levels below 6 mg/dL. This new "treat to target" approach helps facilitate a positive treatment outcome for a patient.[8]

Gout is a complication of CKD. Patients and physicians think of gout as a flare disease but is now seen as a chronic, progressive systemic urate deposition disease. It is viewed as a window into the body. Soluble versus insoluble gout may be a function of what is called visceral gout. This is commonly seen in birds. When uric acid, either soluble or insoluble, causes inflammation to the blood vessels, it is known as vasculopathy. In the kidneys, it is called gout nephropathy.

Crystal deposition can occur in the following areas and organ systems: the spine, eyes, nose, middle ear/Eustachian tube, larynx, pulmonary system, cardiovascular system, breasts, integumentary system, kidneys, GI system, prostrate, penis, and pelvis. It should be noted that uric acid is inflammatory and can occur in the spine 39% of the time causing lumbosacral radiculopathy. Also, it has been documented that SUA in patients with breast cancer is higher than that in patients with benign breast tumor (Figure 1B).[25]

When using the Framingham Risk factors, which includes hypertension, smoking, and diabetes as risk factors for coronary disease, gout should also be included as a risk factor. Although non-specific, when C-reactive protein

is elevated, it is a good predictor of inflammation and can predict heart disease. Hyperuricemia predicts vascular calcification. If serum uric acid is 9 or higher, there is an average loss of 10 years of life.[25,26] The pathway identifying hypercholesteremia, which causes coronary disease occurs via atheromatous inflammation. The specific inflammasome involved has been identified as NLRP3 IL-1B. This pathway is the same exact pathway for gout (Figure 1C).

Urate crystals are deposited predominantly along the surface of the articular cartilage. 65% of the time, gout manifests in the first metatarsal phalangeal joint.[9] 90% of all gout patients will have refractory attacks that occur in the foot. When it occurs in the first metatarsal phalangeal joint, it is known as podagra. Mid-foot (25%-50%) and ankle (18%-60%) attacks can also commonly occur.[1] The total urate burden of the body is comprised of 50% being in the foot and ankle.[23] The current gold standard for the diagnosis of gout is aspiration of the involved joint, followed by polarized light microscopy of the aspirate assessing for needle–shaped negatively birefringent MSU crystals.

Arthrocentesis may technically be challenging in several scenarios, including anatomically difficult-to-access joints such as the spine and sacroiliac joints in certain patients, such as those with immunodeficiencies, patients with inadequate fluid volumes, or patients with severely inflamed joints. In addition, arthrocentesis is a painful invasive technique whose risk factors include infection, hemorrhage, and damage to involved tissues. Experience in diagnosing gout is frequently and definitively made by joint aspiration to rule in the presence of MSU crystals as well as being critically important to rule out septic arthritis or an immune modulation response, which may mimic gout clinically. Samples retrieved by arthrocentesis require immediate analysis to preserve the technique's sensitivity and specificity, introducing practical limitations.[10]

The purpose here is to review the imaging appearances of gout in the clinical presentation to assist in diagnosis and to help the clinician understand what he/she is seeing. With the aid of this advanced imaging, the physician can institute a treatment regimen earlier based on achieving a diagnosis earlier that previously had not been available. Many of the diagnostic techniques available today were previously undeveloped or unknown. Imaging may provide a non-invasive and accurate way to diagnose gout. Different imaging modalities may include x-ray, computed tomography (CT), dual energy CT (DECT), magnetic resonance imaging (MRI), and ultrasound (US).

Incidence and Progression

It is generally recognized that gout prevails in the classical presentation favoring 20:1 men versus women; and in over 80% to 90% of gout patients there is a positive familial history of

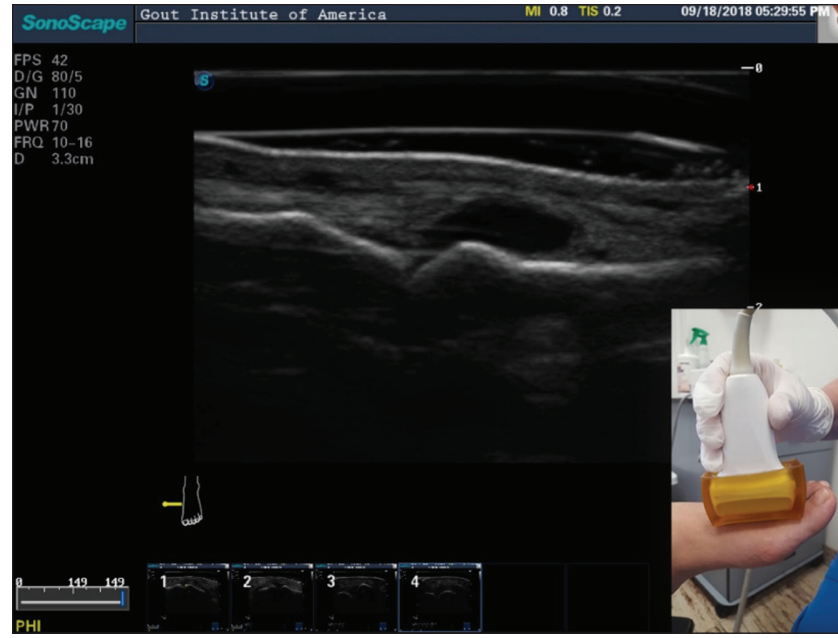


Figure 9: Dorsal long axis imaging with standoff with linear array transducer at 16mgHz demonstrating synovitis.

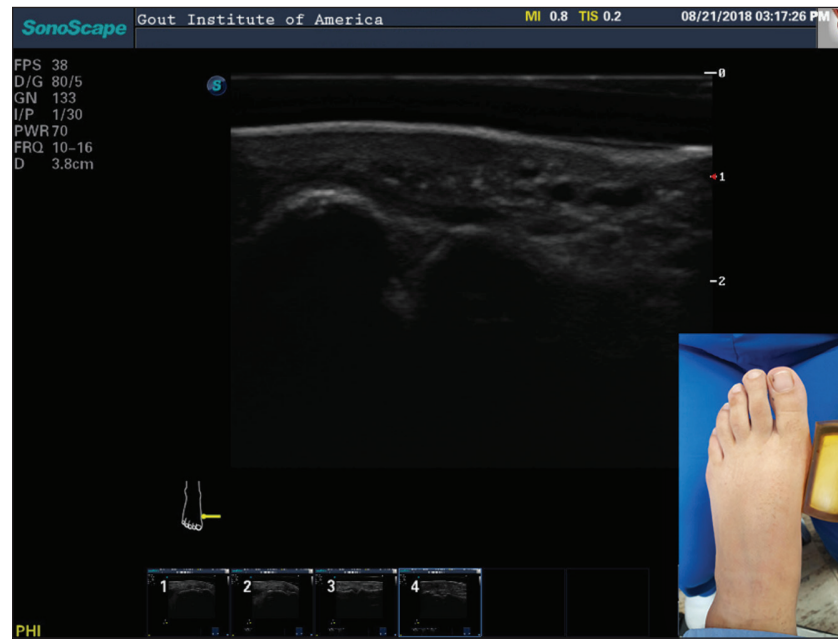


Figure 10: Classic tophus identified with sonoscape 16mgHz linear array transducer with standoff demonstrating varying degrees of hypo and hyper echogenicity noted in the medial long axis position.

gout. The genotype that has been identified is ABCG2. Genetic changes in the ABCG2 gene that can result in hyperuricemia reduce the protein's ability to release urate into the gut. As women become post-menopausal, the rate of prevalence changes with roughly 7% of men and 5% of women. Post-menopausal women no longer produce estrogen, which is thought to be a uricosuric that suppresses the MSU crystal precipitation response.[11] Also, there is another statistical bump in the women's curve due to the use of thiazide diuretics as a first line medical regimen in hypertension.[12]

Gout the disease is basically divided into four phases:

1) Asymptomatic hyperuricemia, 2) Acute gout, 3) Inter-critical gout, and 4) Chronic gout.[13]

Chronic gout may take at least 8 to 10 years to manifest with abnormalities on plain film. Therefore, advanced imaging is frequently employed for early detection, to ascertain a confirmatory diagnosis, and determine the extent of the structural destruction to the joints. By the time the first acute attack occurs, gout is most likely present for 10 to 12 years.

Sites frequently affected are the first metatarsophalangeal joint in the foot. Other frequent sites are the hand, hind foot, pre-patellar bursa, heart, kidneys and at the insertion points for ligaments and tendons.[14] This frequently can cause severe enthesopathies at these sites and may cause significant disabilities. Some of the common pathological findings of gout are juxta-articular erosions, cortical depressions, and overhanging edges with sclerotic margins. These findings are seen routinely and often the cortical depressions are adjacent to a tophus. CT is the most sensitive for detecting boney erosions. Secondarily, synovial proliferation may be demonstrated on imaging as synovial thickening, often with synovial enhancement.

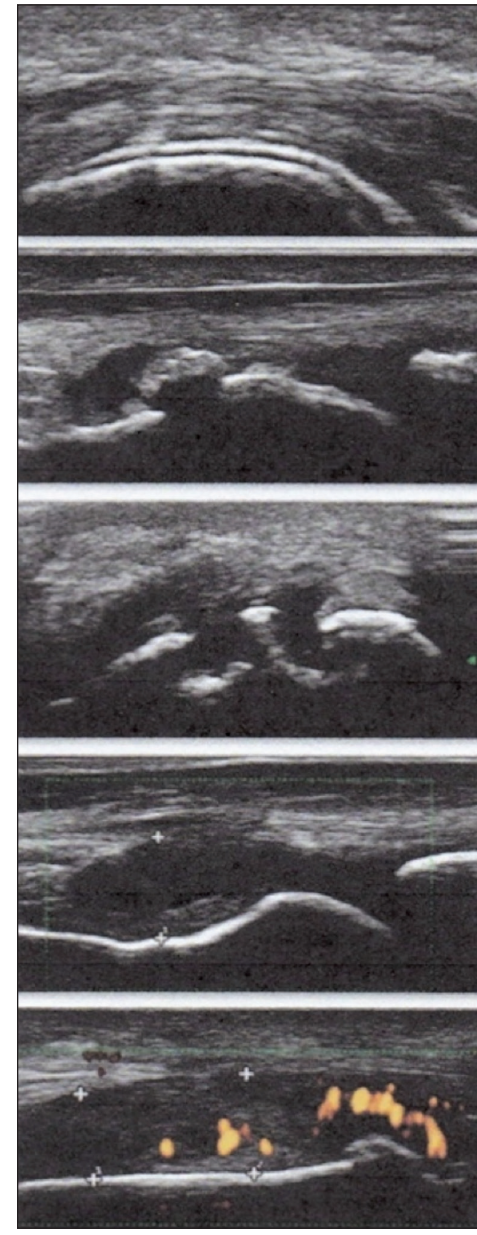
Contrast-enhanced images may increase detection of bone erosions. US Doppler imaging is utilized in gout to assess for increased blood flow and active inflammation. The tophus is visualized (both intra-and extra-articularly) as a high-density soft tissue mass representing the body's chronic immunological response to the MSU crystals. Interarticular presentation is as a hypoechoic return with a halo effect that will have a hyperechoic or heterogenous center. It is now recognized also in axial skeletal imaging of the spine with micro-tophi being imaged.[15]

The characteristics of cartilaginous deposits are not readily demonstrated with conventional diagnostic imaging including roentgenography, computed tomography (CT) or magnetic resonance imaging (MRI). These types of imaging modalities can nevertheless provide helpful diagnostic clues. However, disadvantages include lack of specificity (bone scan, MRI), considerable cost (MRI), and inability to assess early soft tissue changes such as joint effusions, early erosions, synovial hypertrophy, and hypervascularity, or small tophi (roentgenography). Typical well-defined, "punched out," periarticular erosions with overhanging edges are generally not seen radiographically until 10-12 years after the initial acute attack.[16] Podagra, gout, and calcium pyrophosphate disorder arthropathy can be evaluated with radiographic and ultrasound imaging for detection and confirmation.

Radiographic Diagnosis of Gout

Traditionally, plain radiography has been the standard initial imaging technique for assessing structural changes in gouty arthropathy, and a quantitative scoring system has been available since 2007. However, erosive changes on radiographs are a late feature of gout and are frequently only apparent after arthritis in patients has been established for more than 10 years. Radiography is relatively insensitive to the early manifestations of gout. The sensitivity of radiography is only approximately 30%, compared with arthrocentesis, which is considered a gold standard. Gout is often present in the manner reminiscent of psoriatic arthritis without the usually more advanced demineralization and non-uniform joint space narrowing.

Classic osseous radiographic findings demonstrate well defined "punched out" periarticular erosions with sclerotic overhanging edges, normal mineralization, relative preser-



Figures 11 A, B, C, D, E:
A. Typical hyperechoic enhancement on the cartilage surface ("double contour sign")
B. Intra-articular hyperechoic clouds
C. Bony erosions
D. Synovitis
Power Doppler assessing vascular status of acute inflammatory effects of gout

TABLE 1:
Comparison of Different Imaging Modalities in Patients with Gout

Imaging Feature	Pain Radiography	Ultrasonography	MRI	CT	DECT
Erosions	Fair: Erosions might not be detected at complex regions (Carpus/tarsus) +	Good: Some regions not accessible ++	Very good: Detection of erosions in all areas ++	Very good: Detection of erosions in all area +++	Very good: Detection of erosions in all area
Synovitis or Tenosynovitis	Not imaged (apart from soft tissue swelling) –	Very good: Especially using PDUS +++	Very good: Single regions only (intra-venous gadolinium contrast) +++	Not imaged ++	Not imaged
Osteotisis or Bone marrow edema	Not imaged –	Not imaged –	Very good +++	Not imaged –	Not imaged
Cartilage	Poor: Superficial tophi seen adjacent to erosions as asymmetric masses +	Very good: Tophi can be detected at most sites depending on access +++	Fair: Dependent on sequences and acquisitions +++	Poor –	Poor –
Tophus (detection)	Poor: Superficial tophi seen adjacent to erosions as asymmetric masses +	Very good: Tophi can be detected at most sites depending on access +++	Very good at all sites +++	Good: Cannot always be distinguished from background tissue ++	Very good: Highly specific; subcutaneous and intraosseous tophi detected
Tophus (vascularity and measurement)	Poor –	Very good: Vascularity detected using PD US; outlining can measure size and volume +++	Very good: Vascularity detected using Gd–contrast; outlining can measure size +++	Very good: Outlining can measure size (with excellent reproducibility) cannot detect vascularity +++	Very good: Outlining can measure size; cannot detect vascularity
Quantification of urate burden	Poor –	Very good: Site specific only ++	Poor	Poor	Very good +++
Effusion	–	+++	+++	++	++
Synovial Proliferation	–	+++	+++	+	+
Joint Space Narrowing	+++	+++	+++	+++	+++
Overall	Widely used multiple joints imaged; inexpensive; minor radiation exposure	Operator dependent; some joints inaccessible versatile; inexpensive; dynamic and quick no radiation	Single joint area imaged; time consuming; very expensive; claustrophobia; all features well imaged; no radiation	Restricted joint area imaged (but wider than MRI); cannot image inflammation; expensive; radiation exposure	Restricted joint area imaged (but wider than MRI); cannot image inflammation; expensive; radiation exposure; Very specific to urate detection and how to quantify urate burden which is unique to this modality

– Poor + Fair ++ Better +++ Best

vation of the joint spaces, and asymmetric poly-articular distribution. Joint space widening and subchondral bone collapse might occur in later stages of the disease. Such findings take years to manifest after an acute attack. If these findings are present without urate deposits, then it indicates osseous changes due to remote, currently inactive gout.[17] The presence of tophi with underlying bone erosions may indicate the presence of chronic gout.

In patients with acute gout, there is frequently no radiographic change, apart from non-specific soft tissue swelling in the region of the inflamed joint. The hallmark of cartilage damage is joint space narrowing, and this is typically absent in acute gout, but can occur in patients with OA-associated disease, where adjacent sclerosis and osteophyte formation might also be present.

Radiographic presentation of MSU crystals in the synovial membrane in or around ligaments are present in the hands and feet first at the MTPJ and IPJ. As discussed previously, gout may affect numerous joints throughout the body, including the elbow, wrist, olecranon bursa, shoulder, and hip. Gout can also be present in places such as the ear helix or other fleshy areas of the body, and it can have the accumulation of urate crystal deposition that can often resemble xanthoma.[18] This is found in places such as fingers, ears, or eyelids. Soft tissue findings are present with gouty tophi in about 50% of the population.

Descriptions of bone erosions may have overhanging edges as well as punched-out rat bite lesions often accompanied by osteitis and synovitis. The tophus is a reaction that contributes to joint arthritis associated with this malady. Early findings of gout are often adjacent to the tophus and present often as an incidental finding; notably, acute gout flares can mimic septic arthritis, which must be ruled out.

The hallmark radiographic sign of gout is Martel's sign. The presence of tophi is associated with increased osteoclastogenesis. In the presence of urate deposition from gout, affected bone will frequently have erosions that have a punched-out appearance with well-defined overhanging edges. The erosions are due to tophaceous gout of the first metatarsophalangeal joint. It will have typical "overhanging margins" of bone both in the phalanx and in the lateral aspect of the metatarsal head in the case of classic podagra.[19] The other hallmark sign of gout is the double contour sign imaged via ultrasound (Figures 1D and 2).

Ultrasonography

Musculoskeletal ultrasound studies are now performed with triple blended frequency linear array transducers (Figures 3-6). Frequencies are between 7-16 MHz. The transducer is 50mm in length. A standoff is typically utilized to conform to irregular surfaces. The standoff pushes the image down in the near field about 1 cm. This allows better signal to noise and decreases the speckles in the anechoic near field. Standard imaging positioning is distal to the right and proximal to the left. Standard imaging plans are in the short and long axes. All ultrasound exams are operator-dependent and are dynamic in nature. The exams can be reviewed in the cine-loop.

In common with the other advanced modalities, ultrasonography is more sensitive than plain radiography for detecting erosions. Ultrasonography can detect three times as many erosions as radiography, indicating it is superior for sensitivity. There is no gold standard against which to compare ultrasonography.

Power Doppler ultrasonography (PDUS) can detect slow blood flow at the site being imaged, which may indicate inflammatory tissue. Active or "hot" sites will demonstrate PDUS signals. Deposits of MSU crystals can be detected on ultrasonography as tophi and as a fine powder layer over the cartilage, labeled as the "double contour sign". The double contour sign is defined as a highly echogenic line which is detected parallel to the echogenic line of cortical bone, with the interposed low signal representing cartilage. It appears as two convex arcs.

Although this sign has not been compared directly with histopathological appearances, it does seem to correlate with findings from a necropsy study where MSU crystal deposits were seen to overlie the cartilage surface in gouty joints. The double contour sign is present roughly 92% of the time in gouty joints. The double contour sign will be present even if

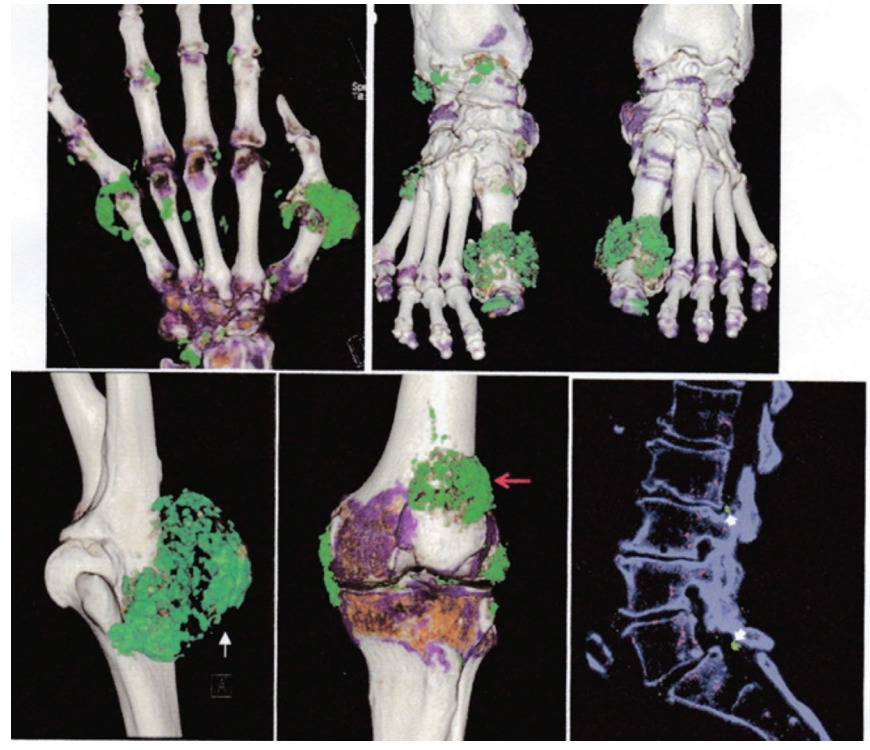


Figure 12: Dual energy computed tomography (DECT) demonstrated gout, in green, in the hand, feet, elbow, knee, and spine.

anisotropy is done at the time of imaging.

Although the double contour sign has mostly been described in patients with long-standing disease, it has been reported to occur in a significant proportion of patients with asymptomatic hyperuricemia and no clinical history of musculoskeletal involvement. This sign has been reported to disappear with effective ULT, once sustained normouricemia has been achieved.[20]

Tophi appear on ultrasonography as hyperechoic nodules, often poorly defined contours and surrounded by an anechoic halo (Figure 7). Tophi can be detected subcutaneously or in deep tissues, where they are non-visible on clinical examination. Utilizing the volume calculation feature on ultrasound machines, the tophaceous volume can be calculated to evaluate if urate-lowering therapy is effective. This modality provides the operator the feasibility to discriminatively measure and evaluate changes in tophus size.

Other classic patterns observed in the joint effusion of gout are an anechoic cavity. Homogenous punctuate echogenic foci of urate sand can also be observed. The "snowstorm" pattern demonstrates rounded aggregates of variable echogenicity superimposed on urate sand.[21]

Ultrasound presents a rather unique ability to be primed for gout remission management. It can be one of the more sensitive and specific imaging modalities to detect MSU intra-articular crystal deposition and early joint destruction. This is especially due to the ability to utilize ultrasound that is high frequency and high resolution to detect changes in the density of the articular surface and synovial fluid as well as changes in density and thickening of the articular cartilage, giving rise to the double contour sign previously mentioned. It also shows the infiltrate into the soft tissue that causes the itching inflammatory response after the presentation of the acute deposition of the gouty crystals.

Ultrasound can also visualize the insertions of ligaments and tendons for urate crystal deposition in patients with an acute flare or to differentiate other diseases such as osteoarthritis. On ultrasound, tophi may demonstrate an anechoic peripheral halo with a heterogeneous hyperechoic center adjacent to a joint and may often be confused with rheumatoid arthritis. Micro-tophi may also be seen in joint effusions, creating hyperechoic foci. This is referred to as a snowstorm appearance. Synovitis and erosions with irregularity of the cortex may be indicative of gout.

Besides detection of synovitis and erosions, ultrasound can also detect the presence of the double contour sign (DC) and peri-intra-articular hyperechoic cloudy areas (HC). DC is defined as focal or diffuse echogenicity on the surface of the joint cartilage. HC is characterized as peri-/intra-articular heterogeneous masses composed of hyper- or hypo-echoic material sometimes possessing posterior acoustic shadows. Synovitis is defined as the presence of either synovial fluid and/or synovial hypertrophy, which is characterized by abnormal hypoechoic intra-articular soft tissue. Volume calculations can be performed both in the long and short axis on a dual screen. The volume calculation occurs with an "x', "y" and "z" axis measurement.

Area calculations of tophus can be accomplished by tracing the tophus. Finally, with the aid of different color maps, three-dimensional scanning is accomplished to image the tophus. If a patient is going to be placed on a uricolytic agent such as Krystexxa®, a pre-treatment image and volume calculation of a tophus can be done and post-treatment, the tophus site can be imaged to show resolution of the tophus (Figures 8-13).

When urate vasculopathy is present in the kidney, the medulla of the kidney will appear hyperechoic. 33% of patients with gout will have these crystals present.

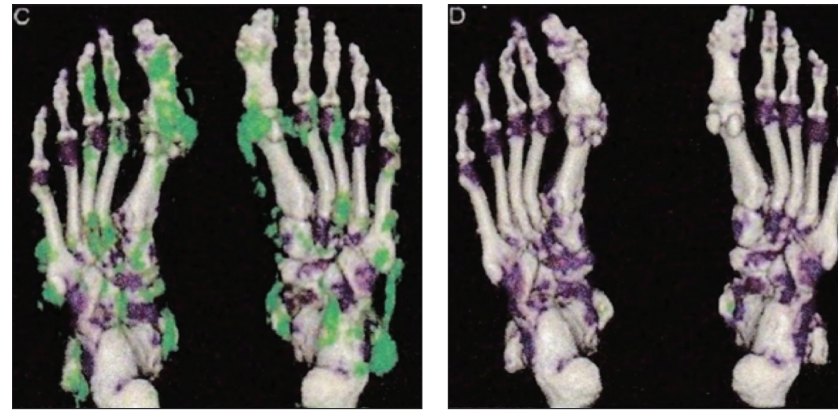


Figure 13 and 14: DECT scan of the feet demonstrating chronic gout (in green). DECT scan of the feet after receiving Krystexxa®; gouty tophus is relatively gone.

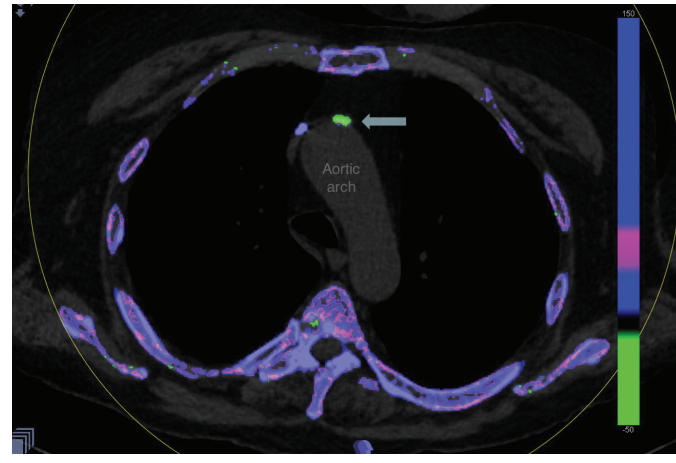


Figure 14A: This patient has multiple discrete spots of MSU crystallization (green), lining his ascending thoracic aorta and in the interior of his coronary artery.

CT

Conventional CT or single energy computed tomography (SECT) is an excellent modality for imaging tophi and erosions in patients with gout,

owing to its multi-planar capabilities. It utilizes a single polychromatic x-ray beam ranging from 70 to 140 kVp with a standard of 120 kVp. CT is probably a more accurate tool of detecting and measuring tophi than MRI and ultrasonography because of its superior definition of tophus-bone interface. Tophi have a typical density on CT of 170 Hounsfield units. CT can detect tophi that are not apparent on clinical physical examination. Unfortunately, CT has a low false-positive rate for detecting tophi,

Calcification in the tophus often is suggestive of renal impairment, which indicates that the kidneys are under secretors. While joint effusions may also be seen, they may not be specific for gout unless accompanied by numerous tophi. (Table 1 summarizes these imaging findings).

CT, especially dual energy, can easily distinguish between crystals and calcification, differentiating between biomechanical abnormalities and crystalline deposition. This could be useful when the clinical presentation is unclear or as an atypical presentation for the clinician treating gout.

While CT may be superior to plain film in detecting abnormalities in gout, it is more expensive than x-ray. It provides, however, the information that can be used to determine the aging extent of the pathological manifestation of the erosions of gout. CT images may show the punched out lytic lesions and overhanging sclerotic margins of early bone erosion. CT can allow the clinician to rule out other diseases such as rheumatoid arthritis or CPPD (calcium pyrophosphate disease). In CPPD, there often is non-uniform joint space narrowing, subchondral sclerosis of the joint, and peri-articular soft tissue swelling due to tophi being deposited around the joints.

DECT

The newest modality in imaging gout is dual-energy computed tomography (DECT). It is also known as spectral imaging. An image is acquired simultaneously using two ray tubes. Two different voltages are utilized, such as 80 kVp and 140 kVp. The beams are 90 degrees to each other. Utilizing this technique, different materials such as bone, soft tissue, and gouty tophus may be discriminated based on their varying absorption of different energies depending on their chemical composition. 22)

DECT is very sensitive and specific for its identification of tophi. However, utilization of DECT imaging may be limited due to the cost and radiation. DECT has the ability to show intra- and extra-articular tophi as well as tophi located at the insertions of the ligaments and tendons, and within the spine. DECT scanning allows the physician to ascertain whether the patent is tophaceous, even if it is not visible on examination.[23] This technique utilizes ionizing radiation and is relatively expensive, so it might not be widely applicable outside of research or teaching hospitals. With this technique, there is a 10% increase in radiation exposure compared to a standard CT examination (Figure 14). With the advent of

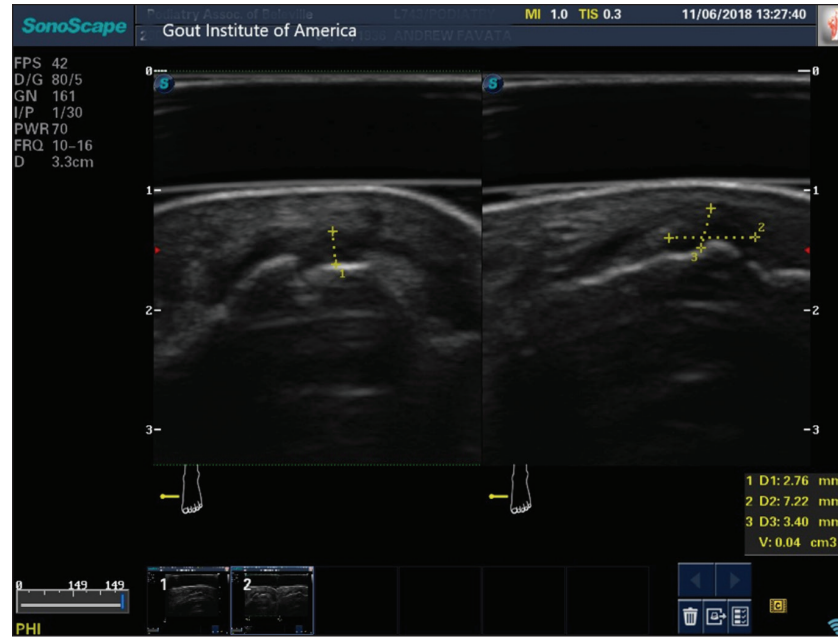


Figure 15: Short axis and long axis scan demonstrating volume of tophus.

Figure 16: 3D image demonstrating tophus of the first MTPJ clearly demonstrating bone erosions by tophus. Image can be independently rotated on the x,y,and z axis.

DECT imaging of the heart, there have been advances in the understanding of the extent and influence of urate deposition. When coronary calcium scoring tests are performed, they reveal urate deposition in the aorta and the coronary vessels. Urate crystals are embedded in arteriosclerotic plaques. When calcification occurs, uric acid co-localizes. 85% of the time gout patients will have urate deposition and these patients will also have a coronary calcium score on average 3.5 times (Figure 14A). On of the newest specialties is cardio rheumatology. Departments specializing in this are now at NYU, Stamford, and the Cleveland Clinic.

MRI

Magnetic resonance imaging may also be used in the diagnosis of gout (Figures 15 and 16). Most tophi are heterogenous in signal secondary to their varying high-protein composition. MRI allows accurate crystalline deposit identification and localization, including within the deeper soft tissues and in areas and in sites atypical for MSU and/or CPPD crystalline deposition. It can allow the clinician to diagnose the extent of gout involvement, including at the insertions of tendons and ligaments into bone.

Gouty tophi, when examined with Tl-weighted imaging post-contrast, frequently yield an image of good quality to clearly demarcate the size borders and depth of penetration of the tophus. A T2-weighted imaging can have a higher signal to noise ratio post-contrast. Detected signal strength is in the mean proportional to the intensity of bone involvement in the structure, especially in the inter-osseous layers of the foot due to the sensitivity of MRI.

MRI modality can utilize fat suppression imaging. With MRI, the progress of treatment for chronic refractory gout can be monitored and assessed continuously. Additionally, with MRI, gout and other crystalline arthropathies such as CPPD can be frequently differentiated between septic arthritis and osteoarthritic conditions of the joint (Figure 17).[24]

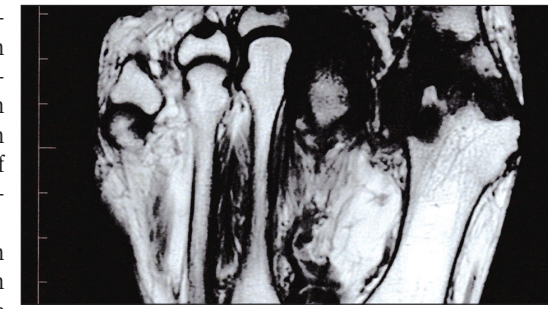


Figure 17: MRI of the foot demonstrating gouty tophus with erosions of the first MTPJ and phalanx.

Conclusion

Gout is an erosive inflammatory arthropathy where long-term damage to joints can have a major negative impact on patient function. Cellular studies have focused on the role of cytokines and inflammatory mediators produced by cells of the innate and adaptive immune systems that are resident within the tophi. MSU crystals can act both directly and indirectly to stimulate an inflammatory response with resultant tissue destruction. Gout should no longer be thought of as a flare disease. The renal and cardiac ramifications are eye opening.

Osteoclasts and osteoblasts in the underlying bone have recently emerged as major players in driving erosion and preventing adequate tissue repair when subjected to an environment of MSU crystal stimulation. Advanced imaging modalities provide additional insights into the pathological processes involved in tissue destruction in patients with gout by providing information about bone erosions, tophi, and MSU deposition on cartilage surfaces. All modalities have advantages and disadvantages. Thus, insights from cellular and imaging studies can complement one another and help improve the clinical management of patients with this painful and potentially disabling disease (Figure 18). **PM**

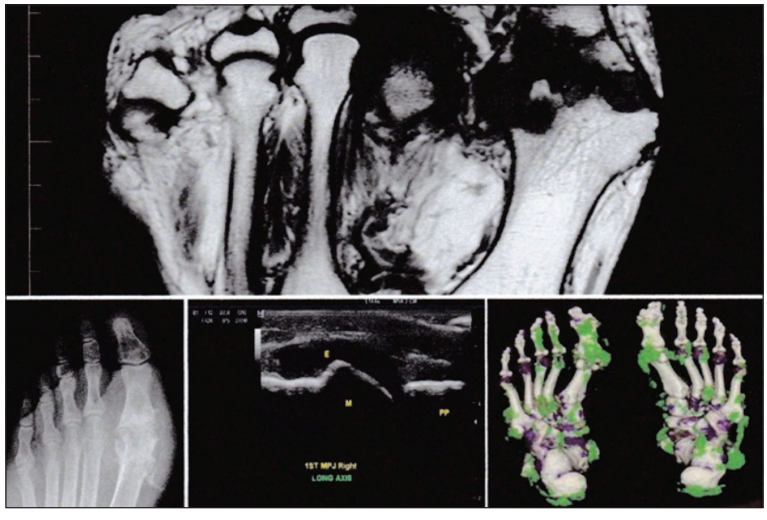


Figure 18: Montage showing MRI, x-ray, ultrasound, and DECT scanning.

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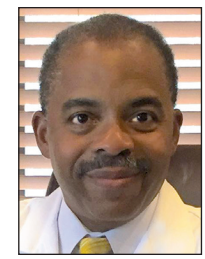


CME EXAMINATION

1) **The presence of tophi is associated with**
   - **A) Osteoporosis**
   - **B) Osteoblastgenesis**
   - **C) Osteoclastgenesis**
   - **D) Osteopenia**

2) **Arthrocentesis is**
   - **A) 22% accurate**
   - **B) 35% accurate**
   - **C) 45% accurate**
   - **D) 74% accurate**

3) **Crystallization of serum uric acid to mono sodium urate at normothermia occurs at:**
   - **A) 6.8**
   - **B) 3.4**
   - **C) 8.1**
   - **D) 5.0**

4) **After consuming a high sugar meal, serum uric acid will spike in:**
   - **A) 10 minutes**
   - **B) 20 minutes**
   - **C) 21 minutes**
   - **D) 30 minutes**
   - **E) 24 hours**

5) **When assessing urolithiasis, the nidus found in kidney stones is comprised of:**
   - **A) Xanthine Dehydrogenase**
   - **B) L-Arginine**
   - **C) Uric Acid**
   - **D) ATP**

6) **Crystal deposition can occur in the human body in the following areas except:**
   - **A) Larynx**
   - **B) Ear**
   - **C) Heart**
   - **D) Brain**

Continuing Medical Education

CME EXAMINATION

7) If a patient has a familial history of gout, the genotype identified is:
   A) ARQ32Z
   B) ABCR45
   C) ABCG2
   D) ABCDEFG8

8) The Double Contour sign is defined as;
   A) As a highly echogenic line which is detected parallel to the echogenic line of cortical bone, with the interposed low signal representing cartilage. It appears as two convex arcs.
   B) As a highly isoechoic line which is detected parallel to the echogenic line of cortical bone, with the interposed low signal representing cartilage. It appears as two concave arcs.
   C) As a low signal which is detected perpendicular to the anisotropic line of cortical bone, with the interposed high signal representing cartilage. It appears as two concave arcs.
   D) None of the above

9) Single Energy Computed Tomography (SECT) has multiplanar capabilities. It utilizes a polychromatic x-ray beam from
   A) 70-140 kVp with a standard of 120kVp
   B) 70-150kVp with standard of 110 Volts
   C) 30 Milli amps
   D) 25-123kVp with a standard of 220V

10) The Percentage of the urate burden that is found to occur in the human body is:
   A) 25% - Kidney
   B) 50% - Foot
   C) 33% - Heart
   D) 75% - Eye
   E) 43.2% Ear

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2.	A	B	C	D		7.	A	B	C	D
3.	A	B	C	D		8.	A	B	C	D
4.	A	B	C	D	E	9.	A	B	C	D
5.	A	B	C	D		10.	A	B	C	D	E

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