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Original Article

Assessment of sensitivity and specificity of ultrasonographic features of gout in intercritical and chronic phases

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Abstract

Aim

To study the usefulness of ultrasonography (US) in the diagnosis of gouty arthritis and to assess its sensitivity and specificity in intercritical and chronic stages and also its use in comparing patients with high serum uric acid (HSUA) and low serum uric acid (LSUA).

Patients and methods

We studied 60 patients known to be gouty in either chronic phase or intercritical phase, diagnosed clinically and through laboratory assessments, and 30 controls. Demographic, clinical, and serological data were evaluated. Knee and first metatarsophalangeal joints were assessed by musculoskeletal US by a blinded radiologist.

Results

A total of 53 (88.3%) patients were in the intercritical stage of gout during the study, and seven (11.6%) patients had chronic gout with clinically detectable tophi. Double contour sign (DCS) was found in 57.5% and tophi were found in 41.6% of first metatarsophalangeal joints. DCS was present in 42 (70%) patients with gout, and in only one of the control group ($P < 0.001$). Comparing patients with HSUA and LSUA subgroups, DCS was detected in 92.3% in HSUA subgroup, but in only 28.5% in LSUA subgroup, with P value less than 0.004. The sensitivity of DCS increased to 92.9% in patients who had HSUA within the past 6 months before the US was done. In the LSUA subgroup, where sensitivity of DCS was low (28.5%), sensitivity of tophi was 48.7%, and it increased in the presence of both tophi and erosion in any joints to 66.6% compared with the control group. Finally, there was a positive correlation between tophi and erosions and disease duration, with $r = 0.81$ and $P = 0.01$ and $r = 0.27$ and $P = 0.035$, respectively.

Conclusion

Musculoskeletal US is useful for diagnosis of gout in intercritical and chronic stages, especially in patients with HSUA level and long disease duration.

Keywords: Double contour sign, gout, gout imaging, ultrasonography in gout, uric acid

Introduction

Gout arthritis is the most common form of inflammatory joint disease that affects ~1% of the population. The prevalence is higher in men and increases with age. The pathogenesis of gout includes disturbed purine metabolism, decreased renal excretion of uric acid, increased blood uric acid levels, and deposition of monosodium urate (MSU) crystals in the joints and soft tissues [1].

Clinically, it is often classified into four phases: asymptomatic hyperuricemia, acute attacks, asymptomatic intercritical, and the chronic, which is characterized by the presence of a tophus or tophi [2].

The gold standard for diagnosis of gout is demonstration of MSU crystals under polarizing microscope in the aspirate from joints or tophi. However, because it is an invasive procedure, diagnosis by demonstrating crystals is infrequently done, and therapy is often started on the basis of clinical profile [3]. In a recent study on dietary influence on acute attack of gout,

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crystal deposition was detected in only 12.3% of the patients with gout [4].

A simple radiography of the involved joint is usually the first and the only imaging study performed in patients with gout, but the sensitivity has been reported to be as low as 31% [5]. Typical radiography features of gout include well-defined 'punched-out' periarticular erosions with overhanging edges. This damage would only be noted in radiographs obtained 6–12 years after the initial acute attack [6].

Computed tomography (CT) and MRI have been used for the evaluation of gout, with the advantages of early detection of tophi and bone erosion. However, the disadvantages include inconvenience (CT and MRI), exposure to radiation (CT), high cost (MRI), and lack of specificity (MRI) [7]. Therefore, musculoskeletal ultrasound (MSUS) has come up in recent years for confirmation of gout in a noninvasive way. The advantages of MSUS include relatively low operational time and costs, ability to scan in multiple planes, feasibility of dynamic scanning, high spatial resolution, and free of radiation hazards [8].

Uric acid exists mainly as the urate ion in plasma and extracellular fluid at the physiological pH. Supersaturation of urate ion occurs when serum uric acid (SUA) level exceeds 6.8 mg/dl [7,8]. These urate ions get deposited as MSU crystals on hyaline cartilage within the joints, causing gouty arthritis, or in extra-articular tissues as a lump of crystals, resulting in tophus [9].

When MSU crystals are deposited over the hyaline cartilage of joints, they form a layer on it, and during US examination, the layer looks like a double contour on the cartilage, which is best seen in metatarsophalangeal joints (MTPJs), knee, and metacarpophalangeal joints [10].

Tophus in MSUS looks like a heterogeneous, globular mass usually hyperechoic (rarely hypoechoic) with a surrounded hypoechoic rim. These double contour sign (DCS) and 'tophi' demonstrated by MSUS are rarely seen in any other type of arthritis [11]. US can also be used for the evaluation of synovial thickness, synovial effusion, and bone erosion. Synovial inflammation could be assessed by power Doppler US [10].

Some studies have reported the disappearance of DCS after achieving sustained normouricemia. However, there is not much available published literature yet regarding the utility of US signs in patients with gout in intercritical or chronic tophaceous stages [12].

The aim of our study is to reveal the sensitivity and specificity of US features of gout in patients who are in intercritical or chronic stages of gout and to compare US features of gout between patients with high serum uric acid (HSUA) and patients with low serum uric acid (LSUA).

Patients and methods

Patients

The study protocol was approved by the Ethics Committee of GOTHI. A total of 60 consecutive patients with age between 18 and 80 years were consecutively recruited from the rheumatology outpatient clinic of Al-Mataria Teaching Hospital. All of them fulfilled the ACR diagnostic criteria of gout [13]. Moreover, 30 controls with matched age and sex were enrolled.

(1) History and clinical examination was done for every patient.
(2) MSUS examination was then performed.
(3) SUA and serum creatinine was noted. All available SUA reports in a given patient, including the maximum value of SUA in the past 6 months, were noted. We screened those patients who had at least two SUA reports available in the past 6 months.

Inclusion criteria

The following were the inclusion criteria:

(1) Patients age more than 18 years with primary gout confirmed by demonstration of MSU crystals at some point during their disease course.
(2) Patients known clinically in intercritical or chronic stage of gout and with disease duration more than or equal to 1 year.

Exclusion criteria

The following were the exclusion criteria:

(1) Hyperuricemia without previous history of acute or subacute gouty attack.
(2) Associated other arthritis, for example, psoriatic arthritis, reactive arthritis, and so on.
(3) History of fracture in or around the examined joints.
(4) Intraarticular corticosteroid injections in the examined joints within 3 months before the study entry.

Ultrasonography image interpretation

All patients subsequently underwent a musculoskeletal US evaluation of both knee joints (transverse suprapatellar view of the femoral cartilage in maximal flexion) and both first MTPJs (longitudinal dorsal and medial views) using a 12.5-MHz linear probe (Philips-ATL, HDI 5000; Philips, Bothell, Washington, USA). During US, the following lesions were assessed: (a) the DCS (defined as an inhomogeneous, hyperechoic layer on the articular cartilage seen in both long and short axes); (b) tophus [defined as heterogeneous globular mass (>1 mm diameter) mostly hyperechoic with a surrounded hypoechoic rim seen in both long and short axes]; (c) bony erosions (defined as breach in the hyperechoic cortical bone within the joint in two perpendicular planes); (d) hypervascularity (defined as increased signal intensity in power Doppler within the joint); (e) synovial proliferation (defined as an uncompressible hypoechoic intraarticular area); and (f) synovial effusion (defined as a compressible anechoic intraarticular area) [14,15].

Statistical analysis

All tabulated data were expressed as mean ± SD. Comparisons between patients and control groups were done by using the Student *t* test. For all statistical tests, significance was assessed using the correlation coefficient (*r*) test, in which

significance is defined as level of *P* value of less than 0.05. Computations were done using an SPSS statistical program, version 12 (USA). Graphs were assessed using Microsoft excel XP version [16].

Results

We studied 60 patients with gout and 30 controls (19 with osteoarthritis, three with rheumatoid arthritis). Fifty-three (88.3%) patients were in the intercritical stage of gout during the study, and seven (11.6%) patients had chronic gout with clinically detectable tophi. Demographic, clinical, and laboratory parameters are shown in Table 1.

All 60 patients with gout were subdivided into two subgroups according to SUA levels. The first subgroup included 39 patients with HSUA of maximum SUA levels more than or equal to 6.9 mg/dl within the past 6 months before recruitment. The remaining 21 patients had maximum SUA levels below 6.9 mg/dl in that specified time. The patients in the HSUA subgroup either never received urate-lowering therapy or were noncompliant to the therapy, whereas the LSUA subgroup was on urate-lowering drugs to maintain SUA less than 6.9 mg/dl for a minimum 6 months before the study entry.

These two subgroups were analyzed separately, and comparisons of their baseline characteristics are shown in Table 2.

A total of 120 first MTP joints and 120 knee joints ofgout patients were examined by US. The DCS was found in 68 (57.5%) first MTPJs and tophi were found in 50 (41.6%) first MTPJs. Among 120 examined knee joints, DCS was detected in 31 (25.8%) joints and tophi in 3 (2.5%) joints only as seen in (Figs. 1-7).

The DCS was present in 42 (70%) patients with gout, in one or more of their examined joints, and in one of the control group ($P < 0.001$). Interestingly, DCS was detected in 36 (92.3%) cases in the HSUA subgroup, but in only six (28.5%) patient in the LSUA subgroup ($P < 0.004$). However, there was no significant difference in presence of tophi demonstrated by US between HSUA and LSUA subgroups ($P = 0.42$).

Bony erosions in the first MTPJs were detected in 26 (43.3%) gout patients and in 3 (10%) subjects in the control group ($P < 0.001$). All of the patients with erosions in the control group had rheumatoid arthritis. Moreover, the low SUA subgroup showed significantly higher occurrence of erosions 9 (42.8%) and tophi 11 (52.3%) in first MTPJs as compared to the control group (Table 3) as seen in (Figs. 1-7).

The sensitivity and specificity of DCS in patients with gout were 70 and 96.6%, respectively. The sensitivity of DCS increased to 92.9% in subgroup of patients who had HSUA within the past 6 months before the US was done. Moreover, tophi in patients with gout were 50 and 93.3%, respectively. In the LSUA group, where sensitivity of DCS was low (28.5%), sensitivity of tophi was 48.7%, and increased in both tophi and/or erosion in any joints to 66.6%, compared with control group, as seen in Table 4.

Table 1: Comparison between patients with gout and control groups regarding demographic, clinical, and laboratory data

	Patients with gout ($n=60$)	Controls ($n=30$)	*P*
Age (years) (mean±SD)	51.5±5.37	52.4±5.94	0.28
Sex, male/female [*n* (%)]	27/33 (45-55)	55/50 (50-50)	0.27
BMI (kg/m^2) (mean±SD)	34.22±8.27	33.9±8.8	0.41
Arthralgia or arthritis in 1st MTPJs [*n* (%)]	9 (6.4)	NR	NR
Serum creatinine (mg/dl) (mean±SD)	0.89±0.24	0.63±0.16	0.04
Serum uric acid (mg/dl) (mean±SD)	7.2±2.6	3.7±0.4	0.001

MTPJ, metatarsophalangeal joint.

Table 2: Comparison between patients with gout with high serum uric acid and patients with gout with low serum uric acid subgroups regarding demographics, clinical, and laboratory data

	HSUA subgroup ($n=39$)	LSUA subgroup ($n=21$)	*P*
Age (years) (mean±SD)	52.38±5.66	49.9±4.47	0.025
BMI (kg/m^2) (mean±SD)	33.1±8.6	36.1±7.2	0.026
Arthralgia/arthritis in 1st MTPJ [*n* (%)]	10 (25.6)	4 (19.04)	0.53
Disease duration (months) (mean±SD)	80.53±37.4	65.2±35.4	0.64
Serum creatinine (mg/dl) (mean±SD)	1.035±0.13	0.63±0.18	0.21
Serum uric acid (mg/dl) (mean±SD)	8.84±1.83	4.35±0.86	0.001

HSUA, high serum uric; LSUA, low serum uric acid; MTPJ, metatarsophalangeal joint.

Also, other ultrasonographic findings were noted in studying our gouty patients in the form of hyper vascularity, joint effusion, synovial proliferation and tenosynovitis in 2 (3.3%), 12 (20%), 32 (53.3%) and two (3.3%) patients, respectively, and their detection was not significantly different from the control group as seen in (Figs. 1-7).

In our study, we found a correlation between SUA level and both tophi and erosions, with $r = 0.43$ and $P =$ and $r = 0.47$ and $P = 0.001$, respectively. Moreover, there was a correlation between both tophi and erosions and disease duration, with $r = 0.81$ and $P = 0.01$ and $r = 0.27$ and $P = 0.035$, respectively (Figs. 1–7).

Discussion

Gout is one of the commonest forms of inflammatory arthritis. The prevalence appears to be rapidly increasing worldwide. Gout is a disease characterized by MSU crystal deposition in

Table 3: Comparison between different groups and subgroups regarding ultrasonographic features

US data	Controls ($n=30$) [n (%)]	Gout patients ($n=60$) [n (%)]	P	HSUA subgroup ($n=39$) [n (%)]	LSUA subgroup ($n=21$) [n (%)]	P
DCS	1 (3.3)	42 (70)	0.001	36 (92.3)	6 (28.5)	0.001
Tophi	2 (6.6)	30 (50)	0.001	19 (48.7)	11 (52.3)	0.7
Erosion	3 (10)	26 (43.3)	0.001	17 (43.5)	9 (42.8)	0.9
Synovial thickness	15 (50)	32 (53.3)	0.8	20 (51.2)	12 (57.1)	0.6
Joint space	18 (60)	33 (55)	0.24	23 (58.9)	13 (61.9)	0.86

DCS, double contour sign; HSUA, high serum uric acid; LSUA, low serum uric acid; US, ultrasound.

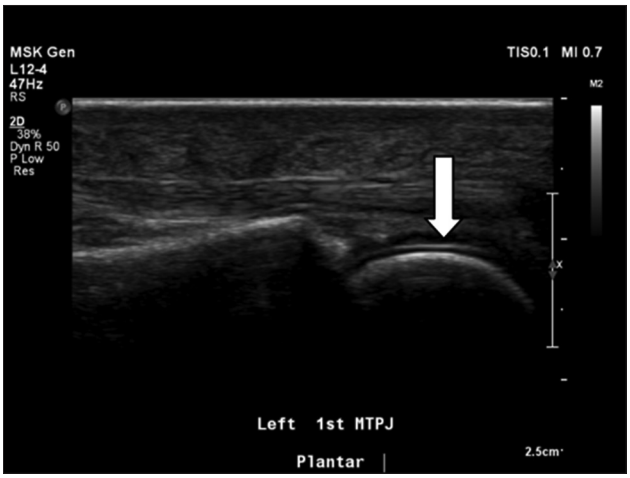

Figure 1: US longitudinal view of first MTPJ, showing double contour sign (white arrow). MTPJ, metatarsophalangeal joint; US, ultrasonography.

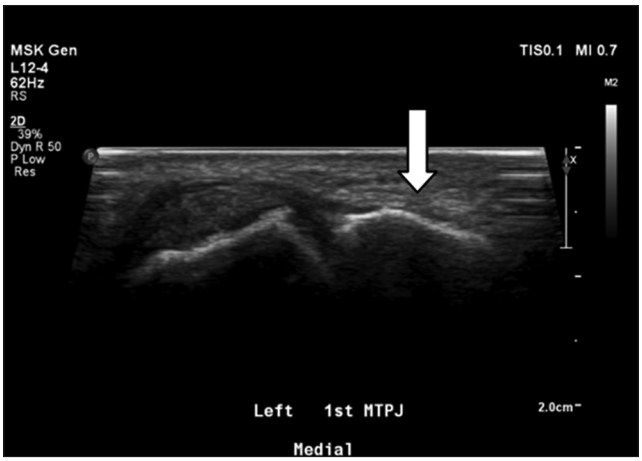

Figure 2: US longitudinal view of first MTPJ, showing synovial Thickness (white arrow). MTPJ, metatarsophalangeal joint; US, ultrasonography.

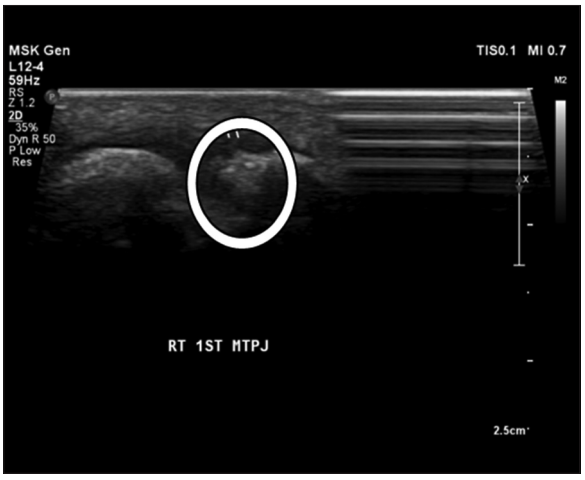

Figure 3: US longitudinal view of first MTPJ, showing echogenic aggregates. MTPJ, metatarsophalangeal joint; US, ultrasonography.

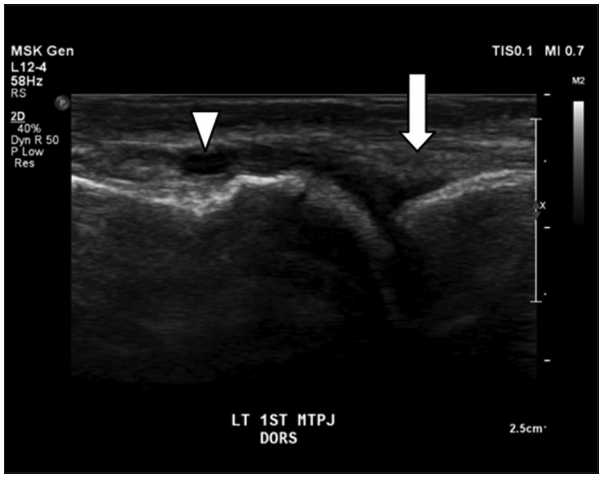

Figure 4: US longitudinal view of first MTPJ, showing synovial Thickness (white arrow) and effusion (head arrow). MTPJ, metatarsophalangeal joint; US, ultrasonography.

articular and periarticular structures, resulting in soft tissue inflammation [4].

US is an evolving noninvasive tool that can confirm diagnosis of gouty arthritis [17]. The sonographic signs of gout include a hyperechoic surface of hyaline cartilage (double contour), hyperechoic spots and bands within soft tissues, a 'snowstorm' appearance of synovial effusion, tophi described as heterogeneous masses containing hypoechoic and hyperechoic areas, with more of them being hyperechoic [18], and bone erosion [7].

Our study assessed the utility of MSUS in diagnosis of gout in the intercritical and chronic stages and compared the US features of gout in patients with HSUA and LSUA.

The presence of DCS and tophi in examined joints ranged from 17.8–92 and 14.3–100%, respectively, in different studies [19,20]. However, in our study, DCS was found in 68 (57.5%) first MTPJs, and tophi were found in 50 (41.6%) first MTPJs.

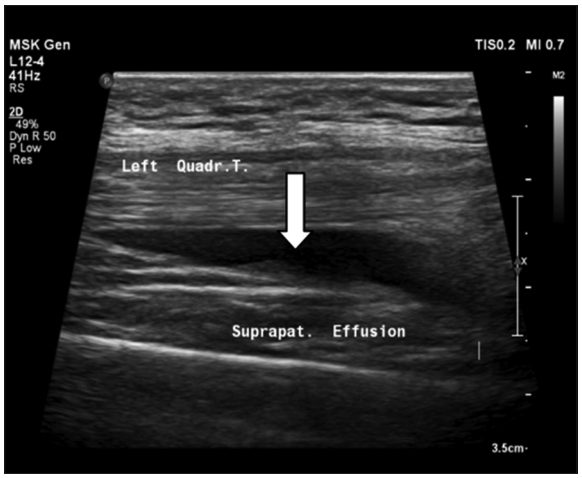

Figure 5: US suprapatellar view of knee joint shows effusion (white arrow). US, ultrasonography.

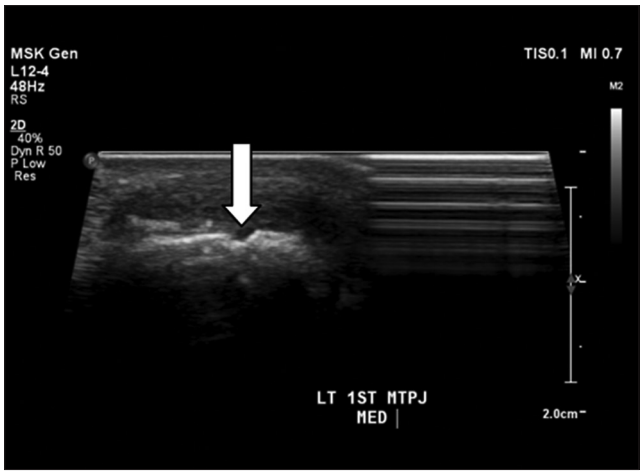

Figure 6: US longitudinal view of first MTPJ, showing bone erosion at medial aspect. MTPJ, metatarsophalangeal joint; US, ultrasonography.

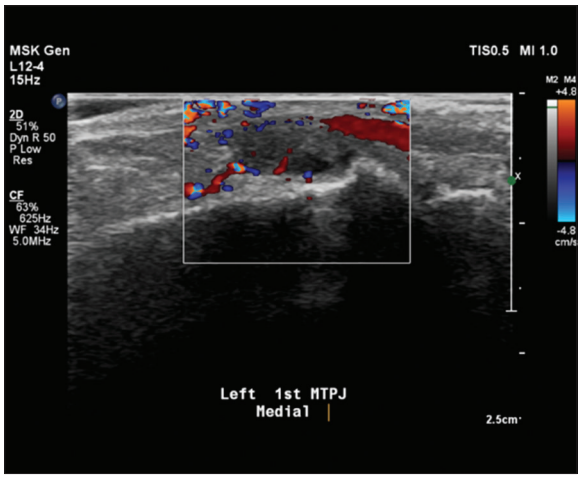

Figure 7: Power Doppler US longitudinal view of first MTPJ revealed slightly increased synovial vascularity. MTPJ, metatarsophalangeal joint; US, ultrasonography.

A recent large meta-analysis study on imaging modalities for gout showed sensitivity and specificity detected by MSUS of DCS were 83 and 76%, respectively, and of tophus were 65 and 80%, respectively [10]. In another study, sensitivity of DCS was detected in 92% and of tophi were detected in 100% of examined joints, which are much higher than the other studies [21]. However, we found that sensitivity and specificity of DCS were 70 and 96.6%, respectively, and those of tophi were 50 and 93.3%, respectively. Similar findings were detected by other authors where they found that sensitivity and specificity of DCS were 69.4 and 100%, respectively, and those of tophi were 66.1 and 100%, respectively. The sensitivity of DCS in our study and the similar one was low than previous studies [12].

Table 4: Values of sonographic signs in diagnosing gouty arthritis

Sonographic signs	Sensitivity (%)	Specificit (%)	PPV (%)	NPV (%)
DCS in any joints				
All gout patient (*n*=60)	70	96.6	97.7	61.7
HSUA subgroup (*n*=39)	92.9	96.6	97.2	90.6
LSUA subgroup (*n*=21)	28.5	96.6	85.7	65.9
Tophi in any joints				
All patients with gout (*n*=60)	50	93.3	93.7	75.6
HSUA subgroup (*n*=39)	48.71	93.3	90	71.8
LSUA subgroup (*n*=21)	52.3	93.3	84.6	73.6
Tophi and erosion in any joints				
All patients with gout (*n*=60)	60	93.3	94.7	75
HSUA subgroup (*n*=39)	64.1	93.3	92.3	54.5
LSUA subgroup (*n*=21)	66.6	93.3	86.6	69.2

DCS, double contour sign; HSUA, high serum uric acid; LSUA, low serum uric acid; NPV, negative predictive value; PPV, positive predictive value.

This can be explained by presence of high mean SUA levels (11.2 mg/dl) compared with our study where mean SUA was 8.84 mg/dl and also asymptomatic joints were not examined in their study. Interestingly, DCS was detected in 92.3% of HSUA subgroup in our study. Similar findings to our results were detected by other authors in the HSUA subgroup. Mean SUA was 8.7 mg/dl, and DCS was detected in 95.2% of them. This is an indirect evidence that persistence of HSUA results in occurrence of DCS and tophi in and around the joints [12].

Filippucci *et al.* [22] reported a sensitivity of 43.7% for the DCS in 32 gouty knee joints. The sensitivity is high compared with our study where DCS was detected in 31 gouty knee joints in 17 patients with sensitivity of 28.3%, and also was detected in 68 gouty first MTPJs in 38 patients with sensitivity of 63.3%. This result may be owing to precipitation of more MSU crystal at first MTPJs in Egyptian patients with gout.

In addition to joint site differences, the severity and duration of hyperuricemia may affect the sensitivity of the DCS because more MSU crystal deposition occurs in advanced gout and long disease duration as found in our study. These results were in agreement with the study of Ogdie *et al*. [23], where US was performed in 824 patients (416 cases and 408 controls). The sensitivity, specificity, positive predictive value, and negative predictive value for the presence of any one of the features were 76.9, 84.3, 83.3, and 78.1%, respectively. Sensitivity was higher among patients with disease more than or equal to 2 years duration and among patients with subcutaneous nodules on examination (suspected tophus).

Patients with LSUA were detected in 35% of patients with gout in our study. The overall sensitivity of DCS is lower than same previous studies, which may be owing to the presence of DCS even in this group who maintained LSUA levels (as a result of urate-lowering therapy) for at least 6 months. Similar results were noted by other authors where they detect LSUA in 30% of patients with gout [12].

This observation supports the finding of a previous study that noticed maintaining SUA level less than 6 mg/dl causes disappearance of DCS which takes 8–18 months after sustained normouricemia is achieved, as observed by Thiele and colleagues in three patients. However, serial MSUS examination at regular intervals were not done in that study to detect the exact time taken for dissolution of crystals from articular cartilage [10].

Furthermore, the presence of tophi in 52.3% of our patients in the LSUA group as a result of urate-lowering therapy compared with the presence of DCS, which was only in 28.5%, suggests that dissolution of tophi takes longer than of DCS. Similar results were detected by Shyamashis *et al*. [12] who found the presence of tophi in 50% of patients with LSUA group compared with the presence of DCS, which was only in 5%.

The presence of erosions and tophi in patients at the intercritical phase even with LSUA means continuous precipitation of MSU crystal at first MTPJs and knee joints. There is great need to continue medication to prevent joint damage.

In our study, we did US assessment of first MTPJs and knee joints bilaterally irrespective of their clinical involvement, as US features of gout have been demonstrated frequently in these joints in the literature, and these in clinical practice would be time efficient [24]. Naredo *et al*. [25] reported that bilateral examination of combination of one joint (radiocarpal joint), two tendons (patellar and triceps), and three articular cartilages (first MTP, talar and second metacarpal/femoral) showed best balance between sensitivity and specificity. However, examination of 12 areas would certainly be more time consuming. There is still no consensus on how many joints to scan for gout diagnosis.

Our recommendation is that a follow-up serial US is needed to detect the time period required for disappearance of DCS and even tophi after urate-lowering therapy and advise patients to avoid stopping of treatment even after improvement to protect joints from erosion.

Conclusion

In conclusion, MSUS is an easy and safe radiological tool and is useful for confirmation of gout in intercritical or chronic stages, where clinical diagnosis is sometimes more difficult than the acute stage. US signs of gout have good sensitivity and specificity, especially in patients with elevated SUA and also correlated with long disease duration.

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Conflicts of interest

There are no conflicts of interest.

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