The Egyptian Rheumatologist (2013) 35, 71–75

Egyptian Society for Joint Diseases and Arthritis

The Egyptian Rheumatologist

www.rheumatology.eg.net
www.sciencedirect.com

ORIGINAL ARTICLE

Role of diagnostic ultrasonography in detecting gouty arthritis

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Received 14 October 2012; accepted 10 December 2012
Available online 29 January 2013

KEYWORDS
Gouty arthritis;
Hyperuricemia;
Ultrasonography;
Double contour sign

Abstract *Introduction:* Gout is a form of inflammatory arthritis that is characterized by attacks of active synovitis related to the presence of monosodium urate (MSU) crystals in the joints and periarticular soft tissues.

Aim of the work: To establish the usefulness of ultrasonography (US) in diagnosing subclinical gouty arthritis and to determine whether there are sonographic features that are characteristic of gout.

Patients and methods: We studied 20 patients known to be gouty (group 1), 20 patients with asymptomatic hyperuricemia (AH) (group 2) and 20 controls (group 3) in a cross sectional study. Demographic, clinical and serological data were evaluated. Knee and 1st MTP joints were assessed by musculoskeletal (US) to detect subclinical gouty arthritis.

Results: Clinical gouty arthritis was found in only (20%) in (group 1), but subclinical gouty arthritis had been found in (75%) in (group1) and (25%) in (group 2). There were statistically significant differences between the examined groups regarding the presence of double contour (DC) sign ($p < 0.001$), joint effusion ($p = 0.04$), serum uric acid (SUA) level ($p < 0.001$), diuretics use ($p < 0.001$), allopurinol use ($p < 0.001$), also it was found that only SUA was the risk factor for the occurrence of the double contour (DC) sign ($p = 0.03$) and cut-off value of SUA was 9.1 mg/dl above which DC sign was detected.

Conclusion: Ultrasonography (US) is a useful tool to detect subclinical gouty arthritis; also serves as a non-invasive, bedside and non-ionizing tool.

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Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.

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1. Introduction

Gout is one of the commonest forms of inflammatory arthritis. The prevalence appears to be rapidly increasing worldwide [1]. It is mediated by the crystallization of uric acid within the joints [2]. Urate crystals are deposited predominantly in the

1110-1164
http://dx.doi.org/10.1016/j.ejr.2012.12.003

superficial portions of the articular cartilage. These characteristic cartilaginous deposits are not readily demonstrated with conventional diagnostic imaging including roentgenography, computed tomography (CT) or magnetic resonance imaging (MRI) [3].

Gout occurs when too much uric acid builds up in the blood and uric acid crystals precipitate in the cooler parts of the body such as the joints of the feet. High levels of uric acid may also build up as lumps under the skin called tophi or as kidney stones. Uric acid is a waste product of the oxidation of purines which are constituents of nucleic acids such as DNA. Uric acid is normally excreted in the urine to maintain a concentration of uric acid in the blood of approximately 4 mg/dl. When the concentration exceeds 7 mg/dl, crystals of monosodium urate start to form in the tissues. This condition is known as hyperuricemia [4].

Several British and American surveys have estimated the prevalence of gout to be 2.6–8.4 per 1000 in adults, with the prevalence increasing with age to rates of 24 per 1000 in men and 16 per 1000 in women aged 65–74 years. Gout has a predilection for the first metatarsophalangeal joint (1st MTPJ), with as many as 50–70% of first gout attacks occurring here [5].

The National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2008 showed a hyperuricemia (serum urate $\geqslant$7 mg/dl) prevalence of 21.1% in men and 4.7% in women [6]. Most individuals with hyperuricemia, however, do not develop gouty arthritis [7]. The reported gouty arthritis prevalence in the 2007 to 2008 NHANES data was 5.9% in men and 2% in women, with an overall prevalence of 3.9% (8.3 million adults) [6]. The risk of developing gouty arthritis is dependent on the severity of hyperuricemia. In the Normative Aging Study, healthy patients with serum urate levels $\geqslant$9 mg/dl upon entry into the study had a cumulative incidence of acute flares that reached 22% after 5 years, whereas those with serum urate levels $\leqslant$7 mg/dl had an annual incidence of only 0.5% [8]. In another study, the 5-year prevalence of gouty arthritis was 30% in individuals with serum urate levels $>$10 g/dl [9].

In patients with the very first manifestations of gout, no radiographic findings are present but for an increase in the soft tissues. Typical plain radiographic features of chronic gout [10] include visualization of tophi as soft-tissue or intraosseous masses, and the presence of a nondemineralizing erosive arthropathy with erosions that are well defined with sclerotic or overhanging margins [11].

The joint space is usually preserved until late in the disease and other features such as periosteal new bone formation, extra-articular erosions, intraosseous calcifications, joint space widening and subchondral collapse may be present [12–14]. Radiographic abnormalities are most frequently present in the feet, particularly in the first metatarsal phalangeal joint. Radiographic damage is a late feature of chronic gout, typically occurring 15 years after the onset of the disease, and is virtually always present in patients with subcutaneous tophi [14].

Over the past several years, there has been a growing interest in musculoskeletal ultrasound (US) in rheumatology. US visualizes tissues as acoustic reflections. Crystalline material reflects US waves more strongly than the surrounding tissues, such as unmineralized hyaline cartilage or synovial fluid. This enables distinction of monosodium urate (MSU) crystal deposition from the less echogenic surrounding soft tissues. MSU crystals are found in the cartilage, tendon sheaths, synovial fluid and subcutaneous tissue. US detects deposition of MSU crystals on cartilaginous surfaces, as well as tophaceous material and typical erosions. A hyperechoic, irregular band over the superficial margin of the articular cartilage, described as a double contour sign or icing, is found exclusively in gouty arthritis [3] and represents crystalline precipitates of MSU. In addition, the presence of hypoechoic to hyperechoic inhomogeneous material surrounded by a small anechoic rim, representing tophaceous material and erosions adjacent to tophaceous material on US, are suggestive of the diagnosis of gouty arthritis. US is superior in detecting changes of gouty arthritis compared with other imaging modalities (magnetic resonance imaging, plain X-ray scans, computed tomography and three-dimensional rendering imaging) [15].

In contrast to gout, calcium pyrophosphate crystals tend to aggregate in the centre of both hyaline and fibrous cartilage. In the hyaline cartilage, this material forms a layer that parallels the bony cortex. Sonographically this appears as a hyperechoic, irregular line embedded in anechoic appearing hyaline cartilage. Chondrocalcinosis can thus be readily distinguished from gout [16,17].

Recent studies into the pathophysiology of acute gout have revealed that MSU, the crystalline form of uric acid, is recognized by immune cells as a danger signal and can initiate an inflammatory response. This response is orchestrated by the intracellular pattern-recognition receptor NLRP3, which upon exposure to MSU, forms a cytosolic multiprotein-complex called the inflammasome, leading to the activation of caspase-1. Caspase-1 then cleaves the highly pro-inflammatory cytokines interleukin (IL)-1β and IL-18, leading to the secretion of their biologically active forms and culminating in an acute gouty attack [18].Aim of the present study was to evaluate the diagnostic capability of ultrasonography in detecting the subclinical gouty arthritis as a safe, easy and bedside diagnostic tool.

2. Patients and methods

2.1. Patients

Forty male patients were consecutively recruited from the Rheumatology department, Cairo and Fayoum University hospitals. Half of them were fulfilling the ACR diagnostic criteria of gout [19], none of them had chronic tophaceous gout and the other 50% had asymptomatic hyperuricemia (AH) only, also 20 controls with matched age and sex were enrolled.

All subjects were asked to complete a questionnaire on demographics and medication use. Serum uric acid was assessed for all subjects.

Subjects were categorized as belonging to 1 of 3 groups: (1) gout (those meeting ACR clinical criteria), (2) AH (no gout per ACR clinical criteria, UA level $\geqslant$6.9 mg/dl), and (3) control (no gout, UA level $\leqslant$6.8 mg/dl). Informed consents were taken from the patients and the study was approved by the local ethics committee.

2.2. Exclusion criteria

1. Rheumatoid arthritis.
2. Seronegative spondyloarthritis.
3. Pseudo gout.

4. Hemochromatosis.
5. History of severe trauma to the affected joint.
6. Malignancy.

2.3. US interpretation

All subjects subsequently underwent a structural musculoskeletal US evaluation of both knee joints (transverse suprapatellar view of the femoral cartilage in maximal flexion) and both 1st MTP joints (longitudinal dorsal and medial views) using a 12.5 MHz linear probe (Philips-ATL®, HDI 5000, Philips®, Bothell, WA, USA).

US definitions described by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Special Interest Group were adopted for the study. Joint effusion was recorded when anechoic or hypoechoic joint cavity widening was detected, while synovial hypertrophy was recognized as the presence of abnormal hypoechoic or hyperechoic tissue within the joint cavity. Additionally, hyperechoic enhancement of the superficial margin of the hyaline cartilage was regarded as a surrogate of MSU crystal deposition (double contour sign), whereas inhomogeneous tendon and/or entheseal thickening and intratendinous hyperechoic bands defined the presence of enthesopathy or tendinopathy. Erosion was defined as a definite cortical interruption with a step-down contour defect in both longitudinal and transverse views [20].

Statistical analysis: Computer software package SPSS 15 was used in the analysis, for quantitative variables, mean (as a measure of central tendency), standard deviation (as measure of variability) were presented. Frequencies and percentages were presented for qualitative variables. ANOVA test was used to estimate differences in quantitative variables. Chi-square and Fisher-exact tests were used to estimate differences in qualitative variables. Logistic regression analysis was used, *P* Value < 0.05 is significant [21].

3. Results

Twenty male patients known to be gouty were examined in the current study, with a mean age of 58.6 ± 7.9 years and mean disease duration of 6.4 ± 2.3 years as well as 20 male patients with asymptomatic hyperuricemia (AH) with a mean age of 59.5 ± 6.7 years and 20 controls with matched age and sex with a mean age of 57.4 ± 6.2 years as shown in Table 1.

All of enrolled subjects gave history of knee osteoarthritis, but clinically they had crepitus only, none of our patients had tophi, renal stones or nephropathy, but five swollen and tender 1st MTP joints were found in 4/20 (20%) of patients in (group 1) and absent in (group 2 and 3); but musculoskeletal US examination revealed MSU deposition in 15/20 (75%) of patients in (group 1) and 5/20 (25%) in (group 2). X-ray examination of the affected joints revealed no specific radiographic findings for gouty arthritis except a mild increase in the soft tissues in 1st MTP joint as shown in Fig. 1.

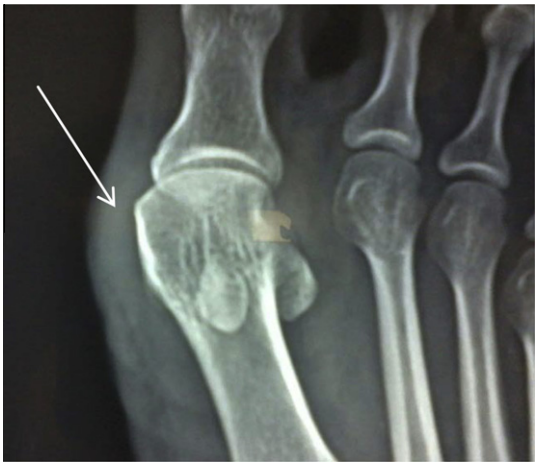

Figure 1 Plain X-ray of the left foot showing soft tissue edema of the first metatarsophalangeal joint (white arrow).

Table 1 Demographics, clinical and laboratory data and management strategy of the study groups.

	Gouty patients (group 1) (20 patients)	AH patients (group 2) (20 patients)	Control group (group 3) (20 subjects)	*P* value
Clinical and demographic data				
Age (mean ± SD)	58.6 ± 7.9	59.5 ± 6.7	57.4 ± 6.2	0.6
Arthritis in 1st MTP joints No. (%)	5/40 (12.5%)	0 (0%)	0 (0%)	0.3
Laboratory data				
SUA (mean ± SD)	11.3 ± 1.8	8.3 ± 1.5	4.5 ± 0.9	$< 0.001^{**}$
Serum creatinine (mean ± SD) (mg/dl)	0.7 ± 0.3	0.6 ± 0.2	0.4 ± 0.2	0.4
Ultrasonography data				
No. (%) of patients with double contour sign.	15 (75%)	5 (25%)	0 (0%)	$< 0.001^{**}$
No. (%)of patients with joint effusion	9 (45%)	3 (15%)	0 (0%)	0.04^{*}
Treatment received				
No. (%)of patients on diuretics	12 (60%)	4 (20%)	2 (10%)	0.001^{**}
No. (%)of patients on allopurinol	12 (60%)	3 (15%)	0 (0%)	0.001^{**}
No. (%) of patients on colchicine	13 (65%)	7 (35%)	0 (0%)	0.06

1st MTP: first metatarsophalangeal, SUA: serum uric acid.
* Significantly different at $p < 0.05$.
** Is significantly different at $p < 0.001$.

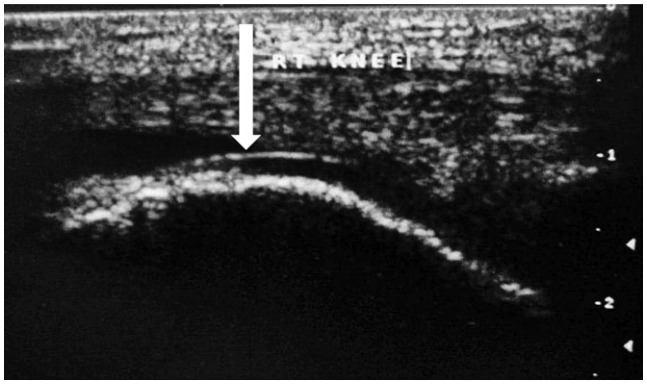

Figure 2 US longitudinal view of the knee joint; showing the double contour (DC) sign (white arrow).

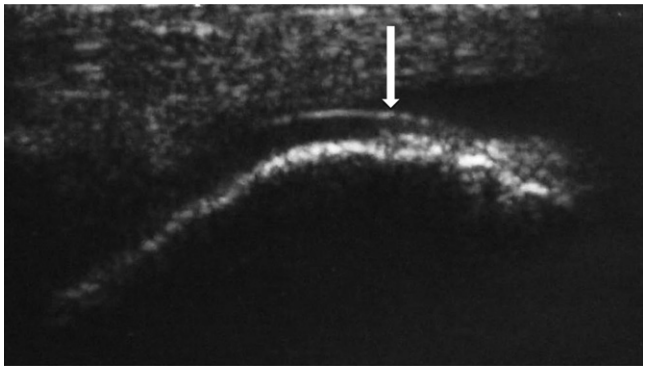

Figure 3 US longitudinal view of the knee joint; showing the double contour (DC) sign (white arrow).

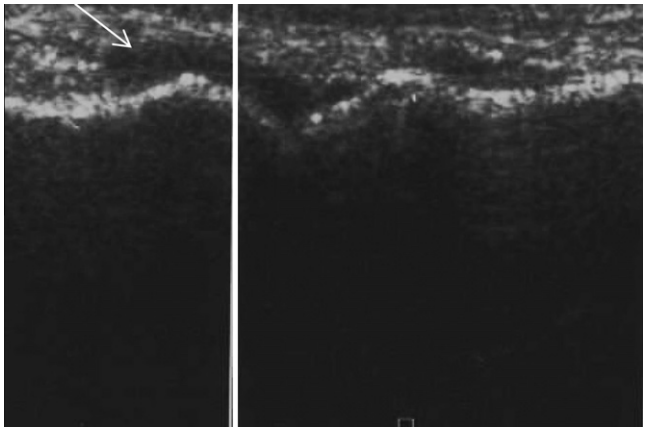

Figure 4 US longitudinal view of first metatarsophalangeal joint; showing joint effusion (white arrow).

Double contour sign as shown in Figs. 2 and 3 and effusion as shown in Fig. 4 were detected by US and the results were shown in Table 1, but neither joint erosion nor tophi were detected by US. Also it was found that, the cut-off value for SUA above which the DC sign was detected was 9.1 mg/dl. On correlating the presence of the double contour sign to age, SUA and intake of diuretics, it was found that only SUA was the risk factor of the occurrence of the double contour sign as shown in Table 2. Also SUA level was significantly higher in patients with AH with DC sign in relation to patients with AH and without DC sign (10.5 ± 1.3 mg/dl and 7.6 ± 0.6 mg/dl, respectively) ($p = 0.005$).

Table 2 Shows that serum uric acid is the only risk factor for occurrence of DC sign.

	P value	Odds ratio	95.0% C.I.
Age	0.6	1.1	
SUA	0.03*	11.6	0.9–1.3
Diuretics intake	0.7	1.8	

* Significantly different at $p < 0.05$.

4. Discussion

In the present study clinical gouty arthritis was found in (20%) of patients known to be gouty and absent in patients with AH; but musculoskeletal US examination revealed DC sign in (75%) of gouty patients and in (25%) of patients with AH who showed significantly higher SUA level; this matched the results of Puig et al. (2008), who examined lower extremity joints of AH patients by US and found DC sign in the knee hyaline cartilage and the first metatarsophalangeals, also emphasized that US changes suggestive of gouty arthritis were found in 25% of hyperuricemic individuals. These changes were found exclusively in the hyperuricemic individuals but not in their control group of normouricemic individuals [22]. Also the results in the present study coincides with the results of a previous study that enrolled 50 male subjects, their knee and 1st MTP joints were assessed by musculoskeletal ultrasound to detect the "double contour" sign as an evidence of MSU crystal deposition. They found the DC sign in 29% of AH subjects [23].

We found the double contour sign exclusively in patients with hyperuricemia especially with SUA level $\geqslant 9.1$ mg/dl ($P < 0.001$). This band had a slightly irregular surface; that was not seen in control patients. This sonographic finding was consistent with older histopathological studies that showed a particular predilection for uric acid to crystallize on the surface of the hyaline cartilage [3]. This could be explained by the fact that; chondroitin sulphates and phosphatidylcholine, constituents of the hyaline cartilage, have been reported to foster crystallization of uric acid in vitro [24].

The results of Neogi (2008), emphasized upon the usefulness of urate-lowering treatment in patients with clinical manifestations of hyperuricemia such as gouty arthritis, but in patients with AH it is still the object of several controversies [25]. This could in part be related to the limited evidence about the subclinical musculoskeletal involvement in asymptomatic individuals with hyperuricemia [26]. In the present study, US detected double contour sign and joint effusion in cases of AH, this may increase the need for use of the urate lowering therapy in this group of patients.

Double contour sign represents SUA crystal deposition in the hyaline cartilages [24]. As confirmation of the presence of MSU in the hyaline cartilage, Thiele and Schlesinger (2010), demonstrated the disappearance of the double contour sign in patients with gout successfully treated with urate-lowering

agents who had maintained SUA levels below 6 mg/dl for at least 7 months [27]. This may strengthen the need for treatment necessity in asymptomatic individuals with hyperuricemia and indisputable US features of MSU crystal tissue deposition such as the double contour sign or the presence of tophi [25].

In the current work diagnostic US detected double contour sign in (75%) and in (25%) of gouty arthritis and AH patients respectively, which was highly suggestive for the articular deposition of monosodium urate crystals, depending on the results of Wright et al. (2007) and Gutierrez et al. (2009), who emphasized that double contour sign had been described solely in gout [28,29]. Despite the fact that; demonstrating the presence of MSU crystals in aspirated joint fluid or tophus is considered the gold standard [30].

In conclusion; ultrasonography which is bedside, easy and a safe radiological tool, can detect MSU deposition in patients with AH, which necessitates the use of urate lowering drugs.

5. Conflict of Interest

The authors have no conflict of interest.

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