Musculoskeletal ultrasonographic assessment of asymptomatic hyperuricemic Egyptian individuals
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Background
Asymptomatic hyperuricemic individuals are discovered accidently on the basis of elevated levels of serum urate. The established use of urate-lowering treatment in patients with gouty arthritis is well documented; however, it is still an issue of research and controversy in individuals with asymptomatic hyperuricemia. Therefore, many attempts have been made to study the influence of asymptomatic hyperuricemia on different musculoskeletal organs.

Objectives
The aim of this study was to view the ultrasonographic musculoskeletal changes in asymptomatic hyperuricemic individuals and to compare them with the findings in normal controls.

Methods
Bilateral ultrasonographic examinations of the first metatarsal–phalangeal joints, ankles and knees, as well as of the related tendons and enthesis of the lower limbs, for 40 asymptomatic hyperuricemic individuals and 40 normal controls, were performed.

Results
A double contour sign was found at the first metatarsal–phalangeal joint in 45% of joints of hyperuricemic individuals but was absent in controls ($P<0.001$). It was also found in the femoral cartilage in 15% of knees of hyperuricemic individuals but was absent in controls ($P<0.0001$). Patellar tendenopathy was recorded in 6.25% of tendons. Intratendinous tophi were significantly reported in the patellar and Achilles tendons of patients. Achilles enthesopathy was reported in 18.75% of tendons of patients compared with 2.5% of tendons of controls ($P<0.001$). Intra-articular tophi were reported in 16 ankle joints (20%) of hyperuricemic individuals but were absent in controls ($P<0.001$).

Conclusion
Musculoskeletal ultrasonography of asymptomatic hyperuricemic individuals helps identify morphostructural changes suggestive of gouty arthritis induced by chronic hyperuricemia occurring in both intra-articular and extra-articular structures.

Keywords:
asymptomatic hyperuricemia, double contour sign, enthesopathy musculoskeletal ultrasonography, tophi

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of asymptomatic hyperuricemia on different musculoskeletal organs.

The best imaging method to investigate MSU crystal deposits during the early stages of gouty arthritis and to diagnose individuals with asymptomatic hyperuricemia has not yet been established [6]; however, ultrasound (US) has been demonstrated to be a valid imaging modality to detect musculoskeletal involvement [7]. The main US findings related to MSU crystal deposition are the appearance of hyperechoic enhancements on the superficial margin of the hyaline cartilage, known as a double contour sign, the appearance of hyperechoic spots within tendons and soft tissues, and the presence of tophi and bone erosions [8]. In addition, an increase in blood flow surrounding the MSU deposits detected by power Doppler has been described as an indicator for inflammatory activity [6,8]. Moreover, in cases of erosive arthropathies, a musculoskeletal US has been shown to confirm early structural tissue damage [9].

**Aim of the work**
The aim of this study was to assess the different musculoskeletal US findings in individuals with asymptomatic hyperuricemia and to compare them with the findings in normouricemic individuals.

**Patients and methods**

**Patients**
This study included 40 individuals who were referred to the outpatient clinic of the Department of Rheumatology and Physical Medicine and Rehabilitation, Ain Shams University hospitals, from different clinics in the hospitals for further assessment. These patients did not show symptoms of gout or any musculoskeletal symptom but showed SUA concentrations of 7.0 mg/dl or higher on at least two occasions within the past 6 months. The study also included 40 healthy control individuals who were volunteers from our hospital staff.

**Exclusion criteria**
Individuals aged less than 18 years; those having diabetes, hypertension, renal disease, urate stones, malignancies, and concomitant rheumatic disease; those on urate-lowering drugs, NSAIDS, and corticosteroids; and pregnant women were excluded from this study.

Both the hyperuricemic individuals and controls were informed about the nature of the study and consent was obtained.

**Methodology**
(1) Clinical and laboratory assessment for all individuals included:
   (a) History taking, especially for a previous gouty attack (e.g. podagra) and for the occurrence of musculoskeletal symptoms (such as joint swelling, hotness, and redness).

(b) Full musculoskeletal examination to record the presence of joint swelling and tenderness, the range of motion, contracture, or the presence of skin lesions (cutaneous tophi) at the corresponding areas of the studied joints to confirm the absence of musculoskeletal involvement.

(c) Assessment of BMI

(d) Venipuncture to collect a venous blood sample of 15–20 ml from the cephalic vein of the left or right arm, no longer than 3 days before US evaluation, for measuring levels of SUA and serum triglycerides (TG) and evaluating the lipid profile.

(e) Musculoskeletal US evaluation. This was performed in both the asymptomatic hyperuricemic group, which was devoid of any clinical evidence of arthritis or enthesopathy, and the normouricemic control group.

(2) US assessment was performed using Philips Apparatus (Phillips HD 11, France) equipped with a 9–12 MHz broadband linear transducer.

All hyperuricemic individuals and controls were examined and scanned by two expert musculoskeletal radiologists and by two rheumatologists (to minimize the interobserver error). The representative ultrasonographic images were acquired, stored, digitally recorded, and electronically filed for each patient using a standardized offline form.

Musculoskeletal US examinations were performed in accordance with the European League Against Rheumatism guidelines [10].

The following areas were scanned bilaterally:
(1) The knee (the proximal and distal patellar tendon insertions and the femoral hyaline cartilage).
(2) The ankle (the tibialis posterior, peroneus longus, brevis, and Achilles tendons and the tibiotalar joint).
(3) The first metatarsal–phalangeal (MTP) joints (the synovial membrane and hyaline cartilage).

Dynamic US examination with flexion and extension was performed for the mentioned joints to investigate parts of the cartilage. Each area was scanned in a grayscale mode to detect any morphostructural changes, and subsequently, the power Doppler technique was used to detect any abnormal blood flow, with special attention to avoid compression of the blood vessels by the pressure of the transducer.

The observations from US examination were as follows:
(1) Joint effusion was recorded when anechoic or hypoechoic joint cavity widening was detected [on a scale of 1–3 (mild, moderate, or severe)].
(2) Synovial hypertrophy was detected as the presence of abnormal hypoechoic or hyperechoic tissue intra-articularly inside the joint cavity.
(3) Enhancement of the hyperechoic superficial margin of the hyaline cartilage, also known as a double...
Table 1 Demographic data of all studied individuals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperuricemic (N=40)</th>
<th>Normouricemic (N=40)</th>
<th>P</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(25–56) 48.5 ± 15.3</td>
<td>(23–58) 51.7 ± 8.3</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>(29–40) 34.7 ± 4.6</td>
<td>(25–32) 28.8 ± 3.6</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

NS, nonsignificant; S, significant.

Table 2 Comparison between the hyperuricemic individuals and controls as regards sex distribution

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperuricemic (N=40) [N (%)]</th>
<th>Normouricemic (N=40) [N (%)]</th>
<th>Z</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27 (75.5)</td>
<td>25 (78.5)</td>
<td>1.002</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>13 (25.0)</td>
<td>15 (12.5)</td>
<td>1.003</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, nonsignificant.

The hyperuricemic group consisted of 27 men (75%) and 13 women (25%), with a mean age of 48.5 ± 15.3 SD, and the normouricemic control group comprised 25 men (78%) and 15 women (12.5%), with a mean age of 51.7 ± 8.3, which was statistically insignificant between the two groups. The BMI of the hyperuricemic group ranged from 29 to 40, with a mean of 34.7 ± 4.6 SD, and that of control group ranged from 25 to 32, with a mean of 28.8 ± 3.6 SD, which showed a significant difference (Tables 1 and 2).

The SUA levels of the 40 asymptomatic hyperuricemic individuals were 7 mg/dl or higher, with a range of 7.1–8.8 mg/dl and a mean value of 7.1 ± 2.7 SD, whereas those of the 40 controls showed a range of 4.4–5.6 mg/dl, with a mean value of 4.71 ± 0.9 SD, which showed a highly significant difference. The other laboratory data of the patients (triglyceride, low-density lipoprotein, and cholesterol levels) showed higher values compared with controls, with a highly significant difference (Table 3).

The bilaterally examined joints in 40 individuals with asymptomatic hyperuricemia and 40 normouricemic control individuals included both first MTP joints, both ankle joints, and both knee joints.

US examination of the 80 MTP joints of asymptomatic hyperuricemic individuals revealed the presence of joint cavity widening in 36 joints (45%) in the form of synovial hypertrophy and in 20 joints (25%) in the form of synovial effusion. These percentages were compared with those obtained for the 80 MTP joints of normouricemic controls: joint cavity widening was observed in 10 joints (12.5%) in the form of synovial hypertrophy and in five joints (6.25%) in the form of synovial effusion, with a P-value of less than 0.05 indicating a significant difference in favor of asymptomatic hyperuricemic individuals. Bone erosions were present in one MTP joint (1.25%) of an asymptomatic hyperuricemic individual but were absent in normouricemic controls, with a P-value of more than 0.05 indicating a nonsignificant difference. A hyaline cartilage double contour sign denoting an aggregation of MSU crystals was reported in 16 joints (20%) of asymptomatic hyperuricemic individuals but was absent in normouricemic controls, with a P-value of less than 0.001 denoting a highly significant difference (Table 4 and Figs 1 and 2).

US examination of 80 ankle joints revealed synovial tissue hypertrophy in the form of synovial cavity widening in 20 joints (25%) of individuals with asymptomatic hyperuricemia but in only two joints (2.5%) of normouricemic controls, which was a highly significant difference. Bone erosions were not detected in any group. Tophi were observed in 20 joints (25%) of individuals with asymptomatic hyperuricemia but were absent in normouricemic controls, with a P-value of less than 0.001 denoting a highly significant difference (Table 5 and Figs 3 and 4).

US examination of 80 knee joints revealed synovial tissue hypertrophy in the form of synovial cavity widening in 10 joints (12.5%) of individuals with asymptomatic hyperuricemia but only in four joints (5%) normouricemic controls, which showed a nonsignificant difference. Bone erosions were not detected in any group. A femoral...
Hyaline cartilage double contour sign denoting aggregation of MSU crystals was reported in 12 of 80 asymptomatic hyperuricemic knees (15%) but was absent in the control group, with a value *P*-value of less than 0.0001, which was highly significant (Table 6 and Figs 5 and 6).

Musculoskeletal US examination of the related tendons around the examined knees, ankles, and first MTP joints of asymptomatic hyperuricemic and normouricemic individuals involved in our study revealed the presence of patellar tendenopathy in five tendons (6.25%), posterior tibial tendenopathy in 10 tendons (12.5%), and peroneal tendenopathy in three tendons (3.75%). However, Achilles enthesisopathy was observed in 15 tendons (18.75%) of individuals with asymptomatic hyperuricemia and in three (3.75%) tendons of normouricemic controls. The values in the normouricemic control group were 0 (0%), 0 (0%), and 2 (2.5%), respectively, with a nonsignificant difference for the patellar tendon, a significant difference for the peroneal tendon, and a highly significant difference for both the posterior tibial and Achilles tendons, in favor of asymptomatic hyperuricemic individuals as shown in (Table 7) and (Fig. 7).

Intratendinous tophi were observed in three (3.75%) patellar, 10 (12.5%) posterior tibial, one (1.25%) peroneal, and five (6.25%) Achilles tendons of asymptomatic hyperuricemic individuals but were not detected in normouricemic controls, showing a significant difference for the patellar, posterior tibial, and Achilles tendons and a nonsignificant difference for the peroneal tendon (Table 7 and Figs 8 and 9).

US assessment of the examined joints using the power Doppler did not show any increase in the vascular markings.

**Discussion**

Gout is a common form of arthritis caused by deposition of MSU crystals within joints secondary to chronic elevated hyperuricemia. Patients with acute gout experience significant pain and swelling that can severely impair their quality of life. Definitive diagnosis of gout requires microscopic identification of MSU crystals in aspirated synovial fluid/tophaceous samples [4]. The presence of MSU crystals in the synovial fluid of asymptomatic individuals with hyperuricemia was first demonstrated in the early 1980s using polarized light microscopy [5].

The incidence of hyperuricemia has been increasing over the past few decades in response to a number of factors...
such as a high purine diet, obesity, diabetes, alcohol use, and kidney disease [11].

Hyperuricemia and blood lipid abnormalities are positively correlated [12]. In our study, there was a significant difference between hyperuricemic individuals and normouricemic controls as regards the SUA, triglyceride, low-density lipoprotein, and cholesterol levels.

Hyperuricemia is also known to be associated with obesity and metabolic syndrome. In this study, the mean BMI of our 40 asymptomatic hyperuricemic patients was 34.7 ± 4.6, with a range of 29–40, which is considered to be an indication of overweight and obesity. This is in agreement with the results of an Indian study that reported a BMI in the range of 28–35 in the studied hyperuricemic patients, indicating that the Indian obese population has a significantly high prevalence of hyperuricemia [13].

Chronically elevated SUA levels were reported by large prospective population studies to be a predictor for renal

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Table 5 Comparison between asymptomatic hyperuricemic individuals and normouricemic controls as regards musculoskeletal findings at the ankle joints

<table>
<thead>
<tr>
<th>Variant</th>
<th>Hyperuricemic</th>
<th>Normouricemic</th>
<th>Z</th>
<th>P</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial hypertrophy</td>
<td>80 (20)</td>
<td>80 (2)</td>
<td>4.132</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>Bone erosion</td>
<td>80 (0)</td>
<td>80 (0)</td>
<td>0</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Tophi</td>
<td>80 (20)</td>
<td>80 (0)</td>
<td>4.781</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

HS, highly significant; NS, nonsignificant.

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Figure 2

Synovial thickening of the first metatarsophalangeal joint (a, b) with tiny erosions (a, white arrow).

Figure 3

Comparison between the hyperuricemic and normouricemic groups as regards the frequency of pathological musculoskeletal ultrasonographic findings at the ankle joint.

Figure 4

Tophi, a soft-tissue swelling with hyperechoic foci on the medial side of the ankle joint without signs of arthritis.
failure [2], coronary artery disease [14,15], and progression of endothelial dysfunction [16].

As a result of this global problem, it is important to establish the wide use of safe, inexpensive, and effective approaches to diagnose and thus prevent and treat gout worldwide [7,8].

Recently, US has been shown to be valuable in detecting subclinical joint and tendon inflammation in inflammatory conditions such as arthritis [17], psoriasis [18], and Sjogren syndrome [19]. The ability of US to identify the involvement of the hyaline cartilage, small joints, and tendons in individuals with asymptomatic hyperuricemia, with no signs of inflammation or musculoskeletal complaints, has been improved. The double contour sign has been shown to be a specific feature of gout [8] and seems to represent the preference of MSU to crystallize on the surface of cartilage, as the normal components of cartilage namely chondroitin sulfate and phosphatidylcholine could facilitate the nucleation and subsequent crystallization of MSU [20]. The disappearance of this double contour sign in patients with gout after sustained normouricemia is achieved using urate-lowering agents was reported recently using US techniques [21].

Our present study aimed to demonstrate a wide spectrum of US changes in asymptomatic individuals with hyperuricemia. We extended the US evaluation to additional sites (polyarticular US) characteristically involved in gout, such as the femoral hyaline cartilage, MTP joints, ankles, and Achilles tendons.

Our US studies on individuals with asymptomatic hyperuricemia have demonstrated clinically undetected synovial effusions of the first MTP joints in 25% of studied joints and synovial hypertrophy of the first MTP, ankle, and knee joints in 45, 25, and 12.5% of the studied joints, respectively. This is in agreement with the findings of Pineda et al. [22], who in their study on 100 asymptomatic hyperuricemic joints reported synovial hypertrophy of the first MTP and knee joints in 52 and 7% of joints, respectively.

In our study, a double contour sign was visualized in 16 and 12 joints (20 and 15%) of 80 examined first MTP and knee joints in asymptomatic hyperuricemic individuals, respectively, which is in agreement with the results of the study by Pineda et al. [22], who reported a double contour sign in 25 and 17% of their examined first MTP and knee joints, respectively. However, the double contour sign was observed most frequently at the first MTP joints (right 60 and left 68%) in the study by Roddy et al. [23], who used polyarticular sonography to assess gouty patients, which explains the higher detection rate of the double contour sign in their study.

Tophi formation was detected in our study in 25% of ankle joints of hyperuricemic individuals, which is in agreement with the results of a previous study by Puig et al. [6], who studied 35 patients with asymptomatic hyperuricemia and reported urate deposits (tophi) in the tendons and synovia of 12 patients (34%).

In our study, examination of the tendons revealed tenosynovitis in 6.25% of patellar, 12.5% of posterior tibial, and 3% of peroneal tendons, with Achilles enthesopathy in 18.75% of tendons, which is higher compared with the results of a previous study by Pineda et al. [22], who reported tenosynovitis in three hyperuricemic patients [in the peroneus longus tendon in two patients (2%) and in the posterior tibialis tendon in one patient (1%)] and Achilles enthesopathy in 15% of tendons. Intratendinous tophi were present in all the examined tendons. In our study, no power Doppler signal was detected in any anatomical area examined, which is in agreement with the results of the study by Pineda et al. [22].

All our US findings confirmed the presence of MSU crystal deposition in both intra-articular and extra-articular

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### Table 6 Comparison between asymptomatic hyperuricemic individuals and normouricemic controls as regards musculoskeletal findings at the knee joints

<table>
<thead>
<tr>
<th>Variant</th>
<th>Hyperuricemic</th>
<th>Normouricemic</th>
<th>Z</th>
<th>P</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial hypertrophy</td>
<td>80 (12.50)</td>
<td>80 (5)</td>
<td>1.679</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Bone erosion</td>
<td>80 (0)</td>
<td>80 (0)</td>
<td>0</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Double contour</td>
<td>80 (15)</td>
<td>80 (0)</td>
<td>3.602</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

HS, highly significant; NS, nonsignificant.
structures of asymptomatic hyperuricemic individuals. This may strengthen the need for development of a treatment protocol in asymptomatic hyperuricemic indi-

dividuals with definite US features of MSU crystal deposition such as a double contour sign or the presence of tophi [22]. The detection of double contour signs
at the first MTP joint and the knee, as well as tendinous tophaceous deposits, suggests that US might help to identify individuals with asymptomatic hyperuricemia at risk of developing gout [22,24]. This could be a topic for further research, and longitudinal follow-up studies to determine the predictive value of US in the development of established gout in previously asymptomatic hyperuricemic individuals should be carried out.

**Conclusion**

Musculoskeletal US of asymptomatic hyperuricemic individuals helps identify morphostructural changes suggestive of gouty arthritis induced by chronic hyperuricemia occurring in both intra-articular and extra-articular structures, such as synovial effusion, synovial hypertrophy, tophi (including intratendinous tophi), double contour signs, tendenopathy, and enthesisopathy.

**Acknowledgements**

**Conflicts of interest**

There are no conflicts of interest.

**References**

21. Thiele RG, Schlesinger N. Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheumatol Int 2010; 30:495–503.