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Role of Diagnostic Musculoskeletal Ultrasound in Assessment of Gouty Arthritis

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ABSTRACT

Background: Gout is a chronic heterogeneous disorder of urate metabolism results in deposition of monosodium urate crystals in the joints and soft tissues, with accompanying inflammation and degenerative consequences.

Aim of work: Assessment of the role of musculoskeletal ultrasound (MSUS) in detecting changes in gouty arthritis patients under anti hyperuricimic treatment. **Patients and methods:** 30 patients with gouty arthritis treated with febuxostat 80 mg once daily for 3 months and 20 (age, sex & body mass index "BMI") matched controls were included. Patients were assessed by clinical examination, pain by visual analogue scale (VAS), tenderness by Ritchie index, functionally assessed using lower extremity functional scale & examination of joint effusion and tophi by palpation. MSUS findings in knee and first metatarsophalangeal "1st MTP" joints of patients and controls were reported before and 3 months after treatment. **Results:** BMI mean in patients group was 28.18 ± 1.49 (25-31) and in controls was 27.67 ± 1.56 (25-31). VAS, tenderness & lower extremity functional scale in patients before treatment in knee & 1stMTP joints significantly improved after treatment ($p < 0.001$). There was a significant improvement in ESR, CRP, serum uric acid, double contour sign & knee effusion in patients after treatment compared to before treatment.

Conclusion: Ultrasonography can detect changes related to treatment of gout with febuxostat. Febuxostat is a safe and efficient anti hyperurecemic drug and is effective in treatment of gouty arthritis. Ultrasound is more sensitive in detecting findings & changes of disease than clinical examination.

Keywords: gout, ultrasonography, gouty arthritis, double contour sign, tophi, febuxostat.

INTRODUCTION

Gout is a chronic heterogeneous disorder of urate metabolism resulting in deposition of monosodium urate crystals in the joints and soft tissues, with accompanying inflammation and degenerative consequences. It is the most common form of inflammatory joint disease in men aged ≥ 40 years [(1)].

Gout is associated with group of conditions which may be characterized by an elevation of serum uric acid (usually), recurrent attacks (flares) of an acute inflammatory arthritis with monosodium urate crystals demonstrated in synovial fluid, bone and joint destruction in some cases and aggregates of uric acid crystals (tophi) in and around joints, soft tissues and various organs. Tophus in bone leading to erosions in some cases [(2)]. The primary goal in management of gout is reduction and maintenance of serum uric acid in a sub-saturating range (usually < 6.0 mg/dl). The two pharmacological methods currently employed for urate lowering in gout are reduction of urate production by use of the xanthine oxidase (XO) inhibitor (allopurinol) and enhancement of urinary uric acid excretion with a uricosuric agent [(3)].

Febuxostat is an orally-active, potent, non-purine, selective xanthine oxidase inhibitor. It is indicated in adults for the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred. Febuxostat 40-120 mg/day rapidly and sustainably reduces serum uric acid by 25-70% in uric acid underexcretors and overproducers [(4)].

Musculoskeletal Ultrasound (MSUS) has recently been identified as a promising new imaging modality for gout, which would help provide an early, non-invasive diagnostic tool. MSUS 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. Monosodium urate (MSU) crystals are found in the cartilage, tendon sheaths, synovial fluid and subcutaneous tissue. Ultrasound detects deposition of monosodium urate (MSU) crystals on cartilaginous surfaces, as well as tophaceous material and typical erosions [(5)].

The aim of this study was to assess the role of musculoskeletal ultrasound (MSUS) in detecting changes in gouty arthritis patients under antihyperuricimic treatment.

PATIENTS AND METHODS

This study included 30 patients with primary gout fulfilled "2015 Gout Classification Criteria: an American College of Rheumatology/European League against Rheumatism Collaborative Initiative" [(6)]. They were selected from the Outpatient Clinics of Physical Medicine, Rheumatology and Rehabilitation Department of Tanta University Hospitals. In addition to 20 apparently healthy volunteers with matched age,

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sex and BMI as a control group. All subjects were asked to complete a questionnaire on demographics and medication use and previous use of urate-lowering drugs. Allopurinol was the drug used by patients but it had been stopped more than one year before the time of study. Serum uric acid was assessed for all subjects. Patients with inflammatory arthritis, history of trauma, malignancy or secondary gout were excluded from the study. Laboratory assessment for exclusion of secondary gout before treatment: Complete Blood Count (CBC), Rheumatoid Factor (RF), Anti- Cyclic Citrullinated Peptide (ANTI-CCP) and Random blood sugar.

Ethical approval:

The study was approved by the Ethical committee of Tanta University Hospital. All patients gave their informed consent prior their inclusion in the study.

All patients were subjected to the following assessment before treatment with febuxostat 80 mg once daily for three months & NSAIDS. After treatment: complete history taking, clinical, functional, laboratory and ultrasonographic assessment were done. Clinical assessment of the patients was performed on knee and 1st MTP joints. Pain was evaluated using the Visual Analogue Scale (VAS) [(7)], assessment of tenderness by Ritchie index [(8)] and examination of joint effusion and tophi by palpation. Tenderness of both knee joints and 1st MTP joints was assessed according to Ritchie: grade 1, no tenderness; grade 2, patient complained of pain; grade 3, patient complained of pain and winced and grade 4, patient complained of pain, winced and withdrew the joint (patients were in intercritical or chronic stages of gouty arthritis with polyarticular disease). Functional assessment was performed using lower extremity functional scale. The Lower Extremity Functional Scale (LEFS) has been used to assess the activities of daily living, especially the functional performance of the lower limb. It is a 20-item self-report measure of physical function. Each item is rated on a five point scale (0-4), with lower scores representing greater difficulty. Total scores can range from 0 to 80. Function is defined as follows: extreme difficulty or unable to perform activity (0-19 points), quite a bit of difficulty (20-39 points), moderate difficulty (40-59 points), a little bit of difficulty (60-79 points) and no difficulty (80 points). Scores: Extreme difficulty or inability to perform activity: 0, quite a bit of difficulty: 1, moderate difficulty: 2, mild difficulty: 3, no difficulty: 4 [(9)]. Laboratory assessment before and after treatment for 3 months: C – Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) by Wintrobe method [(10)] and Serum uric acid. Normal Uric acid levels are 2.4-6.0 mg/dl (female) and 3.4-7.0 mg/dl (male). Fasting for 4 hours prior to uric acid testing is preferred.

Ultrasonographic assessment (MSUS) was done on two joints; knee and 1st MTP, by the same sonographer before and after treatment for three months with febuxostat 80 mg once daily. All the patients and controls underwent sonographic examination under supervision of highly experienced sonographer at Ultrasound Unit of Physical Medicine, Rheumatology and Rehabilitation Department of Tanta University Educational Hospital (SAMSUNG MEDISON (UGEO H60), using linear array transducers (with frequencies ranging between 5-13 MHz). Much gel was applied over the joints to give appropriate contact between the probe and skin. 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.

US definitions described by 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 [(11)].

Statistical analysis

The used tests were Chi-square test, McNemar, Mann Whitney test, Wilcoxon signed ranks test, Pearsons correlation coefficient (r) and Fisher's Exact.

RESULTS

The mean age of the 30 patients (40-75) was comparable to the mean age of the 20 controls (40-75). In patients group, males represented 70% (21 males) and females 30% (9 females) and in control group males represented 65% (13 males) and females 35% (7 females). Our results reported that men have higher urate levels than women and an increased prevalence of gout at all ages. BMI mean in patients group was (25-31) and in control group was (25-31). There was no significant difference between gouty patients and controls regarding gender, age and BMI (table 1).

Table (1): Demographic data and laboratory studies of the two studied groups.

	Gender %		Age (Mean ± SD)	BMI (Mean ± SD)	S. uric acid (Mean ± SD)	ESR (Mean ± SD)	CRP (Mean ± SD)
	Males	Females					
Patients	70.%	30%	53.10 ±7.82	28.18 ±1.49	8.13 ±1.18	34.13 ± 6.66	6.88 ± 0.87
Controls	65%	35%	54.20 ±8.30	27.67 ±1.56	3.75 ±0.50	10.65 ±2.31	2.73 ±0.59
P - value	0.710		0.637	0.247	<0.001*	<0.001*	<0.001*

Disease duration in our study ranged from 2-10 years in gouty patients with mean of 4.50 ± 2.06. The number of flares from onset of disease ranged from 1-5 with mean 2.20 ± 1.32. Tenderness by Ritchie index in patients group before treatment in knee joints was in grades 2, 3 and 4 and represented 23.3%, 63.3% and 13.3% respectively. Tenderness in 1st MTP joints was in grade 2 with 100%. It is significantly improved after treatment in knee joints to grades 1 and 2 with 13.3% and 56.7% respectively and in 1st MTP joints in grades 1 and 2 with 43.3% and 56.7% respectively; p <0.001 (table 2).

Table (2): Assessment of tenderness by Ritchie index in knee & 1st MTP joints before and after treatment in group 1 (n = 30)

	Knee				1st MTP			
	Before		After		Before		After	
Grades	No	%	No	%	No	%	No	%
1	0	0.0	13	43.3	0	0.0	13	43.3
2	7	23.3	17	56.7	30	100.0	17	56.7
3	19	63.3	0	0.0	0	0.0	0	0.0
4	4	13.3	0	0.0	0	0.0	0	0.0
P	<0.001*				<0.001*			

The lower extremity functional scale significantly improved, in patients group before treatment score 3 and 4 were 100% and 0% respectively and after treatment were 20% and 80% respectively; p <0.001 (table 3).

Table (3): Assessment of lower extremity functional scale before and after treatment in group 1 (n = 30)

Scores	Before		After	
	No	%	No	%
0	0	0.0	0	0.0
1	0	0.0	0	0.0
2	0	0.0	0	0.0
3	30	100.0	6	20.0
4	0	0.0	24	80.0
P	<0.001*			

The visual analogue scale (VAS) mean in patients group before treatment in knee joints was 4-9 and in 1st MTP joints was 4-8, which was significantly improved after treatment (0-3) (Table 4).

Table (4): VAS and laboratory studies in patients before and after treatment.

	VAS (Mean ± SD)		ESR (Mean ± SD)	CRP (Mean ± SD)	S. uric acid (Mean ± SD)
	Knee	1st MTP			
Before	6.73 ± 1.44	6.20 ± 1.35	34.13 ± 6.66	6.88 ± 0.87	8.13 ±1.18
After	.63 ± 0.89	1.6 ± 1.0	8.87 ± 2.89	2.76 ± 0.50	4.42 ± 0.56
P	<0.001*	<0.001*	0.002*	<0.001*	<0.001*

Poly articular pattern of involvement included tenderness in upper limb joints in 8 patients and ankle joint in 12 patients. Knee effusion with its degrees: mild, moderate and severe was found in 20% of patients (6 patients) before treatment. 1st MTP effusion was found in 10% of patients (3 patients) before treatment. There was a significant difference in ESR, CRP and serum uric acid in patients group after treatment compared to before treatment, p <0.001 (Table 4). Double Contour sign in knee joints was found in 12 patients before treatment and in 5 patients after treatment. In 1st MTP joints double contour sign was found in 7 patients before treatment and in 1 patient after treatment. There was significant difference in double contour sign after treatment (p 0.016). as shown in table (5).

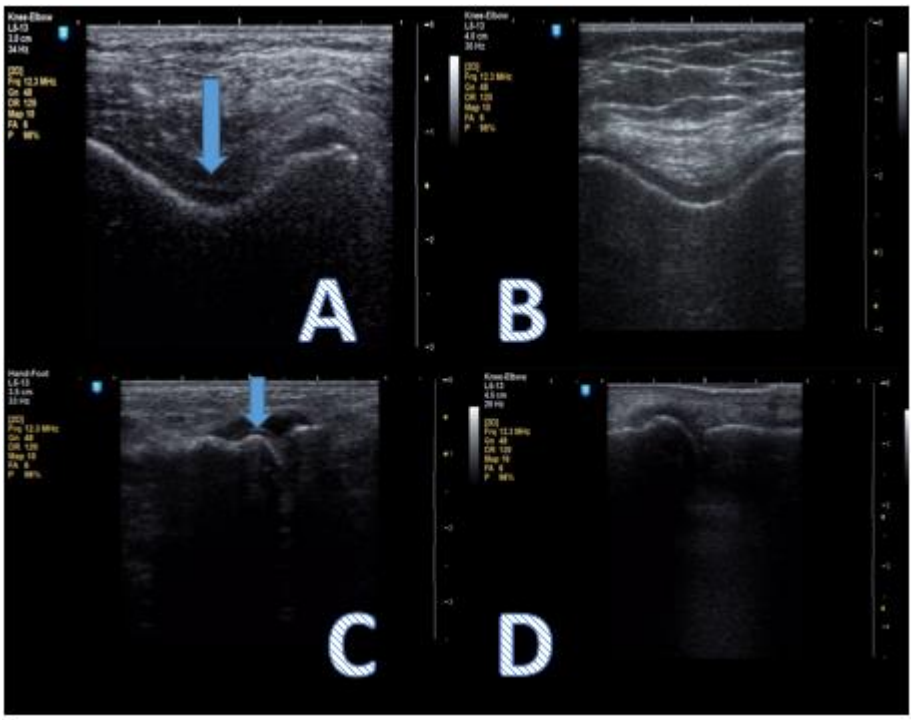

Figure 1: Ultrasounographic findings of the knee (transverse suprapatellar view of the femoral cartilage in maximal flexion) and 1st MTP (longitudinal dorsal view) joints before and after treatment.
A) Double contour sign (hyperechoic enhancement of the superficial margin of the hyaline cartilage) in knee joint by ultrasound before treatment.
B) Disappearance of double contour sign in knee joint after treatment.
C) Double contour sign in 1st MTP joint by ultrasound before treatment. D) Disappearance of double contour sign in 1st MTP joint after treatment.

Table (5): Ultra sonographic findings in patients before and after treatment.

	Double contour%		Effusion %		1st MTP Tophi %
	Knee	1ST MTP	Knee	1ST MTP	
Before	40%	23.3%	36.7%	40%	30%
After	16.7%	3.3%	0%	0%	20%
P	0.016*		0.001*	<0.001*	0.250

Knee effusion was present in 11 patients in patients group before treatment and 1st MTP effusion in 12 patients and all improved after treatment (0%). There was a significant improvement ($p < 0.001$) as shown in table (5). Tophi were present in 30% of patients group before treatment and in 20% after treatment (3 of them decreased in size after treatment). There was no significant improvement ($p = 0.250$) as shown in table (5). Ultrasound was more sensitive in detecting findings and changes of the disease than clinical examination (tables 6 & 7). There was significant difference between knee and 1st MTP effusion detected clinically and by ultrasound in gouty patients before and after treatment. All patients in our study showed that their serum uric acid lowered and effusion disappeared. Patients who had double contour sign not disappeared. They had a follow up by ultrasound and serum uric acid level. Ultrasounographic findings of the knee and 1st MTP joints before and after treatment are shown in figure (1).

Table (6): Comparison between Clinical findings and Ultrasound findings according to Tophi, Knee and 1st MTP effusion before treatment

	Tophi	Knee Effusion	1st MTP effusion
Clinical findings	23.3%	10%	10%
Ultrasound findings	30%	36.7%	40%
p	0.500	0.039*	<0.001*

Table (7): Comparison between Clinical findings and Ultrasound findings according to Tophi, Knee and 1st MTP effusion after treatment.

	Tophi	Knee Effusion	1st MTP effusion
Clinical findings	23.3%	0%	0%
Ultrasound findings	30%	0%	0%
p	0.500	<0.001*	<0.001*

DISCUSSION

Clinical findings in gouty patients in our study, all clinically detected tophi were detected around 1st MTP joint. Clinical tophi were found in 23.7% of patients (7 patients) before treatment. Knee effusion with its degrees: mild, moderate and severe was found in 20% of patients (6 patients) before treatment. 1st MTP effusion was found in 10% of patients (3 patients) before treatment. This coincides with **Stewart *et al.*** [12] who reported that the 1st MTP joint is a common location for sonographic evidence of urate deposition in people with gout and asymptomatic hyperuricemia [12]. There was significant improvement between gouty patients before treatment and 3 months after treatment regarding to assessment of pain by VAS in knee and 1st MTP joints. VAS pain, is a validated outcome measures in patients with chronic gout as **Jasvinder *et al.*** [13] reported that there was a decreases in VAS pain scores after 6-months of treatment. Degree of tenderness in knee and 1st MTP joints of gouty patients was scored on a 4-point scale and our results revealed that there was significant difference between gouty patients before treatment and 3 months after treatment regarding grades of tenderness by Ritchie index. Besides, our study revealed that there was a significant improvement between gouty patients before treatment and 3 months after treatment in regard to lower extremity functional scale. There was significant difference between gouty patients and controls regarding ESR and CRP. This coincides with **Jae *et al.*** [14] who reported that gouty attacks in elderly patients are commonly accompanied by strong systemic inflammatory responses with fever and higher CRP levels and ESRs.

Serum urate level > 6 mg/dl is one of the identified ten key features for discrimination between MSU-positive gout and other MSU-negative conditions in 2016 Gout Classification Criteria: SUGAR study [15]. There was a significant difference between gouty patients before and 3 months after treatment. **Charnelda *et al.*** [16] reported that febuxostat decreased serum uric acid production through selective inhibition of xanthine oxidase enzyme.

Regarding assessment of ultrasound findings before and 3 months after treatment in gouty patients, there was significant difference between gouty patients before treatment and 3 months after treatment. This coincides with **Ralf G and Schlesinger** [17] who reported that sonographic signs of deposition of MSU crystals on the surface of hyaline cartilage disappeared completely if sustained normouricemia was achieved. Knee Effusion was found in 36.7% of patients (11 patients) before treatment and disappeared after treatment. 1st MTP effusion was found in 40% of patients (12 patients) before treatment and disappeared after treatment. **Elsaman *et al.*** [18] reported that gouty arthritis was found by ultrasound (US) in four forms: (i) floating echogenic foci in effusion fluid or Baker cysts, (ii) deposits on the cartilage surface (double contour sign), (iii) erosions and (iv) mature tophus/tophi. Tophi were found in 30.0% of patients (9 patients) before treatment and 3 of them decreased in size after treatment. There was no significant difference between gouty patients before treatment and 3 months after treatment regarding tophi in 1st MTP joints. This coincides with **Gianni & Antonio** [19] who reported that a lower serum UA target (<5.0 mg/dl) is recommended to facilitate faster dissolution of crystals for patients with severe gout until total crystal dissolution and resolution of gout. In our study, ultrasound was more sensitive in detecting findings and changes of the disease than clinical examination. There was significant difference between knee and 1st MTP effusion detected clinically and by ultrasound in gouty patients before and after treatment. This coincides with **Shyamashis *et al.*** [20] who reported that MSUS is useful for confirmation of gout in intercritical or chronic stages, where clinical diagnosis is sometimes more difficult than the acute stage. Ultrasonographic signs of gout have good sensitivity and specificity, especially in patients with persistently high SUA level (> 7 mg/dl). Febuxostat is a non-purine-selective inhibitor of xanthine oxidase. It works non-competitively blocking the active site of xanthine oxidase, which is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid [21]. The most commonly reported adverse effects were: liver function abnormalities, diarrhoea, headache, nausea, dizziness, and/or altered taste. In our study, we used febuxostat,

orally, selective xanthine oxidase inhibitor, with dose 80 mg/day once daily for 3 months. This coincides with **Michael *et al.*** [(22)] who reported that urate-lowering efficacy of febuxostat 80 mg daily was superior to that of febuxostat 40 mg or allopurinol 300/200 mg, and was comparably safe [(22)].

CONCLUSION

Ultrasonography can detect changes related to treatment of gout with febuxostat. Febuxostat is a safe and efficient antihyperurecemic drug and is effective in treatment of gouty arthritis. Ultrasound is more sensitive in detecting findings and changes of the disease than clinical examination.

RECOMMENDATIONS

MSUS is useful tool for diagnosing and detecting changes of gouty arthritis with urate lowering therapy. Febuxostat once daily is an effective treatment in gouty arthritis.

Drawbacks: 3 months treatment were not sufficient for disappearance of tophi with urate-lowering therapy but it needs long time of maintaining serum uric acid within normal ranges.

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