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RESEARCH

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Ultrasonographic findings in patients with chronic kidney disease with asymptomatic hyperuricemia

Nashwa Ismail Hashaad[1*], Sahar Saad Ganeb[1], Saddam A. A. Hassan[2], Shimaa Hamdeen Mohamed[3] and Noha Hosni Ibrahim[1]

Abstract

Background: Musculoskeletal ultrasound is a useful, noninvasive tool to detect anatomical damage in the hyaline cartilage, synovial tissue, and tendons of individuals with asymptomatic hyperuricemia. This study aimed to determine the frequency of musculoskeletal ultrasonographic findings related to hyperuricemia among CKD patients and its relation to chronic musculoskeletal pain and their quality of life.

Results: Double contour (DC) was found in12%,18%, and 22% of the knee, ankle, and 1st MTPs joints, respectively. Hyper-echoic cloud was present in 2% and 6% of the knee and 1st MTPs, respectively. Synovitis was seen in 8%, 4%, and 16% of the knee, ankle, and 1st MTPs joints, respectively. Patellar tendon showed enthesopathy in 14% and tophus in 8% of cases. Tibialis posterior tenosynovitis was in 2% and peroneii tenosynovitis in 2%. Achilles tendon showed calcific foci in 24%, enthesopathy in 20%, and tophi in 4%. First MTPs showed erosion in 10% and tophi in 4%. There were statistically significant relations of pain index to DC, synovial thickening at the knee and at ankle joint. There were statistically significant relations of serum uric acid level to DC.There were statistically significant correlations of serum uric acid level to the 36-Item Short Form Survey (SF-36).

Conclusions: Untreated hyperuricemia might cause musculoskeletal ultrasonographic changes that could cause chronic musculoskeletal pain and decrease quality of life in chronic kidney disease patients.

Keywords: Musculoskeletal, Ultrasonography, Hyperuricemia, Chronic kidney disease

Background

Chronic kidney disease (CKD) is defined as kidney structure or function abnormalities that persists for more than 3 months with implications for health [1]. These abnormalities include decreased glomerular filtration rate ($GFR < 60$ mL/min/1.73 m^2) or evidence of one or more markers of kidney damage (e.g., albuminuria or urine sediment abnormalities) [2]. Renal handling of uric acid is a complex process that accounts for 2/3 to 3/4 of its total excretion, the remainder being excreted via the GIT. It is not surprising then that impaired kidney functions account for up to 90% of hyperuricemia [3]. Asymptomatic hyperuricemia (AH) is a term traditionally applied to settings in which the serum urate concentration is elevated without any symptoms or signs of monosodium urate (MSU) crystal deposition disease, such as gout, or uric acid renal disease [4, 5]. This concept has undergone a significant revision driven by the advances in imaging techniques showing that 30 to 90% of individuals with AH have occult MSU crystal deposition in soft tissues which does not only herald the classic gouty lesions in joints and urinary tract but also incite a low-level widespread systemic inflammation [6]. The evolving role of

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MSUS in acquisition of high-resolution images of articular and periarticular structures has allowed accurate visualization and differentiation of gouty lesions from other pathological entities, thus aiding early and dynamic diagnosis of arthropathy. The symptoms of CKD are non-specific and very variable. Chronic musculoskeletal pain (CMP) is a very common symptom in CKD [7]. The prevalence of pain has been reported to be in more than 60–70% among patients with advanced and end-stage kidney disease, and its underlying etiology is variable [8]. The aim of this study is to determine the frequency of musculoskeletal finding related to hyperuricemia among CKD patients and its relation to chronic musculoskeletal pain and their quality of life.

Methods

Study design

This case–control study was carried on 170 adult participants who were evaluated for enrollment. Ninety subjects were ruled out due to either ineligibility (36) or lack of interest (54) to participate in this study. Eventually, 80 participants were enrolled in the present study where fifty patients with CKD and asymptomatic hyperuricemia (AH) served as cases and (30) age- and sex-matched apparently healthy volunteers with normal serum uric acid served as controls. All the cases were recruited form patients attending clinics at the Nephrology Unit of Internal Medicine Department at our University Hospital, and controls were either patients' relatives or staff members. Persons less than 16 years old and patients with apparent joint swelling or deformity, autoimmune, or blood diseases were excluded from our study.

Clinical assessment

Baseline demographics, present and past medical history, and general examination with emphasis on local musculoskeletal system assessment of the studied joints were performed by two expert senior rheumatologists (once at enrollment and then during MSUS) at the Rheumatology, Rehabilitation and Physical Medicine Department of our University Hospital, and data were collected for both study groups. Height, weight, and body mass index (BMI) were calculated. Musculoskeletal symptoms in different body regions were assessed using an Arabic translation of the 1st part of the standardized Nordic questionnaires for musculoskeletal symptoms [9]. Pain index was assessed using on 100 mm visual analogue scale (VAS) [10]. All participants filled in 36-Item Short Form Health Survey questionnaire (SF-36) written in the Arabic language.

Laboratory investigations

Serum creatinine (Cr), estimated glomerular filtration rate (eGFR), serum parathyroid hormone (PTH), serum calcium, serum phosphorus, and 25(OH) vit. D were measured.

Radiological investigations

Ultrasound assessment of the knee, ankle, and 1st MTP joints was performed bilaterally using Logiq E real-time scanner (General Electric Medical System, Milwaukee, WI, USA) equipped with an 8–13 MHZ linear array transducer. The reported findings were defined and verified based on the EULAR guidelines for musculoskeletal ultrasound in rheumatology [11]. using both gray and power Doppler scale according to the EULAR guidelines. Focus, depth, and gain are adjusted for better image quality for detection of one or more signs of these ultrasonographic features [12]. Examination was done for knee joint, patellar tendon, ankle joint, Achilles tendon, peroneii tendons, and tibialis posterior tendon, and 1st MTP were examined. Synovitis, DC, tenosynovitis, tophi, aggregates, and enthesopathy were diagnosed according to OMERACT definition:DC (abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation, and may be either irregular or regular, continuous or intermittent, and can be distinguished from the cartilage interface sign), tophus (a circumscribed, inhomogeneous, hyperechoic, and/or hypoechoic aggregation which may or may not generate posterior acoustic shadow and may be surrounded by a small anechoic rim, may or may not generate posterior acoustic shadow), aggregates (heterogeneous hyperechoic foci that maintain their high degree of reflectivity, even when the gain setting is minimized or the insonation angle is changed and occasionally may generate posterior acoustic shadow), and erosion (extra-articular discontinuity of the bone surface visible in two perpendicular planes) [13].

Ethical considerations

A written consent in Arabic language was obtained from all participants after explaining the study details and benefits. The study was conducted in accordance with the Code of Ethics Of the World Medical Association (Declaration of Helsinki). This study was approved by the Ethical Committee of the Faculty of Medicine.

Statistical analysis

The statistical analysis was conducted using STATA version 11 (STATA corporation, College Station, Texas). The data were summarized as mean ± standard deviation (SD) when parametric and were compared by one-way ANOVA test or as median and interquartile range (IQR) when nonparametric and were compared by the Kruskal-Wallis test for more than 2 groups or the Wilcoxon signed-rank test for paired data. Qualitative data

were represented as frequency and percentages and were compared by chi-square test. The Student *t*-test and the Mann-Whitney test were used to detect differences between two groups for parametric and nonparametric data respectively. Inter-reader reliability (IRR) between the two operators was calculated using Kappa-coefficient statistics. The Spearman correlation coefficient (rho) was used to examine the correlation between the sUA and the other variables. A multivariate regression analysis was conducted to adjust for any interaction between sUA and MSUS findings and other independent variables. A *P*-value < 0.05 was considered statistically significant (S) and *P*-value < 0.001 as highly statistically significant (HS).

Results

General characteristics of patients and controls

In group 1, there were 18 females (36.0%), 32 males (64.0%), and 16 patients (32.0%) with a history of DM and 26 patients (52.0%) with a history of HTN; their ages ranged between 22 and 70 years with a mean of 47.33 ± 14.19 years, CMP present in 20 patients (40%), pain index ranged between 2 and 8 with a mean of 4.12 ± 2.03, their SF-36 score ranged between 1 and 5 with a mean of 3.2 ± 1.18, the duration of their renal disease ranged between 1 and 10 years with a mean of 3.94 ± 2.42 years, and their BMI ranged between 20.96 and 39.06 with a mean of 28.88 ± 4.45. Chronic musculoskeletal pain (CMP) was documented in 40% of our cases. There was insignificant differences between group 1 and group 2 patients regarding demographic data. Among the fifty CKD patients with AH, the majority (41) of patients had CKD-stage 5 and were on hemodialysis (82.0%), three patients had CKD-stage 2 (6.0%), four patients had CKD-stage 3 (8.0%), and 2 patients had CKD-stage 4 (4.0%).

Ultrasonographic findings in patients and controls

In knee joint, we found double contour in 12 joints (12%) with significant difference and aggregates in 2 joints (2%) with insignificant difference, and synovial thickening was in 8 joints (8%) with significant difference from controls, while Patellar tendon showed enthesopathy in 14 tendons (14%) with significant difference and tophus in 8 joints (8%) with significant difference. On ankle examination, there was double contour sign in 18 joints (18%) with significant difference and synovial thickening in 4 joints (4%) with insignificant difference, while tibialis posterior tenosynovitis was in 2 tendons (2%) with insignificant difference from controls, and peroneii tenosynovitis was in 2 tendons (2%) with insignificant difference from controls. Achilles tendon showed calcific foci in 24 tendons (24%) with highly significant difference, enthesopathy in 20 tendons (20%) with highly significant difference, and tophus in 4 tendons (4%) with insignificant difference. In the 1st MTPs, we found double contour sign in 22 joints (22%) with highly significant difference, erosion in 10 joints (10%) with highly significant difference, and aggregates in 6 patients (6%) with insignificant difference, and synovial thickening was in 6 joints (16%) with insignificant difference and tophus in 4 joints (4%) with insignificant difference from controls (Table 1).

Relationships of ultrasonographic pictures with clinical and laboratory findings in the studied group

There were statistically significant relations between pain index and DC at knee joint, DC at ankle joint and DC at MTP, and knee synovial thickening and synovial thickening at ankle joints, while there were statistically insignificant relations to other findings (Table 2). There were statistically significant relations of serum uric acid and DC at knee joint, DC at ankle joint, and DC at MTP, while there were statistically insignificant relations to other findings (Table 3). In CKD patients, there were statistically significant correlations between SF-36 and age, CMP, serum Cr, serum calcium, vit. D, serum phosphate, urea, GFR, Hb, serum K, and serum uric acid despite insignificant relations to other clinical and laboratory findings (Table 4, Figs. 1, 2, 3, 4 and 5).

Discussion

SU crystallization on the surface of cartilage could be argued to the fact that the normal components of cartilage chondroitin sulfate and phosphatidylcholine ease the nucleation and subsequent crystallization of MSU [13]. Our results showed that DC were found in 12% of examined knees with a statistically significant difference in similarity with Younes et al. [14], who found DC in 15% of knee joints of 40 asymptomatic hyperuricemia patients. Noteworthy, we elucidated that DC was in 8% of ankles with a statistically significant difference in proximity with Wang et al. [15] who concluded that patients with asymptomatic hyperuricemia had subclinical MSU crystal deposits on ankle dual energy CT (DECT) scans with significant difference to controls. This study showed DC at 1st MTP in 22% with a statistically significant difference in accordance with Stewart et al. [16], in their study on 29 patients of asymptomatic hyperuricemia. Tophi and enthesopathy were in 4% and 20% of patellar tendon respectively with a statistically significant difference in agreement with Pinda et al. [17], results in 50 patients with asymptomatic hyperuricemia. We detected cases of synovitis in 16% of our cases with a statistically significant difference and erosion in 10% in contrary to Puig et al. [18], who did not find synovitis or erosion in their study on 35 patients of asymptomatic hyperuricemia. This discrepancy could be

Table 1 MSUS findings of the studied groups

MSUS findings		Group 1 (joints no. = 100)		Group 2 (joints no. = 60)		Chi-square test (FET)	*P*
		No	%	No	%		
Knee	**Double contour sign**	12	12.0	0	0.0	FET	0.004
	Aggregates	2	2.0	0	0.0	FET	0.53
	Synovial thickening	28	28	0	0.0	FET	0.002
Patellar tendon	**Tendinopathy**	14	14	4	6.0	FET	0.007
	Tophus	8	8.0	0	0.0	FET	0.05
Ankle	**Double contour sign**	18	18.0	0	0.0	FET	0.002
	Synovial thickening	4	4.0	0	0.0	FET	0.30
Tibialis posterior tendon	**Tenosynovitis**	2	2.0	0	0.0	FET	0.53
Peroneus tendon	**Tenosynovitis**	2	2.0	0	0.0	FET	0.53
1st MTP	**Double contour sign**	22	22.0	0	0.0	15.30	< 0.001
	Erosion	10	10.0	0	0.0	FET	0.01
	Aggregates	6	6.0	0	0.0	FET	0.08
	Synovial thickening	16	16.0	0	0.0	10.67	< 0.001
	Tophus	4	4	0	0.0	FET	0.30
Achilles' tendon	**Calcific foci**	24	24.0	0	0.0	16.94	< 0.001
	Tendinopathy	20	20	0	0.0	13.71	< 0.001
	Tophus	4	4.0	0	0.0	FET	0.05

MSUS Musculoskeletal ultrasound, *1st MTP* first metatarsophalangeal joint, *FET* Chi-square test. If $P \leq 0.05$ means significant, if $P < 0.001$ means highly significant

Table 2 Relation between CMP with ultrasonographic findings in CKD patients

Variable	Group 1 (no. = 50)	
	Mann–Whitney test	*P*
Double contour sign at knee	4.09	< 0.001
Synovial thickening	3.79	0.003
Patellar tendinopathy	2.27	0.36
Double contour sign at ankle	2.38	0.02
Synovial thickening	2.38	0.02
Double contour sign at 1st MTP	2.13	0.03
Synovial thickening	0.84	0.4
Aggregate at 1st MTP	0.92	0.36
Achilles' tendon calcific foci	0.98	0.33
Achilles' tendinopathy	0.15	0.88

1st MTP first metatarsophalangeal joint if $P \leq 0.05$ means significant, if $P < 0.001$ means highly significant

Table 3 Relation between serum uric acid with ultrasonographic findings in CKD patients

Variable	Group 1 (no. = 50)	
	Mann–Whitney test	*P*
Double contour sign at knee	1.85	0.05
Synovial thickening at knee	3.79	0.06
Patellar tendinopathy	0.19	0.89
Double contour sign at ankle	2.38	0.03
Synovial thickening at ankle	0.18	0.86
Double contour sign at 1st MTP	2.13	0.03
Synovial thickening at 1st MTP	0.84	0.4
Tophi at 1st MTP	0.92	0.36
Achilles' tendon calcific foci	0.98	0.33
Achilles' tendinopathy	0.15	0.88

1st MTP first metatarsophalangeal joint. If $P \leq 0.05$ means significant, if $P < 0.001$ means highly significant

due to difference in size of studied group, different ethnicity, and different operators. We noticed enthesopathy in 20% of Achilles tendon with a highly statistically significant differences in agreement with Mutlu et al. [19]. The current study found tophi in 24% of Achilles tendon with a highly statistically significant difference in a proximity from Hussein et al. [20], who found tophi in 20% of Achilles tendon in their patients. This work demonstrated statistically significant relations between serum uric acid and DC in both of the knee, ankle, and 1st MTP in proximity with Thiele and Schlesinger [21] who emphasized the disappearance of DC in gouty patients taking enough drugs to control serum uric acid. There was significant relation between serum uric acid

Table 4 Relation between quality of life and clinical laboratory findings in CKD patients

Variable	Group 1 (no. = 50)	
	r	*P*
Age (years)	0.33	0.02
Pain index	0.33	0.02
Duration of renal disease (years)	0.26	0.07
BMI (kg/m^2)	0.24	0.09
Creatinine	0.40	0.004
Vit. D	0.87	< 0.001
Serum uric acid	0.47	0.009
GFR (ml/min/1.73 m)	0.33	0.02
Serum Na	0.09	0.55
Serum K	0.35	0.01
Platelets (× 10^3/mm^3)	0.17	0.24
WBCs (× 10^3/mm^3)	0.05	0.74
Serum Ca	0.55	0.01
Hb (gm/dl)	0.76	< 0.001
Serum phosphate	0.35	0.01

K Potassium, *Na* Sodium, *Ca* Calcium, *Hb* Hemoglobin, *GFR* Glomerular filtration rate, *Vit* Vitamin, *BMI* Body mass index, *WBC* White blood cells if $P \leq 0.05$ means significant, if $P < 0.001$ means highly significant

and knee synovitis; the same result was proven by using MRI by Bassioni et al. [22]. Chronic pain in patients with chronic kidney disease may be caused by numerous factors like renal bone disease and ischemic bone pain [23]. In this study, CMP was in 40% of our CKD patients in line with Caravaca et al. (2016) [24, 25] who found CMP in 38% of 1169 patients. There was another point of similarity with Stewart et al. [15], when we demonstrated a statistically significant relation between CMP and DC in the knee, ankle, and 1st MTP. This study emphasized significant correlation between SPF 36 and serum uric level in consistence with Aggarwal et al. [8], on 200 Indian CKD patients. There was another point of similarity with them when we found significant correlation between SPF 36 and serum calcium level. We found significant relation between SPF 36 and urea level in agreement with Cruz et al. [26]. Also, there was significant correlation between SPF3 and hemoglobin in CKD in consistence with Fructose et al. [27] in their study on thirty patients with CKD. At the same time, there was significant correlation between SF-36 and serum 25(OH) vitamin D in CKD in similarity to the result of Oh et al. [28] in their study on 1844 pre-dialysis CKD Korean patients. We emphasized significant correlation between SPF3 and serum phosphate in CKD in consistence with Vides and Martins [29] who documented the same result in 155 CKD patients. Moreover, there was another point of agreement when we found significant correlation between SPF3 and pain score. We observed a significant correlation between SPF3 and GFR in CKD in consistence with Vides and Peng [30, 31] who documented the

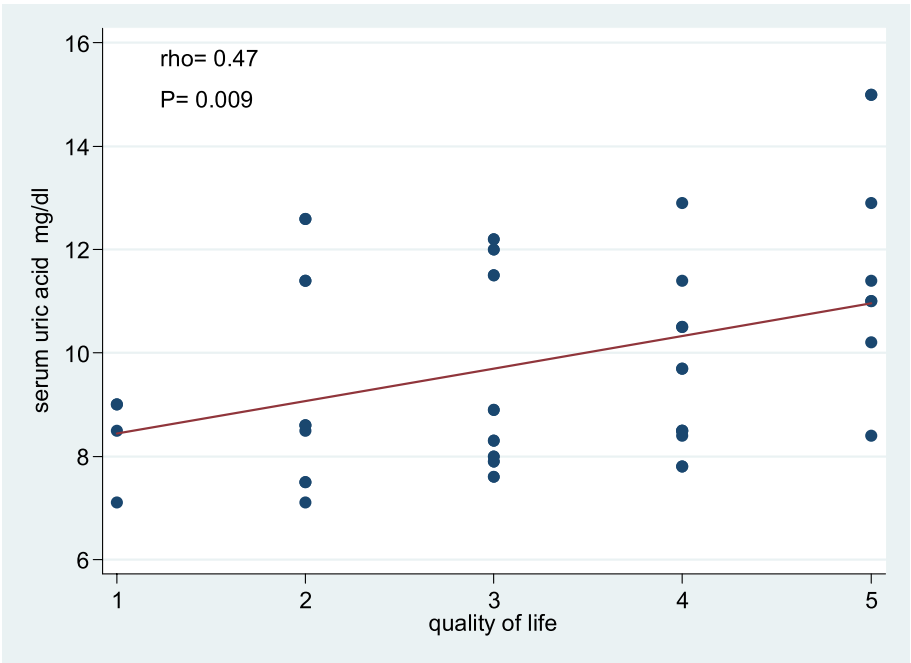

Fig. 1 Correlation between quality of life and serum uric acid

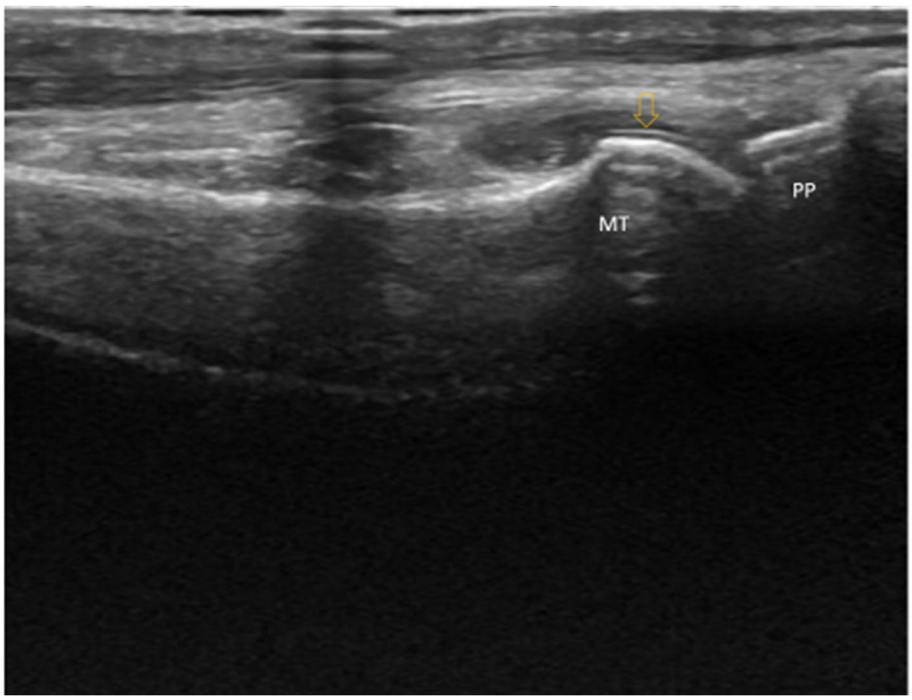

Fig. 2 Dorsal longitudinal gray scale ultrasound scan of the 1st MTP joint showing double contour (arrow)

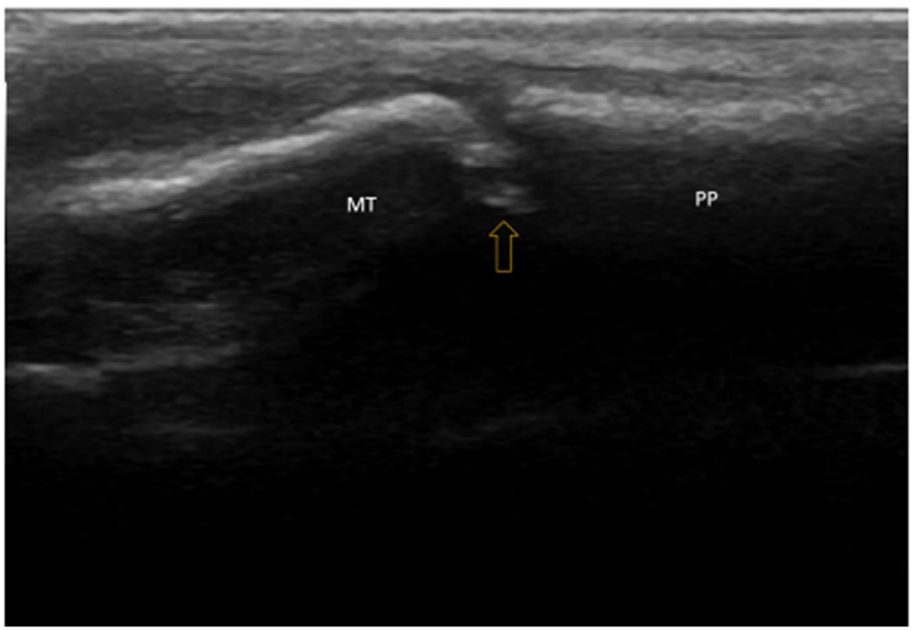

Fig. 3 Dorsal longitudinal gray scale ultrasound scan of the first MTP joint showing erosion (arrow)

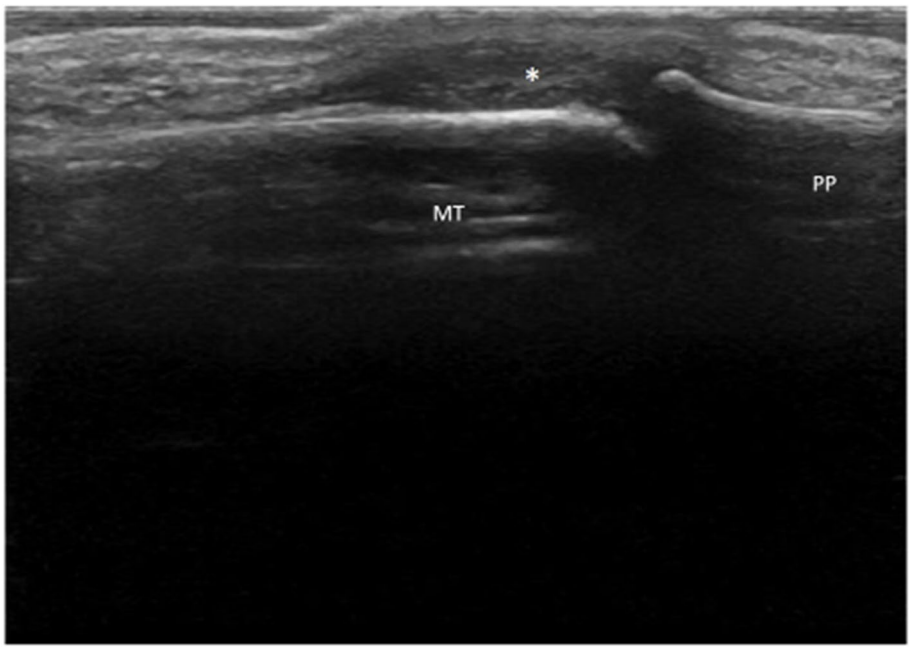

Fig. 4 Dorsal longitudinal gray scale ultrasound scan of the 2nd MTP joint showing synovitis (asterisk)

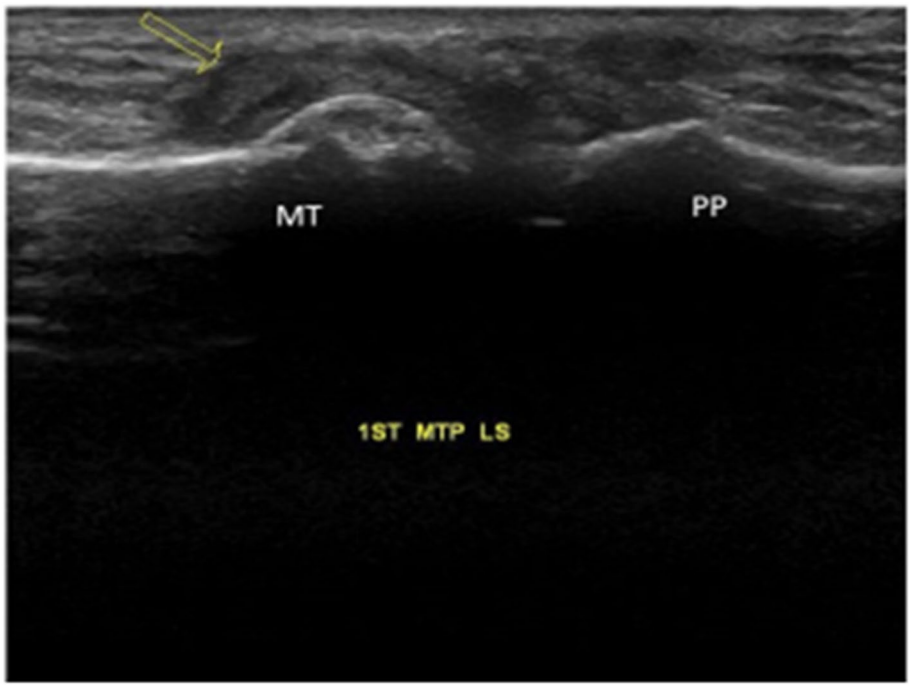

Fig. 5 Dorsal longitudinal gray scale ultrasound scan of the 1st MTP joint showing tophus (arrow)

same result at 39 clinical centers located at 28 cities. We are aware that our study has limitations, including the absence of longitudinal follow-up to determine the predictive value of US in the development of established gout and the lack of MSU crystal diagnosis in those patients with US changes suggestive of gouty arthritis. Furthermore, the sonographers were not blinded to they examined.

Conclusions

Untreated asymptomatic hyperuricemia might cause musculoskeletal ultrasonographic changes that could cause chronic musculoskeletal pain and decrease quality of life in chronic kidney disease patients.

Abbreviations

CKD: Chronic kidney disease; AH: Asymptomatic hyperuricemia; GFR: Glomerular filtration rate; SU: Serum uric acid; MSU: Monosodium urate; CPM: Chronic musculoskeletal pain; The Medical Outcome Study 36-Item Short Form Health Survey SF-36: 36-Item Short Form Health Survey questionnaire; DC: Double contour; MSUS: Musculoskeletal ultrasound; 1st MTP: First metatarsophalangeal joint; FET: Fisher's exact test; K: Potassium; Na: Sodium; Ca: Calcium; Hb: Hemoglobin; Vit: Vitamin; BMI: Body mass index; WBC: White blood cells.

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Authors' contributions

The authors read and approved the final manuscript. Idea suggestion and put the study design, SG; data collection and analysis, NHI and SH; US examination, SG, NIH, and NHI; manuscript writing and final revision, SG, NIH, NHI, and SH. The content of this manuscript has not been published or submitted for publication at anywhere else.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Done, the committee's reference number: 2–2018, date: 28 February 2018. Written consents according to the Helsinki Declaration were taken from all patients and control subjects prior to participation in the study that was approved by the ethical committee of the Faculty of Medicine, Benha University.

Consent for publication

Not applicable.

Competing interests

Dr. Sahar Saad Ganeb is Editor in Chief in the ***Egyptian Rheumatology and Rehabilitation***. The other authors declare that they have no competing interests.

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