Articular cartilage of knee and first MTP joint are the preferred sites to find double contour sign as an evidence of urate crystal deposition in asymptomatic hyperuricemic individuals

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ABSTRACT

Background/Objective: A cross-sectional study to determine the preferred sites of urate crystal deposition in asymptomatic hyperuricemic individuals by ultrasound.

Methods: In two years period, twenty-four asymptomatic hyperuricemic individuals (serum uric acid ≥7mg/dl) and fifty controls (serum uric acid <7mg/dl) aged more than 18 years were included in this study. Double contour sign was examined at three articular cartilage sites (first metatarsophalangeal, tibiotalar and femoral condyle) whereas hyperechoic aggregates were looked for at one joint site (radiocarpal joint) and two tendon sites (patellar tendon and triceps tendon). The Chi-square test was used to compare the categorical variables and discrete variables were compared by one--way analysis of variance. The p-value<0.05 was considered significant.

Results: Eight out of 24 asymptomatic hyperuricemic individuals had ultrasound evidence of urate crystal deposition in first metatarsophalangeal joint area followed by knee joint area which was detected in 6 patients. The detection rate of ultrasound abnormalities in asymptomatic hyperuricemic individuals was 45.8% with two joint area (knee and first metatarsophalangeal) and 50% with six sites assessment. Amongst controls, 16% were found to have these abnormal ultrasound findings.

Conclusion: The highest predilection of urate crystal deposition in asymptomatic hyperuricemic individuals is the articular cartilage of the first metatarsophalangeal and knee joints. This might explain the frequent clinical presentation of arthritis in these joint areas.

Keywords: Musculoskeletal ultrasonography; Asymptomatic hyperuricemia.

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INTRODUCTION

Asymptomatic hyperuricemia (AH) is a term applied to settings in which the serum uric acid (SUA) level is high but without clinical manifestations of uric acid deposition such as gout or uric acid renal disease. The prevalence of hyperuricemia ranges from 2.6% to 47.2% in various populations[1,2]. Ultrasonographic (USG) evidence of urate crystal deposition in the form of double contour sign (DCS) and hyperechoic aggregates (HAGs) in asymptomatic hyperuricemic individuals has been documented in previous studies[3-5]. The detection rate of these ultrasound abnormalities has varied from 25% to 42.3% in AH individuals[3-5].

The study from Naredo et al.[6], has found the best balance between sensitivity and specificity (84.6% and 83.3%, respectively) with the assessment of one joint (ie, radiocarpal) and two tendons (ie, patellar and triceps) for HAGs, and three articular cartilages (ie, first metatarsal, talar and second metacarpal/femoral) for double contour sign (DCS) in intercritical gout patients. The objective of this work was to identify the preferred sites of urate crystal deposition among these six sites in AH individuals.

METHODS

Study population: Thirty AH individuals attending our outpatient department service, either referred for hy-

peruricemia from other department or found to have high uric acid in routine health checkup and had self--referral to consult regarding treatment of hyperuricemia as well as 50 controls (healthy volunteers from general population) who agreed to undergo ultrasound examination and blood investigations, were screened for the study. AH was defined as individuals with SUA ≥7mg/dl by uricase method, at least twice two months apart without articular symptoms suggestive of arthritis (joint pain with morning stiffness > 30 minutes or joint pain with swelling) in the past or present. Historical controls, individual with normal SUA (<7mg/dl by uricase method) and without arthritis were used from a previous study for comparison[7]. Twenty-four AH (17 male and 7 female) individuals who fulfilled inclusion criteria were included in this study. This study was approved by the local institutional ethics committee. Written informed consent of participants taken prior to participation in the study.

Details were collected regarding comorbidities, dietary habits and alcohol intake. Hypertriglyceridemia was defined by serum triglyceride levels >150 mg/dl or above the laboratory reference range and chronic kidney disease (CKD) was defined by eGFR<60 ml/ /min/1.73m2[8]. Intake of 250 ml of milk or equivalent amount of milk products per day was considered as dairy product consumer. Individuals who fulfilled inclusion criteria were asked to come to the department on a separate day after 12 hours overnight fast for blood samples which were collected for biochemical analysis.

USG examination was done and three articular cartilage sites (first metatarsal, tibiotalar and femoral condyle) were looked for DCS whereas HAGs were looked for at one joint site (radiocarpal) and two tendon sites (patellar and triceps). Linear array multi-frequency (8–13 MHz) transducer of Logiq E; GE Medical Systems Ultrasound machine was used for USG examination, on B mode gray scale (GS). Settings of machine were as follows: GS frequency of 11–13 MHz, dynamic range of 40–50 dB and GS gain of 60 dB. Definitions of HAGs and DCS were as per Outcome Measures in Rheumatology Clinical Trials (OMERACT) task force[9]. Heterogeneous hyperechoic foci in USG examination that maintain their high degree of reflectivity, even when the gain setting is minimized or the insonation angle is changed and which sometimes may generate posterior acoustic shadow were considered as HAGs. DCS was defined as abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation, and which may be irregular or regular, continuous or intermittent and can be distinguished from the cartilage interface sign[9]. Positions of joints were as follows: First metatarsophalangeal (1st MTP) in neutral position, tibiotalar joint with slight plantar flexion and probe at medial side of dorsal aspect, knee joint in maximum flexion for femoral condyle cartilage and 30-degree flexion for patellar tendon, triceps tendon in 30-degree flexion of elbow joint while forearm resting on abdomen and radiocarpal joint in prone position. Both horizontal and longitudinal views were taken to minimize any artefactual findings. USG was done by a trained Rheumatologist who has 3 years' experience in musculoskeletal ultrasound. Findings were confirmed by an experienced radiologist simultaneously who has 6 years' experience in musculoskeletal ultrasound. As a part of our previous study 7 intra-reader and inter-reader agreement was done by using Cohen's kappa statistics to test the reliability of lesions. Five patients with crystal proven gout were screened at 6 joint areas (total 30 sites for DCS and 40 sites for HAGs) before the study. Intra-reader agreement was 100% for both DCS and HAGs, while inter-reader agreement was good for both DCS and HAGs (κ0.8 & 0.6 respectively).

Representative still images (Figure 1) were stored on the hard drive of the ultrasound machine.

STATISTICAL ANALYSIS

The results are presented as mean±SD and percentages. The Chi-square test was used to compare the categorical variables. The discrete variables were compared by one-way analysis of variance (ANOVA). The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF STUDY POPULATION

Table I displays demographics, clinical and laboratory findings of study population. Body Mass Index (BMI), high purine diet, hypertension and hypertriglyceridemia were significantly higher among the AH individuals as compared to control subjects (p<0.05).

However, dairy products intake was found significantly lower ($p<0.01$) in AH individuals. There was no significant ($p>0.05$) difference in the prevalence of CKD, diabetes and coronary artery disease (CAD) among the groups.

ULTRASOUND FINDINGS

DCS was found in 11 (45.8%) out of total 24 AH individuals with 6 sites screening and HAGs was found in 1 (4.2%) AH individual only. Any USG abnormality (DCS or HAGs) was present in 12 (50%) out of total 24 AH individuals with 6 sites screening whereas in 11 (45.8%) individuals, it was found at two sites (knee and 1st MTP joint). DCS at knee joint area (femoral condyle) was found in 25% and 6% of AH individuals and healthy subjects respectively whereas the DCS at 1st MTP joint was present in 33.3% and 16% of AH individuals and healthy subjects respectively. The difference was significant ($p<0.05$) between AH and Controls at both knee and 1st MTP joint areas.

DISCUSSION

Hyperuricemia is the commonest cause of urate crystal precipitation in gout. Evidence of urate crystal

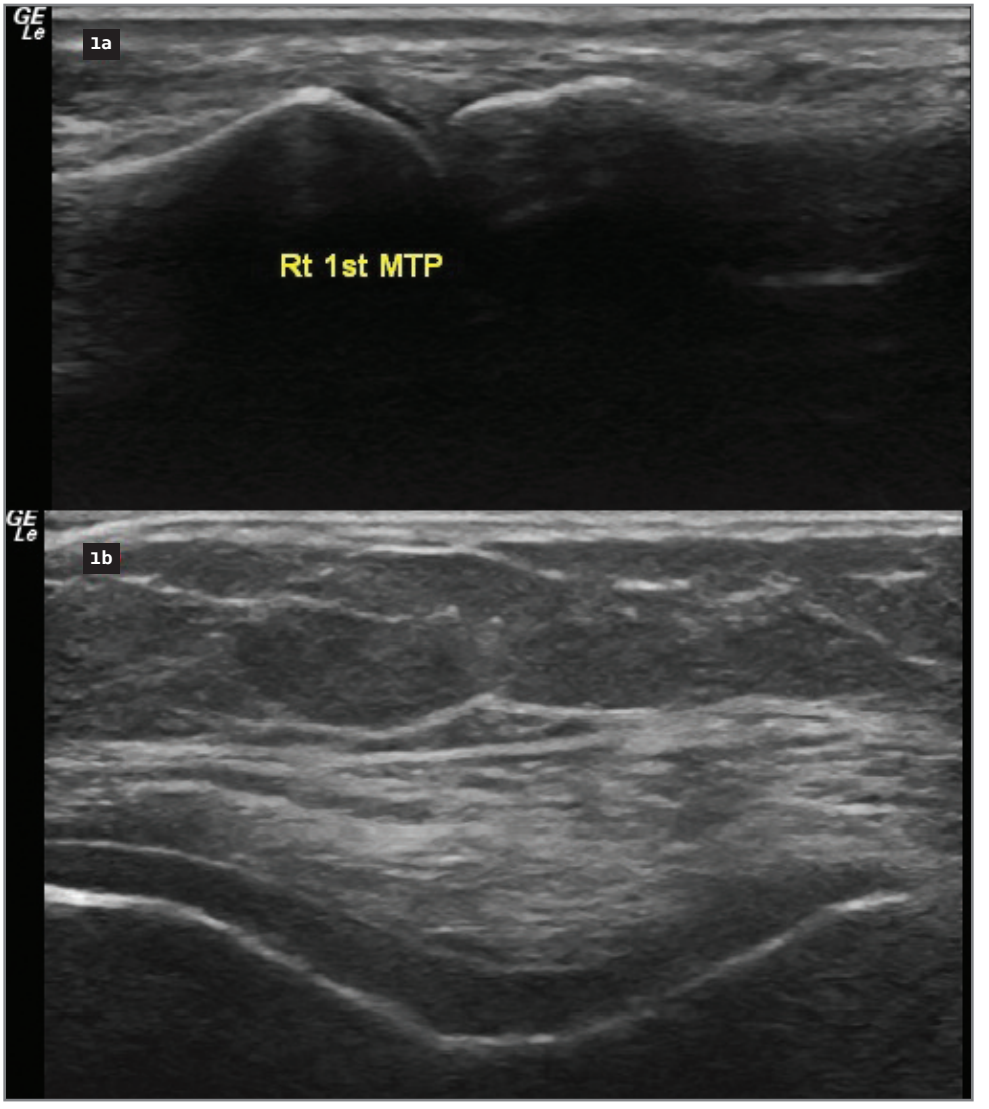

FIGURE 1. 1A) Double Counter Sign of the right first metatarsophalangeal joint on dorsal aspect. 1B) Double Counter Sign of femoral condylar cartilage.

TABLE I. DEMOGRAPHICS AND CLINICAL AND LABORATORY FINDINGS IN STUDY POPULATION

	AH (n=24)		Control (n=50)		p-value
Characteristics	No.	%	No.	%	AH vs Control
Age (year), mean±SD	45.50±13.66		48.52±11.48		0.32
Male gender	17	70.8	43	86.0	0.39
BMI (kg/m^2), mean±SD	27.91±5.83		24.76±3.72		0.006*
Red meat/Sea food	15	62.5	16	32.0	0.01*
Dairy product	10	41.7	45	90.0	0.0001*
Alcohol intake	3	12.5	3	6.0	0.33
Hypertension	11	45.8	8	16.0	0.006*
Diabetes	2	8.3	6	12.0	0.63
CAD	2	8.3	1	2.0	0.19
CKD	2	8.3	0	0.0	0.03*
Hypertriglyceridemia	7	29.2	5	10.0	0.001*
Uric acid (µmol/L), mean±SD	484.16±51.15		302.15±58.88		0.001*

*Significant; AH, asymptomatic hyperuricemia: SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; Unpaired t-test was applied to analyze age, BMI and serum uric acid among groups. Chi-square test was used for other variables.

TABLE II. ULTRASOUND FINDINGS AT DIFFERENT ANATOMICAL LOCATIONS

	AH (n=24)		Control (n=50)		p-value[1]
Anatomical site	No.	%	No.	%	Gout vs Controls
Knee joint DCS	6	25.0	3	6.0	0.0001*
1st MTP Joint DCS	8	33.3	8	16.0	0.0001*
1st MTP joint HAGs	0	0.0	0	0.0	NA
Tibiotalar joint DCS	1	4.2	0	0.0	NA
Patellar tendon HAGs	1	4.2	0	0.0	NA
Triceps tendon HAGs	0	0.0	0	0.0	NA
Radiocarpal joint HAGs	0	0.0	0	0.0	NA
Knee and 1st MTP joint abnormalities	11	45.8	8	16.0	0.0001*
Ultrasound abnormalities at six sites	12	50.0	8	16.0	0.0001*

[1]Chi-square test, *Significant, NA, not applicable; AH, asymptomatic hyperuricemia; DCS, double contour sign; HAGs, hyperechoic aggregates; 1st MTP, first metatarsophalangeal

deposition in articular cartilage has been demonstrated in AH individuals by ultrasound[3-5]. These individuals can also be called asymptomatic gout as per recent proposed gout classification[10]. This suggests that deposition of urate crystal in articular cartilage starts much earlier than symptomatic gouty arthritis. So articular cartilage deposition of urate crystal alone is not sufficient for symptomatic gout and second hit is required for the development of gouty arthritis. There are some evidences which suggest that urate crystal alone is not sufficient to cause gouty arthritis but need some other co-stimulatory agents eg MRP8/14, free fatty acids (FFA) etc[11, 12]. Holzinger et al[11] have found that MRP-8 and MRP-14 are enhancers of MSU crystal–induced IL-1secretion both in vitro and in vivo, whereas Joosten et al[12] have studied the role of FFA in secretion of IL-1 by using human peripheral mononuclear blood cells (PMBC). Hyperuricemia per se is a risk factor for developing CAD coronary artery disease. Andres et al[13] reported that AH individuals with USG evidence of urate crystal deposition had more severe coronary artery calcification as compared to AH individuals

without USG evidence of urate crystal deposition. Improvement in endothelial function and renal function has been shown by Kanbay et al[14] with the use of allopurinol for 4 months in AH individuals. So keeping serum uric acid within normal range is beneficial in terms of reducing CAD and CKD incidences.

In this study we identified urate crystal deposition in 50% AH individuals with six sites screening. The preferred sites were 1st MTP joint (33.3%) and knee joint (25%) in the form of DCS. Combination of knee and 1st MTP joint sites had 45.8% prevalence of urate crystal deposition. Our previous study[7] of in gout patients had found that screening of 1st MTP joint (for DCS and HAGs) and knee cartilage (for DCS) are as good as six sites in detecting urate crystal deposition. Puig et al[4] have found the USG evidence of urate crystal deposition in the form of tophus in 34% of AH individuals (>2 years duration) at knee and ankle joint areas. In a pilot study, Miguel et al[5] have found the USG abnormalities related to urate crystal deposition (eg. DCS and hyperechoic cloudy area) in 42.3% of AH individuals at 1st MTP and knee joint area. These lesions were confirmed for MSU crystals by microscopic examination in 9 out of 11 AH individuals. Higher percentage of DCS in this study as compare to previous studies could be due to screening of more sites. Major limitation of this study is that we have not confirmed these DCS and HAGs by doing microscopic examination for MSU crystals, as false positive DCS could be due to interface sign also. Another limitation is lack of blinding of ultrasonographer. Despite these limitations, this is the only comprehensive study to look for the evidence of urate crystal deposition at multiple sites in AH individuals and compared with normouricemic individuals. Results from this study shows the importance of two joint area screening in AH individuals for proper utilization of resources and time. In future we can focus on these joints to detect urate crystal deposition by using more specific technique e.g. Dual Energy CT.

CONCLUSION

To conclude, articular cartilage of 1st MTP and knee joints are the preferred sites of urate crystal deposition in AH individuals. DCS was seen in 45.8% of AH individuals at 1st MTP and knee joint areas despite absence of articular symptoms. Long-term follow-up studies are required to determine the future development of gout in these individuals.

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REFERENCES

1. Currie W. Prevalence and incidence of the diagnosis of gout in Great Britain, Ann Rheum Dis 38:101, 1979.
2. Klemp P, Stansfield S, Castle B, Robertson M. Gout is on the increase in New Zealand, Ann Rheum Dis 56:22, 1997.
3. Pineda C, Amezcua-Guerra LM, Solano C, et al. Joint and tendon subclinical involvement suggestive of gouty arthritis in asymptomatic hyperuricemia: an ultrasound controlled study. Arthritis Res Ther 2011;13:R4.
4. Puig JG, de Miguel E, Castillo MC, et al. Asymptomatic hyperuricemia: impact of ultrasonography. Nucleosides Nucleotides Nucleic Acids 2008;27:592–5.
5. De Miguel E, Puig J, Castillo C, et al. Diagnosis of gout in patients with asymptomatic hyperuricaemia: a pilot ultrasound study. Ann Rheum Dis January 2012;71:157–8.
6. Naredo E, Uson J, Jiménez-Palop M, et al. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? Ann Rheum Dis 2014;73: 1522–1528.
7. Bhadu D, Das SK, Wakhlu A, et al. Ultrasonographic detection of double contour sign and hyperechoic aggregates for diagnosis of gout: two sites examination is as good as six sites examination. Int J Rheum Dis. 2018: 21; 523-532.
8. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 16: 31–41, 1976
9. Gutierrez M, Schmidt WA, Thiele RG, et al. International Consensus for ultrasound lesions in gout: results of Delphi process and web-reliability exercise. Rheumatology (Oxford) 2015; 54: 1797–1805.
10. Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a new staging system? Ann Rheum Dis 2014;73:1598–1600
11. Holzinger D,Nippe N, Vogl T, et al. Myeloid-Related Proteins 8 and 14 Contribute to Monosodium Urate Monohydrate Crystal–Induced Inflammation in Gout Arthritis Rheumatol. 2014 May;66(5):1327-39
12. Joosten LA, Netea MG, Mylona E, et al. Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1 production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. Arthritis Rheum. 2010 Nov;62(11):3237-48
13. Andrés M, Quintanilla MA, Sivera F, et al. Silent Monosodium Urate Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia: An Exploratory Study. Arthritis Rheumatol. 2016 Jun;68(6):1531-9
14. Kanbay M, Huddam B, Azak A, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration ratein asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol. 2011 Aug;6(8): 1887-94