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Performance of Musculoskeletal Ultrasound in screening for Gouty Arthritis in Chronic Kidney Disease Patients

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ABSTRACT

Background: Gout is a metabolic disorder characterized by disturbance in purine metabolism and urate excretion with manifestations of acute and chronic arthritis and tophus formation. **Aim of work:** To evaluate the role of musculoskeletal ultrasound (MSUS) in early detection of gout in CKD patients. **Subject and methods:** This study was carried out on 50 patients with CKD according to K/DOQI classification of CKD. Musculoskeletal ultrasound assessment for wrists, hands, feet and knees joints was done for all patients then they were divided into 2 groups according to presence or absence of MSUS specific findings of gout as double contour sign (DCS) and/or tophus formation. Statistical analysis carried out for all collected data using SPSS statistical significance was determined at as P value < 0.05. **Results:** Using MSUS revealed that 35 patients (70%) had positive ultrasound findings for gouty arthritis. 10 of this group (28.6 %) were non hyperuricemic. The group of patients with positive sonographic findings had significant higher serum uric acid and older age than other group (P value =0.004), (P value < 0.001) respectively. MSUS reveled sensitivity 80 % and specificity 47 % in the detection of gout in patient with CKD.

Conclusion: MSUS is considered a reliable tool with high sensitivity in screening of gouty arthritis in asymptomatic hyperuricemic patients.

Keywords: gouty arthritis, ultrasound findings of gout, chronic kidney disease.

1. Introduction

Gout is a prevalent rheumatologic illness that is a leading cause of inflammatory arthritis in adults. It is caused by the formation of monosodium urate crystals (MSU) in tissues. It is distinguished by recurrent bouts of swollen, painful, and heated joints. When the serum urate content surpasses the solubility point (6.8 mg/dL), crystals of monosodium urate (MSU) develop and precipitate in the joint tissues, causing gout (Beyl Jr *et al.,* 2016).

Chronic kidney disease (CKD) is a separate risk factor for gout development. It has been demonstrated that 90% of cases of hyperuricemia are caused by poor renal excretion. As a result, detecting silent gout is critical because it can cause bone erosions and joint degeneration even before symptoms arise. Ultrasounds (US), a noninvasive, ionising radiation-free, simple, and low-cost method, have lately been utilised to locate MSU crystal deposits in order to diagnose gout (Davies *et al.,* 2019).

Early in the course of the disease, musculoskeletal ultrasounds (MSUS) can identify crystal accumulation in soft tissues and joints. As a result, it can be utilized not only to guide aspiration but also to diagnose gout. As a result, it was included in the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) (2015) gout diagnostic criteria (Wilson and Saseen, 2016).

The aim of the work to study the role of musculoskeletal ultrasound in screening of asymptomatic gouty arthritis in CKD patients.

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2. Patients and Methods

Type of the Study: Cross sectional study.

This study was conducted on 50 patients with different stages of chronic kidney disease according to K/DOQI classification of CKD.

They were recruited from the Internal Medicine department and hemodialysis unit at Tanta University Hospital after informed consent from every patient in the period from January to June 2021. A total of 50 patients were enrolled for this study (28 men and 22 women).

They were divided into two groups:

Group I: patients who had positive specific MSUS findings for gout (presence of DC sign, gouty tophi or both).

Group II: patients without specific findings of gout by MSUS.

Inclusion criteria:

Our study included 50 patients who had CKD according to K/DOQI classification of CKD with no previous clinical symptoms for gout.

Exclusion criteria:

- Previously symptomatic gouty arthritis.
- Patients with known autoimmune connective tissue disorders
- Previous operations or trauma to the joints.
- Malignancy

Clinical and laboratory assessment

All patients were subjected to the following

1. Full history taking especially for duration of the CKD, diabetes mellitus, hypertension or other comorbidity.
2. Laboratory investigations including the following:

- Serum uric acid. (mg/dl)
- Serum creatinine and blood urea. (mg/dl)
- Total ca.(mg/dl)
- Serum phosphorus (po4). (mg/dl)
- Parathyroid hormone level. (PTH) (pg/dl)
- C – Reactive protein titer (CRP). (mg/l)
- Erythrocyte sedimentation rate (ESR) (1^{st} hour). (mm/hr)
- Complete blood count (CBC): hemoglobin level (g/dl), total leukocytic count (cell/mm^3), platelet count (10^3 / ul)

3. Staging of chronic kidney disease from stage I to V according to K/DOQI classification of CKD.
4. Imaging

Musculoskeletal ultrasound was performed on 42 joints (hands, wrists, knees, ankles and feet) searching for pathological specific findings of gout (double contour sign and/or gouty tophi) in these joints and surrounding soft tissues.

We used Alpinion " ECUBE 5 " device for examination of joint. The target joints were scanned by (L3 - 12T) transducer. All joints were examined longitudinally and transversally.

Ethical considerations

Consent: Informed consent was taken from all patients which includes the following information:

1. The aim of research and steps done.
2. All data were confidential.
3. All data were used in research only.

4. An identified person to whom the relatives will return to at any time for explanations.

For Patient Privacy:

1-There was a code number for each patient in special folder.

2-The results of research were used in scientific publishing only.

For Safety of the Patients:

1-Complete asepsis were practiced during the procedures.

2-Proper healthful disposal of any disposables used.

Unexpected risks that appear during the courses of research were cleared to the participants and the ethical committee.

Statistical considerations

Once data were collected, a code sheet was developed. Organization, tabulation, presentation and analysis of data were performed by using SPSS (Statistical Package for the Social Sciences) V25 of IBM, USA.

1- Mean value (X):

The sum of all observations divided by the number of observations.

2- Standard Deviations (S.D.):

It measures the degree of scatter of individual varieties around their mean.

3-The unpaired student t-test:

It was used to compare between two groups in quantitative data.

4-Chi-square (x^2):

The hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi square and likelihood-ratio chi-square.

3. Results

Hyperuricemia was found in 31 patients of all patients included in the study, it was the highest level with stage I, II and V (22.6 %), then stage III (19.4 %) and lastly stage IV (12.9 %) There was no significant difference between all stages according to presence of hyperuricemia (P value =0.551) (Table 1).

Table 1: Association between hyperuricemia and stages of CKD

	Hyperuricemia				**Fisher's Exact test**
	Yes N=31		**No N=19**		
	N	%	N	%	P value
Stage I	7	22.6%	2	10.5%	0.551
Stage II	7	22.6%	4	21.1%	
Stage III	6	19.4%	4	21.1%	
Stage IV	4	12.9%	6	31.6%	
Stage V	7	22.6%	3	15.8%	

Hyperuricemia considered if serum uric acid level was ≥ 6 in females and ≥ 7 in males.

35 patients (70 %) of our studied patients had gouty arthritis. Our patients were divided into two groups according to the findings of specific ultrasonographic signs of gout as: (presence of double contour sign (DC), gouty tophi with or without underling boney erosions) into:- (Table 2)

- Group I (positive MSUS findings) and Group II (negative MSUS findings). We found that, Comparison between the 2 groups reveled high positive significant difference in the duration of CKD (p value = 0.005) with median 4 years and mean rank (2 -5). So, longer duration of the disease was associated with higher rate of MSUS findings.

- There was significant difference between the 2 groups according to the age (p value = 0.043) with mean ± SD (54.4 ± 11.5) in group I and (46.5 ±14.1) in group II. So, gout was associated with higher age.
- There was no significant difference according to sex. Also, we found that there is no correlation between the presence of DM or hypertension and musculoskeletal findings in all studied patients. (P value = 0.804), (p value = 0.416), (p value = 0.423) respectively.

Table 2: Comparison between the two groups as regards the demographic data, duration of CKD and associated DM or HTN.

		Gouty arthritis by MS ultrasound (double contour or tophi)				*P value*
		Group 1 (N=35.70%)		**Group 2 (N=15.30%)**		
Age (years)	Mean ± SD	54.4 ±11.5		46.5 ±14.1		0.043*[b]
Sex	Female	15	42.9%	7	46.7%	0.804 [c]
	Male	20	57.1%	8	53.3%	
Duration of the disease (years)	Median (IQR)	4.0 (2.0-5.0)		1.5 (1.0-3.0)		0.005* [a]
	Mean rank	29.29		16.67		
Diabetes Mellitus	No	16	45.7%	5	33.3%	0.416 [c]
	Yes	19	54.3%	10	66.7%	

- In our study, when we did correlation between hyperuricemia and MSUS findings in both groups, we found significant positive correlation (P value = 0.036) as we found positive findings in 25 patient (71.4 %) with hyperuricemia and 10 patients with normal uric acid.
- In group I, we found 10 patients of them (28.6%) had positive specific US findings of gouty arthritis but without having hyperuricemia. These findings can prove the role of MSUS in detection of gout even before exceeding normal serum uric acid level (Table 3 and Figure 1).

Table 3: Correlation between presence of hyperuricemia and the ultrasound findings.

			Gouty arthritis by MS ultrasound (double contour or tophi)		Chi-Square test
			Group 1 (N=35.70%)	**Group 2 (N=15.30%)**	P value
Hyperuricemia	No	N	10	9	0.036*
		%	28.6%	60.0%	
	Yes	N	25	6	
		%	71.4%	40.0%	

*Significant at p<0.05.
Hyperuricemia considered as ≥ 6 mg/dl in females and ≥7 mg/dl in males. CRP considered positive ≥ 6 mg/l.

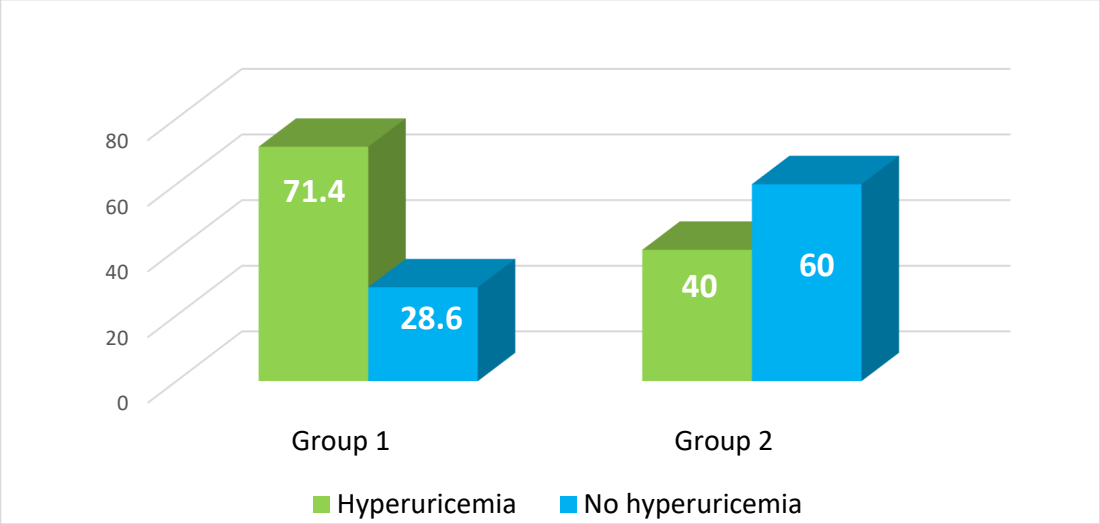

Fig. 1: Correlation between presence of hyperuricemia and the ultrasound findings.

Also, we studied the association between MSUS findings of gout and staging of CKD. We found that there is no significant difference between different stages of CKD and the incidence of gouty arthritis.

In group I we found that 7 patients (20.3 %) were stage I, 8patients (20.3%) were stage II, 7 patients (20.3%) were stage III, 7 patients (20.3%) were stage IV and 7 patients (20.3%) were stage V (Table 4).

We found in this study that musculoskeletal ultrasound had sensitivity 80 %, specificity 47 % and accuracy 63.5 % with positive predictive value 60.15 % and negative predictive value 70.15 %. So, it can be a good predictor for diagnosing gouty arthritis in CKD patients in all stages of the disease (Table 5).

Table 4: Association between stages of CKD and MSUS findings of gout

	Gouty arthritis by MS ultrasound (Double contour or tophi)				Fisher's Exact test
	Group 1 (N=35. 70%)		Group 2 (N=15.30%)		
	N	%	N	%	P value
Stage I	7	20.0%	2	13.3%	0.989
Stage II	7	20.0%	4	26.7%	
Stage III	7	20.0%	3	20.0%	
Stage IV	7	20.0%	3	20.0%	
Stage V	7	20.0%	3	20.0%	

Table 5: Performance of the musculoskeletal ultrasound for diagnosing gouty arthritis in CKD patients

	TP (N)	FP (N)	TN (N)	FN (N)	Sensitivity 95% CI (%)	Specificity 95% CI (%)	PPV 95% CI (%)	NPV 95% CI (%)	Accuracy 95% CI (%)
The MS ultrasound	25/31 80.64%	10/19 52.63%	9/19 47.36%	6/31 19.35%	80.0 (70.82-87.33)	47.0 (36.94 - 57.24)	60.15 (55.05-65.04)	70.15 (60.12-78.55)	63.50 (56.42-70.18)

The gold standard is hyperuricemia
TP: true positive, FP: false positive, TN: true negative, FN: false negative, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval

Specific MSUS findings for gout

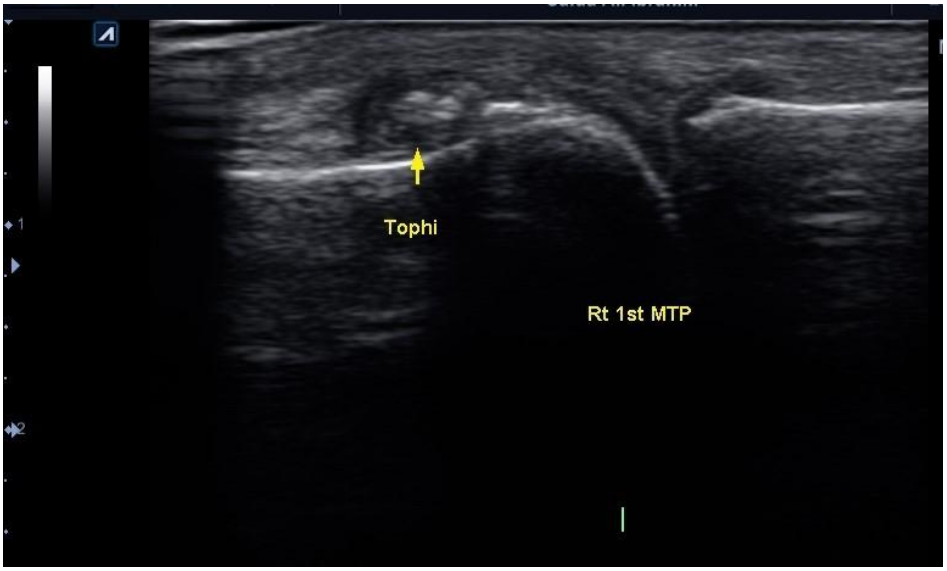

Fig. 2: Right first MTP joint showing tophus formation (heterogenous shadows with surrounding hypoechoic shadow).

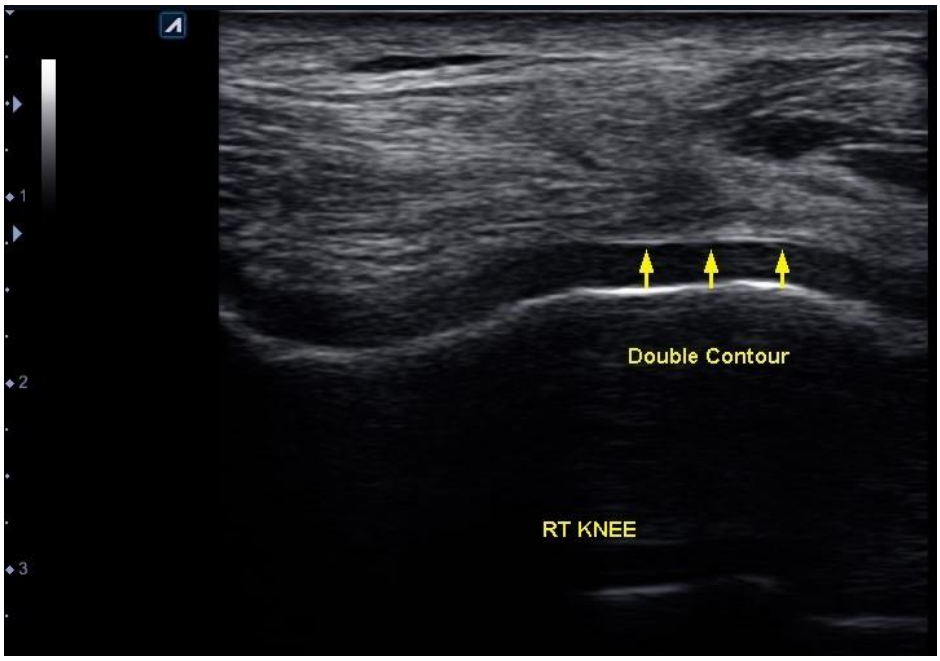

Fig. 3: Double contour sign at right knee joint

4. Discussion

The term "gout" refers to a group of clinical disorders caused by an excess of serum urate (uric acid). Gouty arthritis is the most prevalent clinical manifestation of gout, and it often manifests as acute and episodic arthritis, though it can appear or evolve to chronic arthritis (Wilson and Saseen, 2016).

Gout is the most prevalent cause of inflammatory arthritis in adults and one of the most common rheumatologic illnesses. As the prevalence of gout continues to rise, various innovations and

evidence-based updates for gout diagnosis and management have been addressed (Merdler-Rabinowicz *et al.,* 2017)**.**

Ultrasound (US) is a noninvasive, ionising radiation-free, simple, and low-cost method that has recently been utilised to locate MSU crystal formations in order to diagnose gout (Davies *et al.,* 2019).

As a result, we attempted to assess the relevance of musculoskeletal ultrasonography in the screening for asymptomatic gouty arthritis in CKD patients.

To accomplish this goal, we conducted a study in which 50 individuals with chronic kidney disease (CKD) were examined for pathological specific findings of gout using musculoskeletal ultrasonography.

The study comprised 50 CKD patients ranging in age from 27 to 83 years (mean age: 52.012.7). The participants were mostly men. This contradicted what the National Health and Nutrition Examination Survey (NHANES) of 2004 stated about gender differences in the incidence of CKD in the United States. They discovered that CKD is more common in women. The disparity could be attributed to a bias in his study caused by serum creatinine standardisation, as demonstrated in his study. Another rationale was that the authors of the NHANES study relied on albumin creatinine ratio and s. creatinine rather than serum creatinine alone (Go *et al.,* 2004).

In our analysis, the most common chronic conditions were hypertension (82%), followed by diabetes (58%). Emerging data suggests that hyperuricemia has a pathogenic role in the development of HTN and CKD, as well as the progression of CKD. The increase in serum uric acid in hypertension may be attributable to the hypertensive state's decrease in renal blood flow, because a low renal blood flow stimulates urate reabsorption. Hypertension can also cause microvascular illness, which can lead to local tissue ischemia (Mallat *et al.,* 2016).

In this study, using musculoskeletal ultrasound reveled 70% of patients "35 Ultrasound revealed that 70% of the "35 patients" had gouty arthritis. This was consistent with the findings of Juraschek *et al.* (2013), who discovered that gout was present in up to 75% of CKD patients at various stages. 7. Other studies found a lower prevalence rate of ultrasound-diagnosed gouty arthritis, such as Pineda *et al.* (2011), who reported gouty arthritis by ultrasound in 25 out of 100 CKD patients.

The presence of a double contour sign, tophi, or both was used to screen for gout in the current investigation. This is similar to what Liu *et al.* (2021) reported, but he added other signs and gave points for each parameter as synovial effusion (2 points), synovial hypertrophy (5 points), tophus (3 points), bone erosion (7 points), and first MTP joint: double contour sign (2 points), tophus (9 points), bone erosion (4 points). The highest possible overall score was 42. The ideal gout cut-off score was 6.5. Sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were calculated to be 86.9%, 75.2%, and 0.878, respectively. The patients were divided into groups based on their ultrasonography score (range 0-42). The prevalence of intercritical gout, tophi and bone erosion increased with the increase of the score. In the validation population, 83.20% of 193 patients with gout had ultrasound scores above 6.5; 76.10% of 163 patients with asymptomatic hyperuricaemia had ultrasound scores under 6.5 (Gutierrez *et al.,* 2009; Liu *et al.,* (2021).

Puig *et al.* (2008) investigated 35 asymptomatic hyperuricemia patients and discovered tophi development in both tendons and synovium in 34% of patients, with a preference for the distal patellar tendon.

In this study, there were no significant differences between the two groups based on gender (P value =0.804). So, according to the findings of this study, male gender is not a risk factor for greater crystal deposition or tophi formation. Similarly to our findings, Pineda *et al.,* (2011). There was no statistically significant difference in sex between the two groups, with males predominating in both. Howard et al.,2011 and Lu et al.,2020 got similar results since they did not account for sex variations in crystal deposition and observed no significant difference in hyperuricemia between males and females (Lu *et al.*, 2020; Howard *et al.,* 2011). On the other hand, Jing et al. (2015) reported male sex as a significant risk factor for tophi deposition in CKD patients and also, Kirshnan, (2012) reported higher incidence of crystal depositions among males.

The comparison of the two groups in this study revealed a high positive significant difference in the duration of CKD (p=0.005). Furthermore, Lu *et al.* (2020) found a statistically significant positive link between the presence of tophi or double contour and disease duration, owing to the fact

that hyperuricaemia or gout is a continuous and chronic pathophysiological process that is altered by time. As a result, crystal depositions rose dramatically as hyperuricemia duration increased. [11].

In the current investigation, there was no significant difference between the two groups in terms of the occurrence of diabetes or hypertension (P values =0.416, 0.423, respectively). In contrast to our findings, Pineda *et al.,* (2011) discovered a greater prevalence of diabetes and hypertension among gouty arthritis patients (Kirshnan, (2012). Jing *et al.,* 2015 He established a significant relationship between diabetes and gout, stating that 46.3% of gouty people had diabetes and 97.4% had high blood pressure. He contended that both disorders were linked to CKD and, by coincidence, to gout. Lu *et al.* (2020) found higher prevalence of diabetes among gouty arthritis patients and comparable prevalence of hypertension. The difference could be referred to the high prevalence of hypertension in the total cohort which affected the distribution of cases among both groups.

There was high positive significant difference at the serum uric acid level between the 2 groups (*p=0.004).* Similarly, Liu *et al.* (2021) reported cut-off value equal to 6.5 above which gouty arthritis could develop and his scoring system was based on the differential ultrasound signs can effectively evaluate the severity of joint injury in individuals with gout and asymptomatic hyperuricaemia.

Although people with asymptomatic hyperuricemia might not have clinical symptoms of acute arthritis, ultrasonography can reveal certain structural alterations in joints. Previous research has shown that asymptomatic hyperuricemia and gout have the same acoustic appearance but differ in severity Pineda *et al.,* (2011), Although urate deposition was identified in persons with asymptomatic hyperuricemia, Dalbeth *et al.,* (2015) found that deposits occurred more frequently and in greater amounts in patients with symptomatic gout.

As the study focused primarily on CKD patients, there was no statistically significant difference between the two groups in terms of renal function tests such as s. creatinine and blood urea (P value = 0.799), (P value = 0.844). In another study with a larger sample size, patients with asymptomatic hyperuricemia who had tophi by ultrasound had lower eGFR than those who did not have tophi [11] , and there was a statistically significant negative link between the two. Lower eGFR has also been identified as a significant risk factor for ultrasound-proven gouty arthritis by Jing *et al.,* (2015); Krishnan, (2009) and McAdams-DeMarco *et al.* (2013) verified the occurrence of an inverse connection between eGFR and gout as well as hyperuricemia. The difference may be explained by the relatively smaller sample size in our study in addition to absence of control group with normal s. creatinine.

In the current study, there was no statistically significant association between CKD stage and degree of hyperuricemia or gout (P value =0.551) , In contrary to this result, a study conducted among individuals with CKD identified in the nationally representative population-based National Health and Nutrition Examination Survey (NHANES) found a similar gout prevalence of 35% among those with stage 4 CKD, but lower gout prevalence of 11% among those with stage 3 CKD compared with our estimate of ~25% for CKD stages 3a and 3b [18]. On the other hand, Kirshnan, (2009) reported inverse relationship between grade of nephropathy and degree of hyperuricemia or gout.

In the current study, we reported musculoskeletal ultrasound to have 80 % sensitivity and specificity 47% to diagnose gouty arthritis in asymptomatic gouty CKD patients. Liu *et al.* (2021) reported lower sensitivity 79.3% but more specificity 77.5% to diagnose asymptomatic hyperuricemia. [9]

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