Annals of International Medical and Dental Research
E-ISSN: 2395-2822 | P-ISSN: 2395-2814
Vol-7, Issue-5 | September-October 2021
Page no- 71-80 | Section- Research Article (Orthopaedic)

Serum Uric Acid Levels and Musculoskeletal Manifestations

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Received: 22 May 2021
Revised: 03 July 2021
Accepted: 12 July 2021
Published: 21 August 2021

Abstract

Background: To assess serum uric acid levels in patients with musculoskeletal complaints and study its prevalence and correlation with the complaints. **Materials & methods**: Total 1123 patients complaining of unexplained musculoskeletal problems for duration of more than 4 weeks were enrolled in the study. Patients with known rheumatologic autoimmune disease known gouty arthritis, malignancy, evident cardiovascular disease or any associated endocrine gland disorder apart from diabetes mellitus were excluded. All patients were subjected to full history taking, clinical examination, laboratory tests. Anthropometric measurements were done for assessment of body mass index and central obesity. **Results**: Out of 1123 patients, 657 patients (58.5%) had elevated SUA whereas 466 patients (41.5%) had normal SUA. Elevated SUA were positively correlated with musculoskeletal complaints. Among the study population, around 40% had soreness, bodyaches, 17.9% had interphalangeal & wrist joint pain, stiffness, 13.86 % had bilateral knee pain, 11.4% had low backache and stiffness. Others contributed to <10% each. Prevalence of elevated SUA was higher in male patients than female patients with significant p-value ($p<0.0001$). 619 patients (55.12%) were alcoholics, and mean SUA levels among alcoholics are higher when compared to non- alcoholics which was statistically significant with p value of <0.00001. 266 patients (23.69%) had co-existing diabetes mellitus. **Conclusion**: Majority of the cases with unexplained musculoskeletal complaints were associated with elevated SUA level. Hence, hyperurecemia plays a significant role in the pathophysiology and development of various musculoskeletal manifestations.

Keywords: Serum Uric Acid, Musculoskeletal Complaints, Diabetes, Alcoholism

INTRODUCTION

Uric acidis a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula C5H4N4O3.[1] It is the final step of the purine catabolic pathway in human beings. An abnormality in handling uric acid can cause attacks of

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painful arthritis (gout attack), kidney stones and blockage of the kidney filtering tubules with uric acid crystals, leading to kidney failure. Episodic diffuse musculo-skeletal pain developing in and around a joint region in the absence of clear etiology, diagnosis, and therapy remains a major obstacle in current orthopaedic practice. A clear diagnosed gout is the most common inflammatory arthritic disease, affecting about 1% to 2% of the population.[1]

Hyperuricemia is defined as a serum uric acid level greater than 6.8 mg/dL, as measured by the automated enzymatic (uricase) method. Serum uric acid concentrations rises at puberty from childhood mean values of 3.5 mg/dL to adult levels of 5.0 ± 2.0 mg/dL. In contrast, levels remain constant in women until menopause, when they begin to rise to the level in men. The normal uric acid level in women is 4.0 ± 2.0 mg/dL. The reason is that estrogen promotes excretion of uric acid during the reproductive period.[2]

Although deposition of tophus is a common feature in chronic gout; however, signs and symptoms are not always well pronounced in cases of uncommon sites.[3] In individuals with chronic asymptomatic hyperuricemia, the presence of synovitis and double contour sign by US may represent a subclinical manifestation of monosodium urate crystal nucleation, capable of triggering inflammatory pathways (IL-6 and IL-8) similar to what is observed in patients with gout.[4]

Prevalence is expected to increase due to changes in diet – such as high intake of meat, fructose and beer - and the ageing of the population.[5] Clinically, gout is defined as a deposition disease, *i.e.* diagnosis is confirmed by the presence of monosodium urate crystals in the synovial fluid or tophi in soft tissue.[6] These crystals are responsible for acute episodes of inflammation as well as long-term sequelae due to chronic inflammation of gout.[7]

The deposition of monosodium urate results by crystallization process is temperature and pH-dependent and occurs when the theoretical saturation threshold of 6.8 mg/dL(~400 µmol/L) serum urate at 37°C is exceeded.[7] Accordingly, lowering the serum urate level and depleting the body urate pool are the established goals in the treatment of gout. To achieve this, the serum urate must be reduced below the saturation point of monosodium urate under physiological conditions. Based on these conclusions, the European League against Rheumatism (EULAR) and American Society of Rheumatism Task Forces for Gout recommend lowering serum urate levels to a target of ≤6 mg/dL (360 µmol/L).[8,9] For patients with tophaceous disease manifestation, the British Society of Rheumatology (BSR) and American College of Rheumatology (ACR) proposed an even stricter serumurate target of <5 mg/dL (<300 µmol/L).[8,10]

There are case reports indicating that many people with higher serum urate levels do not develop gout, while others presenting with crystal proven gout have "nearly" normal serum urate levels at the time of investigation.[11] While the usefulness of urate- lowering treatment in patients with clinical manifestations of hyperuricemia has been established, its use in asymptomatic hyperuricemia is still the object of several controversies.[12]

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Since evidence for subclinical musculo-skeletal involvement in otherwise asymptomatic individuals with hyperuricemia is lacking, urate lowering therapy to date is only indicated and reimbursed in cases of confirmed gout.

Current international guidelines do not address the pharmacologic management of asymptomatic hyperuricemia due to a paucity of prospective, randomized, controlled intervention trials in that area.[13] Still there are no data available how many patients with asymptomatic hyperuricemia have to be treated to prevent one patient with gout (number needed to treat/number needed to harm). However, in a cross-sectional controlled study ultrasound findings demonstrate the signs of present monosodium urate crystal tissue deposition in both intra and extra-articular structures from asymptomatic hyperuremic individuals.[14]

There is very limited literature available in this area. Hence true purpose of study was taken up to assess the uric acid levels and musculoskeletal manifestations in territory care hospital.

MATERIALS AND METHODS

Study population

One thousand one hundred and twenty three (1123) patients complaining of unexplained musculoskeletal problems (eg. joint pain, joint swelling, low back pain, enthesitis, muscular pain, and generalized bone ache) for duration ≥ 4 weeks were included in the present study. All patients were recruited from Department of Orthopedicat Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telanagana over period of one year from October 2019 to August 2020. Informed consent was obtained from the patients to be included in the study.

Inclusion criteria: Included age between 20-80 years, both male and female genders, patients with vague musculoskeletal complaints.

Exclusioncriteria: For patients were the presence of known rheumatologic autoimmune disease, known kidney disease, known gouty arthritis, malignancy, or any endocrinal gland disorders apart from diabetes mellitus (DM).

Clinical evaluation

All patients were subjected to full history taking and thorough clinical examination for assessment of the risk factors for hyperurecemia. Age, history of alcoholism and diabetes were documented. Anthropometric measurements (height, weight and waist circumference) were done for assessment of BMI (weight/ hight^2) and central obesity.

Laboratory Methods

Serum Uric Acid calculation:

The uric acid was calculated from serum using uricase/ perioxidase method using an autoanalyser. The principle of the method is:

Uric acid in the sample is subjected to coupled reactions described below, such that a coloured complex is formed. This involves reaction between uric acid and uricase which forms allantoin and peroxide. This peroxide reacts with 4-Aminoantipyrine in the presence of peroxidase to form Quinineimine, a coloured complex, which is measured using a spectrophotometry.

All the data were collected on a proforma prepared for this study and was analysed.

Serum uric acid level was considered normal (if SUA< 6.8 mg/dl in men and < 6.0 mg/dl in women), mild to moderate hyperuricemia (if SUA 6.8-9 mg/dl in men and 6–9 mg/dl in women) and marked hyperuricemia (if SUA> 9 mg/dl in both men and women).

ESR was measured using Westergren method and taking the 1st hour reading. Triglycerides, total cholesterol and high density lipoprotein (HDL) were assayed (Roche Diagnostics). Fasting blood sugar was assayed using commercial kits.

Imaging Methods

Plain radiographs (Antero-posterior views for both feet and sacroiliac joints; and lateral views for both heels) were done for all patients.

Ethics Approval

This study was evaluated and approved by ethics committee of Chalmeda Institute of Medical Sciences

Statistical Analysis

The statistical analysis was performed using SPSS 17.0. The chi-square test was used for an overall approach to compare percentages among the groups. ANOVA test compare the difference between more than two group means in interval and ordinal variables. Risk estimate was done by odds ratio. Correlations were calculated using Spearman's rank correlation coefficient. The level of statistical significance was set at a p level < 0.05.

RESULTS

The present study was conducted in the Department of Orthopedics, Chalmeda Anand Rao Medical College, Karimnagar with the objective of assessing the uric acid levels in patients presenting with musculo skeletal complaints. The results of the study are as follows:

Among the study population, 28.05% belonged to the age group of 40-49 years, followed by 50-59 years (22.53%) and 30-39 years (20%) each. 13.54% belonged to age group of 60-69 years and 9.08% belonged to 70-79 years. Around 6% belonged to 20-29 years. Other age groups contributed to 1% each.

Among the study population, 28.05% belonged to the age group of 40-49 years, followed by 50-59 years (22.53%) and 30-39 years (20%) each. 13.54% belonged to age group of 60-69 years and 9.08% belonged to 70-79 years. Around 6% belonged to 20-29 years. Other age groups contributed to 1% each. 54.05% were males, 45.95% were females.

Among the study population, around 40% had Soreness, Bodyaches, Mild fever, 17.9% had Interphalangeal & wrist joint pain, stiffness. 13.86% had bilateral knee pain. 11.4% had low backache and stiffness. Others contributed to <10% each.

Among the study population, 41.50% serum uric acid levels were within normal limits. 58.50% had increased serum uric acid levels – hyperuricemia.

The prevalence of hyperuricemia is 58.50%

Among the study population, 55.12% were alcoholics

Among the study population, 53.70% were not having any co-morbidities. 23.69% had only diabetes, 9.17% had only hypertension. 13.45% had both diabetes and hypertension.

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Table - 1: Showing the chief complaints:

Chief Complaints	Obs	Mean	Std Dev	P value
Ankle pain and stiffness	17	6.6059	2.3395	<0.000001 (Statistically Significant)
Bilateral knee pain	156	4.0923	1.1573	
Elbow pain & stiffness	9	4.2	0.4444	
Great toe pain and swelling	61	6.9098	2.6798	
Interphalangeal & wrist joint pain, stiffness	201	6.2627	2.1488	
LBA and Stifness	128	4.075	1.2158	
multiple joint pain & stiffness	38	5.8316	0.1358	
Neck pain +metacarpophalangeal stiffness	9	2.3889	0.2421	
Plantar fasciitis	34	4.35	1.1823	
Retrocalcaneal bursitis	48	5.8229	2.3686	
soreness, bodyache, mild fever	422	7.2059	1.9271	

The mean serum uric acid levels according to the chief complaints are at higher end for complaints like soreness, bodyache, mild fever, Great toe pain and swelling, Ankle pain and stiffness, Interphalangeal & wrist joint pain, stiffness suggesting the presence of musculoskeletal disorders.

The mean difference among the chief complaints and mean serum uric acid levels is statistically significant with P value of <0.000001.

Table – 2: Showing the association between the alcoholism and serum uric acid levels:

Alcoholism	Serum Uric acid levels		P value
	Mean	Std Dev	
No	4.902	1.8104	<0.00001 (Statistically significant)
Yes	6.8355	2.2006	

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The mean serum uric acid levels among alcoholics are higher when compared to non-alcoholics. The mean serum uric acid levels among alcoholics and non-alcoholics is statistically significant with p value of <0.00001.

Table – 3: Showing the mean values of serum uric acid according to co-morbidities:

Co-morbidities	Obs	Mean	Std Dev	P value
DM	266	6.3098	2.1312	0.001 (Statistically Significant)
DM,HTN	151	6.3033	2.5256	
HTN	103	5.6883	2.0706	
None	603	5.7806	2.2342	

The mean serum uric acid levels among diabetes and both diabetes and hypertension group are almost similar and are on the higher end when compared to hypertension group and no co-morbidities group. The difference in the mean values is statistically significant with P value of 0.001.

Table – 4: Showing the association between serum uric acid levels and Blood urea values:

Serum Uric Acid levels- With In Normal	Blood urea levels		P value
	Mean	Std Dev	
Yes	28.4588	15.8473	<0.0001
No	35.1931	20.9979	

The mean blood urea level among the hyperuricemic patients was high when compared to the patients with normal serum uric acid levels. The mean difference between the groups is statistically significant with P value of<0.0001.

Table – 5: Showing the association between serum uric acid levels and Blood urea values:

Serum Uric Acid levels- With In Normal limits	Hemoglobin levels		P value
	Mean	Std Dev	

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Yes	12.0915	2.4156	0.01
No	12.4506	2.3218	

The mean hemoglobin levels among the both the groups are almost similar withminor differences in the mean value. The difference in the mean values of both the groups is statistically significant with P value of 0.01.

Table – 6: Showing the association between serum uric acid levels and RBS values:

Serum Uric Acid levels- With In Normal limits	Random Blood Sugar Levels		P value
	Mean	Std Dev	
No	126.7139	50.1903	0.008*
Yes	129.4485	38.6075	

**Mann Whitney U test values

The mean RBS values were higher in patients with higher serum uric acid levels. The difference in the mean is statistically significant with P value of 0.008.

Table – 7: Showing the association between serum uric acid levels and Serum Creatinine values:

Serum Uric Acid levels- With In Normal limits	Serum Creatinine levels		P value
	Mean	Std Dev	
No	1.0401	0.5323	0.07
Yes	1.5485	7.2001	

The mean serum creatinine values were higher in patients with higher serum uric acid levels. The difference in the mean is not statistically significant with P value of 0.07.

DISCUSSION

Hyperuricemia is fairly common, with prevalence ranging between 2.6% and 47.2% in various populations. A variety of factors appears to be associated with high serum urate concentrations. In adults, serum urate levels correlate strongly with the age, alcoholism, diabetes mellitus body weight, height.

Our study included 1123 patients complaining of unexplained musculoskeletal problems, 657 patients (58.5%) had an increased serum uric acid level. The upper cut-off point of uric acid values was at 6.8 mg/dl for men and 6 mg/ dl for women.

Hyperuricemia has been shown to be significantly more common in patients increasing age. In present study, it is

observed that as the age is increasing, the mean serum uric acid levels are increasing. The difference in the mean according to the age is also statistically significant with P value of 0.02.

We have found an association between musculoskeletal complaints and SUA. The increase in odds ratio by increasing SUA level can be compared with greater exposure to a suspected risk factor. Our study has not proven any causal relationship.

In the present study, around 40% had Soreness, Bodyaches, Mild fever, 17.9% had Interphalangeal & wrist joint pain, stiffness. 13.86% had bilateral knee pain. 11.4% had low backache and stiffness. Others contributed to <10% each.

A cross-sectional study was conducted by Comberg HU,[15] in a single German center. Generally healthy subjects (including patients with controlled mild hypertension, hyperlipidemia, and/or not insulin dependent type 2 diabetes) aged 20-75 years presenting for their annual routine check-up were invited to participate. In total, 600 patients (54.7%) male, (55.2% ± 13 7 years) were included in the survey. Urate levels were closely correlated to the number of patients complaining about joint pain (r=0.978). Higher urate levels were associated with a higher percentage of patients with joint pain. There was a marked increase in the percentage of patients experiencing joint pain from urate level 5 (30.8%) to 5.5 (60.9%). Lumbar spine, cervical spine, shoulder, and knee were the most common locations for joint pain. Multivariate analysis indicated weight, purine intake, alcohol consumption, administration of diuretics, creatinine, and triglycerides as factors with significant impact on the urate level. Of all tested variables, only serum urate had a significant impact on jointpain(OR1.996;95%CI1.6262.451;p<0.00 01). A significant correlation between pain in various joints and urate levels was found for all most commonly affected regions.

A cross sectional study was done by Jonsson H et al,[16] to analyze whether hyperuricema in the elderly is associated with joint pain. Participants in the population-based AGES-Reykjavik Study (males 2195, females 2975, mean age 76(6)) answered standardized questions about joint pain. In addition they recorded intermittent hand joint pain by marking a diagram of the hand. In males, no association was found between hyperuricemia and pain. Females however, showed a positive association between hyperuricemia and joint pain at many sites. After adjustment for age, BMI and hand osteoarthritis however, only intermittent hand joint pain (OR 1.30(1.07–1.58), p = 0.008) and intermittent pain in ≥10 hand joints (OR 1.75(1.32–2.31), p<0.001) remained significant. The best model for describing the relationship between serum uric acidlevels (SUA) and in teritten than joint pain in≥10 joints wasnon-linear with a cut-off at 372 µmol/L. The attributable surplus number of symptomatic females with SUA ≥372 µ mol/L was approximately 2.0% of the study population for those reporting pain in ≥10 hand joints. Next after having severe hand osteoarthritis, SUA ≥372 was an independent predictive factor of intermittent pain in ≥10 hand joints. Intermittent hand joint pain was also an independent risk factor for worse general health description. The authors concluded that Results from this population based

study indicate that hyperuricemia in elderly females may be a rather frequent cause of intermittent hand joint pain, often in many joints. The most likely explanation relates to low- grade urate crystal induced inflammation.

A non-randomised multicetric prospective study was carried out by Soni S et al,[17] from December 2015 to May 2018. This is a descriptive study comprising 108 patients with diagnosis of gout according to the American College of Rheumatology (ACR) criteria. The study revealed that male patients was 86 (79.63%) and 22 (20.37%) patient were female. In this study 108 patients with serum uric acid level between 5.5 -9.0 mg/dl with age from 20 yr to 60 yr were studied. Uric acid level between 7 - 9 mg/dl found in 68.48% and it was in age between 30–45 yr of age. 73 patiens (67.59%) had pain at enthesis for at least once before inclusion in the study. Intra-tendinous tophi and hyperechoic aggregates were the most frequent lesions at the tendon in US examinations. In this study Patellar tendon is the most frequently involved tendon followed by quadriceps, Achilles and peroneus tendon. The authors concluded that tophius involvement of tendon in the lower limbs in gout is very frequent, particularly at the patellar tendon, Quadriceps tendon and Achillestendon.

CONCLUSION

The present study gives an indication that uric acid may contribute to development of different patterns of musculoskeletal manifestations and the rise in SUA does not merely indicate gout. The pathophysiological mechanisms underlying the findings are unknown, and merely hypothetical explanations are conceivable. Hyperuricemic patients were exposed to subclinical musculoskeletal manifestations. We support the studies which advised the addition of hyperuricemia to the list of differential responsible for vague musculoskeletal complaints.

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Source of Support: Nil, Conflict of Interest: None declared