

URIC ACID PROFILE IN PATIENTS WITH CHRONIC NONSPECIFIC MUSCULOSKELETAL PAIN

Naeema Afzal, Tafazzul-e-Haque Mahmud**, S Shah Jahan**, Salma Kundi*

Departments of Chemical Pathology and Physiology,* Ayub Medical College Abbottabad

**Department of Biochemistry & Chemical Pathology, Shaikh Zayed, Federal Postgraduate Medical Institute, Lahore-Pakistan

Background: The present study was undertaken to determine the uric acid profile in patients with unexplained chronic musculoskeletal complaints, and to establish any possible causal role for altered uric acid profile in such patients. **Method:** A comparative study of 36 patients and 36 controls of both sexes and ages between 25-60 years was carried out at Shaikh Zayed Hospital, Lahore from November 2001-May 2002. Patient included were those who had at least 4-24 weeks duration of complaints. Uric acid profile for serum uric acid, uric acid excretion, uric acid clearance and total uric acid production was done. Additional tests included renal functions test, liver function test, cardiac enzymes, haematology and serology to exclude other underlying causes of complaints. **Results:** Mean serum uric acid levels were higher in patients as compared to controls ($p=0.05$), with 9 (25%) patients showing hyperuricemia. Uric acid clearance (female patients 5.86 ± 0.42 ml/min, female controls 8.06 ± 0.24 ml/min) and daily uric acid excretion (female patients 412.38 ± 28.52 mg/24 hours, female controls 487.79 ± 18.64 mg/24 hours) in female patients was significantly lower than control females ($P=0.034$ and $P<0.001$ respectively). Twenty patients (55.55%, 3 males and 17 females) were classified as under excretors of uric acid, while there were no under excretors in the control group ($p<0.001$). **Conclusion:** We conclude that abnormalities of uric acid profile, particularly under excretor status may be an underlying biochemical abnormality in a significant number of patients. Female patients appear more predisposed to abnormal uric acid profile such as hyperuricemia and under excretor status.

Key words: Uric acid, musculoskeletal diseases, gout.

INTRODUCTION

Complaints of chronic nonspecific musculoskeletal pain are very common as reported from many communities.^{1,2} The majority of these subjects do not fit in known disease entities and in 40-50% of cases no diagnosis can be made.³⁻⁷ Chronic nonspecific musculoskeletal pain has been defined as “recurrent or persistent pain with more than 4 weeks-24 weeks duration of no discernable cause.”^{2,7,8}

Prevalence of chronic nonspecific musculo-skeletal pain in general population in North England was reported to be 11.2% while it was 20-50% in different districts of Sweden.²

Classification of chronic nonspecific musculo-skeletal pain is based after excluding known cause of musculoskeletal pain^{1-3, 5, 14, 16, 17} such as given in Table 1.

Numerically more women are reported to have myalgia (70%), while 68% males localized pain to low back region.⁵ Mechanism of pain modulation varies in different studies.^{3,14,15} One study correlated myogenic hyperuricemia with elevated levels of xanthine oxidase in injured human skeletal muscles in association with inflammatory events and eccentric exercise.^{3,16}

Table 1: Causes of Generalized Chronic Musculoskeletal Pain^{1-3,5,14,16,17}

No.	Causes	No.	Causes
1.	Inflammatory and collagen disease	9.	Arthralgia
	Osteoarthritis	10.	Post fracture pain
2.	Cervical spondylosis	11.	Enzymatic defects
3.	Epicondylitis	12.	Mental disorders (depression agony)
4.	Neck muscle tension		Migraine
5.	Low back pain	13.	Angina pectoris
6.	Generalized analgia (incl: Fibromyalgia)	14.	Diverticulitis
7.	Myofascial pain syndrome	15.	No finding supporting diagnosis or symptom
8.		16.	

It has been reported that myogenic hyperuricemia may be caused by overproduction of uric acid, which is based on the excessive degradation of purine derivatives in exercising muscle.¹⁷ Eisinger et al associated fibromyalgia (a cause of muscle pain) with hyperuricemia and disturbance of carbohydrate metabolism expressed as decreased lactate and increased pyruvate production.¹²

A paper reviewing the urate metabolism, in hyperuricemia and in normal healthy subjects, describe that the pathogenesis of hyperuricemia consists of overproduction and under excretion of uric acid, which can be estimated using urate clearance test.¹⁸ Average normal urate clearance is 10ml/min.¹⁹

Over production is defined as the urinary urate excretion (Uua)mg/kg/hr being higher than 0.030 and uric acid clearance (Cua) lower than 6.1ml/min.¹⁸

There exists a balance between the production of purine nucleotide, catabolism of purine containing compounds to produce free purine, oxidation of purine to uric acid by xanthine oxidase, tubular reabsorption of urate and finally tubular secretion of urate. Disturbance of this balance can result in hyperuricemia and deposition of monosodium urate crystals in the tissues, leading to painful arthritis, chronic gouty arthritis, tophus formation, nephritis and muscle pain.²⁰ Hyperuricemia is also the biochemical feature of the group of clinical disorders collectively referred to as gout.^{20,21}

It was seen that multiple pain localization had worst prognosis on pain and general health and these patients also showed increased serum urate levels of unclear significance.⁵

A study carried out reported a higher mean serum uric acid level in patients as compared to pain free population.²² There are relatively few basic studies of the metabolism and transport of urate.²³

No studies on uric acid profile in chronic non-specific musculoskeletal pain have been reported from Pakistan. The present study was undertaken to elicit the role of uric acid profile in subjects with musculoskeletal pain in our setting.

MATERIALS AND METHODS

The study was carried out at Shaikh Zayed Hospital, Lahore from November 2001 to May 2002. A total of 72 subjects of both sexes and age groups between 25 to 60 years, comprising of 36 nonspecific pain patients and 36 controls were included in the study.

Patients with musculoskeletal pain of at least 4-24 weeks duration were included in the study group after excluding people with history of injury of over excretion, diabetes mellitus, renal disease, chronic infection, neoplastic condition or any other systemic disease, known cases of arthritic diseases and subjects testing positive for rheumatoid arthritis factor, ANA, ASOT, with raised levels of CPK, LDH, ALAT, AST, BUN, Creatinine, Glucose, and ESR. Detailed history was taken on prescribed Performa assessing the patients' disease status and history of musculoskeletal pain.

Physical examination of the subject was carried out for height, weight, temperature, blood pressure, anaemia, joint swelling, localization of pain, deformity and functional disability.

A 6ml venous blood sample from each subject and control was drawn and allowed to clot in a plastic tube. After 1-2 hours the tubes were centrifuged, serum collected and stored in marked serum storage tubes at -20⁰ C for later analysis.

Calculation for uric acid clearance, uric acid excretion, urine acid production and creatinine clearance were carried out.

Only those patients were included in the study who had no known disease entity.

Uric Acid

Abnormal serum uric acid was estimated by enzymatic colorimetric method using Bayer kit No. 6688/6699 on chemistry analyzer Technicon 2010. Uric acid is converted by Uricase into allantoin and hydrogen peroxide, which in the presence of peroxidase (POD), oxidizes the chromogen (4-aminophenazone/3-hydroxy-2, 4, 6-triodobenzoic acid) to a red colored compound.

Uric acid clearance

Uric acid clearance in ml/min was calculated by the formula $Uua \times V/Sua$, where “Uua” is urinary uric acid concentration expressed as mg/dl, “V” is urine volume per minute of “Sua” serum uric acid level expressed as ng/dl.

Over producers were calculated using the formula: $Uua \text{ mg/kg/hr} > (0.030Cua) + 0.325$, where (Cua) is urinary uric acid clearance expressed as ml/min and Uua is urinary uric acid excretion. *Under excretion* was taken as uric acid clearance $< 6.1 \text{ ml/min}$.

Additional tests

Cardiac Enzymes (LDH, CPK and AST), Kidney function (BUN, Creatinine) were assessed by dimension (AR) Clinical chemistry system

Diabetes mellitus was excluded by blood glucose estimation on dimension (AR) clinical chemistry system.

ANA, ASOT and RA factors were estimated by latex agglutination technique and ESR was estimated by Westergren method.

All data were entered on SPSS ver 8.0 software and were analyzed for frequencies, means and SD; Chi-Square and Student’s t-test were used for hypothesis testing. $P \leq 0.05$ was maintained as significant.

RESULTS

A total number of 36 patients with nonspecific musculoskeletal pain (10 males and 26 females) and 36 controls subjects. (12 males and 24 females) were included in the study. Basic demographic data are summarized in Table 2.

Table 2: Basic demographic data of subjects; values are expressed as Mean \pm SEM

Groups	Sex	Ages	Heights	Weights
		(years)	(cms)	(kgs)
		Mean \pm SEM	Mean \pm SEM	Mean \pm SEM
Controls (36)	Male	39.92 \pm 1.90	161.67 \pm 1.40	74.25 \pm 2.23
	(12)	38.00 \pm 1.36	158.95 \pm 1.00	67.13 \pm 2.34

	Female (24)			
Patients (36)	Male (10)	36.40 ± 3.58	170.92 ± 4.23	66.50 ± 3.88
	Female (26)	37.96 ± 1.77	157.36 ± .75	64.35 ± 2.17

Uric acid profile is given in Table 3. It shows significant differences between the control and patient groups with respect to their serum uric acid levels ($p=0.05$), even though the mean levels are within the normal ranges. Daily urinary uric acid clearance also showed a significant difference between control and patient females ($p=0.034$). The uric acid clearance showed a highly significant difference between control and patient groups, largely due to a difference in the females of these two groups ($p<0.001$).

Table 3: Uric acid profile of subjects; values are given as Mean ± SEM

Groups	Serum uric acid (mg/dl)	Daily urinary uric acid excretion (mg/24 hours)	Uric acid clearance (ml/min)
Controls	4.59±0.17	495.83±15.86	7.83±0.20
Males (12) 7.36±0.34	5.23±0.32	511.92±30.23	
Female (24) 8.06±0.24	4.27±0.24	487.79±18.64	
Patients 6.15±0.34**	5.24±0.27*	457.78±25.90	
Male (10) 6.90±0.52	6.08±0.31	575.80±37.40	
Female (26) 5.86±0.42†	4.91±0.34	412.38±28.52***	

* $p=0.05$ & ** $p<0.001$ as compared to controls, *** $p=0.034$ & † $p < 0.001$ as compared to female controls

When patients and controls were divided according to upper cutoff serum uric acid values of ≥ 7.0 mg/dl and ≥ 5.7 mg/dl for males and females respectively, only 3 male patients out of 10 (30.0%) showed a higher serum uric acid level, while 6 out of 26 females (23.08%) showed abnormal levels; whereas no male controls and only two out of 24 (8.3%) female controls had higher uric acid level (Table 4). Thus a total of 11 subjects (15.27%) were hyperuricemic, of which 9 (81.82%) were patients; 8 subjects (11.11%) were females, out of which 6 (75%) were in the patient group.

Table 4: Hyperuricemia in controls and patients by gender

Groups		Normal serum uric acid values	High serum uric acid levels
		M: < 7.0 mg/dl F: < 5.7 mg/dl	M: ≥ 7.0mg/dl F: ≥ 5.7 mg/dl
Controls	Male (12)	12 (100%)	0 (0%)
	Female (24)	22 (91.7%)	2 (8.3%)
Total	36	34 (94.45%)	02 (5.555%)
Patients	Male (10)	07 (70%)	03 (30%)
	Female (26)	20 (76.92%)	06 (23.08%)
Total	36	27 (75%)	09 (25%)

When patients and controls were classified as over producers and under excretors of uric acid, none of the patients were found to be over producers, while only 2 (8.33%) controls fell in the category. Three male (30.0%) and 17 female (65.4%) patients were classified as under excretors, none of the controls showed under excretion of uric acid. Only one female patient out of 26 (3.84%) was classified as having both under-excretion and over-production of uric acid (Table 5).

Table 5: Distribution of subjects into Over Producers, Under Excretors, Combined Over Producers and Under Excretors or Normal Uric Acid Producers and Excretors, on the basis of Uric Acid Profile (Over Producers = Uua mg/kg/hr > (0.03Cua) + 0.325; Under Excretors = Uac < 6.1 ml/min)

Groups	Over Producers	Under Excretors	Combined	Normal
Controls				
Male (12) (100%)	Nil	Nil	Nil	12
Female (24) (91.66%)	02 (8.33%)	Nil	Nil	22
Patients				
Male (10) (70.0%)	Nil	03 (30.0%)	Nil	07
Female (26) (30.76%)	Nil	17 (65.4%)	01 (3.84%)	08

Total	(72)	02 (2.78%)	20* (27.78%)	01 (1.38%)	49
	(68.06%)				

*p<0.001 as compared to controls

DISCUSSION

Our results indicate that patients with chronic non-specific musculoskeletal pain differ from control group in several aspects including parameters of uric acid profile.

In the present study, a significant difference in the mean serum uric acid values was seen between patient and control groups (5.24 ± 0.27 and 4.59 ± 0.17 , $p=0.05$, Table 3). Earlier studies have reported a significantly higher uric acid level in females with chronic nonspecific pain.²² In another study from Sweden, a significantly higher serum uric acid was reported in patients with chronic nonspecific pain taken as a single group as compared to controls.⁵

Nine subjects (3 male and 6 female, 25%) showed hyperuricemia in the patient group, as compared to two female controls (5.5%) having higher than normal uric acid level. Aarflot et al reported from Norway a higher incidence of hyperuricemia in chronic nonspecific musculoskeletal complaints in 40-42 years age group.²² Both 24 hours urinary uric acid excretion and uric acid clearance in female patients was significantly ($P<0.034$ and $P<0.001$) respectively) lower as compared to controls (Table 3). Both lower excretion and lower clearance of uric acid may be reciprocally related to each other. In our study an inverse correlation between the serum uric acid levels and uric acid clearance in patients was observed, but this was not significant ($r = -.285$, $p = 0.092$).

In gouty patients showing hyperuricemia, under-excretion of uric acid was reported in 60% of this group.¹⁸ This tallies well with the results of our study, where of the 36 patients with chronic musculoskeletal pain, 20 (55.55%) were classified as under excretors (Table 5). Aloaka and Kamataini have shown an association between hyperuricemia and superactivity of enzymes involved in nucleotide synthesis and deficiency of enzymes in salvage pathway responsible for converting purines and thus nucleosides to mononucleotides.²⁵ Some other workers^{18, 22, 23} also describe similar mechanism of hyperuricemia. Many workers have reported a higher uric acid level in chronic nonspecific musculoskeletal pain subjects, but this could not be classified as hyperuricemia, as also seen in the present study.^{5, 22}

Earlier studies by Aarflot and Anderssen et al showed a significant association between high serum uric acid and presence of disability in chronic nonspecific musculoskeletal pain cases.^{5, 22} The present study indicates that abnormal uric acid metabolism may be a contributing factor to status of mild disability found in some of the patients, particularly females, with chronic nonspecific musculoskeletal pain. This also agrees with the finding that there were more females in both the under excretor and hyperuricemic groups.

CONCLUSION

We conclude that abnormal uric acid profile may be a contributory factor to the underlying biochemical abnormalities of patients with nonspecific musculoskeletal pain. It is tempting to identify a high-risk group

of females with an under excretor status contributing to hyperuricemic profile as the prototype for chronic nonspecific musculoskeletal pain syndromes. Further in-depth studies should be undertaken to explore the role of abnormal uric acid profile and metabolism as causal factors in the development of chronic musculoskeletal pain syndromes.

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Address for correspondence:

Dr. Naeema Afzal, Department of Pathology, Ayub Medical College Abbottabad 22040, Pakistan.