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Research Article

EFFECT OF URATE LOWERING THERAPY ON GOUT AND RELATED CO-MORBIDITIES- A RETROSPECTIVE STUDY OF 200 PATIENTS

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A B S T R A C T

Background: There is an increasing prevalence of hyperuricemia and gout worldwide. A substantial body of epidemiological and experimental evidence suggests that serum uric acid is an important, independent risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD) especially in patients with hypertension (HTN), heart failure or type II diabetes melitus (DM).
Materials and Methods: 200 patients with diagnosis of gout, with at least 3 years of follow up were reviewed. They were divided into 2 groups; 60 patients with mean serum uric acid level (sUA) < 6 mg/dL and 140 patients with mean sUA ≥ 6 mg/dL.
Results: The long term ULT maintaining the serum urate level under 6 mg/dL leads to significant decrease in the incidence of gout related comorbidities.
Conclusion: There exists an association between gout and subsequent CVD and HTN. Retaining control of uric acid decreases the incidence of acute gouty attacks and related co-morbidities.

INTRODUCTION

Gout is the most prevalent inflammatory arthritis, affecting an estimated 1-2% of adult men in the Western world. It is generally characterized by acute onset of pain in joint, erythema and swelling of the first metatarsophalangeal joint [1, 2].

Gout is frequently associated with hypertension (HTN), chronic kidney disease (CKD), type II diabetes mellitus (DM), obesity and ischaemic heart disease. Epidemiological studies examining the relationship between gout and CVD report conflicting findings, with a significant association reported by some[2-5], but not others,[6-8] and investigations for risk of CVD or peripheral vascular disease (PVD) in patients with gout are comparatively fewer [9-11]. Consequently, the risk intrinsic to gout itself, compared to that from hyperuricaemia or vascular risk factors, such as HTN and obesity commonly found in patients with gout, and remains unclear. Additionally, many of these studies have been conducted in secondary care populations, who may be characterized by more severe disease, rather than primary care where the majority of patients with gout are managed. Further work is required to establish the effect of optimum management of both vascular risk factors and gout itself on the long-term health of gout patients, clarifying the nature of the relationship between gout and PVD, and the mechanism by which gout patients are at greatest risk.

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MATERIAL AND METHOD

This retrospective cross sectional study was done on 200 patients diagnosed with gout during 2014 to 2016 at Sri Aurobindo Medical College and PG Institute, Indore after getting clearance from Institutional Ethical Committee and Academic Review Board. The board exempted informed consent because it was a retrospective study with minimal risk. Patients were diagnosed to have gout on the basis of classical triad of acute monoarthritis, hyperuricaemia and a dramatic response to colchicine therapy. They were divided into 2 groups; 60 patients with mean serum uric acid level (sUA)<6mg/dL and 140 patients with mean sUA≥6mg/dL. Comorbidities of gout such as HTN, DM, CKD, CVD and urolithiasis were compared in each group at baseline and at last follow-up visit. Frequency of acute gout attacks were also compared between the groups. Patients on drugs which increase the serum uric acid were excluded from the study. Data was collected from patient's record file which includes the demographic details, anthropometric data, clinical details and laboratory investigations findings.

The characteristics of the patients in each group, including sex, age, height, weight, body mass index (BMI), duration of gout (calculated from first gout attack), duration of urate lowering therapy (ULT) (calculated from the first date of starting ULT),

presence of tophi, family history of gout, history of smoking or alcohol, medication possession ratio (MPR) and frequency of acute gout attack during follow up period were collected through chart review. History of comorbidities of gout such as HTN, DM, CKD, CVD and urolithiasis were investigated at baseline and at the last follow up visit.

Diagnosis of HTN was made if the patient was on anti-hypertensive medication or if the patient showed continuous stage I hypertension or above [SBP over 140 mmHg or DBP over 90 mmHg (JNC 7 guideline)]. Diagnosis of DM was made if the patient was on oral hypoglycemic agent or insulin, if the patient showed continuous elevation of fasting glucose above 126 mg/dL or if HbA1c was over 6.5% (American Diabetes Association 2013 guidelines). CKD was defined as glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m² calculated by modification of diet in renal disease (MDRD) formula. CVD consisted of myocardial infarction (MI), angina, heart failure (HF) and cerebrovascular disease. Diagnosis of urolithiasis was made if the stone was visualized by computed tomography, intravenous pyelogram or abdominal sonography or when confirmed by a physician.

MPR was calculated by dividing the number of medication consumed days by the number of total clinic follow up days and converted into percentage. The MPR was dichotomized at 80%, with MPR of<80% considered non-adherence [8-10]. Gout flare was defined as an incidence with 3 or more of the following criteria: any patient-reported warm joint, any patient-reported swollen joint, patient-reported pain at rest of >3 (0-10 scale) intensity and patient-reported flare [11] or if directly diagnosed by a physician.

Statistical analysis

Data was presented as mean and standard deviation for Continuous variables and number and percentages for discrete variables. Normality of data was checked by KolmogorovSimonov test. Student t test and Mann Whitney U test was applied to see the significant difference in mean and median of continuous data for parametric and non-parametric data respectively. Chi Square test was used to see the significant difference in discrete variables between two groups. P value <0.05 was considered significant.

RESULT

Total 200 gout patients 60 patients whose mean serum uric acid level sUA< 6 mg/dL mean age were 52.12±11.5 and 140 patients whose mean sUA ≥ 6 mg/dL mean age were 42.42±11.4. There was no significant difference in presence of tophi (20% vs15%, *P*=0.111), family history of gout (10% vs8%, *P*=0.341), smoking (20% vs 25%, *P*=0.225), alcohol consumption (40% vs32%, *P*=0.112) and hypercholesterolemia (47% vs84%, *P*=0.401) between the adequately treated group and the inadequately treated group (Table 1). Patients in the adequately treated group was older (52.12 ± 11.5yr vs42.42 ± 11.14yr, *P*<0.001), lighter (72.4 ± 9.8kg vs78.0 ± 12.6kg, *P*=0.004), shorter (168.1 ± 8.4cm vs169.4 ± 8.1cm, *P*=0.035) with lower BMI(26.0 ± 1.8kg/m² vs28.4 ± 1.3 kg/m², *P*=0.002). There was no significant difference in the duration of gout (12.6 ± 1.1yr vs12.9 ± 2.3yr, *P*=0.194) and ULT duration(7.1 ± 2.1yr vs7.9 ± 8.8yr, *P*=0.080). The MPR (96 ±0.11% vs 62 ± 0.41%, *P*<0.001) and the percentage of patients with MPR≥80% (78% vs 29%, *P*<0.001) were both higher in the adequately treated group.There was no difference in the frequency of sUA measurement between the adequately and inadequately treated group (36±12.14vs 36±22.1, *P*=0.654). In the inadequately treated group, 78% (n=110), 8.3% (n=5) and 14% (n=20) of the patients were treated with allopurinol, benzbromarone and febuxostat respectively. In the adequately treated group, 88.3% (n=53) and 2.1% (n=3) of the patients were treated with allopurinol and benzbromarone respectively. There was no significant difference in the dosage of allopurinol between the adequately and inadequately treated group (252± 94 mg vs 251±100 mg, *P*=0.780).

During the mean follow up period of 3years, the average frequency of acute attack and the yearly rate of acute attack were both lower in the adequately treated group compared to the inadequately treated group (2 ± 3 vs4 ± 6, P<0.001 and 0.38 ± 0.22 vs0.69 ± 0.33, P<0.001). In baseline HTN (53.3% vs 27.1%, p= 0.001), DM (10% vs8.6%, p= 0.718), CVD (20% vs5.7%, p= 0.001), urolithiasis (10% vs5.7%, p= 0.001) and CKD (31.6% vs 18%, p= 0.004) (Table 1).

Table 1 Characteristics of patients in each group

Parameters	Mean sUA< 6 mg/dL n = 60	Mean sUA ≥ 6 mg/dL n = 140	p value*
Male	27 (45)	56 (40)	0.095
Female	33 (55)	84 (60)	0.092
Age (yr)	52.12 ± 11.5	42.42 ± 11.14	0.001
Weight (kg)	72.4 ± 9.8	78.0 ± 12.6	0.004
Height (cm)	168.1 ± 8.4	169.4 ± 8.1	0.035
BMI (kg/m²)	26.0 ± 1.8	28.4 ± 1.3	0.002
Duration of gout (year)	12.6 ± 1.1	12.9 ± 2.3	0.194
ULT duration (year)	7.1 ± 2.1	7.9 ± 8.8	0.080
Tophi	12 (20)	24 (15)	0.111
Family history of gout	6(10)	11 (8)	0.341
Smoker	12 (20)	35 (25)	0.225
Alcohol	18 (40)	45 (32)	0.112
Hypercholesterolemia	28 (47)	85 (61)	0.401
Mean serum uric acid (mg/dL)	5.5 ± 0.40	7.3 ± 0.11	0.001
MPR (%)	96 ±0.11	62 ± 0.41	0.001
MPR ≥ 80%	47 (78)	40 (29)	0.001
Average frequency of acute attack	2 ± 3	4 ± 6	0.001
Yearly rate of acute attack	0.38 ± 0.22	0.69 ± 0.33	0.001
Baseline HTN	32 (53.3)	38 (27.1)	0.001
Baseline DM	6 (10)	12 (8.6)	0.718
Baseline CVD	12 (20)	8 (5.7)	0.001
Baseline Urolithiasis	6 (10)	8(5.7)	0.327
Baseline CKD	19 (31.6)	25 (18)	0.004

*P value by Mann-Whitney U test or chi-square test. Values are presented as mean ± SD or number (%). sUA- serum uric acid; BMI- body mass index; ULT- uric acid lowering therapy; MPR- medication possession ratio.

In the adequately treated group HTN increased from 53.3% to 63.3%, DM from 10% to 16.6%, CVD from 20% to 30%, urolithiasis from 10% to 13.3% and 3 patients showed decrease in CKD stage (Table 2). However, McNemar's test showed no significant increase in incidence of HTN, DM, CVD, and urolithiasis or significant decrease in incidence of CKD stage.In the inadequately treated group HTN increased from 27.1% to 57.8% (P<0.001), DM from 8.6% to 21.4% (P<0.001), CVD from 5.7% to 12.1% (P=0.004) and urolithiasis from 5.7% to 12.8 % (P=0.001). McNemar's test showed significant increase in incidence of each comorbidity. Only 2 cases showed increase in CKD stage (Table 2).

Age and the frequency of baseline HTN which could have influenced the CVD outcome were all higher in the adequately

treated group. However BMI was higher in the inadequately treated group which could influence on the HTN, DM and CVD state. Generalized estimating equation analysis after adjusting for BMI also showed higher incidence of HTN and CVD (P<0.001, P=0.002, respectively) in the inadequately treated group. There was no difference in the DM outcome (P<0.634).

Table 2 The number of patients with comorbidities of gout according to uric acid level at baseline and at last follow up visit

Comorbidities		Mean sUA< 6 mg/dL n = 60		Mean sUA ≥ 6 mg/dL n = 140	
		No. (%)	p value	No. (%)	p value
HTN	Baseline	32 (53.3)	0.083	38 (27.1)	0.001
	Last visit	38 (63.3)		81 (57.8)	
DM	Baseline	6 (10)	0.128	12 (8.6)	0.001
	Last visit	10 (16.6)		30 (21.4)	
CVD	Baseline	12 (20)	0.157	8 (5.7)	0.004
	Last visit	18 (30)		17 (12.1)	
Urolithiasis	Baseline	6 (10)	0.300	8 (5.7)	0.001
	Last visit	8 (13.3)		18 (12.8)	
CKD*	Baseline	19 (31.6)	0.711	25 (18)	1.000
	Last visit	22 (36.6)		27 (19)	

*P value by McNemar's test comparing before and after uric acid lowering therapy

DISCUSSION

Although the optimal uric acid level to be achieved with ULT has been controversial [12-14], the 2012 ACR guideline and 2013 multinational evidence-based recommendations [15] recommends the uric acid treatment target of <6 mg/dL with ULT in gout patients. Our study demonstrated that tight control of uric acid decreased the development of acute gout attacks which was correlated with the study by Shoji *et al*. [16]. Patients with high MPR of urate lowering agent consequently achieved mean uric acid level of <6 mg/dL and effectively reduced the risk of acute gout attacks. Theoretically serum is supersaturated for monosodium urate at concentrations >6.8 mg/dL at 37°C and urate levels below this can be considered appropriate target for treatment [17].

Hyperuricemia is common in patients with HTN. Among patients with gout, 40% have hypertension [18, 19]. Kanbay *et al*. [20] reported significant reduction in blood pressure in hyperuricemic patients treated with allopurinol and Feig *et al*. [21] reported reduction in blood pressure in adolescents with newly diagnosed essential hypertension treated with allopurinol. Treatment with xanthine oxidase inhibitor allopurinol may contribute to reduction in blood pressure. However, there is yet to be a study on blood pressure in gout patients treated with allopurinol. This study also showed no significant increase in the prevalence of HTN in the group tightly treated with ULT. However, in the inadequately treated group there was a significant increase in the prevalence of HTN after mean follow up period of 3yr. In this study 90.4% of patients were treated with allopurinol and early treatment with allopurinol could have prevented the new development of HTN.

Serum uric acid level increases with increasing hemoglobin A1c (HbA1c) up to 6-6.9% and then decreases with a further increase in HbA1c [22]. Whether optimal management of gout with ULT reduces the risk of future DM is unknown. The Finnish diabetes prevention study, based on 557 overweight or obese individuals with impaired glucose tolerance, reported that baseline uric acid predicted the risk of diabetes after adjusting for age, gender, blood pressure, BMI, triglyceride levels, baseline creatinine, physical activity and dietary variables (*P*=0.037) [23]. Choi *et al*. [24] reported that men with gout and high cardiovascular risk are at risk of developing type II DM independent of other known risk factors compared with men without gout. Our study showed significant increase in prevalence of DM in the inadequately treated group compared to the adequately treated group at the end of follow up period. After adjusting for BMI, there was no significant difference in the incidence of DM between the 2 groups. However, our study did not include other risk factors for DM such as HDL cholesterol level <35 mg/dL, triglyceride level>250 mg/dL, or family history of DM.

This study showed significant increase in prevalence of CVD in the inadequately treated group compared to the adequately treated group. In vitro and animal studies suggest that uric acid is a biologically active compound that can increase inflammatory mediators such as monocyte chemoattractant protein-1 and nuclear factor-kappa B [25] known to lead to vascular damage. Framingham study [26] found 60% increased risk of coronary artery disease among gout patients and Edwards [27] reported that hyperuricemia is an independent risk factor for CVD. Hyperuricemia itself is associated with cardiovascular risk factors such as HTN and DM. Allopurinol itself through its ability to reduce myocardial oxygen demand also appears to be beneficial in patients with ischemic heart disease [28].

The most frequent type of gout related nephropathy is urolithiasis (10%-20%) and its prevalence is much higher than that observed in the general population [29]. In 1967, Yu and Gutman[30] investigated 1,258 patients with primary gout and reported a 22% prevalence of urolithiasis, based on history of urolithiasis during the course of gout. Shimizu *et al*. [31] reported the prevalence of urolithiasis calculated from stone history was 16.2%. Our study showed urolithiasis prevalence of 13%. At baseline, we included the patients who reported medical history of urolithiasis. During the follow up period, we only included radiologically proven urolithiasis or urolithiasis confirmed by a physician. This could explain the lower prevalence of urolithiasis in our study. This study shows that strict control of uric acid level below 6.0 mg/dL with ULT is beneficial in decreasing the new development of urolithiasis. Hyperuricemia, also contributes to renal impairment. Zhu *et al*. [32] reported that of the estimated 8.3 million Americans effected with gout, 71% had CKD greater than stage 2 (GFR<60 mL/min per 1.73 m²), using 2007-2008 data from the National Health and Nutrition Examination Survey. With increasing levels of sUA, there were graded increases in the prevalence of CKD. In our study there was a decrease in the frequency of CKD in the adequately treated group from 31.6% to 36.6% of patients and in the inadequately treated group there was an increase from 18% to 19% of patients. Although there was no statistical difference in the adequately treated group, this shows that renal function can be recovered by intensive ULT therapy.

The ideal MPR is 100% and good adherence is generally defined as an MPR of 80% or higher. Gout is among the chronic diseases with a low treatment adherence rate which is interestingly lower in younger patients [33]. In studies of pharmacy dispensing gout medications, the percentage of patients with good adherence ranged from 18% to 44% [34]. In a comparative study showing a 36.8% adherence rate among

gout patients, patients with HTN or type II DM had higher rates of 72.3% and 65.4% respectively [33]. In our study 29% of patients showed good adherence compared to78% of patients in the adequately treated group who showed good adherence. The patients in the adequately treated group were also older, with higher prevalence of HTN and DM at baseline which could have influenced the drug adherence rate, in accordance with other studies.

The mean age of the patients in the adequately treated group was higher than the age of the inadequately treated group. This could explain the reason why higher percentage of patients in the adequately treated group had HTN, DM, CVD, urolithiasis and CKD compared to the inadequately treated group at baseline. However, only HTN, CVD and CKD showed significant difference (P<0.001) between the 2 groups at baseline.

CONCLUSION

In summary, the long term ULT maintaining the serum urate level under 6 mg/dL leads to significant decrease in the incidence of gout comorbidities such as HTN and CVD after adjusting for BMI. New development of DM and urolithiasis tends to decrease in the well-treated group despite the older age and preexisting comorbidities. Retain control of uric acid also decreases the development of acute gout attacks and can also potentially lead to recovery of renal function. Prospective randomized study is needed to confirm these results, taking into consideration other confounding factors for each comorbidity of gout.

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