

Renal Function of Patients with Gout on Initial Visit at a Rheumatology Clinic

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Abstract

Background and Objectives: Gout is an inflammatory arthritis involving the deposition of uric crystals. It has been known to cause renal disease in the form of acute or chronic urate nephropathy, or urolithiasis. Numerous studies have been published worldwide, defining proper handling and management of such cases. Despite such recommendations, the renal function of these patients complicates the management. Administration of the properly-adjusted medications and referrals to appropriate services are delayed because of lack of data at the patient's initial visit. This study therefore aims to describe the renal function at index consult of Filipino patients with gout, and identify the factors that correlate with a depressed kidney function in such patients.

Methods: This study is a retrospective descriptive study involving gout patients seen in four rheumatology clinics. A total of 485 patients were identified. Records of the patients' index consult, were reviewed. Demographic and disease characteristics were noted. Renal function was identified using the Cockcroft-Gault equation for estimated glomerular filtration rate. Univariate analysis was done, characteristics of patients with good and poor renal function were compared.

Results: A total of 485 patients were studied. Most were males with presenting with a monoarticular joint

involvement, with attacks occurring more than three times a year. Tophi were present in 28.2% of patients at the initial consult. The most commonly reported co-morbidity was hypertension. At index consult, the average serum creatinine and uric acid are 1.7mg/dL and 9.1 mg/dL, respectively. The average creatinine clearance is 65.0 ± 34.1 mL/min, and 51.3% presented with an eGFR of <60 mL/min at index consult. Poor renal function (eGFR <60 mL/min) was associated with late onset ($p < .0001$) and prolonged disease duration ($p < .0001$), higher serum uric acid ($p < .0001$), a history of urolithiasis ($p < .035$), frequent attacks ($p < .0001$), with coexisting hypertension ($p < .0001$) or diabetes mellitus ($p < .013$). Interestingly, results also showed that females tend to have poorer renal function at index consult compared to males ($p < .0001$).

Conclusion: In this cohort of 485 Filipino patients with gout, 51.3% have eGFR <60 mL/min on first consultation. The clinical findings with significant associations with poor renal function should alert Filipino physicians to the high probability of renal disease among Filipino patients with gout and make the necessary adjustments in treatment plans.

Keywords: gout, renal disease, chronic kidney disease, hyperuricemia, renal function, initial visit

Introduction

Gout is a clinical disease associated with hyperuricemia and deposition of urate crystals in the joints. Although the disease classically affects middle-aged male patients, this disease can be seen in other groups such as those in their second and third decade (early-onset gout), and in post-menopausal women. Gout has been well-known to cause renal disease manifesting as acute or chronic urate nephropathy, or uric acid nephrolithiasis. Increases in

serum uric acid (SUA) have been directly correlated with increased risk for urate nephropathy.¹ In a study done in the United States in 2009 involving gout patients², 24% was noted to have an impaired renal function, defined as an eGFR <60 mL/min. In Taiwan, the incidence of end-stage renal disease (ESRD) among gout patients is 1.73 per 1000-patient years.³

According to the Veterans Affairs medical database in the United States, only 2.0% of patients with gouty arthritis were without co-morbid illness.⁴ Even in the absence of co-morbid illnesses, in another study involving 1,410 Chinese patients with gout, 11.9% have decreased renal function.⁵ A smaller cohort of Taiwanese patients ($n = 152$) showed that the presence of tophi and advanced age correlated well with advanced renal disease.⁶

Given the increased risk of renal disease among patients with gout and the resulting dilemma in the choice of anti-inflammatory drug for acute arthritis during the initial consult,

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it is important to establish the incidence of kidney disease among patients with gout in the Philippines and establish clinical clues to its presence. In particular, this research will describe the renal function of Filipinos with gout during their initial visit at the Rheumatology clinic (index consult) and will identify clinical and demographic characteristics that are associated with poor renal function.

Objectives

General:

To determine the estimated glomerular filtration rate (by Cockcroft-Gault formula) of Filipino patients diagnosed with gout seen in adult Rheumatology clinics

Specific:

A) To describe the demographic and disease characteristics of the patients

B) To identify the factors and/ or characteristics that correlate with decreased renal function

Patients and Methods

Study Design

Cross- sectional study

Setting:

Adult rheumatology clinics

Study Population

The study included all patients diagnosed with gout based on the American College of Rheumatology Classification Criteria. The records of these patients must contain all necessary information such as the weight, serum uric acid and serum creatinine, all taken at index consult. Patients diagnosed with gout, but had incomplete records were excluded from the study.

Sampling Procedure

The study used a non-probability sampling of all patients diagnosed with gout, who satisfied the inclusion criteria.

Method

The study was done through review of records of gout patients seen in rheumatology clinics in the Philippines. Demographic and disease characteristics were noted in the data collection form (Appendix 1). The patients' social history, co- morbid illnesses, serum uric acid and creatinine from the initial consult were also recorded. The creatinine clearance was computed using the Cockcroft-Gault equation for the estimated glomerular filtration rate (eGFR).

Statistical Analysis

Demographic and disease characteristics were described using means, standard deviations, and percentages. Logistic regression analysis was done to identify factors related to poor renal function.

Definition of Terms

Age of symptom onset - age in years when gout symptoms were first noted.

Age of disease diagnosis - age in years when the diagnosis of gout was made.

Index consult - first two consults when the diagnosis of gout was made.

Renal function - the estimated *glomerular filtration rate* or eGFR (estimated renal creatinine clearance) computed using the Cockcroft-Gault equation.

Poor renal function - is an eGFR of <60 mL/min, and good renal function is an eGFR of $\geq$ 60 mL/ min.

History of urolithiasis - documented urolithiasis through imaging (ultrasound/ CT scan/ MRI/ X-ray), or a history of passage of stones.

Monoarthritis - is arthritis involving only one joint. *Oligoarthritis* is arthritis involving two to three joints. Involvement of four joints or more is classified as *polyarthritis*.

Ethical Consideration

This study is a retrospective study involving gout patients seen at four rheumatology clinics. The patients' names are coded to ensure confidentiality of records. This study was funded by the authors. The conduct of the study was approved by the UP Manila Ethics Review Board.

Results

A total of 485 patients with gout were included and their demographic characteristics are summarized in Table I. The majority of the patients are males (90.9%). Most are non-smokers and 55.7% have a history of drinking alcoholic beverages. Family history of gout in was noted in 23.3% of the patients. The most commonly reported co-morbid illnesses are hypertension and diabetes mellitus.

Table I: Demographic characteristics of 485 Filipino patients with gout

	Frequency (%) n= 485
Gender	
Male	441 (90.9)
Smoking	
Yes	174 (35.9)
No	224 (46.2)
Not stated	87 (17.9)
History of alcohol drinking	
Yes	270 (55.7)
No	128 (26.4)
Not stated	87 (17.9)
Family history of gout	
Yes	113 (23.3)
No	237 (48.9)
Not stated	135 (27.9)
Co- morbid illnesses	
Hypertension	211 (43.5)
Diabetes mellitus	43 (8.9)

Disease characteristics are summarized in Table II. The average age of onset of symptoms is 45 years old, with the first attack mostly presenting as a monoarthritis (72.37%). The average age of diagnosis is 52 years old, with the disease occurring for approximately 48 months from the onset of symptoms to diagnosis. At the initial consult, most patients presented with polyarticular joint involvement (34.23%). Attacks occurred more than three times a year in the majority of patients (51.34%). Only 28.25% of patients presented with tophi on the first visit. Although most patients were not initially requested an ultrasound, only 65 patients (13.4%) reported to have urolithiasis.

Table II: Disease characteristics of the study population at index consult

Characteristics	Frequency (%) n= 485
Age at onset of symptoms (years), n=459	
Mean (SD)	45.3
Median	44
Range	14 - 80
Age at diagnosis of gout (years), n=465	
Mean (SD)	52.1
Median	53
Range	15 - 80
Duration of gout prior to diagnosis (mos.), n=449	
Mean (SD)	77.6 ± 92.1
Median	48
Range	0 - 62.4
Joint involvement at onset of symptoms	
Monoarticular	351 (72.4)
Oligoarticular	11 (2.3)
Polyarticular	4 (0.8)
Not stated	119 (24.5)
Joint involvement at index consult	
Monoarticular	140 (28.9)
Oligoarticular	141(29.1)
Polyarticular	166 (34.2)
Not stated	38 (7.8)
Frequency of attacks	
< 3 attacks/ year	130 (26.8)
>3 attacks / year	249 (51.3)
Not stated	106 (21.9)
History of urolithiasis	
With	65 (13.4)
Without	211 (43.5)
Not stated	209 (43.1)
Presence of tophi	
With	137 (28.2)
Without	346 (71.3)
Not stated	2 (0.4)
Mean serum uric acid (mg/dL), n=464	
Mean (SD)	9.06 (2.5)
Median	8.98
Range	2 - 17.9

Four hundred and eighty-five records provided data for creatinine clearance. Table III summarizes the estimated renal function at index consult of the patients. The mean serum creatinine at index consult is 1.66 ± 1.46 mg/dL (median= 1.3, range= 0.11-21.7). Using the Cockcroft-Gault formula for estimating glomerular filtration rate, the mean

eGFR is 65.02 ± 34.11 mL/min (median=59.33, range= 4.58-187.8). More than half of the total study population (51.34%) had poor renal function (eGFR< 60 mL/min), most of the patients eGFR of 30-59 mL/min at index consult, or CKD Stage III, based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI).

Table III: Renal function of study population at index consult

Estimated GFR(mL/min)	Results n= 485
≥ 90	104 (21.4)
60- 89	132 (27.2)
30- 59	181 (37.2)
15- 29	52 (10.7)
< 15	16 (3.3)

Characteristics of patients with good versus poor eGFR are shown in Table IV. Several parameters differ between the two populations. Univariate analysis was done (Table V). A history of drinking alcohol ($p= 0.0046$) and a family history of gout ($p= 0.003$) are associated with good renal function. There are multiple factors that are associated with a poor GFR at the initial consult, namely, female gender, delayed age at onset, longer disease duration, tophi, a history of urolithiasis, higher serum uric acid, polyarticular joint involvement at consult, and a history of frequent attacks.

To determine independent association of the variables with renal function, multivariate logistic regression was done. A variable of the univariate test with a p- value of ≤ 0.25 was considered as a candidate for the multivariable model. Using the stepwise backward selection, the results of the analysis is shown in Table VI. Females and those with prior use of steroids are at increased risk of having poor renal function. Those patients with higher serum uric acid, especially if more than 9.0 mg/dl, older age at onset of symptoms, and longer duration of symptoms prior to diagnosis, are also at slightly higher risk of having poor renal function. Frequency of attacks more than three times a year is not associated with renal function.

Discussion

The results of this study show that most patients who suffer from gout present with an impaired eGFR at index consult.

Factors contributing to poor renal function

Univariate analyses show that poor renal function correlates with a delayed age of onset, late diagnosis, and longer disease duration. These results are to be expected as it has been well- documented that creatinine rises with increasing age. This impairment is additionally burdened with hyperuricemia, which has also been well- established to negatively affect renal function. Through the univariate analysis, it has also been identified that patients with

Table IV: Characteristics of gout patients with good versus poor renal function

	eGFR ≥60 mL/ min (n = 236)	eGFR < 60 mL/min (n = 249)
Sex		
Male	227 (96.2)	214 (85.9)
Female	9 (3.82)	35 (14.1)
Smoking history		
With	82 (41.0)	92 (46.5)
Without	118 (59.0)	106 (53.5)
History of alcohol drinking		
With	145 (61.4)	125 (50.2)
Without	55 (23.3)	73 (29.3)
Family history of gout		
With	70 (29.7)	43 (17.3)
Without	106 (44.9)	131 (52.6)
Age of onset of symptoms Mean (SD)	40.38 (12.7)	50.03 (14.6)
Age at diagnosis Mean (SD)	45.52 (11.9)	58.44 (12.2)
Duration of prior to diagnosis(mos.) Mean (SD)	60.74 (77.1)	94.50 (102.4)
Presence of tophi		
With	45 (19.1)	92 (36.9)
Without	190 (80.5)	156 (62.6)
History of urolithiasis		
With	22 (9.3)	43 (17.3)
Without	103 (43.6)	108 (43.4)
Mean BUA Mean (SD)	8.58 (2.2)	9.53 (2.7)
Joint involvement at onset of symptoms		
Monoarticular	177 (75.0)	174 (69.9)
Oligoarticular	3 (1.3)	8 (3.2)
Polyarticular	1 (0.4)	3 (1.2)
Joint involvement at index consult		
Monoarticular	87 (36.9)	53 (21.3)
Oligoarticular	71 (30.1)	70 (28.1)
Polyarticular	60 (25.4)	106 (42.6)
Frequency of attacks		
< 3 attacks/ year	78 (33.1)	52 (20.9)
>3 attacks / year	116 (49.1)	133 (53.4)
Co- morbid illnesses		
Hypertension	82 (34.8)	129 (51.8)
Diabetes mellitus	13 (5.5)	30 (12.1)
Medications taken prior to consult		
Urate- lowering therapy		
With	29 (12.3)	43 (17.3)
Without	178 (75.4)	43 (17.3)
Colchicine		
With	64 (27.1)	61 (24.5)
Without	143 (60.6)	155 (62.3)
COX- inhibitors		
With	69 (29.2)	75 (30.1)
Without	138 (58.5)	141 (56.6)
Other NSAIDs		
With	106 (44.9)	119 (47.8)
Without	101 (42.8)	97 (39.0)
Steroids		
With	12 (5.1)	40 (16.1)
Without	195 (82.6)	176 (70.7)

Table V: Univariate analysis of factors contributing to changes in renal function

	Odds Ratio	95% CI	p- value
Female	4.13	1.94 – 8.79	<0.0001
Smoking history	1.25	0.84 – 1.86	0.272
History of alcohol drinking	0.65	0.42 – 0.99	0.046
Family history of gout	0.50	0.31 – 0.78	0.003
Age of onset of symptoms	1.05	1.04 – 1.07	<0.0001
Age at diagnosis	1.09	1.07 – 1.11	<0.0001
Duration of prior to diagnosis (mos.)	1.00	1.002 – 1.007	<0.0001
Presence of tophi	2.49	1.64 – 3.77	<0.0001
History of urolithiasis	1.86	1.04 – 3.33	0.035
Mean BUA	1.17	1.08 – 1.26	<0.0001
Monoarticular at onset	2.71	0.71 – 10.39	0.222
Oligoarticular at onset	3.05	0.31 – 29.62	
Oligoarticular at index consult	1.62	1.006 – 2.60	
Polyarticular at index consult	2.9	1.82 – 4.62	<0.0001
>3 attacks / year	1.72	1.12 – 2.64	0.014
Hypertension	2.02	1.40 – 2.91	<0.0001
Diabetes mellitus	2.35	1.19 – 4.62	0.013
Medications taken prior to consult			
Urate- lowering therapy	1.53	0.91 – 2.55	0.108
Colchicine	0.88	0.58 – 1.34	0.546
COX- inhibitors	1.06	0.71 – 1.59	0.763
Other NSAIDs	1.17	0.80 – 1.71	0.424
Steroids	3.69	1.88 – 7.26	<0.0001

Table VI: Results of Multiple Logistic Regression

	Odds Ratio	95% CI	p- value
Female	2.77	1.006 – 7.618	0.049
Age at onset of symptoms	1.08	1.054 – 1.107	<0.0001
Duration of symptoms prior to diagnosis(mos.)	1.01	1.006 – 1.014	<0.0001
Mean BUA	1.26	1.116 – 1.424	<0.0001
Frequency of attacks			
>3 attacks / year	1.53	0.837 – 2.801	0.167
Steroids	5.49	1.767 – 17.037	0.003

urolithiasis have depressed eGFR compared to those without. This finding correlates with that of Rule et al in which patients with urolithiasis were more likely to develop chronic kidney disease. The significant correlation of tophi and impaired renal function at the initial visit is understandable, as tophaceous deposits mostly develop in patients with longstanding and poorly-controlled hyperuricemia, hence a decreased GFR. Although Tarng et al.⁶ reported the same data on subcutaneous tophi and chronic kidney disease, conversely, a report by Nickeleit et al. stated otherwise, in that renal tophi, and not subcutaneous tophi, was the factor established to contribute to poorer renal function.

Our univariate analysis also showed that polyarticular gout and frequent attacks also have implications in a patient's renal function. This finding is very important in that this stresses the need for earlier and aggressive control of

patients' symptoms. Although pain is the patient's primary concern, it should be stressed that attention on kidney function is equally important. This also implies that in this subset of patients, effective and safe (renally-adjusted) medications should be advised as a great proportion of these patients suffer from impaired kidney function at presentation.

It has been widely accepted that hypertension and diabetes mellitus, with or without hyperuricemia, directly contribute to kidney disease. Although a study by Zhang et al. reported that kidney disease in hyperuricemic patients was common even in the absence of co-morbidities, we found that most of our patients suffer from either hypertension or diabetes mellitus. Our findings of co-existing co-morbidities in patients suffering from gout with poor renal function was similar to that of Targ et al.¹², and, similar to his study, it can be pointed that hypertension caused more impact on these patients' kidney function. Gout is a risk factor for hypertension, or hypertension and gout may have co-existed at the onset as part of metabolic syndrome.

More interestingly, univariate analysis and multiple logistic regression showed that at the initial visit, female patients with gout were more likely to suffer from depressed renal function ($p=0.049$) than males. This is probably due to the later age of onset of gout in females compared to males. In addition, there may have been some delay in recognition of gout among these female patients because of their rheumatoid arthritis-like polyarticular joint involvement.

Factors contributing to good renal function

Our study showed that patients who have a family history of gout have better kidney function ($p=0.003$) than those without (Table IV). Our presumption is that their knowledge of the disease and of the appropriate health facility where they can consult allows them to seek consultation earlier. Appropriate management is given early during the disease course and this helps prevent disease progression.

A history of drinking alcohol was also found to be significantly associated with good renal function ($p=0.046$). We expected that alcohol consumption would correlate with poor renal function as it has been well-established that this contributes to hyperuricemia and exacerbation of symptoms. Alcohol has been known to influence kidney function negatively, although recent reports show that moderate consumption of alcoholic beverages has no significant effects on kidney function. It is difficult to conclude because 17% of the records did not have information on alcohol intake.

Limitations of the Study

Although the study has interesting findings, its limitations are recognized. First, because this is a retrospective study, some data were missing. In addition, as we utilized multiple study sites with different physicians in charge of each, there might be differing definitions of some of the parameters. An

estimate, rather than a direct measure, of the glomerular filtration rate as is customary in our setting was used. Since this is an index consult, the creatinine elevation may be acute and therefore Cockcroft-Gault formula may not be used appropriately to measure eGFR.

Conclusion

In conclusion, this study showed that 52% of our patients with gout have decreased kidney function on consultation at a rheumatology clinic. Most patients already have Chronic Kidney Disease Stage III. At presentation, there is a higher probability of poor renal function when the patient is female, with older age or long-standing disease, with higher serum uric acid, and with previous use of steroids. Polyarticular arthritis on index consultation, the presence of tophi, history of urolithiasis, hypertension, diabetes mellitus, and more frequent attacks were also associated with poor renal function initially on univariate analysis but their association cancelled out when multivariate analysis was done. History of alcohol intake and family history of gout seemed to be "protective" for the kidneys but these effects were not upheld on multivariate analysis.

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Appendix I: Data collection form

Patient No.:		Clinic:
Ht:	Wt.:	Age at diagnosis (index consult):
Present Age:	BMI:	Date of diagnosis (Index consult):
Sex:	Civil Status:	Date of last follow- up:
Education: ☐ Elementary ☐ HS ☐ Vocational ☐ College		Occupation: ☐ Never employed ☐ Previously employed ☐ Presently employed
		Family hx of Gout? Y N
Smoking History:	Y N	Duration of Gout in months: _____
Alcohol Drinking:	Y N	Age of onset of symptoms: _____
Co- morbidities: ☐ HTN ☐ DM ☐ BPH ☐ OTHERS: _____		Type of arthritis at onset: ☐ Monoarticular ☐ Oligoarticular ☐ Polyarticular
Type of arthritis at index consult: ☐ Monoarticular ☐ Oligoarticular ☐ Polyarticular		Joints Involved from onset to index consult: ☐ PIP ☐ DIP ☐ MCP ☐ Wrist ☐ Elbow ☐ Knee ☐ Ankle ☐ 1st MTP ☐ Other MTPs
Frequency of attacks:	<3 >=3	Tophi: Present Absent
Presence of nephrolithiasis?	Y N	Duration to tophi formation: _____
Laboratories BUA: _____ Crea: _____ eGFR: _____ CKD Stage: _____		Medications prior to index consult: ☐ NSAIDS ☐ COX2 ☐ ULT ☐ Colchicine ☐ Steroids ☐ Others