Gout Severity in Recipients of Kidney Transplant

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ABSTRACT

Purpose. This retrospective analysis of medical chart data was performed to compare severity and treatment of gout in patients with or without a history of kidney transplantation (KT).

Methods. Via an online survey, a panel of board-certified US nephrologists (N = 104) provided the following deidentified chart data for their 3 most recent patients with gout: age, sex, serum uric acid, numbers of swollen or tender joints, visible tophi, gout flare events (prior 12 months), gout drug treatment history, and KT history. The presence of "severe, uncontrolled gout" was defined as: serum uric acid $\geq$ 7.0 mg/dL, $\geq$1 tophi and $\geq$2 flares in the last 12 months, and history of xanthine oxidase inhibitor treatment.

Results. Twenty-five out of 312 (8.0%) gout patients had a history of KT. Univariate analysis found that patients with gout and history of kidney transplants had: greater prevalence of severe uncontrolled gout (27% vs 8%, $P = .007$) and tophi (36% vs 17%, $P = .030$), and higher rates of failure or physician perceived contraindication to allopurinol (44% vs 23%, $P = .028$).

Conclusion. This study provides preliminary evidence that gout in patients with history of KT is more severe and poses greater challenges to pharmacologic management. Although gout has been linked to worse outcomes among kidney recipients in the literature, there are presently no publications on gout severity among patients with KT in comparison to other patients with gout. Further investigation of disease severity and appropriate, effective treatment options in recipients of kidney transplant with a diagnosis of gout, especially prior to the transplant, is warranted.

GOUT is a disorder that manifests as a spectrum of clinical and pathologic features caused by the deposition of urate crystals in the joints and other tissues [1]. The presentation varies in severity from intermittent flaring of acute joint inflammation to chronic, debilitating pain and structural damage caused by crystal deposits (tophi) in numerous joints, tendons, and soft tissue [1,2].

Gout is a frequent comorbidity among recipients of kidney transplant [3]. New-onset gout following kidney transplantation (KT) has been observed in 4% to 17% of recipients [3–8] and the overall prevalence of gout in patients who have undergone renal transplantation is an estimated 13% [9]. By comparison, among the general US

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population, annual and lifetime gout prevalence has been estimated at 1% and 4%, respectively [10,11]. Among the Medicare population with KT, 7% developed new-onset gout within 3 years posttransplantation [3]. A dramatic increase in hyperuricemia prevalence in patients with a history of KT, from 47% pretransplantation to 84% posttransplantation in one study, highlights the significantly elevated risk of developing gout for recipients of transplantation [5]. Chronic use of calcineurin inhibitors, especially cyclosporine, are a frequently cited explanation for the high rates of gout seen in the population with history of KT, as cyclosporine and tacrolimus are known to cause hyperuricemia through decreased renal excretion of urate [12–15]. Other proposed drivers of increased gout in patients with history of KT include treatment with diuretics and compromised renal function, both of which may also raise serum urate levels [16–18]. In contrast, patients with history of kidney transplant are often on corticosteroids, which would be expected to reduce gout flares. Nevertheless, gout is more common in the kidney transplant population than in the general population [9].

Gout is associated with higher mortality rates in patients with severe kidney disease [3,19]. Patients who developed new-onset gout following KT were found to have higher all-cause mortality compared to patients without gout [3]. Similarly, new-onset gout was associated with an increased risk of cardiovascular mortality among patients on dialysis for end-stage renal disease [19].

Among the general population with gout, greater gout severity is associated with poorer health outcomes [20–23]. Serum uric acid (SUA) level and the presence of visible tophi were associated with increased mortality among patients with gout in a prospective study [21]. Similarly, the risk of acute myocardial infarction increased with each of several gout severity metrics, including SUA level, number of affected joints, and presence of tophi, in a cross-sectional study of the population with gout [20]. Gout severity has also been found to correlate with poorer quality of life and greater disability [23].

Less well understood are any differences in gout severity and treatment success between patients with gout either with or without KT. Clive et al [15] provide anecdotal evidence that patients with gout and history of KT are particularly prone to tophi. Other qualitative differences reported among patients with gout and a history of KT include presentation with enthesitis and tenosynovitis, arthritis of the hips, shoulders and sacroiliac joints, and dermal tophi [15,24–26]. However, there are no comparative studies published to date studying gout in patients with or without history of KT.

This retrospective analysis of medical patient chart data in the real-world setting was performed to compare disease severity and treatment history in patients with gout and a history either with or without KT.

METHODS

An initial noninterventional retrospective medical chart review of patients with gout was conducted among a panel of 104 board-certified nephrologists in the United States with the purpose of understanding gout symptomology and current treatments.

Nephrologists who qualified for the quantitative, web-based research study, provided deidentified clinical information from the medical charts of patients presenting with gout by entering the data in an online survey form. Nephrologists were asked to access their 3 most recent gout patient charts to avoid selection bias and provide a point-in-time random sample of charts. Eligible patient charts included gout patients of all ages, with or without a history of KT. Chart data was collected between December 1, 2017 and February 1, 2018.

Institutional Review Board approval was obtained for post-hoc analysis of the available data. The following medical data were analyzed from the previously collected patient chart data: age, sex, SUA level, presence of swollen or tender joints at most recent visit, presence of visible or palpable tophi at most recent visit, history of gout flare events in the prior 12 months, gout pharmacologic treatment history, and history of KT.

To capture a broader view of gout disease burden, the presence of uncontrolled gout among the patient chart samples was analyzed. Uncontrolled gout definitions were based on previously published criteria, extended to include additional symptomology and treatment history not available in larger population-based studies. “Uncontrolled gout” was defined as SUA $\geq$ 6.0 mg/dL ($\geq$0.357 mmol/L); 1 or more tophi at the most recent visit; or 2 or more gout flares in the prior 12 months, plus a history of xanthine oxidase inhibitor (XOI) treatment. “Severe, uncontrolled gout” was defined as SUA $\geq$ 7.0 mg/dL ($\geq$0.417 mmol/L); 1 or more tophi at the most recent visit; and 2 or more gout flares in prior 12 months, plus a history of XOI treatment.

Continuous variables were summarized as mean $\pm$ SD. Categorical variables were summarized as proportions. Differences in means and proportions were tested using Student t test and Fisher exact test, respectively. Difference in distribution of chronic kidney disease stage, based on ordinal estimated glomerular filtration rate data, was tested using the Mann-Whitney U test.

RESULTS

Nephrologist respondents had an average of 15 years of experience and were primarily focused on clinical practice (Table 1).

The basic demographic characteristics of gout patients with (n = 25) or without (n = 287) KT are summarized in Table 2. The KT cohort was 6.9 years younger on average (55.1 vs 62.0 years, P = .028), but had a similar proportion of male patients.

Clinical characteristics and basic treatment histories among patients with gout and with or without KT are summarized in Table 2. Patients with gout and a history of KT were more likely to have severe uncontrolled gout compared to patients with gout and lacking a history of KT (27% vs 8%, P = .007). Univariate analysis found that patients with gout and a history of KT had a higher prevalence

Table 1. Nephrologist Respondent Characteristics

Characteristic	Nephrologist Respondents (N = 104)
Time in practice (y), mean ± SD	15.0 ± 6.4
Proportion of time spent in clinical practice (%), mean ± SD	94.4 ± 4.7

of tophi (36% vs 17%, $P = .030$), and greater rates of failure or contraindication to allopurinol (44% vs 23%, $P = .028$).

Although the prevalence of uncontrolled gout (see Table 2 for uncontrolled and severe, uncontrolled gout criteria), prevalence of SUA ≥ 7.0 mg/dL, and incidence of ≥2 flares in the prior 12 months were all observed to be greater in the KT cohort, the differences were not statistically significant ($P = .319$, $P = .196$, $P = .330$, respectively). Similarly, although the KT cohort was observed to have a lesser proportion of patients on allopurinol, a greater proportion of patients on febuxostat, and a greater rate of failure or contraindication to febuxostat, these differences were not statistically significant ($P = .209$, $P = .674$, $P = .231$, respectively).

Further details on gout treatment history, including overall history of urate-lowering therapy and allopurinol and febuxostat dosages are summarized in Table 3. Nearly all patients in each cohort had some history of urate-lowering therapy (94% vs 92%, $P = .645$). Allopurinol dosages varied widely within each cohort and, although the mean current allopurinol dosage was greater in the KT sample (260 ± 128 vs 215 ± 134 mg/day, $P = .336$), any observed differences were not statistically significant. Similarly, no significant differences in febuxostat dosages were observed.

Reasons for allopurinol discontinuation were analyzed among patients with or without history of KT who were previously, but no longer treated with allopurinol (n = 9 and n = 61, respectively). Results are summarized in Table 3. Lack of efficacy (patient inadequately controlled) was the most common reason for allopurinol discontinuation in both cohorts, followed by hepatic impairment among patients with KT (33% vs 0%, $P = .002$) and renal impairment among patients without KT (11% vs 36%, $P = .254$). Reasons for febuxostat discontinuation were not analyzed due to lack of sample (n = 1) among the KT cohort.

Prevalence and stage of chronic kidney disease (CKD) among patients with gout and with or without KT are summarized in Table 4. No significant difference in the proportion of patients with a current CKD diagnosis was observed (68% vs 72%, $P = .652$). However, CKD stage was significantly lower among patients with gout and a history of KT (Mann-Whitney U test, $P = .003$).

DISCUSSION

Previous studies have found that greater gout severity is associated with poorer health outcomes, including higher mortality and increased risk of major cardiovascular events [20–23]. However, despite a large body of evidence of high gout prevalence among patients with KT [3–8], gout severity among patients with KT has not been previously evaluated.

This study finds that patients with gout and a history of KT are more likely to have severe, uncontrolled gout compared to patients with gout that do not have a history of KT. The presence of palpable tophi is a characteristic of more severe gout [1]. In the present study, the increased presence of tophi among patients with gout and a history of KT highlights higher gout disease burden in these patients. The high prevalence of gout among patients with KT and increased health risks associated with severe gout

Table 2. Patient Demographics, Gout Severity, and Treatment History

Category	Criteria	No KT History (n = 287)	KT History (n = 25)
Demographics	Age (y), mean ± SD	62.0 ± 13.0	55.1 ± 14.1*
	Sex (% male)	75	72
Uncontrolled gout†	SUA ≥ 6.0 mg/dL,	32	41
	1+ tophi or 2+ flares, previous or current XOI treatment, (%)		
Severe uncontrolled gout†	SUA ≥ 7.0 mg/dL,	8	27‡
	1+ tophi and 2+ flares, previous or current XOI treatment, (%)		
SUA level§	≥6.0 mg/dL, (%)	76	79
	≥7.0 mg/dL, (%)	50	67
Symptoms/findings	Presence of swollen/tender joints, (%)	37	40
	Presence of tophi, (%)	17	36*
	≥2 flares in prior 12 mo‖,(%)	31	43
Treatments	On allopurinol, (%)	55	40
	Failed or contraindicated, (%) allopurinol	23	44*
	On febuxostat, (%)	39	44
	Failed or contraindicated febuxostat, (%)	6	12

Abbreviations: KT, kidney transplantation; SUA, serum uric acid; XOI, xanthine oxidase inhibitor.
*Difference is statistically significant: $P < .05$.
†Among patients with SUA level and flare history data (n = 206 and n = 22 for no KT history and KT history cohorts, respectively).
‡Difference is statistically significant: $P < .01$.
§Among patients with SUA level data (n = 250 and n = 24 for no KT history and KT history cohorts, respectively).
‖Among patients with flare history data (n = 227 and n = 23 for no KT history and KT history cohorts, respectively).

Table 3. Additional Urate-Lowering Therapy History, Dosages, and Reasons for Discontinuation

Category		Criteria/Answer	No KT History (n = 287)	KT History (n = 25)
History of ULT		Current or previous treatment with any ULT, (%)	94	92
		Current treatment with any ULT, (%)	94	88
Dosages	Allopurinol	Current dosage (mg/day), mean ± SD	215 ± 134	260 ± 128
		Physician-stated max dosage (mg/day)*, mean ± SD	300 ± 187	315 ± 127
	Febuxostat	Current dosage (mg/day), mean ± SD	50.4 ± 18.4	49.1 ± 19.8
		Physician-stated max dosage (mg/day)*, mean ± SD	71.1 ± 17.6	65.5 ± 19.2
Reasons for allopurinol discontinuation†		Patient inadequately controlled, (%)	66	56
		Patient could not tolerate therapy, (%)	10	0
		Patient showed side-effects while on therapy, (%)	11	22
		Renal impairment, (%)	36	11
		Hepatic impairment, (%)	0	33‡
		On other drugs that might interact with treatment, (%)	2	0
		Cost: reimbursement/insurance issues, (%)	0	0
		Patient requested a change, (%)	3	0
		Unknown [exclusive], (%)	3	22

Abbreviations: Urate-lowering therapy included allopurinol, febuxostat, probenecid, lesinurad, and pegloticase, KT, kidney transplantation; ULT, urate-lowering therapy.
*Nephrologists were asked to state the maximum dosage they would prescribe for each patient, if escalation were to become necessary.
†Among patients previously, but no longer, treated with allopurinol (n = 61 and n = 9 for no KT history and KT history cohorts, respectively). Nephrologists were asked to "select all that apply" with exception of "unknown." Reasons for febuxostat discontinuation not summarized due to sample size (n = 1) of KT history cohort.
‡Difference is statistically significant: $P < .05$.

compound the potential importance of these findings and underscores the need for further investigations in this area.

An analysis of gout treatment histories in the present study highlights the perceived challenges for physicians managing gout among recipients of kidney transplant. The finding that patients with gout and a history of KT were more likely to have discontinued or be contraindicated to allopurinol is consistent with known prescribing challenges for allopurinol in the KT population [15,27–31]. XOIs, allopurinol, and febuxostat are contraindicated in patients receiving azathioprine, which is still used as a second line antirejection agent after mycophenolate in patients with solid organ transplantation [27,28]. Hepatic impairment has been noted in the literature as a reason for allopurinol discontinuation [29,30]. Instances of hepatic impairment observed in the present study may be consistent with these previous reports, but it should be noted that the current study did not distinguish between hepatotoxicity caused by allopurinol and hepatic impairment of other etiologies that may have led to a precautionary change in treatment. Recent findings of increased risk of cardiovascular death associated with febuxostat [31] in patients with known significant cardiovascular disease might further reduce its use among the clinically complicated KT population. Future study of unmet needs with regards to appropriate, effective treatment options in gout patients with KT is warranted.

Although renal function does not appear to explain the higher rates of allopurinol failure and contraindication among the KT cohort in the present study (renal function was poorer among patients with CKD and no history of KT; the proportion of patients discontinuing allopurinol due to renal impairment was not greater in the KT cohort) the finding of renal impairment as a reason for allopurinol discontinuation merits discussion nonetheless. There is evidence that significant renal insufficiency poses specific risks to patients on XOIs such as allopurinol hypersensitivity syndrome and febuxostat-related myopathy (myositis or rhabdomyolysis) [32–34]. We presume that the instances of allopurinol discontinuation due to renal impairment in the present study are derived from such concerns, that is, that allopurinol hypersensitivity may be more common among subjects with CKD. Some nephrologists may also be concerned that allopurinol could be nephrotoxic [35–37] or that it may exert a blocking effect on the renin-angiotensin

Table 4. Chronic Kidney Disease Among Patients With Gout

Category	Criteria/Answer	No KT History (n = 287)	KT History (n = 25)
CKD prevalence	Current CKD diagnosis, (%)	72	68
CKD stage*,†	Stage 1 (eGFR > 90 mL/min/1.73 m^2), (%)	0	0
	Stage 2 (eGFR 60–89 mL/min/1.73 m^2), (%)	3	6
	Stage 3a (eGFR 45–59 mL/min/1.73 m^2), (%)	28	65
	Stage 3b (eGFR 30–44 mL/min/1.73 m^2), (%)	40	24
	Stage 4 (eGFR 15–29 mL/min/1.73 m^2), (%)	21	0
	Stage 5 (ESRD) (eGFR < 15 mL/min/1.73 m^2), (%)	8	6

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; KT, kidney transplantation.
*Difference between distributions is statistically significant: $P < .01$.
†Among patients with a current CKD diagnosis (n = 206 and n = 17 for No KT history and KT history cohorts, respectively).

system resulting in a hemodynamically-mediated reduction in estimated glomerular filtration rate [38]. However, a recent study showed that the use of allopurinol does not appear to increase the risk of CKD decline, but rather may slow progression [39].

Higher rates of XOI failure and contraindication among patients with gout and a history of KT suggest that pharmacologic challenges may be contributing to greater disease severity, but undertreatment is unlikely to fully explain the observed results. For example, the proportion of patients with gout currently on urate-lowering therapy was only slightly lower in the KT cohort and those on XOIs were not receiving lower dosages. Similarly, age and renal function seem unlikely to explain the greater gout severity observed among the KT cohort, as this group was younger and had better renal function among the large proportion of patients with CKD. Several factors previously cited as risks for hyperuricemia and increased gout prevalence among patients with a history of KT (eg, cyclosporine, tacrolimus, diuretics) were not available in the current data set, but could be contributing to greater gout severity [12–18]. Importantly, the present study does not capture whether hyperuricemia was present prior to KT and, if so, whether a lack of appropriate management at that time was associated with the more severe gout seen in the transplantation cohort. Alternatively, it is possible that increased gout severity leads to greater risk of renal failure and hence, the need for transplantation to restore renal function, which would be consistent with evidence of hyperuricemia and gout as risk factors for the development and progression of CKD and end-stage renal disease [40,41].

Limitations

Several limitations of this study are worth noting. This preliminary study is retrospective and small and is thus subject to the potential biases and power limitations associated with such a design. There are factors that might influence gout severity that were not available in the present study, including, but not limited to: immunosuppressant use (eg, calcineurin inhibitors) and other concomitant medications (eg, diuretics), timing and persistence of urate-lowering therapy, duration of disease and onset relative to transplant, and relevant comorbidities (eg, obesity and cardiovascular disease). A study that includes other types of solid organ transplantation could help determine the specific role of KT and other types of solid organ transplantation in driving gout disease severity.

CONCLUSIONS

Although gout has been linked to higher worse outcomes among patients with a history of KT in the literature [3], there are presently no publications on gout severity among patients with KT in comparison to other patients with gout. This study offers preliminary data that kidney recipients frequently have more advanced, difficult to treat gout.

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