The Effect of Thiazide and Potassium Citrate Use on the Health Related Quality of Life of Patients with Urolithiasis

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Abbreviations and Acronyms

BMI = body mass index

GI = gastrointestinal

HRQOL = health related quality of life

Kcit = potassium citrate

SF-36 = 36-Item Short Form Health Survey

WISQOL = Wisconsin Stone Quality of Life

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Purpose: To our knowledge it is unknown whether the benefits of medical management of urolithiasis outweigh the potential side effects of the medications used, including potassium citrate and thiazide diuretics. Therefore, we evaluated the relationship between potassium citrate or thiazides and overall stone related health related quality of life.

Materials and Methods: Cross-sectional data were obtained on stone forming enrollees in the North American Stone Quality of Life Consortium. We used the WISQOL (Wisconsin Stone Quality of Life) questionnaire to compare health related quality of life between patients treated and not treated with potassium citrate or thiazide type diuretics. Additionally, the likelihood of gastrointestinal complaints was compared between those prescribed and not prescribed potassium citrate. The likelihood of fatigue and sexual complaints was also compared in those prescribed and not prescribed thiazides.

Results: Of the 1,511 subjects, including 787 males and 724 females, 279 were on potassium citrate and 238 were on thiazides at study enrollment. Patients prescribed potassium citrate had higher health related quality of life in each domain vs those not prescribed potassium citrate ($p < 0.001$). Patients prescribed thiazides had higher health related quality of life in each domain compared to those not prescribed thiazide (all $p < 0.01$). Those prescribed potassium citrate were less likely than those not prescribed potassium citrate to report nausea, stomach upset or cramps (OR 0.57, $p < 0.001$). Patients prescribed thiazides were less likely than those not prescribed thiazides to report fatigue (OR 0.63, $p = 0.004$) or reduced sexual interest and/or activity (OR 0.64, $p = 0.005$).

Conclusions: Among stone formers the use of potassium citrate and thiazides was associated with better health related quality of life across all WISQOL domains without an increased likelihood of gastrointestinal complaints and fatigue or sexual complaints, respectively. These findings may be useful when counseling patients regarding the initiation of potassium citrate or thiazides for medical management of nephrolithiasis.

Key Words: kidney calculi, surveys and questionnaires, sodium chloride symporter inhibitors, potassium citrate, quality of life

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UROLITHIASIS has been associated with reduced HRQOL.[1,2] A systematic review of randomized controlled trials and observational studies indeed confirmed that patients with kidney stones experience impaired HRQOL but results regarding patient preference for and experience with medical management were mixed.[2] When treatment regimen outcomes meet the expectations of stone forming patients, the patients are more likely to be satisfied, which may then affect HRQOL.[3] Therefore, in addition to traditional clinical outcomes, HRQOL has been proposed as an important end point in the management of urolithiasis.[1]

The SF-36 has been used to assess HRQOL in patients who form stones but it was unable to differentiate between those with and without stones, and/or stone associated symptoms.[4] Such discriminatory failure prompted development of the WISQOL questionnaire. This internally consistent and externally validated instrument has been demonstrated to differentiate among a continuum of statuses and symptoms of patients with stones.[5] It further identifies stone specific decrements in HRQOL that are not identified by the SF-36.[6]

One area of management for recurrent nephrolithiasis that has been well studied for its efficacy has been pharmacological therapy. According to the AUA (American Urological Association) guidelines on the medical management of kidney stones there is grade B evidence for offering thiazide type diuretics and Kcit to patients with recurrent hypercalciuric calcium stones while expert opinion has stated that Kcit can be administered to raise urinary pH in patients with uric acid and cystine stones.[7] A meta-analysis of 6 randomized controlled trials showed a 47% risk reduction in stone recurrence with thiazides.[8] In a randomized controlled trial Barcelo et al observed decreased stone formation in patients on Kcit compared to those on placebo (72% vs 20%, $p < 0.001$).[9] Adherence to medication therapy has been associated with fewer emergency care visits, hospitalizations and surgery compared to patients nonadherent to medication therapy.[10]

Unfortunately these medications may be associated with side effects that are troubling and potentially difficult to tolerate, including fatigue[11] and loss of libido[12] for thiazides, and GI upset, abdominal pain and diarrhea for Kcit.[13] Such side effects could reduce a perceived benefit as well as ultimate medication compliance.[14] Therefore, in contrast to the anticipated long-term benefits for stone prevention, medications could have a potentially negative impact on perceived HRQOL among stone forming patients.[15]

We sought to determine whether administering these commonly prescribed medications to medically manage stone disease was associated positively or negatively with stone specific patient HRQOL.

METHODS

We performed a multi-institutional, cross-sectional cohort study in a population of established stone forming patients seen at tertiary urology centers participating in the North American Stone Quality of Life Consortium. Institutional review board approval was obtained at all participating sites for data collection and study participation.

Each patient completed an initial intake WISQOL survey at the time of study enrollment. Additionally, data related to demographics, past medical history, current stone and symptom status, history of stone events and prescribed medications were gathered. HRQOL scores were calculated in the WISQOL domains of social, emotional and disease impact, and vitality. Items on the WISQOL are scored by respondents on a Likert scale of 1—worst to 5—best HRQOL. A full accounting of each question in each domain and question validation has been previously published.[5,6]

Using the Student t-test mean domain scores were compared between patients who were and were not prescribed thiazide type diuretics and those who were and were not prescribed Kcit. The chi-square test was used to analyze categorical variables.

We also assessed responses to individual WISQOL survey items reflecting commonly reported side effects associated with the medications. Specifically we compared respondents with any report of side effect (a score of 1 to 4 on the WISQOL survey) to no reported side effects (a score of 5). Univariate and multivariate logistic regression were used to evaluate the likelihood of complaints of nausea and stomach upset between those prescribed and not prescribed Kcit. This was also done to assess the likelihood of complaints of fatigue and reduced sexual interest/activity between patients prescribed and not prescribed thiazides.

Statistical significance was considered at $\alpha = 0.05$. All statistical data were obtained using STATA®, version 13.1.

RESULTS

A total of 1,511 stone forming patients were included in analysis, including 787 males and 724 females (table 1). Of the total population 279 patients were receiving Kcit, 238 were receiving thiazide-type diuretics, 82 were receiving each type of medication and 1,076 were receiving neither at the time of study enrollment. Patients on thiazides had a significantly higher BMI and a higher median number of prior stone events than patients not on thiazides (table 1). Those on Kcit were significantly younger and also had a significantly higher number of prior stone events than those not receiving Kcit (table 1).

When comparing WISQOL domain scores between patients on vs not on thiazides, those on the medication had significantly higher scores across all domains. These findings maintained significance on multivariate analysis when adjusting for age, gender, BMI and number of prior stone events. Scores were higher in the domains of social,

Table 1. *Demographics of patients receiving thiazide diuretic and potassium citrate*

	Medication		
	Yes	No	p Value
Thiazide diuretic:			
No. pts	238	1,076	—
Median age	59.7	59.0	0.67
% Male	55	51.5	0.32
% Female	45	48.5	
Median BMI (kg/m^2)	31.8	30.0	<0.001
Median No. stone events	4	3	<0.001
Potassium citrate:			
No. pts	279	1076	—
Median age	56.0	59.8	0.008
% Male	54.8	51.5	0.31
% Female	45.2	48.5	
Median BMI (kg/m^2)	31.1	30.1	0.06
Median No. stone events	5	3	<0.001

emotional and disease impact, and vitality by 1.9 (4.8%), 2.3 (6.6%), 2.1 (5.3%) and 1.0 points (6.7%), respectively (all p <0.01). Similarly for Kcit we found that patients on the medication had significantly higher scores across all WISQOL domains compared to those not on the medication. Again, these differences maintained significance on multivariate analysis when adjusting for the mentioned factors. Domain scores were higher for social, emotional and disease impact, and vitality by 2.3 (5.8%), 2.5 (7.1%), 2.6 (6.5%) and 1.2 points (8.0%), respectively (all p <0.001, table 2).

Interestingly we found that patients prescribed thiazides were less likely to report any fatigue (59.4% vs 68.3%, p = 0.008) or reduced sexual activity/interest (33.2% vs 44.1%, p = 0.002) compared to those not on the medication. On multivariate logistic regression patients on thiazides were 37% less likely to report fatigue (p = 0.004) and 36% less likely to report reduced sexual activity/interest (p = 0.005) compared to those not on the medication (table 3). GI complaints are a side effect often associated with Kcit but patients prescribed Kcit reported fewer GI complaints than those not on the medication (43.1% vs 55.5%, p = 0.002). On multivariate logistic regression patients on Kcit were 43% less likely to report GI complaints compared to those not on the medication (p <0.001, table 3).

DISCUSSION

There have been conflicting impressions about the effect of medications for stone prevention on HRQOL in patients with urolithiasis. In a study by Bensalah et al thiazides did not impact HRQOL when using the SF-36 while Kcit showed improved scores for physical functioning, bodily pain and social functioning.[16] However, those findings lost significance on multivariate analysis. In a study that underscored these results Bryant et al found that

Table 2. *Domain scores*

	Mean Score			
Medication (domain)	No Medication	Medication	Multivariate Mean Improvement	p Value
Thiazide diuretic:				
Social	32.7	34.6	1.9	0.008
Emotional	25.4	27.8	2.3	0.001
Disease	29.4	31.7	2.1	0.002
Vitality	10.6	11.6	1.0	0.001
Potassium citrate:				<0.001
Social	32.5	34.8	2.3	
Emotional	25.3	27.8	2.5	
Disease	29.2	31.8	2.6	
Vitality	10.6	11.7	1.2	

medical therapy had no positive or negative association with HRQOL across any SF-36 study domains.[17]

To our knowledge this is the largest study looking at the effect of medication use on HRQOL in patients with urolithiasis and the first to use a stone specific HRQOL instrument. Based on these results patients on medications to manage urolithiasis do not appear to have impaired HRQOL. In fact, we identified statistically significant higher scores reflecting better HRQOL in patients on thiazide diuretics and those on Kcit compared to those not currently receiving those medications. These improvements maintained significance when adjusting for potential confounding factors, including patient age, gender, BMI and number of prior stone events. Interestingly patients on these medications were significantly less likely to report the side effects commonly associated with thiazides (fatigue and reduced libido) and Kcit (GI upset) compared to patients not prescribed these medications.

Potential medication related side effects are often cited as the limitations of medical therapy for the prevention of nephrolithiasis. In fact, our study shows the opposite. Not only did medicated patients have higher HRQOL but they also reported fewer side effects than those not on Kcit or thiazides.

Urolithiasis is in a unique category of chronic conditions known for decreased HRQOL on its own as well as for the use of medications rife with potential side effects. An analogous condition in the field of urology is overactive bladder.[18] Patients with overactive bladder were found to have better HRQOL with anticholinergic medication if overall side effects were fewer.[19] Similarly epilepsy management often involves medications with significant potential side effect profiles. These adverse effects have a predominant role in determining HRQOL in this patient population and the frequent assessment of such is essential to maximize HRQOL.[20] Appropriate medication selection, regular monitoring for adverse effects and continued assessment of HRQOL as an outcome measure are equally important in the

Table 3. *Thiazide diuretic and potassium citrate side effect reporting*

Medication (side effect)	% Medication		p Value	OR (95% CI)	p Value
	Yes	No			
Thiazide:					
Fatigue	59.4	68.3	0.008	0.63 (0.46–0.86)	0.004
Reduced sexual activity/interest	33.2	44.1	0.002	0.64 (0.47–0.88)	0.005
Potassium citrate (gastrointestinal complaint)	43.1	55.5	0.002	0.57 (0.43–0.77)	<0.001

management of epilepsy.[21] This can certainly be said for the management of recurrent urolithiasis.

One explanation for the results of this study is that patients on chronic medications to manage recurrent urolithiasis may experience fewer stone episodes. Fewer stone events, an increased interval between events and fewer surgical interventions have been associated with better HRQOL.[15,16,22] In other words, it could be that patients who experience a reduction in stone events after starting a medication have better HRQOL regardless of the prior number of stone events. Indeed, in our study patients on thiazide diuretics and/or Kcit had a higher number of lifetime stone events than those not prescribed these medications. This likely reflects that patients with more aggressive stone disease were prescribed Kcit and thiazides. Additionally, it highlights the anticipated benefits of pharmacological therapy to prevent recurrent urolithiasis.

Furthermore, it is not uncommon for patients with urolithiasis to experience symptoms of GI upset, fatigue and reduced sexual interest during recurrent stone episodes. Although a report has shown no significant difference in sexual side effects in women receiving antihypertensive medications,[23] our data suggest that thiazides to prevent stones are not associated with increased sexual side effects. Despite commonly associated side effects the receipt of Kcit and thiazides to prevent recurrent stones may paradoxically lead to fewer symptoms.

Alternatively the observed improvements in quality of life may reflect a psychological component. The patients in our study were followed at tertiary, multidisciplinary or specialty urology stone clinics where prescribing chronic medications may be more likely. It is possible that our results reflect the effects on patient HRQOL of more proactive management of urolithiasis, the so-called stone clinic effect. More favorable patient perceptions of an illness and more confidence in prescribed treatment regimens can equate to improved HRQOL, as seen in studies of other chronic medical conditions.[24,25]

We recognize that our study has a number of limitations. Its cross-sectional nature enabled us to assess patient HRQOL only at study enrollment. Thus, the potential effect of medication on decreasing stone episodes or recurrence could not be directly measured. Prospective studies are needed to follow these patients with time to see whether improvements in HRQOL are maintained and side effect reporting remains lower, and to assess for reductions in stone recurrence. As new patients continue to be enrolled in the North American Stone Quality of Life Consortium we can better evaluate these trends, especially in those who are started on medication at study enrollment.

Given the cross-sectional design of the study, it is conceivable that some patients tolerated the medications at the time of enrollment without respect to a change in the side effect profile. Also, the study design did not enable us to account for the number of prior stone visits per patient and time that they had been followed. Additionally, the design did not impart the ability to determine whether a patient had previously been on a medication but discontinued it due to intolerance of side effects or some other reason. Our data also did not provide the granularity required to assess the pharmacological therapy duration or dose regimen. Furthermore, we did not discern among specific thiazide-type diuretic formulations, which could differ in side effect profiles. Therefore, it is possible that varying doses or formulations of the study medications could have affected patient reported HRQOL and side effect reporting. For example, this would potentially explain why the cohort on Kcit reported significantly fewer GI complaints when the opposite would be expected.

Finally, while patients on thiazides or Kcit had statistically significant higher HRQOL domain scores, the clinical significance of the reported magnitude of the change remained undefined. As in any observational study unmeasured patient, provider or system factors may be sources of additional unrecognized confounding. These factors include patient comorbidities, and the duration and severity of stone events. Nevertheless, our data provide important reassurance that patients who receive and tolerate these medications can anticipate improved stone specific quality of life.

CONCLUSIONS

Despite the association of thiazide diuretics and Kcit with significant side effects, patients on these medications to manage urolithiasis may experience

higher HRQOL. They are also less likely to report the side effects commonly associated with these medications. Our findings can be used to reassure patients regarding the initiation of Kcit or thiazides for medical management of stones. Further prospective studies are needed to evaluate whether these findings maintain significance with time with respect to stone prevention and improved HRQOL.

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EDITORIAL COMMENT

This is an informative study based on a multi-institutional cross-sectional study of stone formers. It summarizes their health related quality of life as measured by the well-defined WISQOL survey instrument. It included 1,511 patients with some on potassium citrate and/or thiazide diuretics. It provides a good snapshot of these patients at the time of the survey.

Overall those on medication were experiencing better quality of life than those not using medicines. Many factors could not be clarified with this study design. For example, it was not known whether treatment had failed earlier in the patients not on medication. Similarly the dose and duration of treatment were unknown. It was not known whether there was a difference in the severity of stone episodes. These and many other factors can affect the tolerance of medicines.

The authors have clearly stated the limitations of the study. It does, however, present the status of patients at the time of the survey across many institutions and raises multiple areas for future study.

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