Thiazide Diuretic Prophylaxis for Kidney Stones and the Risk of Diabetes Mellitus

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Abbreviations and Acronyms

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

BMI = body mass index

DM = diabetes mellitus

HTN = hypertension

Accepted for publication June 24, 2014.

Supported by the National Institute of Diabetes and Digestive and Kidney Diseases (Mayo Clinic O'Brien Urology Research Center, DK100227 and DK83007) and the Rochester Epidemiology Project (AG034676) from the National Institutes of Health, U.S. Public Health Service.

Study received institutional review board approval.

* Financial interest and/or other relationship with Histosonics.

† Financial interest and/or other relationship with OxThera, Otsuka, IDEXX and Gentian.

‡ Financial interest and/or other relationship with GenomeDx.

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Purpose: Thiazide diuretics used to treat hypertension are associated with a modest risk of diabetes mellitus. It is unknown if there is a similar risk with kidney stone prevention.

Materials and Methods: We identified and validated incident stone formers in Olmsted County, Minnesota from 1984 to 2011 with manual review of medical records using the Rochester Epidemiology Project. The risk of diabetes mellitus after thiazide therapy was evaluated with and without multivariate adjustment for hypertension, age, gender, race, family history of stones, body mass index and number of stone events.

Results: Among 2,350 incident stone formers with a median followup of 10 years, 332 (14%) were treated with thiazide diuretics at some point after the first stone event and 84 (3.6%) received the thiazide diuretic only for kidney stone prevention. Stone formers who received thiazide diuretics were more likely to be older, have hypertension, have higher body mass index and have more stone events. The incidence of diabetes mellitus at 10 years after the first stone event was 9.2% in the group that received thiazide diuretics vs 4.2% in those who did not (HR 2.91; 95% CI 2.02, 4.20). After multivariate adjustment the risk of diabetes mellitus was attenuated (HR 1.20; 95% CI 0.78, 1.83). The risk of diabetes mellitus among those receiving thiazide diuretics solely for kidney stones was further attenuated (multivariate adjusted HR 0.80; 95% CI 0.28, 2.23).

Conclusions: Thiazide diuretic use for kidney stone prophylaxis was not associated with a high risk of diabetes mellitus. Larger studies are needed to determine if there is a modest risk of diabetes mellitus with thiazide diuretics.

Key Words: calculi, thiazides, diuretics, diabetes mellitus

Nephrolithiasis is a common condition worldwide with a prevalence of 5% to 10%.[1] Recent evidence has shown that kidney stones are becoming more common.[2] With the increasing burden of stone disease, the need for effective therapy is paramount. Clinical trials have demonstrated the benefit of thiazide diuretics (and thiazide-like diuretics) for the prevention of recurrent stone disease (only half were done in patients with confirmed hypercalciuria).[3–7] Thiazide diuretics are commonly used for stone prevention since they are generally well tolerated, inexpensive, and effectively reduce urine calcium excretion and stone recurrence risk. However, thiazide diuretics may be underused for the prevention of recurrent kidney stones in the general population due

0022-5347/14/1926-1700/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.06.078
Vol. 192, 1700-1704, December 2014
Printed in U.S.A.

to patient or physician concerns regarding the side effects of this class of medications.

There is a lack of data regarding adverse, long-term side effects of thiazides used for stone prevention. However, the side effect profile of thiazide diuretics has been well studied in the setting of hypertension. The ALLHAT, which followed more than 30,000 patients with hypertension and randomized them to an angiotensin converting enzyme inhibitor, calcium channel blocker or thiazide diuretic therapy, showed that thiazide diuretics resulted in a modest increased risk of diabetes mellitus. ALLHAT showed an increase in the incidence of new onset diabetes after 4 years in the chlorthalidone group compared with the amlodipine and lisinopril groups (11.6% vs 9.8% and 8.1%).[8] Indeed, the potential for a disturbance in glucose metabolism has been a concern since the introduction of thiazides as a class of antihypertensive agent,[9,10] and has been described in nondiabetic, pre-diabetic and diabetic patients, although the mechanism for this association is unknown.[9,11–13] Since an association between insulin resistance and HTN has been described,[14–16] hypertensive individuals might be more susceptible to any hyperglycemic potential of this medication class compared to individuals without HTN in whom the medication is used solely to reduce urine calcium excretion. Thus, we assessed the risk of new onset DM among stone formers in relation to thiazide use and hypertension.

MATERIALS AND METHODS

Study Population

The Rochester Epidemiology Project is a long-standing medical records linkage system that encompasses nearly all medical care delivered to the residents of Olmsted County.[17] More than 95% of the population receives health care in Olmsted County every 2 to 3 years, allowing enumeration of the local population. Diagnostic codes (manually or automatically coded from the final diagnoses in clinical notes) dating back to 1935 are indexed and linked among virtually all Olmsted County providers.[17] The population of Olmsted County increased from 92,006 in 1980 to 144,288 in 2010. After receiving Mayo Clinic institutional review board approval, Olmsted County residents with their first diagnosis of a kidney stone from 1984 to 2011 were identified using ICD-9 codes 592, 594 and 274.11. Comprehensive medical records were then reviewed by a dedicated nurse abstractor who confirmed stone forming status and then collected details of care. A validated incident symptomatic stone event was defined as having documented recovery of a stone after passage, or visualization of a stone in the ureter or renal pelvis with features consistent with obstruction or intermittent obstruction. Symptomatic criteria included gross hematuria, abdominal or flank pain, or documented urinary tract infection with a urease splitting organism.

Among the validated incident symptomatic stone formers, several groups were excluded from the study such as 1) patients with uric acid stones since they are known to be associated with diabetes mellitus[18–20] and are not typically treated with thiazide diuretics, 2) patients who had diabetes mellitus diagnosed before the first stone event, 3) patients with DM within 90 days after their first stone event since they might have resulted from a finder-effect for preexisting DM, and 4) patients who were on thiazide diuretics before or up to 90 days after their first stone event. The study sample was then followed for initiation of thiazide diuretic therapy (as documented in patient care notes) and, specifically, for thiazide diuretics initiated only for stone prophylaxis (and not hypertension). Thiazide diuretic therapy initiation had to be more than 90 days after the incident stone event and could occur at any time during followup (including after subsequent stone events).

Outcome

Followup for onset of DM was captured through the comprehensive medical record as long as the stone former remained a resident of Olmsted County. Followup was censored at the last care visit, death or onset of DM. DM onset was identified by a fasting blood glucose value greater than 126 mg/dl on at least 2 separate but consecutive readings, or when therapy with an antidiabetic medication was initiated.

Comorbidities

Onset of HTN was identified as the first date of 2 systolic blood pressure readings of 140 mm Hg or greater, or 2 diastolic blood pressure readings of 90 mm Hg or greater, or when a physician diagnosed an individual with hypertension. BMI based on height and weight closest to the first stone event was identified. The number of symptomatic kidney stone events (validated with chart review using the same criteria as the incident stone event) was also ascertained as a marker of kidney stone disease severity. Stone composition (oxalate, apatite or brushite) and 24-hour urine calcium excretion for each stone former were characterized to the extent possible.

Statistical Analysis

Cox proportional hazard models were used to estimate the risk of DM associated with thiazide diuretics. Thiazide diuretic use was analyzed as a time dependent variable, as were hypertension and stone events. Only hydrochlorothiazide, chlorthalidone, trichlormethiazide and indapamide were classified as thiazide (or thiazide-like) diuretics. Analyses were done with and without adjustment for hypertension. Multivariate models further adjusted for age, gender, race, number of stone events and BMI. An interaction term for thiazide diuretic use and hypertension was included in a Cox model to estimate the thiazide HR for those with and without prior hypertension. Additional analyses looked at the risk of DM in stone formers who received thiazide diuretics only for stone prophylaxis. A sensitivity analysis excluded stone formers with cystine or struvite stones. Analyses were performed using SAS® version 9.3.

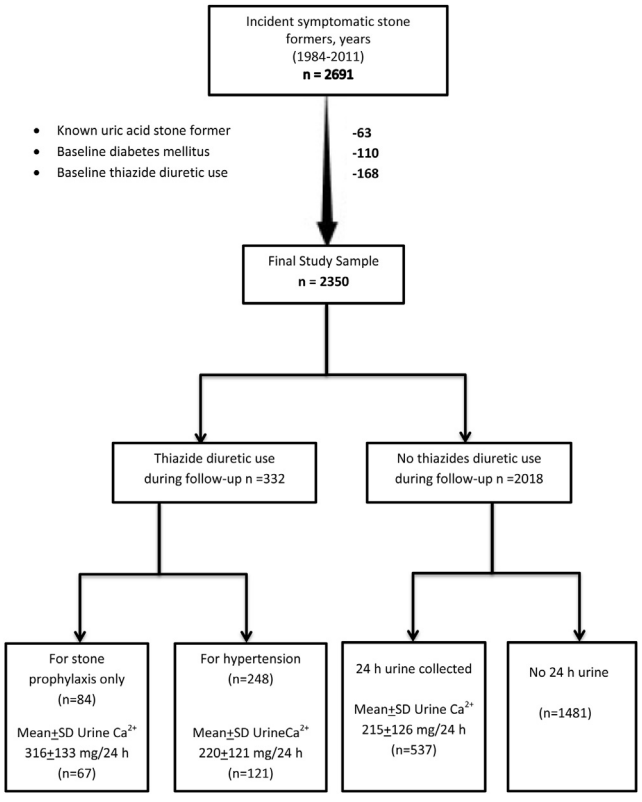
RESULTS

During the study period (January 1, 1984 to December 31, 2011) 2,691 patients were identified and validated as first time stone formers in Olmsted County. The 63 stone formers with known uric acid stone composition were excluded from study. After excluding patients with baseline DM or thiazide diuretic use, 2,350 stone formers remained, of which 332 (14%) received thiazide diuretics at some point during followup (see figure). Urine calcium was higher in those who received thiazide diuretics only for stone prophylaxis (mean 316 mg/24 hours) compared to those who received thiazide diuretics for HTN (mean 220 mg/24 hours, p <0.001) or who did not receive thiazide diuretics (mean 215 mg/24 hours, p <0.001). There were 84 (3.6%) stone formers who received thiazide diuretics during followup specifically to prevent kidney stone recurrence.

The stone formers who received thiazide diuretics during followup were more likely to be older, white race, have a family history of stone disease, have a higher BMI, have hypertension at baseline or during followup, and have more total stone events (table 1). Stone formers who received thiazide diuretics during followup had a longer overall followup than those who did not receive thiazide diuretics (mean 13.9 vs 9.8 years, p <0.001). This was expected since receiving a thiazide diuretic after the first stone event predicates followup time on a future event. Stone composition was known in 1,154 stone formers (49%), of whom 1,091 had calcium stones. Those who received thiazide diuretics were more likely to have a known calcium component of the stones than those who did not receive thiazide diuretics.

There were 163 DM events during followup. The risk of DM was increased among incident stone formers who had prevalent or new onset hypertension, received thiazide diuretics, were older, were male or had a higher BMI. The risk of DM was not associated with a family history of stones or the number of stone events (table 2). The risk of DM after initiation of thiazide diuretics was not statistically significantly increased after adjusting for hypertension or hypertension plus other DM risk factors. Use of thiazide diuretics solely for kidney stone prophylaxis was not associated with an increased DM risk. There was a trend toward an increased risk of subsequent DM among those stone formers given thiazide diuretics who also had hypertension but not among those stone formers in whom HTN never developed (table 3).

There were 9 struvite and 2 cystine stone formers excluded from the sensitivity analysis. The multivariate adjusted risk of DM with thiazide diuretic



Study sample of incident stone formers in Olmsted County, Minnesota.

Table 1. *Characteristics of incident symptomatic stone formers*

	Thiazide Diuretics	No Thiazide Diuretics	p Value
Mean ± SD age	47 ± 15	41 ± 15	<0.001
No. male gender (%)	213 (64.2)	1,230 (61.0)	0.27
No. nonwhite race (%)	11 (3.4)	124 (6.6)	0.024
No. family history of kidney stones (%)	108 (32.5)	515 (25.5)	0.007
Mean ±SD kg/m^2 BMI	29.2 ± 6.0	27.7 ± 6.1	<0.001
No. hypertension at first stone event (%)	44 (13.2)	147 (7.3)	0.0002
No. hypertension ever (%)	264 (79.5)	446 (22.1)	<0.001
Mean ± SD total stone events	2.0 ± 1.6	1.5 ± 1.1	<0.001
No. known calcium stone composition (%)	171 (51.5)	920 (45.6)	0.045

Table 2. *Association of characteristics in incident symptomatic stone formers with risk of DM*

	HR (95% CI)	p Value
Thiazide diuretic (time dependent)	2.91 (2.02, 4.20)	<0.001
HTN (time dependent)	4.37 (3.12, 6.12)	<0.001
Age per 10-yr increase	1.38 (1.26, 1.54)	<0.001
Male gender	1.38 (0.99, 1.93)	0.06
Nonwhite race	1.77 (0.93, 3.37)	0.08
Family history of kidney stones	0.96 (0.68, 1.35)	0.80
BMI per 5-unit increase	1.83 (1.65, 2.02)	<0.001
No. stone events (time dependent) per unit increase	1.01 (0.88, 1.16)	0.88
Known calcium stone composition	1.36 (0.33, 5.52)	0.67

Table 3. *Risk of DM in stone formers who received thiazide diuretics during followup*

	HR (95% CI)	p Value
Thiazide diuretic for any indication:		
Unadjusted	2.91 (2.02, 4.20)	<0.0001
HTN adjusted	1.48 (0.98, 2.23)	0.06
Multivariate adjusted:*	1.20 (0.78, 1.83)	0.40
Estimated HR without HTN	1.10 (0.49, 2.48)	Not applicable
Estimated HR in those with HTN	1.24 (0.76, 2.04)	Not applicable
Multivariate adjusted†	1.13 (0.65, 1.99)	0.65
Thiazide diuretic only for kidney stone prevention:		
Unadjusted	1.02 (0.42, 2.49)	0.97
Multivariate adjusted*	0.80 (0.28, 2.30)	0.68

* Adjusted for HTN (time dependent), age, male gender, race, family history of stones, BMI and number of stone events.
† Further adjusted for known calcium composition.

for any indication (HR 1.16; 95% CI 0.65, 2.03) or for kidney stone prophylaxis (HR 0.84; 95% CI 0.29, 2.40) did not change substantively with these exclusions.

DISCUSSION

While thiazide diuretic use among stone formers was associated with an increased risk of DM, this association was no longer evident after adjusting for confounding factors, including the presence of HTN. In particular, stone formers who received thiazide diuretics solely for kidney stone prophylaxis were not at increased risk for subsequent DM. There was an increased unadjusted risk of DM with the use of thiazide diuretics among stone formers with concurrent hypertension, but this finding likely reflects the association between hypertension severity (need for a diuretic) and DM risk.

The use of thiazide diuretics to treat hypertension has been associated with impaired glucose tolerance.[10,21,22] A large randomized controlled trial (ALLHAT) demonstrated a statistically significant increase in the incidence of new onset DM after 4 years of treatment with a thiazide diuretic compared to amlodipine and lisinopril (11.6% vs 9.8% and 8.1%, respectively).[8] Analysis of the Nurses' Health Study and Health Professionals Follow-Up Study cohorts confirmed that the use of thiazides in patients with hypertension was associated with an increased DM risk.[23] Verdecchia et al observed that treatment with thiazide diuretics was an independent predictor of new onset diabetes in hypertensive patients.[24] However, these studies were performed in hypertensive populations already at high risk for diabetes, and results may not be applicable to those in whom thiazide diuretics are used to reduce urinary calcium excretion and kidney stone risk.[25]

The mechanism of thiazide diuretic induced glucose intolerance is not understood.[25,26] It has been hypothesized that hypokalemia is the most likely cause of thiazide induced hyperglycemia, perhaps leading to impaired beta-cell insulin release.[27] Unfortunately we did not have serum potassium levels in our study to evaluate for a potential link between hypokalemia and DM risk. There is no definitive evidence of a mechanistic chain between thiazide diuretics and hyperglycemia, potassium dependent or independent.[26] The clinical relevance of possible thiazide induced diabetes has been debated since analysis from ALLHAT did not reveal an increased risk of cardiovascular events among patients with impaired fasting glucose or diabetes mellitus who received thiazides.[8] Thus, many have concluded that the cardiovascular benefit of better HTN control when thiazide diuretics are used may outweigh any potential cardiovascular harm from a modestly increased risk of DM. However, normotensive stone formers who take thiazide diuretics will probably not benefit from lowering a blood pressure that is already normal. Thus, an increased risk of DM with thiazide diuretic use in stone formers without HTN is of particular concern. However, our results revealed no increased DM risk among stone formers when thiazide diuretics were used solely for kidney stones.

Calcium stone formers are at increased risk for DM, independent of thiazide diuretic use.[28] The association between nephrolithiasis and subsequent DM may be due to a common metabolic defect that contributes to the development of both diseases.[28,29] Regardless of the underlying mechanism(s) for the association between DM and nephrolithiasis, we did not find any evidence that thiazide diuretic use for stone prophylaxis further increases the risk of diabetes.

Our study has potential limitations. The population of Olmsted County is predominantly white and findings may not be generalizable in other race groups. Kidney stone disease is more common in white than in nonwhite race groups.[30] With a historical cohort study design the detection of DM was passive and dependent on fasting blood glucose levels obtained through usual clinical care. We may have not been able to detect a modest but clinically important risk of DM, although the trend in the nonhypertensive group was protective (HR 0.80). Any increased detection of DM in stone formers from having more clinical care would have biased our data toward detecting an increased risk of DM and we found none. The period of adherence to thiazide therapy could not be determined from the medical record. Finally, stone composition was unknown in approximately half of the stone formers as the stone was not always available or obtained for analyses.

CONCLUSIONS

Thiazide diuretic use to prevent recurrent calcium nephrolithiasis is supported by randomized controlled trials. As the prevalence of kidney stone increases, so will the need for effective, affordable, long-term prevention therapies. Concern for DM may discourage the use of thiazide diuretics. Indeed we found only 3.6% of predominantly calcium stone formers received thiazide diuretic therapy to prevent stone recurrence. However, we found no increased risk of DM when thiazide diuretics were used solely for kidney stones. A study with a larger sample size is needed to clarify if there is a modest risk of DM in stone formers receiving thiazide diuretics.

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