Adverse Metabolic Side Effects of Thiazides: Implications for Patients With Calcium Nephrolithiasis

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Purpose: Thiazide use to prevent recurrent calcium nephrolithiasis is supported by randomized, controlled trials. Concerns regarding adverse metabolic effects of thiazides, which are also used to treat hypertension, have reemerged with analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. The risks posed by thiazide induced hyperglycemia, hyperuricemia, hypokalemia and dyslipidemia may decrease the expected cardiovascular benefit of lowering blood pressure in hypertensive patients. Whether these side effects occur and are clinically significant in nonhypertensive patients with kidney stones treated with thiazides is unclear.

Materials and Methods: A review of the literature was performed for randomized, controlled trials with thiazides for calcium nephrolithiasis. We sought data regarding metabolic effects in this population, including hyperglycemia, hyperuricemia, hypokalemia and dyslipidemia.

Results: Nine randomized, controlled trials of thiazide treatment for kidney stones were included. Mean patient age was 42 years and followup was 2.6 years. Only 2 of the 9 studies measured glucose and lipid levels, which did not significantly change with treatment. Three studies measured serum potassium and 2 showed a significant decrease. Three of the 9 studies measured serum uric acid levels, which increased in all 3. None of the trials studied the development of diabetes mellitus or cardiovascular disease.

Conclusions: There is a lack of data on the metabolic effects of thiazides used to prevent recurrent calcium nephrolithiasis. It remains unclear if metabolic effects occur and increase the risk of cardiovascular disease in otherwise healthy patients with recurrent nephrolithiasis on thiazide prophylaxis. Further research is needed to elucidate other alternatives for the treatment of recurrent nephrolithiasis.

Key Words: kidney, kidney calculi, diabetes mellitus, hyperlipidemia, hyperuricemia
Hypokalemia is a well-known side effect of thiazide treatment. In the setting of thiazide induced secondary hyperaldosteronism and thiazide induced hypomagnesemia increased Na delivery to the distal nephron is responsible for thiazide induced hypokalemia. The decrease in serum K is dose dependent and longer acting thiazides such as chlorthalidone tend to cause greater degrees of hypokalemia than other thiazides. The range of the decrease in serum K can be 0.3 to 1.2 mEq/l with up to 50% of patients experiencing serum K less than 3.5 mEq/l, while 7% have levels less than 3.0 mEq/l. ALLHAT showed a 12.7% prevalence of hypokalemia (serum K less than 3.5 mEq/l) at 2 years and 8.5% at 4 years of thiazide treatment. It occurred more frequently in patients treated with chlorthalidone than in patients treated with lisinopril and amlodipine. At 5 years 8% of the subjects in the chlorthalidone group were receiving K supplementation compared to 4% in the amlodipine group and 2% in the lisinopril group. To our knowledge data have not been reported on the effects of K supplementation in this study.

Thiazide induced hypokalemia continues to have controversial clinical significance. It has been implicated in arrhythmias as well as in hyperglycemia. The arrhythmogenicity and risks of hypokalemia have been a topic of great debate since the 1970s, when early trials demonstrating the benefits of decreasing blood pressure suggested that diuretics were not associated with the expected decrease in the incidence of myocardial infarction. Later doubts arose in the Multiple Risk Factor Intervention Trial, in which an association of thiazides with sudden death in hypertensive men with baseline electrocardiographic abnormalities was suggested. Subsequent analyses failed to prove the hypothesis that hypokalemia is associated with less cardiovascular benefit, ventricular ectopy or sudden death. Meta-analysis also showed that diuretics were superior to other antihypertensive agents for decreasing total mortality, cardiovascular mortality and other end points. In ALLHAT the investigators suggested that an adverse cardiovascular effect of hypokalemia was not observed.

Although normotensive stone formers treated with thiazides may not have the cardiovascular benefit associated with the drug, they could still be at risk for adverse effects of hypokalemia. The presumed mechanism of the putative adverse effects of diuretics on cardiovascular outcomes is the arrhythmogenic potential of hypokalemia. Studies of the acute effects of hypokalemia on arrhythmogenicity and ventricular ectopy are also inconsistent. At this time we do not believe that a consensus exists regarding the danger of mild to moderate degrees of hypokalemia.

Hypokalemia promotes the proximal reabsorption of citrate, which is an inhibitor of calcium oxalate and calcium phosphate precipitation. Hypocitraturia in the setting of thiazide induced hypokalemia may counter the benefit of the decrease in calcium excretion and it can be effectively countered by K supplementation with the chloride or citrate salt. To our knowledge whether patients with hypercalciuria and stones are equally susceptible to thiazide induced hypokalemia compared to those with hypertension has not been established. Patients with essential hypertension may have a higher prevalence of mild primary hyperaldosteronism and, therefore, they may be more susceptible to renal K excretion than nonhypertensive stone formers.

Glucose Intolerance
Disturbances in glucose metabolism with thiazide treatment have been well known since the introduction of thiazides as antihypertensive agents. Impaired glucose tolerance has
been seen in nondiabetic, prediabetic and diabetic patients. ALLHAT showed a statistically significant 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%, respectively). Analysis of the Nurses Health Study and Health Professional Studies confirmed that thiazide use in hypertensive patients is associated with an increased multivariate relative risk of diabetes. The relative risk was 1.20 in the Nurses Health Study I, 1.45 in the Nurses Health Study II and 1.36 in the Health Professionals Study.

The mechanism of thiazide induced glucose intolerance is not completely understood. Decreased insulin secretion by pancreatic β cells and decreased tissue insulin sensitivity have been implicated. Thiazide induced K depletion is likely to have a role in impaired glucose metabolism, perhaps by impairing β-cell insulin release, as in experimentally induced K deficiency. K supplementation was shown to attenuate glucose intolerance in thiazide induced hypokalemia.

The significance of thiazide induced diabetes, like that of hypokalemia, has been debated. ALLHAT did not show differences in cardiovascular outcomes in patients with diabetes or impaired fasting glucose treated with thiazides vs amlodipine or lisinopril. Most groups have concluded that despite an increased incidence of diabetes associated with thiazides the cardiovascular benefits are still evident. However, complications from glucose intolerance and diabetes may take more years to emerge. As critics of ALLHAT point out, it is unlikely that mortality and cardiovascular end points from the development of diabetes would become evident in such a short period, such as 4.9 years in ALLHAT. Again, to our knowledge whether nonhypertensive stone formers with lesser cardiovascular risk would be adversely affected if they experienced new onset of diabetes has not been determined.

On the other hand, although many patients with calcium nephrolithiasis are younger and normotensive, large prospective cohort study analyses suggest that this population may actually be at higher risk for hypertension and diabetes even after adjusting for thiazide use. These positive associations in population studies suggest a possible common underlying metabolic disorder. Abnormal calcium metabolism and dietary factors, such as high Na and low K intake, may contribute to nephrolithiasis and hypertension. The predisposition to diabetes in patients with calcium nephrolithiasis was proposed to be due to hyperinsulinemia, which may increase urinary calcium excretion. Obesity may be an additional risk factor for stones because it is independently associated with hyperoxaluria. Our knowledge whether the predisposition to diabetes in patients with nephrolithiasis is exacerbated by thiazide use and whether K supplementation ameliorates this risk are not known.

Hyperuricemia

Hyperuricemia is another common side effect of diuretic treatment. The mechanism appears to be the promotion of proximal tubular Na reabsorption due to extracellular fluid volume depletion with resultant proximal tubular urate re-absorption. Decreased uric acid secretion secondary to thiazide use was also suggested. It remains controversial whether thiazide induced hyperuricemia is of clinical significance. Hyperuricemia treatment is not considered to be indicated in asymptomatic patients. Analysis of data from the Framingham cohort and Normative Aging Study supported conservative treatment for asymptomatic hyperuricemia and showed that diuretic use did not significantly increase the risk of gouty arthritis. A retrospective cohort study indicated that the use of hydrochlorothiazide at doses of 25 mg daily or higher was associated with a significantly increased risk of the initiation of anti-gout therapy, suggesting that symptomatic hyperuricemia may be more prevalent than once thought. To date ALLHAT has not provided any data on serum uric acid levels before or after therapy.

An association of increased serum uric acid with cardiovascular risk has been suggested for decades. New data implicate increased serum uric acid as an independent risk factor for cardiovascular disease. The Systolic Hypertension in the Elderly Program showed that higher serum uric acid at baseline predicted cardiovascular events with increases greater than 0.06 mmol/l, offsetting any benefits attributable to blood pressure lowering. Postulated mechanisms are endothelial dysfunction, platelet aggregation and impaired oxidative metabolism. Further studies are needed to determine whether increased uric acid has a pathogenic role in CHD.

Hyperuricemia was also recently proposed as a contributing factor in the pathogenesis of hypertension. Studies suggest that increased serum uric acid induces endothelial dysfunction, causing renal afferent arteriolaropathy and tubulointerstitial disease. There is also considerable evidence linking diuretic induced hyperuricemia to progressive renal disease compared with other agents used to treat hypertension. Patients with nephrolithiasis who are on life long thiazide treatment for preventing recurrent renal calculi may be exposed to a long-term increase in serum urate. Further studies are needed to determine whether asymptotically increased uric acid concentrations carry a significant risk of chronic kidney disease.

Changes in Lipid Profiles

Many studies of thiazides consistently show increases in lipid profiles, mainly increased total cholesterol, LDL and triglycerides. Before ALLHAT whether the increases in lipids and lipoproteins persisted beyond 1 year of treatment was not clear. During chlorthalidone treatment for mild hypertension total cholesterol, triglycerides and LDL were found to increase by approximately 10 to 18, 10 to 20 and 12 to 14 mg/dl, respectively. The most substantial increase in lipid levels occurred in younger patients with lower baseline cholesterol, a group that might more closely resemble stone formers.

ALLHAT showed significantly higher cholesterol in the chlorthalidone group than in the amlodipine and lisinopril groups at 2 and 4 years. Furthermore, there were more patients with total cholesterol greater than 240 mg/dl in the chlorthalidone group than in the amlodipine group at 2 years, and in the lisinopril group at 2 and 4 years. LDL and triglyceride levels were not reported. The difference in cholesterol levels was confounded by the fact that 35% to 36% of the participants in all 3 groups were on lipid lowering drugs.
as part of the ALLHAT lipid trial. Data were not differentiated among those receiving versus not receiving lipid lowering agents.

The mechanism responsible for increased lipids with thiazide treatment is not well understood. Hemoconcentration was postulated as a cause of hyperlipidemia. However, sufficient volume contraction, as measured by hematocrit and albumin, has been found inconsistently.14,15 Furthermore, the differential effects in different lipoproteins argue against hemoconcentration. The effects of thiazides on insulin secretion or sensitivity may be responsible for the change in lipids since insulin activates lipoprotein lipase, which hydrolyzes triglycerides in LDLS.14

For illustrative purposes we calculated from the studies cited that the average patient on thiazides for recurrent calcium nephrolithiasis is a 42-year-old normotensive, normoglycemic male with a total cholesterol of 220 mg/dl, which was the mean baseline cholesterol of all subjects in the trial by Borghi et al,5 the only trial to report total cholesterol. According to the Framingham risk prediction algorithm, given the worst case scenario of this average patient in whom diabetes develops with an accompanying average 10 to 15 mg/dl increase in total cholesterol from thiazide use, the overall 10-year CHD risk increases from 4% to 7%. To our knowledge this 3% increase in CHD risk has yet to be included in any decision analysis model to calculate the overall cost-effectiveness of thiazide use in recurrent calcium nephrolithiasis.

Other Thiazide Induced Adverse Effects
Recently concern was raised about hyponatremia, which is a less common but often missed and potentially fatal side effect of thiazide use.35 A review of 129 reported cases of severe diuretic induced hyponatremia (serum Na less than 115 mEq/l) reported in the literature between 1962 and 1990 showed that thiazides were responsible for 94%.36 Risk factors include increased water intake, older age and female sex. Contributing to this disorder, the drugs may up-regulate aquaporin-2 in the collecting duct.37 Unlike furosemide, thiazides do not interfere with generation of the corticomedullary concentration gradient and, therefore, they are associated with persistence of a normal ability to fully concentrate urine. Stone formers may be particularly at risk because they are usually advised to increase fluid intake. However, we note that this complication has not been reported as a problem in thiazide trials for hypercalciuria.

Since thiazide use to prevent calcium stones is likely to be life long, serious complications and side effects affecting patient adherence to treatment should be accounted for during the decision to initiate treatment. According to 15 years of experience with more than 300 patients with calcium stones, Yendt and Cohanim reported a 30% incidence of side effects in thiazide treated patients with approximately 10% discontinuing thiazide therapy due to side effects.38 Most common side effects necessitating discontinuation of treatment were weakness, loss of energy and dizziness. In clinical trials there was a significant dropout rate in the treatment groups due to these side effects.39 Erectile dysfunction and decreased libido are also common reasons for terminating thiazide treatment.

The incidence of thiazide induced sexual dysfunction is reported to be 3 to 9%.39 Vasodilation of vascular smooth muscle, decreased extracellular fluid volume or zinc depletion causing decreased testosterone production may be involved in thiazide induced sexual dysfunction. Decreased vaginal lubrication and libido due to thiazides have also been reported in women.

Toward a Cost-Effectiveness Analysis
A recent analysis estimated that the cost of nephrolithiasis in 2000 exceeded $5.3 billion, including the direct costs of medical and surgical procedures, and the indirect costs of work loss.40 Medical therapy is considered cost-effective in patients with recurrent nephrolithiasis. Although it is difficult to assess monetarily, patient morbidity and quality of life are also improved by preventing stone recurrence. Other benefits of thiazide treatment, such as its effect on bone metabolism, may further contribute to a risk-benefit analysis. Prospective studies showed that thiazide treatment decreases the incidence of hip fractures in hypertensive and normotensive patients.41

How one enters potential long-term risks of thiazide treatment into the calculation remains unclear. If these metabolic disturbances do in fact increase cardiovascular risk in this population, the decision analysis model would need to account for long-term costs of cardiovascular disease as a result of thiazide use for stone prevention. Given the lack of data, this cost-effectiveness analysis is currently impossible. Such analysis would involve data from large-scale studies with long-term followup, weighing not only stone recurrence and other benefits of thiazide treatment, but also metabolic side effects, the development of diabetes and cardiovascular end points. Furthermore, more studies are needed to define the increased risk of hypertension and diabetes in this population independent of thiazide use.

K and Mg Supplementation in Thiazide Treatment
Because K depletion is implicated as a potential cause of some of the adverse metabolic side effects, adequate K supplementation during thiazide treatment is imperative. As discussed, disturbances in carbohydrate metabolism are hypothesized to be due to hypokalemia, while K repletion was shown to attenuate glucose intolerance in thiazide induced hypokalemia.23 While lipid disturbances may be linked to insulin activation of lipoprotein lipase, hypokalemia induced insulin resistance may be responsible for hyperlipidemia in thiazide treatment.

K supplementation is also important for preventing calcium nephrolithiasis since hypokalemia promotes hypocitraturia. Whether supplemented as K chloride or citrate, repleting K increases urinary citrate excretion, inhibiting calcium salt precipitation. K citrate provides a more significant increase in urinary citrate than K chloride. However, while K citrate increases urinary citrate excretion and inhibits calcium salt crystallization, it may enhance urinary lithogenicity for calcium phosphate stones by increasing urinary pH.42 A study of the relative effects of K citrate vs K chloride supplementation on the risk of calcium phosphate stones is needed. K-Mg citrate was formulated and shown to be effective for preventing calcium kidney stones but it is not yet commercially available.43 K-Mg citrate may be advantageous because it increases urinary citrate excretion and corrects thiazide induced hypomagnesemia, enhancing K
repletion. It may also have better gastrointestinal tolerance.

An additional means of decreasing the prevalence of hypokalemia is the concurrent use of K sparing drugs with thiazides. The available options are amiloride, which blocks the epithelial Na channel in the distal tubule, and the mineralocorticoid antagonists spironolactone and eplerenone. Amiloride has the advantage of being available in a combination tablet with hydrochlorothiazide. Triamterene, another epithelial Na channel inhibitor, is specifically contraindicated in stone formers because it is poorly soluble and can be associated with triamterene stones or nucleation of calcium oxalate stones. Spironolactone is associated with a decrease in cardiovascular end points in patients with congestive heart failure, presumably due to its inhibition of aldosterone. This may theoretically be a superior way of avoiding hypokalemia in thiazide users.

Dose choice is another factor in avoiding metabolic side effects. Most metabolic side effects of thiazides, especially hypokalemia, are dose related. Optimal dosing of diuretic therapy was proposed to treat hypertension, for which doses of more than 50 mg daily are seldom recommended. Similarly the dosing of thiazides for recurrent nephrolithiasis should be weighed against the risk of metabolic side effects.

Other Treatment Modalities for Recurrent Calcium Nephrolithiasis

New treatment options for recurrent calcium nephrolithiasis with fewer adverse effects should be developed. Bisphosphonates could be another treatment option since in a small study of patients with hypercalciuric calcium nephrolithiasis alendronate decreased urinary calcium excretion. Whether these drugs cause long-term decreases in urinary calcium is not known since to our knowledge no long-term studies with stone recurrence and growth as primary outcomes have been performed.

A randomized, controlled trial of diet for stone prevention in hypercalciuric men was successful. A diet with restricted intake of animal protein, salt and oxalate with 1,200 mg calcium daily was superior to a diet restricted in oxalate with 400 mg calcium daily intake. The high calcium diet was associated with an approximately 50% decrease in stone recurrence at 5 years. It would be of interest to compare the high calcium diet with thiazides and determine their comparative benefit and the associated incidence of metabolic side effects.

Given the links among obesity, insulin resistance and stone formation, it seems likely that any diet associated with weight loss and improved glucose tolerance would be associated with a decrease in stone recurrence but to our knowledge such a causal effect has not been demonstrated. Diets high in animal protein intake are expected to be associated with increased urinary calcium, uric acid and oxalate, and with decreases in urinary citrate. Diets with increased content of fruits and vegetables are associated with greater urine volume, more urinary citrate excretion and higher urine pH, and they may be preferable in the short term. We can speculate that successful weight loss by whatever means will be shown to have a net benefit on eventual stone recurrence as well as the avoidance of diabetes, hypertension and hyperlipidemia.

CONCLUSIONS

It remains unclear if metabolic side effects increase the risk of CHD in otherwise healthy patients with recurrent nephrolithiasis on thiazide prophylaxis. Further long-term studies with metabolic and cardiovascular end points would be needed to determine whether this risk exists and whether it is of clinical importance. However, large trials for hypertension treatment have still not resolved these questions. Physiology suggests that supplementation with K and Mg can attenuate some of these metabolic side effects, namely hypokalemia, glucose intolerance and dyslipidemia. These and other side effects may limit long-term adherence to therapy. Further research is needed to elucidate other alternatives in the treatment of recurrent nephrolithiasis.

Abbreviations and Acronyms

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<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</td>
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<td>CHD</td>
<td>coronary heart disease</td>
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<td>LDL</td>
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REFERENCES


