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

Thiazide use to prevent recurrent calcium nephrolithiasis is supported by randomized, controlled trials. As the prevalence of kidney stones increases, thiazide use for this purpose is likely to increase. Concerns regarding the adverse metabolic side effects of thiazides, which were also recommended as first line treatment for hypertension by the Seventh Joint National Committee Report,[1] reemerged with analysis of ALLHAT.[2] Although they are inexpensive and fairly well tolerated, they have long been known to have undesirable metabolic side effects, such as hypokalemia, glucose intolerance, new onset diabetes, dyslipidemia and hyperuricemia. These metabolic disturbances are thought to increase the risk of cardiovascular disease. Despite the effects of treatment on these other risk factors ALLHAT revealed no significant differences in cardiovascular end points in hypertensive patients with risk factors for CHD treated with chlorthalidone vs amlodipine or lisinopril. Patients treated with chlorthalidone had the same cardiovascular benefit as those treated with amlodipine or lisinopril. At 4 years despite a significantly higher incidence of new onset diabetes in the chlorthalidone treated group there was no increase in all cause mortality or cardiovascular end points. The investigators proposed that decreased blood pressure in hypertensive patients offsets the concomitant risks of the metabolic effects of thiazides.

Whether these side effects occur and are clinically significant in nonhypertensive patients with recurrent kidney stones treated with thiazides is unclear. We reviewed the literature on the metabolic side effects of thiazide for preventing recurrent calcium nephrolithiasis. We reviewed the individual side effects occurring with thiazide use and discuss the costs and benefits associated with stone prevention. We do not intend this to be an exhaustive review of these many effects, all of which are reviewed elsewhere.

REVIEW OF STUDIES OF THIAZIDE PROPHYLAXIS IN NEPHROLITHIASIS

Thiazides, chlorthalidone and indapamide (the latter 2 are nonthiazide sulfonamides with similar diuretic and hypocalciuric properties, and they are included under the designation thiazides) have been shown to prevent recurrent calcium stones in 6 of 9 randomized, controlled trials.[3–11] A meta-analysis including 8 of the 9 trials confirmed the prophylactic benefit of thiazides.[12]

We reviewed all 9 randomized, controlled trials to determine if the adverse effects of thiazides were reported in

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studies of stone prevention. The main end point of the trials was recurrent stone formation. Secondary end points in some but not all of the trials were urinary calcium, urate and oxalate excretion. Mean patient age was 37 to 49 years (overall mean approximately 42). Mean followup was 1 to 3 years (overall average approximately 2.6).

Only 2 of the 9 studies measured baseline and treatment levels of serum glucose and lipids, which did not significantly change with treatment in 50 and 51 cases, respectively.[5,11] Borghi et al studied indapamide,[5] which has been said to have a better side effect profile in terms of glucose and lipid metabolism compared to thiazides. Scholz et al only measured serum triglyceride.[11]

Three of the 9 studies measured serum uric acid, which was significantly increased in all 3.[5,6,11] Four of the 9 studies measured serum K[3,5,6,11] and 3 of the 4[3,5,11] showed a significant decrease in serum K. K supplementation was given as part of the treatment arm in 2 studies. However, neither study measured serum K before or after treatment.[7,9] Scholtz et al supplemented K after serum concentrations decreased below 3.0 mEq/l.[11] Ohkawa et al did not replete K in any study subject.[6]

DISCUSSION

Overall there is a lack of data on the metabolic side effects of thiazide treatment used to prevent recurrent calcium nephrolithiasis. To our knowledge whether these side effects occur at all in this population with different underlying risk factors than in patients with essential hypertension is unknown. If they occur, we do not know what the long-term consequences of these effects are. In the 2 studies that reported serum glucose and cholesterol no significant difference was found between the treatment and control groups. However, after accounting for dropout rates glucose and cholesterol were assessed in only 88 patients, of whom 19 received indapamide. Due to small sample size these studies lacked the power to detect, for example, the average 10 mg/dl increase in total cholesterol seen in prior studies of thiazide treatment in mildly hypertensive patients.[13,14] Despite the small numbers the studies showed significantly lower serum K and increased serum uric acid. None of these trials studied the development of diabetes or cardiovascular disease as end points.

Mean followup in these randomized studies was less than 3 years. Followup was shorter than that in ALLHAT, which was 4.9 years. Since stones require years to nucleate and grow, thiazide prophylaxis is a long-term treatment. Because these mostly normotensive patients are not expected to benefit from blood pressure lowering, the consequences of adverse effects caused by thiazides may not be countered by lowering blood pressure, as they are in hypertensive patients. Given the potential for these side effects to increase cardiovascular risk with long-term thiazide use for preventing recurrent nephrolithiasis, these thiazide induced metabolic disturbances were reviewed.

Hypokalemia

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.[15] 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.[16] Subsequent analyses failed to prove the hypothesis that hypokalemia is associated with less cardiovascular benefit, ventricular ectopy or sudden death.[17] Meta-analysis also showed that diuretics were superior to other antihypertensive agents for decreasing total mortality, cardiovascular mortality and other end points.[18] In ALLHAT the investigators suggested that an adverse cardiovascular effect of hypokalemia was not observed.[19]

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.[17] 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.[20]

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