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

Sarah C. Huen and David S. Goldfarb*

From the Department of Medicine, New York University School of Medicine (SCH, DSG) and Nephrology Section, New York Harbor Veterans Affairs Medical Center (DSG) and Department of Urology, St. Vincent's Hospital (DSG), New York, New York

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

Submitted for publication May 11, 2006.

* Correspondence: Kidney Stone Prevention Programs, Nephrology Section/111G, New York Veterans Affairs Medical Center, 423 East 23 St., New York, New York 10010 (telephone: 212-686-7500, extension 3877; FAX: 212-951-6842; e-mail: david.goldfarb@med.va.gov).

DOI:10.1016/j.juro.2006.11.040

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

been seen in nondiabetic, prediabetic and diabetic patients.[15] 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).[2] 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.[21] 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.[22] K supplementation was shown to attenuate glucose intolerance in thiazide induced hypokalemia.[23] To our knowledge no data are yet available regarding any possible effect of K supplementation on the incidence or prevalence of glucose intolerance in ALLHAT.

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.[24] 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[25,26] and diabetes even after adjusting for thiazide use.[27] 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.[28] Obesity may be an additional risk factor for stones because it is independently associated with hyperoxaluria.[29] To 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 reabsorption. 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[30] and Normative Aging Study[31] 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.[32] 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.[33] 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.[34] Studies suggest that increased serum uric acid induces endothelial dysfunction, causing renal afferent arteriolopathy and tubulointerstitial disease. There is also considerable evidence linking diuretic induced hyperuricemia to progressive renal disease compared with other agents used to treat hypertension.[34] 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 asymptomatically 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.[13,14] Before ALLHAT whether the increases in lipids and lipoproteins persisted beyond 1 year of treatment was not clear.[13] 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.[13,14] The most substantial increase in lipid levels occurred in younger patients with lower baseline cholesterol,[13] 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 between those receiving vs 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.[3,6] 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.[44] 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.[45] Spironolactone is associated with a decrease in cardiovascular end points in patients with congestive heart failure, presumably due to its inhibition of aldosterone.[46] 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.[47] 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.[48] 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.[49] 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.[50] 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.[51] 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

ALLHAT	=	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
CHD	=	coronary heart disease
LDL	=	low density lipoprotein

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; **42:** 1206.
2. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. JAMA 2002; **288:** 2981.
3. Ettinger B, Citron JT, Livermore B and Dolman LI: Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J Urol 1988; **139:** 679.
4. Laerum E and Larsen S: Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. Acta Med Scand 1984; **215:** 383.
5. Borghi L, Meschi T, Guerra A and Novarini A: Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. J Cardiovasc Pharmacol 1993; **22:** S78.
6. Ohkawa M, Tokunaga S, Nakashima T, Orito M and Hisazumi H: Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. Br J Urol 1992; **69:** 571.
7. Robertson WG, Peacock M, Selby PL, Williams RE, Clark P, Chisholm GD et al: A multicentre trial to evaluate three treatments for recurrent idiopathic calcium stone disease: a preliminary report. In: Urolithiasis and Related Clinical Research. Edited by PO Schwille, LH Smith, WG Robertson and W Vahlensieck. New York: Plenum Press 1985; p 545.
8. Wilson DR, Strauss AL and Manuel MA: Comparison of medical treatments for the prevention of recurrent calcium nephrolithiasis. Urol Res 1984; **12:** 39.
9. Mortensen JT, Schultz A and Ostergaard AH: Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. Int Urol Nephrol 1986; **18:** 265.
10. Brocks P, Dahl C, Wolf H and Transbol I: Do thiazides prevent recurrent idiopathic renal calcium stones? Lancet 1981; **2:** 124.

11. Scholz D, Schwille PO and Sigel A: Double-blind study with thiazide in recurrent calcium lithiasis. J Urol 1982; **128:** 903.
12. Pearle MS, Roehrborn CG and Pak CY: Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. J Endourol 1999; **13:** 679.
13. Goldman AI, Steele BW, Schnaper HW, Fitz AE, Frohlich ED and Perry HM Jr: Serum lipoprotein levels during chlorthalidone therapy. A Veterans Administration-National Heart, Lung, and Blood Institute cooperative study on antihypertensive therapy: mild hypertension. JAMA 1980; **244:** 1691.
14. Grimm RH Jr, Leon AS, Hunninghake DB, Lenz K, Hannan P and Blackburn H: Effects of thiazide diuretics on plasma lipids and lipoproteins in mildly hypertensive patients: a double-blind controlled trial. Ann Intern Med 1981; **94:** 7.
15. Perez-Stable E and Caralis PV: Thiazide-induced disturbances in carbohydrate, lipid, and potassium metabolism. Am Heart J 1983; **106:** 245.
16. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. Am J Cardiol 1985; **55:** 1.
17. Papademetriou V: Diuretics, hypokalemia, and cardiac arrhythmia: a 20-year controversy. J Clin Hypertens (Greenwich) 2006; **8:** 86.
18. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH et al: Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003; **289:** 2534.
19. Alderman M, Piller L, Ford C, Davis B, Einhorn P, Cushman W et al: The relation of hyperkalemia at 1 year to morbidity and mortality: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) experience. Eur Heart J, suppl., 2005; **26:** 671.
20. Lim PO, Dow E, Brennan G, Jung RT and MacDonald TM: High prevalence of primary aldosteronism in the Tayside hypertension clinic population. J Hum Hypertens 2000; **14:** 311.
21. Taylor EN, Hu FB and Curhan GC: Antihypertensive medications and the risk of incident type 2 diabetes mellitus. Diabetes Care 2006; **29:** 1065.
22. Rowe JW, Tobin JD, Rosa RM and Andres R: Effect of experimental potassium deficiency on glucose and insulin metabolism. Metabolism 1980; **29:** 498.
23. Helderman JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Shocken D et al: Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983; **32:** 106.
24. Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB et al: Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005; **165:** 1401.
25. Madore F, Stampfer MJ, Rimm EB and Curhan GC: Nephrolithiasis and risk of hypertension. Am J Hypertens 1998; **11:** 46.
26. Madore F, Stampfer MJ, Willett WC, Speizer FE and Curhan GC: Nephrolithiasis and risk of hypertension in women. Am J Kidney Dis 1998; **32:** 802.
27. Taylor E, Stampfer M and Curhan G: Diabetes mellitus and the risk of nephrolithiasis. Kidney Int 2005; **68:** 1230.
28. Kerstetter J, Caballero B, O'Brien K, Wurtman R and Allen L: Mineral homeostasis in obesity: effects of euglycemic hyperinsulinemia. Metabolism 1991; **40:** 707.
29. Lemann J Jr, Pleuss JA, Worcester EM, Hornick L, Schrab D and Hoffmann RG: Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. Kidney Int 1996; **49:** 200.
30. Hall AP, Barry PE, Dawber TR and McNamara PM: Epidemiology of gout and hyperuricemia. A long-term population study. Am J Med 1967; **42:** 27.
31. Campion EW, Glynn RJ and DeLabry LO: Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987; **82:** 421.
32. Gurwitz JH, Kalish SC, Bohn RL, Glynn RJ, Monane M, Mogun H et al: Thiazide diuretics and the initiation of anti-gout therapy. J Clin Epidemiol 1997; **50:** 953.
33. Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW et al: Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000; **18:** 1149.
34. Johnson RJ, Segal MS, Srinivas T, Ejaz A, Mu W, Roncal C et al: Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? J Am Soc Nephrol 2005; **16:** 1909.
35. Gross P and Palm C: Thiazides: do they kill? Nephrol Dial Transplant 2005; **20:** 2299.
36. Sonnenblick M, Friedlander Y and Rosin AJ: Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. Chest 1993; **103:** 601.
37. Kim GH, Lee JW, Oh YK, Chang HR, Joo KW, Na KY et al: Antidiuretic effect of hydrochlorothiazide in lithium-induced nephrogenic diabetes insipidus is associated with upregulation of aquaporin-2, Na-Cl co-transporter, and epithelial sodium channel. J Am Soc Nephrol 2004; **15:** 2836.
38. Yendt ER and Cohanim M: Prevention of calcium stones with thiazides. Kidney Int 1978; **13:** 397.
39. Wartman SA: Sexual side effects of antihypertensive drugs. Treatment strategies and strictures. Postgrad Med 1983; **73:** 133.
40. Saigal C, Joyce G and Timilsina A: The Urologic Diseases in America Project: direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int 2005; **68:** 1808.
41. Schoofs MW, van der Klift M, Hofman A, de Laet CE, Herings RM, Stijnen T et al: Thiazide diuretics and the risk for hip fracture. Ann Intern Med 2003; **139:** 476.
42. Parks JH, Worcester EM, Coe FL, Evan AP and Lingeman JE: Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int 2004; **66:** 777.
43. Ettinger B, Pak CY, Citron JT, Thomas C, Adams-Huet B and Vangessel A: Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J Urol 1997; **158:** 2069.
44. Wuermser LA, Reilly C, Poindexter JR, Sakhaee K and Pak CY: Potassium-magnesium citrate versus potassium chloride in thiazide-induced hypokalemia. Kidney Int 2000; **57:** 607.
45. Carr MC, Prien EL Jr and Babayan RK: Triamterene nephrolithiasis: renewed attention is warranted. J Urol 1990; **144:** 1339.
46. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; **341:** 709.
47. Salvetti A and Ghiadoni L: Thiazide diuretics in the treatment of hypertension: an update. J Am Soc Nephrol 2006; **17:** S25.
48. Weisinger JR, Alonzo E, Machado C, Carlini R, Martinis R, Paz-Martinez V et al: Role of bones in the physiopathology of idiopathic hypercalciuria: effect of amino-bisphosphonate alendronate. Medicina 1997; **57:** 45.
49. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U et al: Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med 2002; **346:** 77.
50. Assimos DG and Holmes RP: Role of diet in the therapy of urolithiasis. Urol Clin North Am 2000; **27:** 255.
51. Meschi T, Maggiore U, Fiaccadori E, Schianchi T, Bosi S, Adorni G et al: The effect of fruits and vegetables on urinary stone risk factors. Kidney Int 2004; **66:** 2402.