Published in final edited form as:

Curr Opin Nephrol Hypertens. 2008 September ; 17(5): 470–476. doi:10.1097/MNH.0b013e328305b9a5.

Do Thiazides Worsen Metabolic Syndrome and Renal Disease?

The pivotal roles for Hyperuricemia and Hypokalemia

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Abstract

Purpose of review—1. To review the current controversies related to the use of thiazide diuretics as first-line treatment of hypertension

2. To discuss the causal roles for hyperuricemia and hypokalemia on the adverse consequences of thiazide usage

Recent findings—Thiazides significantly reduce morbidity and mortality in hypertensive subjects. However, there remains debate about thiazide usage as first line treatment of hypertension. This negative impact of thiazides may be partially attributed to the ability of thiazides to exacerbate features of metabolic syndrome and/or increase the risk for developing diabetes. Several clinical trials suggest that thiazide-induced hyperuricemia and hypokalemia may account for some of these negative effects. Thiazide treatment is also associated with a decline of renal function in spite of a lowering blood pressure. In this review, we discuss the clinical and experimental evidence supporting a potential role of hyperuricemia and hypokalemia on the development of renal injury and worsening of the metabolic syndrome..

Summary—Hyperuricemia and hypokalemia may have pivotal roles in the exacerbation of the metabolic syndrome in response to thiazides. We propose that controlling serum uric acid and serum potassium could improve thiazide efficacy and also reduce its risk for inducing metabolic syndrome or diabetes.

Keywords

Thiazides; metabolic syndrome; endothelial dysfunction; renal injury; hypokalemia; hyperuricemia

Introduction

Thiazides, the distal convoluted tubule diuretics, were introduced as antihypertensive drugs in 1957 [1]. Thiazides are often favored as first-line monotherapy or as a part of combined antihypertensive treatment for hypertension. Several prospective randomized trials have documented the benefit of thiazides in reducing cardiovascular morbidity and mortality in subjects with hypertension [2-6]. Additionally, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends thiazide diuretics as the first-line therapy for most patients with

uncomplicated hypertension [7]. However, because thiazides can cause a variety of adverse metabolic derangements, some have challenged this recommendation [8••-12]. The purpose of this review is to discuss the current controversies on diuretic use [8••,13••]. In addition, we discuss recent studies suggesting a role for hyperuricemia and hypokalemia in mediating metabolic abnormalities and renal disease induced by thiazides.

Clinical uses of thiazides

Thiazides primarily inhibit sodium reabsorption at the renal distal convoluted tubule, thereby reducing plasma volume and lowering blood pressure (BP). Chronic thiazide use also reduces peripheral vascular resistance which also contributes to the lowering of BP [14-16].

Hydrochlorothiazide (HCTZ) is the most commonly used thiazide in clinical practice, although others include chlorthalidone, quinethazone, metolazone and bendroflumazide. Chlorthalidone has a longer half-life (40-60 hours) compared to HCTZ (3.2-13.1 hours) [17] and thus may be more effective at lowering systolic BP at night [18,19]. Additionally, most clinical trials demonstrating the benefits of thiazides in reduction of cardiovascular end points used chlorthalidone rather than HCTZ. Therefore, the substitution of HCTZ with chlorthalidone in clinical practice has been encouraged [8••,20-22].

Thiazides are particularly beneficial in controlling hypertension in certain groups, including African Americans, females and the elderly [23,24]. In addition, other predictors for lowering BP in response to thiazides include shorter duration of hypertension, a higher baseline BP level, a lower baseline plasma renin activity, a lower baseline urinary aldosterone excretion, and a relatively higher urinary sodium excretion in response to HCTZ [24].

Because of the effects of thiazides to lower urinary calcium excretion, thiazides are also used to prevent recurrence of calcium nephrolithiasis, especially in hypercalciuric subjects [25]. Thiazide treatment is associated with a positive calcium balance with an increase in cortical bone mineral density and therefore has been used to treat osteoporosis and prevent fractures in postmenopausal women [26-28]. Additionally, thiazides directly stimulate osteoblast differentiation and bone mineral formation, further slowing the course of osteoporosis [29].

Controversies related to thiazide diuretics usage as a first-line treatment of hypertension

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large randomized double-blind study which included a total of 42,418 hypertensive subjects initially treated with four different drug classes (thiazide; chlorthalidone, calcium channel blocker (CCB); amlodipine, angiotensin- converting enzyme inhibitor (ACEI); lisinopril and α -blocker; doxazosin) and followed for a mean of 4.9 years. ALLHAT demonstrated similar primary outcomes (coronary heart disease mortality or non fatal myocardial infarction) for all four drugs. Nevertheless, when secondary outcomes were analyzed, chlorthalidone-based treatment was superior in the prevention of heart failure to the other three drugs and was also associated with less stroke rates compared with lisinopril and doxazosin [6]. Additionally, a post hoc analysis of ALLHAT showed that amlodipine, lisinopril and chlorthalidone were not different in the rate of development of end stage renal disease (ESRD) or reduced ($>50\%$) GFR [30]. Similarly, a subgroup analysis of hypertensive patients with metabolic syndrome could not demonstrate differences in outcome regardless of whether subjects were initially treated with CCB, α -blocker, or ACEI compared with thiazide-type diuretics, particularly in black participants [31]. These findings have led many authorities to conclude that thiazides should be preferred for the initial treatment of uncomplicated hypertension [7].

However, some critics have challenged this conclusion. For example, it has been argued that the superior benefit of thiazides to reduce stroke and heart failure might be due to the fact that the chlorthalidone treated group had lower systolic BP (2-3 mmHg) than the lisinopril treated group. In addition, despite lower BP in the chlorthalidone group, the morbidity and mortality of coronary heart disease were similar with those treated with ACEI, suggesting the possibility of a superior effect of the ACEI over thiazides on coronary heart disease [8•]. Using chlorthalidone as one of the initial drugs rather than the add on drug for the ACEI or CCB may have also prevented the optimal use of the ACEI or CCB in hypervolemic subjects needing diuretics [9•]. Because the combination of antihypertensive drugs used in ALLHAT is not common in clinical practice, the interpretation of the results should be cautious [8•]. Finally, the average age of participants at entry in ALLHAT was 67 years; therefore the results of ALLHAT may be not applicable to the younger hypertensive population [8•].

While there is no doubt that thiazides reduce mortality in hypertensive subjects, thiazides also may cause a number of metabolic abnormalities that increase cardiovascular risk, including hyperlipidemia, insulin resistance, new onset diabetes mellitus, hypokalemia, hyperuricemia and stimulation of the renin-angiotensin-aldosterone system (RAAS) [9•,11,12,32]. While these effects can be lessened by using low doses of thiazides, they still occur to an alarming degree [33,34]. In the ALLHAT study, for example, a significant increase in the development of type 2 diabetes was observed in the thiazide-treated group compared to the other treatment groups (11.6% vs. 9.8% and 8.1%, for 4-year incidence in chlorthalidone, amlodipine and lisinopril groups, respectively; $P<0.05$). Some have argued that these metabolic effects did not translate into a greater frequency of cardiovascular events, and that thiazides as initial therapy for hypertension offers possibly superior cardiovascular disease outcomes in older hypertensive adults even with the metabolic syndrome, as compared with treatment with CCB and ACEI [35]. However, if one also considers that 1) antihypertensive management is usually life-long; that 2) hypertension and metabolic syndrome are rampant (involving 31% and 27% of the US population, respectively); and that 3) increasing numbers of adolescents are developing obesity and hypertension, then one must be concerned about the long term consequences of thiazide therapy. In fact, it has been also shown that longer treatment with thiazides (up to 16 years) is significantly associated with an increased incidence of new onset diabetes mellitus [34]. In this study, thiazide use increased the incidence of cardiovascular events to the same extent as pre-existing diabetes in treated hypertensive subjects [34].

Additional unfavorable effects of thiazides include lack of improvement in insulin resistance in obese hypertensive patients [36], the development of atherosclerosis in subjects [37-39], the activation of the RAAS, and an increase in serum plasminogen activator inhibitor type I (PAI-1) activity and homocysteine levels [38-43].

Hyperuricemia and hypokalemia: common abnormalities even with low dose thiazide use

Hypokalemia is a well-known complication of thiazides. While it is more common with higher doses of HCTZ (100 mg/d), hypokalemia is still observed with low doses (12.5 to 25 mg/d). For example, in ALLHAT 12.7% of subjects treated with low dose chlorthalidone developed hypokalemia [6]. In turn, hypokalemia may have several significant cardiovascular consequences. For example, hypokalemia increases the risk for sudden death and cardiovascular events in hypertensive patients [44-46]. Hypokalemia may also counter the beneficial cardiovascular effect of thiazides in elderly patients with isolated systolic hypertension [47]. Additionally, hypokalemia may also reduce the effectiveness of thiazides in lowering BP, and potassium supplementation has been shown to augment the BP-lowering effects of thiazides [48]. Furthermore, the known effect of low dose thiazides to increase the risk for diabetes [34] may be due in part to hypokalemia. For example, Zillich *et al*, have

evaluated 59 clinical trials which were conducted between 1966 and 2004, and observed that thiazide-induced hypokalemia is commonly associated with increased blood glucose [49].

Thiazides also induce hyperuricemia, even at low dose [50]. The elevation in mean serum uric acid caused by low dose of diuretics (12.5mg hydrochlorothiazide, or 1.25 mg of bendroflumazide) may occur without any significant changes in serum potassium concentration [51-53], thereby suggesting that alterations in serum uric acid may be more sensitive to the action of diuretics than serum potassium. Recent studies suggest that thiazide induced hyperuricemia can be associated with increased cardiovascular risk. For example, in the WORKSITE study in which 7978 mild-moderate hypertensive subjects were followed on treatment for 20 years, the risk for cardiovascular events was markedly increased in those who had high serum uric acid levels [54]. Similarly, in the Systolic Hypertension in Elderly Program (SHEP) trial, the reduction in coronary artery disease events observed with chlorthalidone was completely abrogated in those subjects whose uric acid increased more than 1 mg/dl during treatment [47]. These studies emphasize the potential importance of hyperuricemia and hypokalemia in increasing the risk for cardiovascular events in subjects on thiazide treatment.

Hyperuricemia and hypokalemia: Potential role in mediating features of the metabolic syndrome in thiazide treated subjects

One interesting complication of thiazide usage is the increased risk for developing features of the metabolic syndrome. Thiazides are associated with an increase in serum triglycerides and in fasting glucose and insulin resistance which may be related with potassium depletion [55-58]. Since thiazides are commonly administered to subjects with metabolic syndrome, identifying ways to prevent exacerbation of these metabolic derangements could theoretically improve the efficacy and benefit of diuretic therapy.

Recently it has been shown that endothelial dysfunction itself can cause features of the metabolic syndrome. A rise in blood glucose after eating stimulates insulin which then acts on endothelial cells to release nitric oxide (NO) that then causes systemic vasodilation and facilitates glucose uptake into peripheral muscle and fat [59]. Hence, one third of insulin's action is thought to act by stimulating the NO-mediated vasodilation. Mice lacking endothelial NO synthase can not produce NO and develop all characteristics of the metabolic syndrome. In this regard, both hypokalemia [60,61] and hyperuricemia [62,63] can cause endothelial dysfunction and low NO levels. This led us to hypothesize that thiazide induced hypokalemia or hyperuricemia might provide the mechanism by which thiazides might cause metabolic syndrome.

To test this hypothesis, we first administered HCTZ to rats with metabolic syndrome induced by a high fructose diet [64]. As expected, we found that HCTZ treatment worsened hypertriglyceridemia, insulin resistance, hyperglycemia, hypokalemia and hyperuricemia in spite of lowering BP [64]. We next examined the effect of lowering serum uric acid (using allopurinol, a xanthine oxidase inhibitor) or of correcting the hypokalemia (with supplemental potassium). Interestingly, both correcting the hyperuricemia with allopurinol and improving the hypokalemia with potassium supplementation could improve the insulin resistance and hypertriglyceridemia along with a further reduction of BP [64].

HCTZ has been reported to cause endothelial dysfunction in animal and human experiments [65-69]. We confirmed this finding and also showed that thiazide usage reduced urinary nitrite/nitrate excretion. More importantly, we found that correction of hyperuricemia, or of hypokalemia, could largely reverse the endothelial dysfunction as measured by the vasodilatory response of aortic segments in response to acetylcholine [60,62]. These studies suggest that correction of hypokalemia and hyperuricemia might be able to improve the blood pressure in

response to thiazides and to reduce the risk for metabolic syndrome, cardiovascular complications and diabetes associated with thiazide use. The proposed mechanism by which hypokalemia and hyperuricemia may account for thiazide-associated exacerbation of the metabolic syndrome is shown in Figure 1.

Do thiazides cause renal injury?

Both clinical and population-based studies have reported that diuretics usage are not renal protective, but rather are associated with acceleration of renal disease in the population. Indeed, the usage of diuretics in the EWPHE [70], Syst-Eur [71], SHEP [72] and INSIGHT [73] studies were all statistically associated with a greater decline in renal function, mainly assessed by a rise in serum creatinine, compared to the other treatment groups. More recently Hawkins and Houston published a highly controversial paper demonstrating that thiazide usage was epidemiologically associated with the increasing incidence of ESRD in the United States. In particular, they noted a time-lag between the use of diuretics and the future development of ESRD [74,75]. These data suggest that thiazides might cause renal injury in spite of lowering BP.

Evidence that thiazides can cause renal structural changes has now been shown in several animal models. For example, Loffing *et al*, have demonstrated that thiazide administration provoked apoptosis in distal tubule cells in the rat, suggesting a direct toxic effect [76]. More recently our group found that chronic HCTZ administration to rats could cause mild renal injury as evidenced by glomerular ischemia, and medullary tubular and interstitial injuries [60••].

The mechanisms responsible for the thiazide associated renal injury remain unclear. The fact that apoptosis has been observed in the distal tubular cells suggests a potential direct toxic effect. However, a more likely mechanism could be due to the chronic effects of thiazides on metabolic abnormalities (hypokalemia, hyperuricemia, hyperglycemia) or volume (volume depletion, stimulation of the RAAS) systems. Hypokalemia, which is one of the main side effects of thiazides, is a likely candidate because it is well known that chronic hypokalemia can cause renal hypertrophy and tubulointerstitial fibrosis, especially in the outer medulla. However, in our study we compared rats with chronic HCTZ-associated hypokalemia and dietary hypokalemia, and only the HCTZ rats displayed renal injury at sacrifice [60••]. It is known that longer periods of dietary hypokalemia will cause renal injury, but this was not observed with the length of this particular study [60••]. In our study, several findings provided suggestive evidence for mechanisms, including volume depletion (as noted by hemoconcentration), increased aldosterone levels (suggesting activation of the RAAS), hypomagnesemia, and chronic hyperglycemia [60••]. Other potential mechanisms could include hyperuricemia, renal ischemia, and oxidative stress [60••].

One important mechanism to consider in HCTZ-associated renal injury is the effects of chronic hyperuricemia. Although HCTZ failed to induce fasting hyperuricemia in our study [60], there is no doubt that diuretics increase serum uric acid in humans. Recent experimental and clinical studies suggest that chronic elevations in uric acid may cause renal dysfunction. For example, we have reported that raising uric acid levels in rats with a uricase inhibitor can induce glomerulosclerosis, tubulointerstitial and microvascular disease [77,78]. Raising uric acid levels can also accelerate renal injury in rats with chronic kidney disease [79,80]. More recently, studies in humans have reported that hyperuricemia predicts the development of kidney disease [81] and that lowering uric acid can slow renal progression in subjects with chronic kidney disease [82]. Thus, uric acid is also an attractive candidate to explain the observation that thiazides do not improve (and may worsen) renal function despite controlling blood pressure. The proposed mechanism for how hyperuricemia and hypokalemia may cause renal disease is shown in Figure 2.

Conclusions

Thiazides are useful agents for the treatment of hypertension either as monotherapy or in combination with other antihypertensive drugs. Thiazides reduce cardiovascular mortality, heart failure, and stroke in subjects with uncomplicated hypertension. However, thiazides may also carry toxicity by inducing endothelial dysfunction, worsening the metabolic syndrome, increasing the risk for diabetes, and accelerating renal disease. Clinical and experimental studies suggest that thiazide-induced hypokalemia and hyperuricemia may be responsible for some of these effects. Clinical studies are needed to determine if correction of hyperuricemia, and/or hypokalemia, can improve blood pressure control and the metabolic syndrome profile in patients on thiazides.

Acknowledgments

Dr Johnson and Dr Nakagawa are listed as inventors on several patent applications related to lowering uric acid in hypertension and cardiovascular disease.

References and recommended reading

- of special interest
 - of outstanding interest
1. Hollander W, Wilkins RW. Chlorothiazide: a new type of drug for the treatment of arterial hypertension. *BMQ* 1957;8:69–75. [PubMed: 13471453]
 2. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255–3264. [PubMed: 2046107]
 3. Patel AB, Kostis JB, Wilson AC, et al. Long-term fatal outcomes in subjects with stroke or transient ischemic attack: fourteen-year follow-up of the systolic hypertension in the elderly program. *Stroke* 2008;39:1084–1089. [PubMed: 18309155]
 4. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation* 1990;82:1616–1628. No authors listed. [PubMed: 2225366]
 5. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systemic review and meta-analysis. *JAMA* 1997;277:739–745. [PubMed: 9042847]
 6. ALLHAT Investigators. 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). *JAMA* 2002;288:2981–2997. [PubMed: 12479763]
 7. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. *JAMA* 2003;289:2560–2572. [PubMed: 12748199]
 8. Campese VM. Diuretics are preferred over angiotensin II-converting enzyme inhibitors for initial therapy of uncomplicated hypertension. *Am J Kidney Dis* 2007;50:197–202. [PubMed: 17660021] ••
The argument of thiazides used as initial antihypertensive drug in those with obesity and the metabolic syndrome
 9. Hebert LA, Rovin BH, Hebert CJ. The design of ALLHAT may have biased the study's outcome in favor of the diuretic cohort. *Nat Clin Pract Nephrol* 2007;3:60–61. [PubMed: 17251990] • This review suggests the flaws of the ALLHAT which make the outcome in favor the diuretics.
 10. Rovin BH, Hebert LA. Thiazide diuretic monotherapy for hypertension: diuretic's dark side just got darker. *Kidney Int* 2007;72:1423–1426. [PubMed: 18046421]
 11. Houston MC. ALLHAT debate: diuretics are not preferred, first-line initial therapy for hypertension. *Arch Intern Med* 2004;164:570–571. [PubMed: 15006839]

12. Morganti A. Should a diuretic always be the first choice in patients with essential hypertension? The case for no. *J Am Soc Nephrol* 2005;16(Suppl 1):S70–S73. [PubMed: 15938039]
13. Grimm R. Diuretics are preferred over angiotensin II-converting enzyme inhibitors for initial therapy of uncomplicated hypertension. *Am J Kidney Dis* 2007;50:188–196. [PubMed: 17660020] •• The concise review to support thiazide diuretics as the first-line treatment of hypertension
14. Hughes AD. How do thiazide and thiazide-like diuretics lower blood pressure? *JRAAS* 2004;5:155–160. [PubMed: 15803433]
15. Zhu Z, Zhu S, Liu D, et al. Thiazide-like diuretics attenuate agonist-induced vasoconstriction by calcium desensitization linked to Rho kinase. *Hypertension* 2005;45:233–239. [PubMed: 15611360]
16. Puscas I, Coltau M, Baican M, et al. Vasodilatory effect of diuretics is dependent on inhibition of vascular smooth muscle carbonic anhydrase by a direct mechanism of action. *Drugs Exp Clin Res* 1999;25:271–279. [PubMed: 10713865]
17. Chen TM, Chiou WL. Large differences in the biological half-life and volume of distribution of hydrochlorothiazide in normal subjects from eleven studies. Correlation with their last blood sampling times. *Int J Clin Pharmacol Ther Toxicol* 1992;30:34–37. [PubMed: 1551742]
18. Ernst ME, Carter BL, Goerdts CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;47:352–358. [PubMed: 16432050]
19. Khosla N, Elliott WJ, Bakris GL. Are chlorthalidone and hydrochlorothiazide equivalent blood pressure-lowering medications? [Commentary]. *J Clin Hypertens (Greenwich)* 2005;7:354–356. [PubMed: 16088299]
20. Sica DA. Chlorthalidone: has it always been the best thiazide-type diuretic? *Hypertension* 2006;47:321–322. [PubMed: 16446394]
21. Choi K, Chua D, Elliott WJ. Chlorthalidone vs. other low-dose diuretics [Letter]. *JAMA* 2004;292:1816–1817. [PubMed: 15494575]
22. Elliott WJ. Systemic hypertension. *Curr Probl Cardiol* 2007;32:201–259. [PubMed: 17398315]
23. Freis ED, Reda DJ, Materson BJ. Volume (weight) loss and blood pressure response following thiazide diuretics. *Hypertension* 1988;12:244–250. [PubMed: 3049338]
24. Chapman AB, Schwartz GL, Boerwinkle E, Turner ST. Predictors of antihypertensive response to a standard dose of hydrochlorothiazide for essential hypertension. *Kidney Int* 2002;61:1047–1055. [PubMed: 11849460]
25. Arrabal-Martín M, Fernández-Rodríguez A, Arrabal-Polo MA, et al. Extracorporeal renal lithotripsy: evolution of residual lithiasis treated with thiazides. *Urology* 2006;68:956–959. [PubMed: 17113886]
26. Bolland MJ, Ames RW, Horne AM, et al. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. *Osteoporos Int* 2007;18:479–486. [PubMed: 17120180]
27. Feskanich D, Willett WC, Stampfer MJ, Colditz GA. A prospective study of thiazide use and fractures in women. *Osteoporos Int* 1997;7:79–84. [PubMed: 9102069]
28. Schoofs MW, van der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. *Ann Intern Med* 2003;139:476–482. [PubMed: 13679324]
29. Dvorak MM, De Joussineau C, Carter DH, et al. Thiazide diuretics directly induce osteoblast differentiation and mineralized nodule formation by interacting with a sodium chloride co-transporter in bone. *J Am Soc Nephrol* 2007;18:2509–2516. [PubMed: 17656470]
30. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005;165:936–946. [PubMed: 15851647]
31. Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008;168:207–217. [PubMed: 18227370]
32. Salvetti A, Ghiadoni L. Thiazide diuretics in the treatment of hypertension: an update. *J Am Soc Nephrol* 2006;17(4 Suppl 2):S25–S29. [PubMed: 16565243]

33. Lindholm LH, Persson M, Alaupovic P, et al. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens* 2003;21:1563–1574. [PubMed: 12872052]
34. Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension* 2004;43:963–969. [PubMed: 15037557]
35. Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Diabetes Care* 2008;31:353–360. [PubMed: 18000186]
36. Fogari R, Derosa G, Zoppi A, et al. Effect of delapril/manidipine vs olmesartan/hydrochlorothiazide combination on insulin sensitivity and fibrinogen in obese hypertensive patients. *Intern Med* 2008;47:361–366. [PubMed: 18310964] • The paper demonstrates the benefit of delapril/manidipine combination but not the olmesartan/HCTZ combination on reduction of insulin resistance and plasma fibrinogen levels in obese hypertensive patients.
37. Fonseca FA, Ihara SS, Izar MC, et al. Hydrochlorothiazide abolishes the anti-atherosclerotic effect of quinapril. *Clin Exp Pharmacol Physiol* 2003;30:779–785. [PubMed: 14516418]
38. Kaşifoğlu T, Yalçın AU. The effects of thiazide and thiazide-potassium sparing diuretics on fibrinolytic system parameters. *Anadolu Kardiyol Derg* 2006;6:143–147. [PubMed: 16766279]
39. Mugellini A, Preti P, Zoppi A, et al. Effect of delapril-manidipine combination vs irbesartan-hydrochlorothiazide combination on fibrinolytic function in hypertensive patients with type II diabetes mellitus. *J Hum Hypertens* 2004;18:687–691. [PubMed: 15071488]
40. Brown NJ, Kumar S, Painter CA, Vaughan DE. ACE inhibition versus angiotensin type 1 receptor antagonism: differential effects on PAI-1 over time. *Hypertension* 2002;40:859–865. [PubMed: 12468570]
41. Lottermoser K, Hertfelder HJ, Vetter H, Düsing R. Fibrinolytic function in diuretic-induced volume depletion. *Am J Hypertens* 2000;13:359–363. [PubMed: 10821336]
42. Dierkes J, Luley C, Westphal S. Effect of lipid-lowering and anti-hypertensive drugs on plasma homocysteine levels. *Vasc Health Risk Manag* 2007;3:99–108. [PubMed: 17583180]
43. Westphal S, Rading A, Luley C, Dierkes J. Antihypertensive treatment and homocysteine concentrations. *Metabolism* 2003;52:261–263. [PubMed: 12647260]
44. Grobbee DE, Hoes AW. Non-potassium-sparing diuretics and risk of sudden cardiac death. *J Hypertens* 1995;13:1539–1545. [PubMed: 8903607]
45. Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;330:1852–1857. [PubMed: 8196728]
46. Cohen HW, Madhavan S, Alderman MH. High and low serum potassium associated with cardiovascular events in diuretic-treated patients. *J Hypertens* 2001;19:1315–1323. [PubMed: 11446723]
47. Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 2000;18:1149–1154. [PubMed: 10954008]
48. Kaplan NM, Carnegie A, Raskin P, et al. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1985;21(312):746–749. [PubMed: 3883170]
49. Zillich AJ, Garg J, Basu S, et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006;48:219–224. [PubMed: 16801488]
50. Reyes AJ. Diuretics in the therapy of hypertension. *J Hum Hypertens* 2002;16:S78–S83. [PubMed: 11986901]
51. Carlsen JE, Køber L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990;300:975–978. [PubMed: 2344503]
52. Girvin B, Johnston GD. A randomized comparison of a conventional dose, a low dose and alternate-day dosing of bendrofluazide in hypertensive patients. *J Hypertens* 1998;16:1049–1054. [PubMed: 9794747]

53. Scholze J, Breitstadt A, Cairns V, et al. The East Germany Collaborative Trial Group. Short report: ramipril and hydrochlorothiazide combination therapy in hypertension: a clinical trial of factorial design. *J Hypertens* 1993;11:217–221. [PubMed: 8385183]
54. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 1999;34:144–150. [PubMed: 10406838]
55. Amery A, Birkenhäger W, Brixko P, et al. Glucose intolerance during diuretic therapy in elderly hypertensive patients. A second report from the European Working Party on high blood pressure in the elderly (EWPHE). *Postgrad Med J* 1986;62:919–924. [PubMed: 3534842]
56. Andersson OK, Gudbrandsson T, Jamerson K. Metabolic adverse effects of thiazide diuretics: the importance of normokalaemia. *J Intern Med Suppl* 1991;735:89–96. [PubMed: 2043227]
57. Helderma JH, Elahi D, Andersen DK, et al. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. *Diabetes* 1983;32:106–111. [PubMed: 6337892]
58. Norbiato G, Bevilacqua M, Meroni R, et al. Effects of potassium supplementation on insulin binding and insulin action in human obesity: protein-modified fast and refeeding. *Eur J Clin Invest* 1984;14:414–419. [PubMed: 6441716]
59. Roy D, Perreault M, Marette A. Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO dependent. *Am J Physiol Endocrinol Metab* 1998;274:E692–E699.
60. Reungjui S, Hu H, Mu W, et al. Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. *Kidney Int* 2007;72:1483–1492. [PubMed: 17928827] •• The paper demonstrates the subtle renal injury seen with hydrochlorothiazide use in normal Sprague Dawley rats and the suggested potential mechanisms.
61. Yang BC, Li DY, Weng Y, et al. Increased superoxide anion generation and altered vasoreactivity in rabbits on low-potassium diet. *Am J Physiol* 1998;274:1955–1961.
62. Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006;290:F625–F631. [PubMed: 16234313]
63. Khosla UM, Zharikov S, Finch JL, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005;67:1739–1742. [PubMed: 15840020]
64. Reungjui S, Roncal CA, Mu W, et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. *J Am Soc Nephrol* 2007;18:2724–2731. [PubMed: 17855639] •• Thiazides precipitate the fructose-induced metabolic syndrome and the potential mechanism may be both thiazide-induced hypokalemia and hyperuricemia.
65. Semenkina AA, Zhivilova LA, Golevtsova ZSh, et al. Comparative assessment of hypotensive, metabolic, and endothelial effects of indapamide-retard and hydrochlorothiazide in patients with essential hypertension. *Kardiologiia* 2006;46:35–39. [PubMed: 16858352]
66. Semenkina AA. Possibilities of using indices of vascular wall function as markers of negative metabolic effects of treatment with thiazide diuretics in patients with essential hypertension. *Ter Arkh* 2007;79:31–38. [PubMed: 17564015]
67. Zhou MS, Schulman IH, Jaimes EA, Raij L. Thiazide diuretics, endothelial function, and vascular oxidative stress. *J Hypertens* 2008;26:494–500. [PubMed: 18300860] • This study demonstrates that thiazide diuretics do not reduce oxidative stress, improve endothelial function, or prevent the expression of pro-atherogenic molecules, although their use reduces blood pressure, left ventricular hypertrophy and proteinuria.
68. Klingbeil AU, John S, Schneider MP, et al. Effect of AT1 receptor blockade on endothelial function in essential hypertension. *Am J Hypertens* 2003;16:123–128. [PubMed: 12559678]
69. Muiesan ML, Salvetti M, Monteduro C, et al. Effect of treatment on flow-dependent vasodilation of the brachial artery in essential hypertension. *Hypertension* 1999;33:575–580. [PubMed: 9931168]
70. Fletcher A, Amery A, Birkenhager W, et al. Risks and benefits in the trial of the European Working Party on High Blood Pressure in the Elderly. *J Hypertens* 1991;9:225–230. [PubMed: 1851785]
71. Voyaki SM, Staessen JA, Thijs L, et al. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Follow-up of renal function in treated and untreated older patients with isolated systolic hypertension. *J Hypertens* 2001;19:511–519. [PubMed: 11288822]
72. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term low-dose diuretic-based antihypertensive therapy on glucose, lipid, uric acid and potassium levels in older men and women with isolated

- systolic hypertension. The Systolic Hypertension in the Elderly Program. *Arch Intern Med* 1999;158:741–751. [PubMed: 9554680]
73. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366–372. [PubMed: 10972368]
 74. Hawkins RG, Houston MC. Is population-wide diuretic use directly associated with the incidence of end-stage renal disease in the United States? A hypothesis. *Am J Hypertens* 2005;18:744–749. [PubMed: 15925729]
 75. Hawkins RG. Is population-wide diuretic use directly associated with the incidence of end-stage renal disease in the United States? *Curr Hypertens Rep* 2006;8:219–225. [PubMed: 17147920]
 76. Loffing J, Loffing-Cueni D, Hegyi I, et al. Thiazide treatment of rats provokes apoptosis in distal tubule cells. *Kidney Int* 1996;50:1180–1190. [PubMed: 8887276]
 77. Mazzali M, Kanellis J, Han L, et al. Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 2002;282:F991–F997. [PubMed: 11997315]
 78. Nakagawa T, Mazzali M, Kang DH, et al. Uric acid--a uremic toxin? *Blood Purif* 2006;24:67–70. [PubMed: 16361844]
 79. Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002;13:2888–2897. [PubMed: 12444207]
 80. Kang DH, Nakagawa T. Uric acid and chronic renal disease: possible implication of hyperuricemia on progression of renal disease. *Semin Nephrol* 2005;25:43–49. [PubMed: 15660334]
 81. Iseki K, Ikemiya Y, Inoue T, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004;44:642–650. [PubMed: 15384015]
 82. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006;47:51–59. [PubMed: 16377385]

Thiazide exacerbates Metabolic syndrome.

Figure 1.
Proposed Mechanism for how thiazides exacerbates Metabolic syndrome.

Thiazide causes renal injury.

Figure 2.
Proposed Mechanism for how thiazides causes renal injury.