Hypertension, Hypokalemia, and Thiazide-Induced Diabetes
A 3-Way Connection
Rajiv Agarwal

Reduction in the dose of diuretics to treat essential hypertension occurred with the recognition that higher doses of thiazides cause hypokalemia, glucose intolerance, and hyperuricemia but little additional reduction in blood pressure.1 Subsequently, large randomized, controlled trials have demonstrated a higher incidence of diabetes mellitus with thiazide diuretics compared with other antihypertensive drugs.2 A meta-analysis done with 143 153 participants without diabetes mellitus in 22 clinical trials showed that thiazide diuretics and β-blockers had similarly high risks of developing new-onset diabetes mellitus, followed by placebo and calcium channel blockers; the most protective were angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors.3 This detrimental effect on glucose tolerance together with the growing epidemic of diabetes and obesity has reined in the wider use of thiazides despite being effective and inexpensive antihypertensive drugs with strong cardiovascular benefits.

Whether thiazide-induced diabetes mellitus has the same adverse prognostic significance as spontaneously occurring diabetes mellitus is not known with certainty.2 If thiazide diuretics unmask the presence of underlying diabetes mellitus, then the earlier detection of diabetes with more aggressive hypertension, lipid, and metabolic control may in fact, instead of being harmful, be protective. There is also some evidence that, although new-onset diabetes mellitus is associated with cardiovascular mortality, treatment of such patients with diuretics has survival benefits. In a long-term analysis of the Systolic Hypertension in Elderly Program with a mean follow-up of 14.3 years, the long-term fatality rate was higher in those with had diabetes mellitus at baseline, followed by patients who developed diabetes during follow-up.4 However, diabetes mellitus that developed among subjects during diuretic therapy (n=258) did not have significant associations with cardiovascular mortality rate (adjusted hazard ratio: 1.043; 95% CI: 0.745 to 1.459) or all-cause mortality rate (adjusted hazard ratio: 1.151; 95% CI: 0.925 to 1.433). Furthermore, diuretic treatment in subjects who had diabetes mellitus was strongly associated with lower long-term cardiovascular and all-cause mortality rates. Given the protective effects of low-dose diuretics through blood pressure lowering, even among patients with diabetes mellitus, but their propensity to cause or unmask diabetes mellitus, interest has been rekindled to explore the provenance of thiazide-induced diabetes.

A previous analysis of the Systolic Hypertension in Elderly Program reported that the incidence of diabetes mellitus in the active treatment group of 8.6% was no different from the placebo group (7.5%; P=0.25).5 The study of Shafi et al6 fills an important gap in our understanding of diuretic-induced diabetes mellitus by providing evidence that incident diabetes in Systolic Hypertension in Elderly Program participants is related to the severity of hypokalemia, even after adjusting for baseline glucose and the dose of diuretic. This risk appears to be log-linear. Thus, the absolute increase in the incidence of diabetes mellitus was much less when serum potassium concentration dropped from 5.0 to 4.5 mEq/L but much higher when serum potassium dropped from 4.0 to 3.5 mEq/L; however, the increase in relative risk was similar. To interpret the log-linear relationship between serum potassium and incident diabetes mellitus requires consideration of balance studies that relate cumulative negative potassium balance with a fall in serum potassium in healthy volunteers.7 Such studies indicate that, with dietary depletion of potassium, it takes ≥1 week to manifest hypokalemia, at which time ≈150.0 mEq of potassium is lost, and serum potassium falls to ≈0.5 mEq/L. Persistent dietary potassium restriction produces an additional 100-mEq potassium loss with only slight, if any, change in serum potassium over the ensuing week. Thus, it would appear that people with hypokalemia, as reported by Shafi et al,6 may have remarkable depletion of total body potassium. A meta-analysis demonstrates a strong inverse relationship between glucose and potassium with the use of thiazides, which is also consistent with the notion that total body potassium stores may mediate insulin sensitivity.8 Was hypokalemia a marker or a mediator of the development of diabetes mellitus? Although the authors did not find a difference in the incidence of diabetes mellitus in those who used potassium supplements versus those who did not, it remains to be seen in large randomized trials whether prevention or treatment of hypokalemia can avoid the development of diabetes mellitus. In fact, mechanistic studies suggest that potassium may have a mediating role as proposed by the epidemiological observations of Shafi et al.6 For example, Helderman et al9 have evaluated the effect of potassium supplementation on glucose tolerance in 7 healthy volunteers receiving high-dose hydrochlorothiazide—100 mg for 10 days. Using a glucose clamp, the investigators demonstrated that, when potassium losses were prevented, thiazides induced no alterations in glucose tolerance.


β-cell sensitivity to glucose, or tissue sensitivity to insulin. Two controlled studies in which hypokalemia was allowed to ensue after hydrochlorothiazide ingestion revealed a diminution in glucose tolerance, a consequence of diminished pancreatic β-cell response to glucose. Pathophysiologically, potassium depletion can also cause dysglycemia as a result of altered skeletal muscle blood flow. Potassium is released from contracting skeletal muscle fibers, and its rising concentration in interstitial fluid is thought to dilate arterioles, thereby mediating the normal rise of muscle blood flow during exercise. Knochel and Schlein\textsuperscript{16} have demonstrated that, in normal dogs, muscle blood flow and potassium release rise sharply during exercise. In contrast, muscle blood flow and potassium release were markedly subnormal in potassium-depleted dogs despite brisk muscle contractions. Thus, a possible but so far little researched mechanism of new-onset, hypokalemia-mediated, thiazide-induced diabetes mellitus may simply be attributable to a reduction in the perfused mass of muscle—a large, glucose-metabolizing organ. Finally, a meta-analysis reported that trials that intervened on hypokalemia due to thiazides had nearly half the changes in potassium and glucose compared with trials that did not.\textsuperscript{8}

To settle the question of potassium being a marker or mediator of thiazide-induced diabetes mellitus requires conducting adequately powered randomized, controlled trials.\textsuperscript{11} The data of Shafi et al\textsuperscript{10} suggest that thiazide is likely to induce diabetes mellitus within a year, so such trials need not last long. However, until such trials are done, the message for patients who care for the patient with hypertension is to avoid hypokalemia, especially when using thiazide or thiazide-like diuretics. In fact, participants in the Systolic Hypertension in Elderly Program trial who experienced hypokalemia after 1 year of treatment with a low-dose diuretic did not have a reduction in cardiovascular events compared with those who did not have hypokalemia.\textsuperscript{12} Recomrnending a diet rich in potassium, such as the Dietary Approaches to Stop Hypertension diet,\textsuperscript{13} would not only avoid hypokalemia but would also lower blood pressure by enhancing natriuresis, modulating baroreflex sensitivity, directing vasodilatation, or lowering cardiovascular reactivity to norepinephrine or angiotensin II.\textsuperscript{14} Likewise, potassium supplementation in patients with thiazide-induced hypokalemia can lower blood pressure and may improve dysglycemia.\textsuperscript{15} Using potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers or switching to a dihydropyridine calcium channel blocker are other logical strategies for the management of the patient who develops thiazide-induced hypokalemia. Restoring total body potassium stores may reverse thiazide-induced diabetes mellitus, but if the 3-way connection is indeed operative (Figure), treatment of hypokalemia may have other benefits, such as reducing the severity of spontaneous diabetes mellitus and lowering blood pressure.

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### References
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