Thiazide diuretics have been recommended as the preferred class of antihypertensive (AHT) drugs for initial therapy and for inclusion in a regimen of multiple drugs.1 This recommendation is based on 4 decades of randomized clinical events trials with placebo (or usual care) comparators, meta-analyses of such trials, and active-controlled trials, including the very large Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT).2-3 In the latter, treatment beginning with the thiazide-like diuretic chlorthalidone reduced the risk for major coronary events (the primary outcome) similar to treatment based on representatives of newer drug classes (amlodipine, doxazosin, and lisinopril); diuretic-based treatment was more effective at preventing heart failure, and in some comparisons, other cardiovascular disease (CVD) events.

However, in ALLHAT mean fasting blood glucose (FBG) and incident diabetes mellitus (IDM) were slightly but significantly increased in the chlorthalidone compared with the other arms.3 Although the design precluded distinguishing between a benefit of the alternate drugs (especially lisinopril) and an adverse effect of the diuretic, previous evidence suggested that thiazides can cause dysglycemia (impaired glucose tolerance, impaired fasting glucose, or diabetes).4 One point about the ALLHAT results that has not received enough emphasis is that if the calcium channel blocker is taken as metabolically neutral, the 4-year IDM rates in the diuretic and calcium channel blocker arms (11.6% and 9.8%, respectively) imply that 83% of IDM occurring in association with thiazide use is not because of the diuretic.

Nevertheless, based on the assumption that there is a direct relationship between thiazide exposure and dysglycemia, several key questions need to be addressed: (1) What are the long-term morbidity/mortality consequences, if any? (2) What are the mechanisms? and (3) Are the changes preventable and/or reversible? The role of potassium may be important to addressing each of these issues.

Evidence is conflicting on the relationship between dysglycemia and CVD risk in the context of AHT treatment. Perhaps relevant are the clear findings that the relative CVD benefits of thiazide-based treatment are equally apparent in patients with normal FBG, impaired fasting glucose, and diabetes.5 More directly, 3 clinical epidemiologic studies have compared the risk conferred by DM6-8 observed in subjects before they were placed on AHT drugs to that while taking such medications (a thiazide alone or with other drugs). In these 3 studies, the relative risk (RR) conferred by DM at baseline was greater than that of DM occurring during treatment, and in 2 of them,6,7 the risk of IDM during treatment was not statistically significant, whereas that of baseline DM was significant. Although this difference could have been influenced by differential diabetes duration, these 2 studies did have very long total follow-up (22 and 14 years, respectively). The analyses from the Systolic Hypertension in the Elderly Program Extension (SHEP-X) were the most robust by far, because of the large sample size and hard end points (especially, CVD mortality); IDM in the group randomized to chlorthalidone during the 5-year trial had no effect on subsequent risk, in contrast to the effect of IDM occurring on placebo.7 Also, SHEP-X had the least contamination with other drugs in the regimen, whereas in the other studies, most patients were on multidrug regimens, and the percentage on thiazide alone was small. Another study found the effect of FBG change on risk of myocardial infarction to be higher in treated hypertensive patients compared with nonhypertensive persons, but it has been criticized for this design and because it adjusted differentially for blood pressure in the 2 groups.9

So what might be different about FBG changes and IDM because of thiazide use versus “naturally occurring” diabetes? In the latter situation, the major causes are established to be adiposity, a sedentary lifestyle, and genetics, but no role of potassium balance has been generally cited. However, the article by Zillich et al10 in this issue of Hypertension points out that a direct relationship between hypokalemia and glucose intolerance has been observed in experimental and clinical studies for >40 years, a relationship that seems to be of some importance in the setting of diuretic treatment. In the diuretic-treated patient, hypokalemia is likely to be intermittent because of dietary and drug adherence variation and potassium-sparing therapeutic intervention. This may also translate to dysglycemia that is intermittent (as argued below) and, thus, confers little risk of diabetic complications. Studies that have measured hemoglobin A1c would be useful in examining this hypothesis.

In the newly reported analyses, a close statistical association between serum potassium decrease and blood glucose increase has now been well demonstrated in this quantitative review of 59
treatment trials published over 38 years. Using a variety of analytic approaches, they consistently found moderately high negative correlation coefficients across trials of mean change in serum potassium (from baseline or versus placebo) and mean change in blood glucose. The magnitude of the association can be estimated from their Figure 2 as ~10 mg/dL glucose increase for a 1 meq/L decrease in potassium. Sensitivity analyses involved a variety of weighting procedures, correlational techniques, exclusions (the largest trials and those using doses beyond what would be currently acceptable), and stratification. The latter divided the trials into those that did or did not report use of potassium supplements or potassium-sparing agents, and the changes in both potassium and glucose were ~50% smaller in the subset that intervened on hypokalemia, a finding relevant to preventability of dysglycemia.

As the authors acknowledge, the association robustly demonstrated in their analysis does not establish a causal relationship between potassium depletion/repletion and dysglycemia, although the subset analysis just mentioned does point in that direction. A noncausal association could result, for example, from parallel responses to variation in prescribed thiazide dose or patient adherence. However, a series of small clinical experiments in healthy volunteers (in 1 study also with risk factors for diabetes) published in 1961 to 1980 provided strong evidence that (1) potassium depletion induced by a variety of means worsens glucose tolerance, (2) potassium repletion reverses the glucose changes in the short term, and (3) the mechanism involves reduced pancreatic insulin release and not reduced insulin sensitivity.11–14 These studies had pre–post designs, but in a subsequent parallel control, nonrandomized study, 100 mg of hydrochlorothiazide for 10 days accompanied by full replacement of potassium losses produced no glucose intolerance, whereas subjects with no potassium replacement developed significant hypokalemia along with glucose intolerance and decreased β-cell responsiveness.15 With regard to reversibility of glucose intolerance after much longer thiazide exposure, Murphy et al16 performed glucose tolerance tests in 10 hypertensive patients after 14 years of thiazide treatment and then retested them 7 months after thiazide withdrawal, at which time potassium had risen from 3.7 to 4.0 meq/L, FBG declined 10% to 6.0 mmol/L, and 2-hour glucose fell 25%, to 7.1 mmol/L; despite any aging effect over the 14 years, the area under the glucose curve returned about halfway toward the baseline. With regard to preventability, in the study by Murphy et al,16 those who maintained potassium levels consistently above 3.6 meq/L at 1, 6, and 14 years of follow-up had a minimal increase in 2-hour glucose. Similarly, in a 10-year follow-up study of 53 thiazide-treated hypertensive patients who received 8 to 16 meq of potassium chloride throughout, serum potassium was maintained in a 4.0 to 4.2 meq/L range, there was no decline in total body potassium, and glucose tolerance did not change.17

Despite the consistency of the evidence cited, definitive studies have not been conducted. There are few clinical trials in thiazide-treated patients with randomization to potassium supplements or potassium-sparing drugs, and they were not designed to address the glucose changes specifically. In a small 6-week placebo-controlled crossover study in hypokalemic patients treated with hydrochlorothiazide or chlorthalidone, supplementation with 60 mmol of potassium chloride raised mean serum potassium from 3.0 to 3.6 meq/L; glucose, insulin, and HbA1c all changed in expected directions, but not significantly so.18 Another modest-sized trial produced not very helpful results. This 2-month, placebo-controlled trial found that neither serum glucose nor insulin changed in the 4 arms using 50 mg of hydrochlorothiazide regardless of whether or what kind of potassium-sparing regimen was added. Not surprisingly, glucose and insulin did deteriorate on the high dose of chlorthalidone (50 mg) administered without any potassium supplementation/sparing agent.19

Thus, well-designed randomized trials are sorely needed testing combinations of a thiazide (in appropriate doses) with various potassium-conserving regimens, including supplements, potassium-sparing diuretics, and ACE inhibitors and/or angiotensin receptor blockers, for effects on glycemia and glucose tolerance. Although Zillich et al20 are correct that testing such interventions on IDM would require substantial sample sizes and long follow-up, trials with the more subtle changes as outcomes and their relationship to potassium changes would be valuable in themselves and may also lead to the larger trial. They would also provide stronger evidence than the correlational analyses that the authors suggest for performing in ALLHAT and SHEP, because the biochemical measures in those large clinical events trials were likely not collected frequently enough for definitive answers. Until such trials are conducted, I concur with the authors and others to the effect that the proven value of thiazides as central drugs in AHT regimens may be enhanced by careful attention to prevention or management of potassium losses.

Disclosures

None.

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Thiazide-Associated Glucose Abnormalities: Prognosis, Etiology, and Prevention: Is Potassium Balance the Key?
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