Effects of Potassium-Sparing Versus Thiazide Diuretics on Glucose Tolerance
New Data on an Old Topic

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In the United States, thiazide (or thiazide-like) diuretics have been recommended for ~40 years as initial antihypertensive drug therapy by guideline committees. In other locales, however, concern about potential metabolic effects, including hypokalemia, hyperglycemia, hypercholesterolemia, hypercalcemia, and hyperuricemia, has recently led to a re-evaluation of the “default first-line choice” for uncomplicated hypertension and (in the United Kingdom treatment guidelines since 2006) to favor either an angiotensin-converting enzyme inhibitor or a calcium channel blocker instead.

In this edition of Hypertension, Stears et al report the results of 2 double-blind, placebo-controlled, crossover trials comparing 4 weeks of amiloride versus a thiazide diuretic on oral glucose tolerance tests in hypertensive patients. Their principal conclusions are that both thiazides had a significant hyperglycemic effect (compared with placebo), which was not seen with equipotent hypotensive doses of amiloride. Despite the small numbers of subjects, the authors’ observations fit nicely with much previous work (including oral glucose tolerance testing in treated hypertensive subjects in the European Working Party on Hypertension in the Elderly trial). Like recent reviews, the hyperglycemic effect of both thiazides was significantly correlated with decreases in serum potassium. In contrast, the potassium-sparing diuretic, amiloride, had no significant effect on oral glucose tolerance tests. The authors’ inclusion of a β-blocker arm in each trial (to explore a secondary objective) suggested that β-blockers have less of an effect on glucose tolerance tests than thiazides. They concluded that amiloride, either alone or in combination, may prevent thiazide-induced diabetes mellitus.

One can quibble with some aspects of the authors’ work. Unfortunately, 81% of their subjects were taking “background” antihypertensive drug therapy; 33% were being treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, which blunts hypokalemia and probably also hyperglycemia attributed to thiazides. However, this should “bias toward the null.” Some believe that the acute increase in blood glucose concentrations is mediated by hemoconcentration, which dissipates over time. A longer duration of treatment than 4 weeks would have been interesting but more time consuming and difficult for the subjects and investigators. Some previous crossover studies of diuretics have been confounded by significant carryover effects, because complete “washout” of diuretics can take longer than the allotted 4 weeks; this is not discussed by the authors.

Although interesting and possibly clinically important, the authors’ suggestion to treat hypertension with amiloride, rather than (or in addition to) a thiazide, is likely to generate controversy. Glucose-tolerance testing was chosen as the end point for this study because it can be measured easily and repeatedly, at reasonably short intervals, in a cohort randomized to different treatments, with the expectation that the 4-week “placebo washout phase” between active treatments will allow glucose tolerance to revert to baseline. In the United States, oral glucose tolerance tests are not routinely used to diagnose diabetes mellitus in nonpregnant individuals, although this procedure may have better performance characteristics than the serum A1c, which the American Diabetes Association recommended recently. As such, the oral glucose tolerance test in these studies is but a surrogate end point that correlates (in large populations) with incident diabetes mellitus.

The differential role of various classes of antihypertensive drug therapy in preventing or causing diabetes mellitus remains quite controversial. Many meta-analyses (including the most recently updated network and Bayesian models) have concluded that the incidence of diabetes mellitus in long-term clinical trials is significantly lower for subjects randomized to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, particularly when compared with thiazide diuretics. The absolute risk difference observed in randomized trials in hypertension, however, is small (~1% per year, according to Stears et al). This small point estimate, albeit significant, is often coupled with the observation (from many trials and cohort studies) that individuals who develop “chemical diabetes” (typically based on a single fasting blood glucose level) do not significantly increase their risk of cardiovascular events during longer-term follow-up. Some have suggested that chemical diabetes is, therefore, different from “true diabetes mellitus” (eg, diabetes present, usually for a number of years, at initial randomization) and should not cause clinical concern. Other investigators have pointed out that, at least in placebo-controlled randomized trials, like the
Systolic Hypertension in the Elderly Program, cardiovascular prognosis was better among individuals randomized to a diuretic who developed incident diabetes mellitus than those who were randomized to placebo, suggesting that the long-term benefits of blood pressure lowering with thiazides outweigh the short- and long-term risks of new-onset diabetes mellitus. A recent large cohort study, with 26 years of follow-up, concluded that it took 9.1 years for cardiovascular risk to increase significantly, after an initial diagnosis of antihypertensive drug-associated diabetes mellitus. The logical link, therefore, among oral glucose tolerance test results, new-onset diabetes mellitus (whether chemical or true), and increased cardiovascular risk is not as clear as proponents of surrogate end points would like. The traditional counterargument is that, even if new-onset diabetes mellitus does not immediately increase cardiovascular risk, the new diagnosis increases healthcare costs, from more frequent healthcare visits and blood tests, and lower targets for dyslipidemia and blood pressure, which often require more intensive (and expensive) drug treatment. Such recommendations for diabetics to achieve lower targets are currently under review in the United States, because several arms of the National Institutes of Health–funded Action to Control Cardiovascular Risk in Diabetes trial, as well as several recent systematic reviews and meta-analyses, all suggest that these traditional lower targets are not justified by proper clinical trial evidence and may, in fact, be harmful.

The authors’ discussion of differences across diuretics in their diabetogenic potential does not include recent reanalyses of the Multiple Risk Factor Intervention Trial, in which hypertensive subjects were randomized to either Stepped Care (typically in university-based centers) or Referred Care (ie, usual care in the local community). Because the choice of the initial diuretic in the Stepped Care group was not prespecified, some centers used hydrochlorothiazide (in doses similar to those chosen by Stears et al), and others used chlorthalidone (also at doses higher than those in common use today). The Multiple Risk Factor Intervention Trial Steering Committee undertook a formal review of morbidity and mortality at ≈5 years of average follow-up and decided that all of the Stepped Care subjects should be withdrawn from hydrochlorothiazide and instead given chlorthalidone. Data supporting this decision were obtained recently from governmental archives, reanalyzed, and published, and show that (in nonrandomized comparisons of the 2 cohorts), the average serum potassium and glucose were both higher in the hydrochlorothiazide group. These data are consistent with the authors’ hypothesis that there are potential differences between diuretics that are clinically important. The 500-patient prospective clinical trial, PATHWAY 3 (Prevention And Treatment of Hypertension With Algorithm-based therapY), may help shed further light on whether amiloride, hydrochlorothiazide, or their combination has differential effects on blood pressure and glucose tolerance. Many American authorities would prefer that physicians simply prescribe less hydrochlorothiazide and more chlorthalidone, as this was the agent that demonstrated “superiority of thiazide-type diuretics in preventing one or more major forms of cardiovascular disease” in the “largest and most important clinical trial in hypertension ever done in the United States.”

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