Metabolic Impact of Adding a Thiazide Diuretic to Captopril

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Thiazide diuretics are among the antihypertensive agents that demonstrate effectiveness in improving cardiovascular morbidity and mortality. However, there has been concern regarding adverse metabolic effects of thiazide diuretics on insulin sensitivity in those predisposed to diabetes mellitus, such as those individuals who are overweight and have hypertension.\(^1\)\(^2\) In this regard, population-based studies suggest that incident or new-onset diabetes mellitus increased in groups randomized to thiazide-type diuretic treatment.\(^3\) Although the exact mechanism for thiazide-induced impairments in glucose metabolism has yet to be determined, groups have traditionally explored alterations in insulin metabolic signaling mechanisms, as it relates to (1) reductions in glucose disposal and (2) impairments in pancreatic \(\beta\)-cell insulin secretion (Figure). In contrast, therapies directed at reducing renin–angiotensin–aldosterone system (RAAS) have been observed to improve glucose metabolism.\(^4\)

Diuretic-induced diuresis stimulates the RAAS, and it has been suggested that the addition of an angiotensin-converting enzyme (ACE) inhibitor (ACEi) or an angiotensin receptor blocker (ARB) to a thiazide diuretic would negate the adverse metabolic effects of thiazide diuretics on insulin sensitivity through attenuation of diuretic-induced hypokalemia, oxidative stress, and inflammation.\(^5\)\(^6\) In this issue of *Hypertension*, McHenry et al\(^7\) build on their previous work,\(^8\) exploring the addition of an ACEi captopril to bendrofluazide and utilizing hyperinsulinemic, euglycemic clamps to evaluate insulin sensitivity. The authors utilized a prospective randomized, crossover design with a 6-week wash-in, followed by 12 weeks of treatment in each arm with clamp studies to evaluate glucose disposal and endogenous glucose production as a marker of hepatic insulin sensitivity. In the authors’ previous report,\(^9\) individuals were up-titrated to 100 mg per day of captopril, and then randomly assigned to either 5 mg of bendrofluazide or placebo. Clamp studies in a cohort of 15 mildly hypertensive (newly diagnosed or currently on <2 antihypertensive agents), overweight (body mass index \(\approx 29\) kg/m\(^2\)) individuals showed no difference when comparing the addition of captopril with high-dose bendrofluazide (eg, 5 mg) to captopril alone. However, the authors observed that the combination increased postabsorptive endogenous glucose production as a marker for hepatic insulin resistance.

In the current study,\(^7\) the authors utilize a similar paradigm of mildly hypertensive, overweight (eg, body mass index \(\approx 29\) kg/m\(^2\)) individuals, but this time randomize to 1.25 mg of bendrofluazide instead of the 5 mg and, as a blood pressure (BP) control, doxazosin was used when systolic BP was \(>160\) mmHg and diastolic BP was \(>95\) mmHg. Only 12 of 23 enrolled patients completed the study protocol, but notably, there were no differences in BP, glycemic, or lipid measures between the 2 treatment groups. Similarly, there were no differences on clamp studies between the 2 groups with either exogenous glucose infusion (glucose disposal) or endogenous glucose production (hepatic insulin sensitivity). There are similarities between the 2 reports that adding bendrofluazide, at any dose, to ACEi had a neutral impact on glucose disposal. However, the addition of 5 mg of bendrofluazide compared with 1.25 mg to ACEi increased hepatic insulin resistance.\(^8\)

Data from these 2 mechanistic applications of systemic insulin sensitivity in humans can be viewed in 1 of 3 ways: (1) addition of an ACEi does truly negate the adverse metabolic impact of thiazides in the treatment of hypertension, (2) thiazides may not influence glucose disposal at all, or (3) thiazides influence insulin sensitivity through a mechanism other than glucose disposal, such as through hepatic or even pancreatic \(\beta\)-cell insulin resistance. Recent data from our group\(^9\) suggest that the addition of an ARB to hydrochlorothiazide in obese, hypertensive individuals prevented glycemic excursions after a glucose load. Approximately 400 individuals were randomized to either an ARB/hydrochlorothiazide or amlopidine/hydrochlorothiazide combination and titrated to goal BP with an oral glucose tolerance test administered at baseline and after 4 months. Those allocated to the ARB/hydrochlorothiazide arm had substantially lower fasting glucose and 2-hour glucose, and postprandial insulin responses, suggesting the combination improves peripheral \(\beta\)-cell insulin secretion. Another recent report from a Japanese cohort of insulin-resistant, hypertensive individuals also suggests that treatment with ARB improves early-phase insulin secretion.\(^9\)

Although our understanding of the mechanisms of thiazide-induced abnormalities on glucose metabolism are evolving, it is becoming evident that there is an impact on systemic and local tissue inflammatory responses in the liver and pancreas (Figure).\(^1\)\(^2\) In light of recent data,\(^6\) results from the current study would suggest that the addition of RAAS inhibition to thiazide-type diuretics may not impact glucose disposal, but may improve hepatic or pancreatic insulin sensitivity. The

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reasons for this are unclear. Whether RAAS inhibition acts through direct reductions in angiotensin II and aldosterone’s adverse effects (eg, inflammation and oxidative stress) on pancreatic β-cells or through preventing reductions in circulating potassium and magnesium, the precise protective mechanism by which RAAS inhibition improves islet insulin secretion remains to be elucidated.10

In summary, the use of thiazides has been clearly linked to new-onset diabetes mellitus in clinical trials and impairments in insulin sensitivity, especially in those at increased risk, such as overweight, hypertensive individuals, as seen in the current study.7 Although these observational results from a relatively small cohort should be viewed cautiously, the use of mechanistic clamp studies in larger cohorts will be necessary to help elucidate the pancreatic β-cell and insulin-sensitive tissue effects of diuretics and RAAS blockers. The finding in the current study that the addition of an ACEi to low-dose bendrofluazide had no impact on measures of insulin sensitivity should help guide clinicians in choosing an antihypertensive regimen in at-risk populations. This being said, previous work results from the current group4 and others1,2 would continue to suggest the use of higher dose thiazide-type diuretics alone or in combination should be avoided in these same at-risk populations.

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**Disclosures**

Dr Sowers is a member of the Advisory Board of Merck Pharmaceuticals.

**References**


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