Thiazide-Induced Dysglycemia

Call for Research From a Working Group From the National Heart, Lung, and Blood Institute

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There are >70-million hypertensive individuals in the United States, and >45-million persons take antihypertensive medications.1,2 Despite the results of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), other trials, and the recommendations in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, well under 50% of these regimens include a thiazide-type diuretic.2,3 In the Department of Veterans’ Affairs, which participated in several of the studies supporting the use of thiazide diuretics, ∼35% of hypertensive patients on pharmacotherapy had a thiazide diuretic included in their hypertension treatment regimens in 2003.4 In private patient encounters, thiazide diuretic use rose from 19% of all of the antihypertensive patient visits in 2002 to 26% in 2004.5

The recommendations for preferred use of thiazide-type diuretics are based on >4 decades of clinical trials, including active-controlled trials, where diuretics were tested against other drugs for their efficacy in preventing hard clinical outcomes, such as myocardial infarction, death, stroke, heart failure, and renal failure. ALLHAT, a randomized, double-blind, active-controlled antihypertensive treatment trial in 42,418 patients assigned to a thiazide-type diuretic, an angiotensin-converting enzyme (ACE) inhibitor, a calcium channel-blocker, (average follow-up: 4.9 years), or the doxazosin/chlorthalidone comparison (terminated early, average follow-up: 3.2 years) showed that the diuretic was at least as beneficial as the comparator drugs in lowering blood pressure (BP) and preventing cardiovascular (CV) and renal outcomes and was superior for preventing heart failure (versus each comparator arm), combined CV events (versus α-blocker and ACE-inhibitor arms), and stroke (versus ACE inhibitor [black subjects only] and α-blocker).6 The ongoing success of thiazide-type diuretics in large, adequately powered hypertension outcome trials and new guidelines have created the basis for increased diuretic use.2,6

However, clinical trials have also frequently shown potentially undesirable metabolic biochemical effects during diuretic treatment compared with other drugs, including an increase in serum glucose levels (dysglycemia).6–14 Diuretic-induced increases in serum glucose levels are small and appear to attenuate over time (“diuretic-induced” indicates the part of the diuretic-associated increase in serum glucose levels that is above the increase related to aging, weight gain, sedentary lifestyle, and other risk factors). Nevertheless, opinion leaders in the medical community have raised concerns about the potential for long-term adverse CV and renal effects of the observed dysglycemia.15 They argue that the average length of follow-up in clinical trials, 4 to 5 years, is not long enough to recognize the potential long-term adverse effects of the known biochemical changes. In addition, they express a concern that patients who develop thiazide-associated diabetes will require monitoring and treatment for diabetes that they would not have experienced without the thiazide.

In contrast to the above concerns, the evidence on whether the development of dysglycemia with any antihypertensive drug treatment produces adverse CV effects is mixed, and there are no direct outcome data for diuretic-induced dysglycemia.6 Among large-sample follow-up studies, the largest (ALLHAT) and the longest (from the Systolic Hypertension in the Elderly Program [SHEP]) show no significant adverse CV events from new diuretic-associated diabetes.17,18 Importantly, 83% of the new-onset diabetes that occurred in the ALLHAT diuretic arm was apparently not because of the diuretic. Although many of these patients had only 3- to 4-mg/dL increases in blood sugar over baseline that tipped them over the threshold, the vast majority who developed

Received April 3, 2008; first decision April 19, 2008; revision accepted May 7, 2008.

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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.108.114389
new-onset diabetes (NOD) had a \( \geq 10 \text{-mg/dL} \) increase in glucose.\(^{18,19} \) Thus, most NOD occurs regardless of medication used. Diuretic-based therapy still afforded similar or superior major CV benefits compared with losartan or amlodipine, even in patients with diabetes and in those with the metabolic syndrome.\(^{20–23} \) Conversely, a small study with only 63 events suggested that NOD carried the same CV risk as diabetes when present before therapy.\(^{15} \) These findings are in contrast to those of the much larger SHEP study (see below).\(^{17} \)

This ongoing debate hampers adoption of the hypertension treatment guidelines, and prescribing momentum for diuretic therapy has been slowed by this controversy.\(^{6,13,24} \) Avoidance of diuretics leaves millions of patients on diuretic-free regimens that may impart a higher risk of new-onset heart failure and, especially in black patients, also a higher risk of stroke, while providing no clear advantages. It is possible that the clinical advantages of the thiazide-type diuretics could be enhanced by eliminating or diminishing their biochemical effects. Evidence suggests that hypokalemia may be a contributing cause of NOD.\(^{6,10} \) The purpose of this article was to review the possible mechanisms for diuretic-induced dysglycemia, especially hypokalemia, and to outline recommendations for a proposed research agenda developed by a working group appointed by the National Heart, Lung, and Blood Institute (NHLBI). The details of the NHLBI Working Group process, additional references, and information about basic science and observational and clinical studies are included in the data supplement available online at [http://hyper.ahajournals.org]. Further details of the meeting and deliberations of the working group can be found at [http://www.nhlbi.nih.gov](http://www.nhlbi.nih.gov).

### Observational Studies

We conducted a literature search using Medline (1950 to December 2007) to identify observational studies that examined the relationship of thiazide diuretics to the incidence of diabetes. A total of 12 observational studies (11 cohort and 1 case-control) were evaluated. None of the observational studies specifically addressed the relationship between hypokalemia and NOD. A table that summarizes the design and results of these studies is included in the data supplement.

In general, observational studies showed an increased risk of NOD among hypertensive patients taking diuretics who received no antihypertensive therapy (relative hazard: 0.91; 95% CI: 0.73 to 1.13). On the other hand, Taylor et al\(^{31} \) reported that the relative risk of incident diabetes in hypertensive participants taking a thiazide diuretic compared with those not taking a thiazide was 1.20 (95% CI: 1.08 to 1.33) in the Nurses’ Health Study I, 1.45 (95% CI: 1.17 to 1.79) in the Nurses’ Health Study II, and 1.36 (95% CI: 1.17 to 1.58) in the Health Professionals Follow-Up Study.

Overall, there was no consistent evidence from observational studies that thiazide diuretics increased the risk of diabetes among hypertensive patients. However, observational studies are subject to selection and diagnostic bias, underscoring the need for evidence from prospective, randomized, controlled trials.

### Clinical Trials

Several large intervention studies did not find an increased risk of diabetes with thiazides, usually after posthoc analyses.\(^{11,32,33} \) The European Working Party Study found a nonsignificant elevation in blood sugar with triamterene plus hydrochlorothiazide compared with placebo.\(^{33} \) In the SHEP Trial, NOD occurred in 8.6% of those treated with chlorthalidone and in 7.5% of those treated with placebo (hazard ratio [HR]: 1.2; 95% CI: 0.9 to 1.5; \( P=0.25 \)).\(^{11} \) In addition, CV mortality was not increased in those who received chlorthalidone and developed diabetes (HR: 1.04; 95% CI: 0.75 to 1.46). Treatment with a diuretic in subjects who had diabetes was associated with lower CV mortality (HR: 0.69; 95% CI: 0.53 to 0.85) and total mortality (HR: 0.81; 95% CI: 0.68 to 0.95).

Multiple Risk Factor Intervention Trial investigators found that NOD was nonsignificantly higher in the special intervention group (11.5%) compared with the usual care group (10.8%) after 6 years of follow-up (HR: 1.08; 95% CI: 0.96 to 1.20); there was heterogeneity in this outcome depending on smoking status at baseline, with a lower rate in special intervention nonsmokers but a higher rate among special intervention smokers, presumably because of weight gain among those who quit smoking.\(^{34} \) In ALLHAT, the odds ratio for developing NOD at 2 years with lisinopril (0.55; 95% CI: 0.43 to 0.70) or amlodipine (0.73; 95% CI: 0.58 to 0.91) versus chlorthalidone was significantly <1.0 (\( P<0.01 \)).\(^{35} \) However, by 4 and 6 years, the odds ratios were no longer significant. The odds ratio at 6 years for lisinopril:chlorthalidone was 0.86 (95% CI: 0.40 to 1.86) and for amlodipine:chlorthalidone was 0.96 (95% CI: 0.58 to 1.20).

The Intervention as a Goal in Hypertension Trial found fewer cases of NOD with nifedipine (4.3%) versus the potassium-sparing/thiazide combination coamilozide (5.6%; \( P=0.023 \)).\(^{35} \) The Study of Tamoxifen and Raloxifene Trial evaluated glucose tolerance in people with the metabolic syndrome and hypertension. This study found an incidence of NOD of 11% with trandolapril/verapamil compared with 26.6% with losartan/hydrochlorothiazide after 52 weeks of treatment (\( P=0.002 \)).\(^{34} \)

Elliott and Meyer\(^{36} \) recently conducted a meta-analysis of 22 clinical trials involving 143 153 participants and found that placebo groups had a significantly lower odds ratio of developing diabetes (0.77; 95% CI: 0.63 to 0.94) when compared with thiazide-assigned groups as the referent. The
odds ratio for β-blockers (0.90; 95% CI: 0.75 to 1.09) compared with diuretics was not significantly different than 1.0, but the corresponding odds ratios for calcium channel blockers (0.75; 95% CI: 0.62 to 0.90), ACE inhibitors (0.67; 95% CI: 0.56 to 0.80), and angiotensin II receptor blocker (0.57; 95% CI: 0.46 to 0.72) were significantly reduced.

Possible Relationship to Hypokalemia

Compounding the difficulty in establishing a clinical link between diuretic treatment and NOD is the absence of a defined mechanistic link between diuretics and hyperglycemia. Potassium is perhaps the most attractive variable to begin with in developing a hypothesized mechanism. Diuretic-related reductions in serum K⁺ are typically dose related and usually range from 0.2 to 0.6 mmol/L. This well-described relationship is depicted by arrow “A” in Figure 1. A recent meta-analysis of 59 studies involving 83 thiazide diuretic treatment arms found a significant correlation between the degree of diuretic-induced hypokalemia and the increase in plasma glucose, and there was evidence that prevention of hypokalemia with K⁺ supplementation or potassium-sparing agents lessened the degree to which plasma glucose increased consequent to diuretic therapy. Thus, the change in plasma K⁺ appears to be related inversely to blood glucose, but how? The well-described effects of hyperkalemia to stimulate insulin secretion and to impair insulin secretion and thereby increase plasma glucose 13,42,43 (arrow “B” in Figure 1) and insulin to induce cellular uptake of potassium 4-45 suggest that low plasma potassium could impair insulin secretion and thereby increase plasma glucose. Hypothesis A+B=C is denoted in Figure 1. However, several challenges remain for this hypothesis, including the incompleteness of experimental evidence that hypokalemia in the range measured in these patients actually decreases insulin secretion as shown in Figure 2.

Insulin and Potassium

Potassium infusions increase insulin secretion, and removal of potassium by insulin from the extracellular fluid (ECF) compartment may help protect against hyperkalemia after a meal. However, insulin is not required for potassium movement from the ECF into the intracellular fluid, as shown by the demonstration that potassium exits from the ECF of dogs with pancreatectomy and clamped insulin infusion. The mechanism for that effect is not known, but the removal of potassium from the ECF is facilitated by insulin.

The more relevant question in the context of this hypothesis is whether potassium controls insulin release. Here, the evidence is not as clear, particularly regarding the potential for decreased plasma potassium to decrease insulin. Most studies have focused on the effects of increased potassium to stimulate insulin, but there has not been consistent evidence that physiological increases in plasma potassium, on the order of 1 to 2 mmol/L, can stimulate insulin secretion, even in studies that have demonstrated stimulation by larger increases. However, if basal insulin is decreased with somatostatin, then low-dose potassium infusions that have minimal effects on plasma potassium in intact conditions have been shown to cause significant hyperkalemia. The effect of decreased potassium in impairing insulin secretion has not been studied as extensively. Although dietary potassium deprivation has been shown to decrease plasma insulin levels, others have shown that potassium deprivation impairs insulin-mediated potassium uptake in skeletal muscle without affecting glucose uptake. Remarkably, the significant hypokalemia that accompanies chronic hyperaldosteronism is not associated with hyperglycemia. However, insulin resistance and an impaired glucose response to an oral glucose load have been reported in such patients.

Thus, the effect of elevated potassium in stimulating insulin is well supported, but whether the 1- to 2-mmol/L changes in plasma potassium that are most relevant physiologically are significant controllers of insulin secretion is not established. It is possible that there is a multiplicative interaction between potassium and glucose in the control of insulin secretion, just as has been described for the effects of potassium and angiotensin II on aldosterone secretion. This is particularly intriguing given the role of K⁺ ATPase channels in glucose-mediated control of insulin secretion, but it also makes the study of potassium-regulated insulin secretion more difficult.
Other Possible Mechanisms

There are other potential mechanisms or covariables that should be considered as intermediaries in the relationship among diuretic therapy, hypokalemia, and hyperglycemia, including hypomagnesemia.\textsuperscript{57,58} In addition, it has been proposed recently that increases in free fatty acids (related to increased serum triglycerides) may damage pancreatic β-cells.\textsuperscript{59,60} The sympathetic nervous system and renin angiotensin systems are stimulated by diuretic-induced decreases in BP, and Figure 2 shows potential mechanisms through which they could be linked to increased blood glucose. Interestingly, the sympathetic nervous system actually could contribute to the hypokalemic response to diuretic treatment, because it is known to be a powerful driving force for moving potassium from the ECF to the intracellular fluid and minimizing hyperkalemia during exercise.\textsuperscript{61} Importantly, Figure 2 shows potential ways that hypokalemia could induce insulin resistance and hyperglycemia independent of a direct effect to decrease insulin secretion. Although there are data to support each of the individual relationships depicted in Figures 1 and 2, it is important to highlight that there is no integrative evidence to construct a mechanistic causal chain that links diuretics to hyperglycemia, whether it be potassium dependent or not.

Minimizing Dysglycemia by Preventing Hypokalemia

The lowest rates of CV risk and glucose intolerance appear to occur at serum K⁺ values between 4.0 and 4.5 mmol/L.\textsuperscript{5,62} Hypokalemia can be prevented or treated with K⁺ supplements or combinations of thiazides together with K⁺-sparring diuretics or aldosterone-receptor antagonists.\textsuperscript{63,64} It should be noted, however, that in a controlled, randomized trial, changes in potassium were not related to the risk of NOD.\textsuperscript{24} Whether this finding was related to the fact that the patients had the metabolic syndrome at baseline, the use of the losartan combination or some unmeasured factor remains to be investigated. However, in ALLHAT, hypokalemia (K⁺ <3.2 mEq/dL), whether associated with potassium supplementation, had no significant effect on the odds of developing diabetes, although the odds ratios for years 4 to 6 tended to be increased for those taking supplements (suggesting that hypokalemia was persistent enough to trigger clinical action).\textsuperscript{18} Potassium-sparing agents may also correct hypomagnesemia, an important factor in how these compounds normalize K⁺ homeostasis in the hypokalemic patient.\textsuperscript{57}

In the meta-analysis by Zillich et al.\textsuperscript{8} there was a significant association between hypokalemia and hyperglycemia in patients treated with thiazide diuretics. This assessment found an average reduction in serum K⁺ of 0.23 mmol/L and an increase in glucose of 3.26 mg/dL in studies using K⁺ supplements or K⁺-sparing agents. In studies that did not use K⁺ supplements or K⁺-sparing agents, the average reduction in serum K⁺ was 0.37 mmol/L, with a corresponding average increase in serum glucose of 6.01 mg/dL (\(P=0.03\)). The degree to which preexisting glucose intolerance affected these results is not known. Although by no means definitive, these findings suggest that preventing diuretic-related hypokalemia not only reduces the risk of hyperglycemia but also might decrease the likelihood of developing NOD.

Future Research Directions

There are many unanswered questions regarding the role of potassium and the development of hyperglycemia in the context of diuretic administration. Additional research is needed to determine the following: (1) whether preventing hypokalemia (keeping serum K⁺ between 4.0 and 4.5 mEq/L) can reduce or eliminate the risk for diuretic-induced dysglycemia or diabetes; (2) to what extent diuretic-induced volume depletion and resulting vasosconstriction contribute to insulin resistance; (3) the comparative effects of methods to correct diuretic-induced hypokalemia, such as potassium supplementation, K⁺ sparing diuretics (triamterene, amiloride, and/or spironolactone), ACE inhibitors and angiotensin II receptor blockers, and issues related to coadministration of these drugs; (4) whether thiazides independently cause or exacerbate hyperglycemia and whether potassium controls insulin release; (5) whether diuretic-induced increases in glucose should be defined by the magnitude of the change in glucose levels (usually averaging 5 to 15 mg/dL) or by the percentage of those who cross a glycemic threshold; and (6) whether populations at greater risk for diuretic-induced glucose changes can be identified (obese versus nonobese, with or without the metabolic syndrome, glucose levels, ethnicity, and/or dietary patterns) and whether the magnitude and mechanisms for the glucose change are uniform across the various subpopulations.

Proposed Experimental Approaches From the NHLBI Working Group

There was unanimous enthusiasm for support of a short-term clinical trial initiative, as described below. The primary research question is whether preventing hypokalemia can minimize or prevent hyperglycemia, NOD, and, ultimately, clinical end points. The need for and design of a definitive trial of the latter question would have to be considered by an advisory group after the short-term trial. Nevertheless, we considered it an important public health priority responsive to ≥2 goals and 3 challenges identified in the NHLBI Strategic Plan.\textsuperscript{69} These were as follows: to promote translation of clinical research findings back to the laboratory (goal 2, challenge 2.1); to enhance the evidence available to guide the practice of medicine and improve public health (goal 2, challenge 2.4); and to promote the development and implementation of evidence-based guidelines (goal 3, challenge...
3.3). We also concluded that there are many unanswered mechanistic questions that will be best pursued in the laboratory through animal and in vitro experimentation, optimally in collaboration with the clinical trial investigators. Finally, we identified several areas of opportunities within existing population cohorts.

**Basic Science Studies**

The presence of several potential mechanistic pathways points to the need for controlled studies, predominantly in animal models, run in conjunction with clinical trials. The latter will establish the relationships among changes in plasma potassium, plasma insulin, plasma renin activity, and glycemic control under conditions of diuretic therapy when potassium balance is maintained or when hypokalemia occurs. To establish independent cause-and-effect relationships, particularly regarding the insulin-potassium hypothesis, chronic blockade and clamp studies will be needed. For example, to study the effect of changes in potassium status independent of the renin-angiotensin system, an intriguing experiment would be to clamp the system chronically, by administering an ACE inhibitor together with a fixed dose of angiotensin II. That model would reveal the effect of diuretic treatment on BP, potassium, insulin, and glucose independent of a change in angiotensin II, as well as the angiotensin-independent response to potassium supplementation. Another important direction for animal studies would be to establish the link among potassium, insulin, and glucose independent of changes in aldosterone. Such studies can be accomplished with adrenalectomy and chronic supplementation with fixed doses of glucocorticoid and mineralocorticoid. A critical issue is whether the changes in plasma potassium caused by diuretic therapy and potassium supplementation cause changes in blood glucose through insulin, angiotensin II, or neither, and isolating those mechanisms likely requires the control and precision afforded by chronic animal models.

**Short-Term Clinical Trials**

Short-term clinical trials assessing clinically relevant strategies to preventing diuretic-induced dysglycemia are feasible and have a high likelihood of informing both science and clinical practice. A single multarm, parallel design randomized trial, with a thiazide-type diuretic alone as a control arm powered to detect a minimum effect size of 5 mg/dL difference between the control and each of the intervention arms would be ideal, and a primary end point of fasting serum glucose levels after 3 months of intervention would be most practical. Other outcomes would include serum potassium, magnesium, and renin levels; 2-hour glucose tolerance test; serum insulin; hemoglobin A1C; triglyceride and free fatty acid levels; and urine potassium and magnesium levels (timed specimens), as well as incident diabetes, BP, and body weight (body mass index).

We recommended a washout before the intervention period and a potential postintervention washout to test persistence of the effects. We propose 4 treatment arms that are most relevant to clinical practice: a thiazide-type diuretic alone, a thiazide-type diuretic plus a potassium-sparing diuretic, a thiazide-type diuretic plus an angiotensin II receptor blocker or an ACE inhibitor, and a calcium channel blocker alone (metabolically neutral control). The dose of the thiazide-type diuretic should be an equivalent of 12.5 to 25.0 mg of chlorthalidone and lifestyle advice provided for all of the participants.

Although this design does not include an arm with thiazide plus tight potassium control achieved by direct replacement of losses, these data will provide considerable insight into the hypothesis in Figure 1 simply through the combined measurements of potassium, insulin, and glucose. Measurement of hypokalemia, hyperglycemia, and low or normal plasma insulin give credence to the hypothesis in Figure 1, whereas increased insulin under those conditions would not be supportive. Thus, in addition to providing a controlled test of the link between low-dose thiazide diuretics and glycemic control, this trial provides strong direction for animal studies that can quantify the cause-and-effect relationships between the study variables.

More details on the deliberations of the working group about the clinical trial design, the use of existing population cohorts, and the areas of opportunities for mechanistic research can be found in the working group report on the NHLBI Web site at http://www.nhlbi.nih.gov.

**Perspectives**

Thiazide diuretics reduce CV events in patients with hypertension. However, their potential association with a modest risk of NOD and heavy promotion of other agents have caused many physicians to avoid their use. This practice likely exposes these patients to excess risk for heart failure, stroke, and other CV outcomes, because diuretics minimize CV risk and are usually required to achieve current BP goals. Better understanding of the complex relationships between diuretics and dysglycemia and the potential for its minimization or prevention should make clinicians become more comfortable with prescribing diuretics and may also lead to further improvement in major clinical outcomes of hypertension.

The relationship between hypokalemia and elevated plasma glucose and the suggestion that hyperglycemia might be mitigated by potassium replacement offer intriguing possibilities for the prevention of NOD. The existing literature does not provide results from a properly conducted, prospective trial designed to address whether NOD attributable to thiazides can be prevented. The working group convened by NHLBI has proposed possible research to answer questions raised by the literature.

**Sources of Funding**

The National Heart, Lung, and Blood Institute convened the working group and provided travel expenses related to the 1-day meeting. Participants received no honoraria, and there was no financial support for the writing activity.

**Disclosures**

B.L.C. receives significant support in the form of grants from the Adherence to BP Guidelines and Continuity of Care from the National Heart, Lung, and Blood Institute. B.L.C. also receives modest payment for speaking bureau appointments from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Dissemination Speakers’ Bureau and modest honoraria payment for Antihypertensive and Lipid-Lowering Treatment to Prevent...
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Hypertension. 2008;52:30-36; originally published online May 26, 2008; doi: 10.1161/HYPERTENSIONAHA.108.114389

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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