Glucose and Insulin Levels During Diuretic Therapy in Hypertensive Men

David Siegel, Patricia Saliba, Steven Haffner

Abstract
We investigated serum glucose and insulin levels resulting from thiazide or thiazide-like diuretic administration and determined whether they were associated with serum or intracellular potassium or magnesium values. We also explored the role of obesity both alone and with thiazides on serum insulin and glucose. Hypertensive men were withdrawn from diuretics and replaced with oral potassium and magnesium and then randomized to 2 months of treatment with (1) hydrochlorothiazide, (2) hydrochlorothiazide with oral potassium, (3) hydrochlorothiazide with oral potassium and magnesium, (4) hydrochlorothiazide and triamterene, (5) chlorthalidone, or (6) placebo. Serum was available from 202 participants for insulin and glucose determinations. Mean fasting serum glucose and insulin did not change significantly after 2 months of randomized therapy with the exception of participants randomized to chlorthalidone, who had significant increases in both serum insulin and glucose (P<0.05 and P<0.01, respectively). As body mass index increased, there was a corresponding increase in serum insulin and to a lesser degree in serum glucose. Also, as body mass index increased, participants taking hydrochlorothiazide had a corresponding increase of serum insulin (P<0.05). After treatment, intracellular potassium and magnesium were both associated with higher serum insulin (P<0.001 for each), and serum potassium was associated with higher and serum magnesium with lower serum glucose (P<0.01 for each). In most hypertensive men, treatment with 50 mg chlorthalidone increases glucose and insulin levels, whereas administration of 50 mg hydrochlorothiazide, with or without potassium and/or magnesium conserving strategies, does not. Obesity has a deleterious effect on insulin metabolism both in hypertensive men not taking diuretics as well as in those receiving hydrochlorothiazide. (Hypertension. 1994;23[part 1]:688-694.)

Key Words: hypertension, essential • diuretics • hydrochlorothiazide • chlorthalidone • insulin • glucose

Results of most drug trials of blood pressure lowering have not achieved the decreases in coronary heart disease (CHD) mortality predicted by epidemiologic studies.1 The reasons for this are unclear. Some authorities have postulated that this less-than-expected benefit from blood pressure lowering is due to the shorter duration of observations in drug treatment compared with epidemiologic studies.2 Alternatively, it has been hypothesized that thiazide or thiazide-like (ie, chlorthalidone) diuretics and nonselective β-blockers, the drugs primarily used in these trials, might have metabolic effects that negate some of the beneficial effects that would be expected from decreases in blood pressure. Thiazide diuretics have been used for more than 30 years and are considered appropriate initial therapy for many of the 58 million people in the United States with elevated blood pressure; therefore, potential toxic effects are an important therapeutic question.

Recent prospective data suggest an increased prevalence of non–insulin-dependent diabetes mellitus (NIDDM)4-7 and impaired glucose tolerance7,8 in patients with hypertension. Both hypertension and diabetes mellitus are important risk factors for CHD.9-11 The increased risk of NIDDM in hypertensive patients might be due to obesity, to an adverse body fat distribution, or to hyperinsulinemia or insulin resistance.12 An alternative or additional explanation for the increased prevalence of NIDDM in hypertensive patients is that some antihypertensive agents might increase the risk of diabetes by increasing insulin resistance. In prospective studies, hypertensive subjects on thiazide diuretics or β-blockers have had an increased risk of NIDDM or impaired glucose tolerance relative to other antihypertensive drugs in some1-6,8 but not all.13,14 To support this hypothesis, some investigators have found an association between thiazides and impaired insulin sensitivity and/or hyperinsulinemia, primarily in short-term studies, leading to hyperglycemia,14-16 but others have not.7,17

Other effects of thiazides on the risk of diabetes and insulin sensitivity could relate to differences in diuretic dosage or to other factors that may increase the risk of glucose intolerance, such as hypokalemia,18 hypomagnesemia,19,20 or obesity. Although it has been studied in relation to lipids, less is known about the effects of the thiazide-like diuretic chlorthalidone on glucose and insulin metabolism. Chlorthalidone remains in clinical use, and it was the primary antihypertensive agent used in a recent major clinical trial.21 In this study we examined the serum glucose and insulin levels that resulted from thiazide or chlorthalidone treatment in hypertensive men. We used a randomized design to discover whether supplementation of diuretics with oral potassium, oral potassium and magnesium, or triamterene affected these levels. We also examined the role of obesity in patients receiving thiazide diuretics as well as the effects of serum and
intracellular potassium and magnesium levels as a consequence of diuretic treatment on serum insulin and glucose levels.

**Methods**

**Selection of Study Subjects**

Details of the study design and participant selection process have been presented previously. Briefly, the Hypertension Arrhythmia Reduction Trial is a clinical trial designed to assess the frequency and severity of ventricular arrhythmias associated with the use of various diuretic combinations. Hypertensive men aged 35 to 70 years with resting electrocardiographic abnormalities were selected as the study participants because the Multiple Risk Factor Intervention Trial (MRFIT) suggested, in subgroup analysis of participants receiving hydrochlorothiazide, that they might be especially at risk for sudden death with diuretic use. The study group was recruited from both clinical populations and by direct mail campaign. Participants were included in the study if they had been taking diuretics for at least 6 months and their diastolic blood pressure was <95 mm Hg or if they had not been on diuretic therapy but had a history of hypertension and were either taking nondiuretic antihypertensive drugs or had a diastolic blood pressure ≥90 mm Hg but <105 mm Hg.

We excluded men who were taking medications that might influence the development of ventricular arrhythmias, such as antiarrhythmic drugs, β-blockers, thalidomine preparations, digitalis preparations, phenothiazines, and tricyclic antidepressants. We also excluded men with a history of myocardial infarction, congestive heart failure, angina pectoris, renal insufficiency (creatinine >2.0 mg/dL), or other serious illness including psychiatric disability and men who were unable or unwilling to give informed consent. The study was approved by the University of California, San Francisco, Committee on Human Research.

**Design Overview**

The men were withdrawn from diuretic treatment, and all participants received 1 month of oral electrolyte repletion with both 40 mmol potassium chloride and 400 mg magnesium oxide (containing 241.3 mg elemental magnesium) daily. Fasting baseline serum glucose and insulin levels were then measured.

Participants were then assigned study medication with the use of a randomized block design. Treatment assignment was blinded from participants, clinicians, and laboratory staff by having another member of the staff dispense and count the blinded labeled medications, which were identically packaged. The six treatment regimens were (1) 50 mg/d hydrochlorothiazide, (2) 50 mg hydrochlorothiazide plus 40 mmol potassium chloride in capsule form per day, (3) 50 mg hydrochlorothiazide plus 40 mmol potassium chloride plus 400 mg magnesium oxide in capsule form per day, (4) 50 mg hydrochlorothiazide plus 100 mg triamterene per day, (5) 50 mg/d chlorthalidone, or (6) placebo (10 mg/d thiamine). After 2 months of randomized treatment, fasting serum glucose and insulin levels were again measured. The hydrochlorothiazide and chlorthalidone doses chosen were the same as those used in MRFIT.

**Serum and Intracellular Electrolytes**

Peripheral venous blood was drawn from the antecubital fossa after the tourniquet was removed and without fist clenching. Serum magnesium was measured with a model 2280 atomic absorption spectrophotometer (Perkin-Elmer) and serum potassium on a model 455 flame photometer (Corning).

Because mononuclear intracellular electrolyte levels are difficult to measure accurately, we instituted special steps to assure the precision of the values used in our analysis. Duplicate 10-mL samples of heparinized blood for each participant were drawn in a single venipuncture and processed indepen-
Body mass index was used as a continuous measure for analysis of glucose and insulin levels in linear regression equations. Continuous measures of serum and intracellular potassium and magnesium were also used as predictors of glucose and insulin levels in both bivariate and multivariate models.

Results

Study Sample
Clinical characteristics of the study sample by randomized group after 1 month of repletion with oral potassium and magnesium were examined (Table 1). Tests of equality across the six groups did not reveal any statistically significant differences in baseline characteristics. Mean age ranged from 58.1 to 62.2 years, and the proportion of participants who were white ranged from 65% to 76%. A minority of participants were current cigarette smokers (14% to 25%), and the majority consumed some alcohol (61% to 79%). The proportion of participants who were white ranged from 66% to 74%, and 7.3% of the entire cohort, 7.3% were taking methyldopa, and 5.6% were taking clonidine; these drugs were continued at a constant dosage throughout the study.

| Table 1. Characteristics of Study Sample by Randomized Group |
|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Characteristic | HCTZ | HCTZ/K | HCTZ/K/Mg | HCTZ/TriaM | CTD | Placebo | All HCTZ |
| n (N=232)*     | 66   | 32    | 35    | 32    | 34   | 33    | 165      |
| Age, y*        | 60.8 (7.9) | 62.1 (6.3) | 62.2 (6.2) | 58.1 (9.4) | 61.4 (7.8) | 60.8 (8.5) | 60.8 (7.7) |
| White          | 76    | 72    | 72    | 65    | 67   | 74    |
| Black          | 9     | 16    | 11    | 22    | 20   | 21   | 13       |
| Other          | 15    | 12    | 17    | 6     | 15   | 12   | 13       |
| Current smoker, % | 14   | 25    | 20    | 22    | 18   | 21   | 19       |
| Current alcohol use, % | 61   | 69    | 63    | 75    | 79   | 70   | 66       |
| Body mass index, kg/m²* | 27.7 (3.6) | 27.8 (2.5) | 27.4 (4.3) | 28.2 (5.0) | 28.0 (4.7) | 28.0 (3.6) | 27.8 (3.9) |
| Nondiuretic antihypertensive drugs during study, % | 35   | 25    | 37    | 34    | 24   | 30   | 33       |

HCTZ indicates hydrochlorothiazide, 50 mg/d; K, oral potassium chloride, 40 mmol/d; Mg, oral magnesium oxide, 400 mg/d; TriaM, triamterene, 100 mg/d; and CTD, chlorthalidone, 50 mg/d.

*Mean (SD).

After 2 months of randomized treatment with the different diuretic combinations or placebo, mean fasting serum glucose and insulin levels had not changed significantly from baseline with the exception of participants randomized to chlorthalidone, who had significant increases in both serum insulin and glucose (P<.05 and P<.01, respectively) (Table 2). The proportion of participants with serum insulin levels ≤104 pmol/L (≤14.5 μU/mL) but <215.3 pmol/L (≤30 μU/mL) and ≥215.3 pmol/L (≥30 μU/mL) and serum glucose levels ≥5.8 mmol/L (≥105 mg/dL) but <7.8 mmol/L (≤140 mg/dL) and ≥7.8 mmol/L (≥140 mg/dL) before and after randomized therapy was also explored (data not shown). Again, the only group to change significantly were those participants randomized to chlorthalidone, of whom 3% had insulin levels ≥215.3 pmol/L (≥30 μU/mL) at baseline and 15% after randomization (P<.05).

| Table 2. Serum Insulin and Glucose Levels Before and After 2 Months of Randomized Treatment |
|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Characteristic | HCTZ | HCTZ/K | HCTZ/K/Mg | HCTZ/TriaM | CTD | Placebo | All HCTZ |
| n (N=202)*     | 57   | 29    | 34    | 27    | 28   | 27   | 147      |
| Serum insulin, pmol/L | 169.3 | 134.9 | 117 | 119.1 | 80.4 | 145.7 | 141.3    |
| Baseline mean  | 174.4 | 119.1 | 134.9 | 152.1 | 144.9 | 201.6 | 150.7    |
| Mean change    | 5.1 | -15.8 | 17.9 | 33 | 64.5† | 55.9 | 9.4       |
| 95% Confidence interval | (-58.1, 68.2) | (-71.8, 40.2) | (-21.5, 57.4) | (-51.7, 117) | (7.2, 120.5) | (-50.9, 162.9) | (-23.7, 40.9) |
| Serum glucose, mmol/L | 5.4 | 4.4 | 5.4 | 4.7 | 4.6 | 5.0 | 5.1       |
| Baseline mean  | 5.4 | 4.6 | 5.7 | 4.8 | 5.3 | 5.3 | 5.2       |
| Mean change    | . . . | . . . | . . . | . . . | . . . | . . . | . . .     |
| 95% Confidence interval | (-0.1, 0.5) | (-0.2, 0.9) | (-0.3, 0.4) | (0.2, 1.3) | (-0.04, 0.5) | (-0.1, 0.4) |

HCTZ indicates hydrochlorothiazide, 50 mg/d; K, oral potassium chloride, 40 mmol/d; Mg, oral magnesium oxide, 400 mg/d; TriaM, triamterene, 100 mg/d; and CTD, chlorthalidone, 50 mg/d.

*Only participants with both baseline and after-treatment values included in analysis.
†P<.05, ‡P<.01.
The proportion of participants in different quartiles of body mass index (kilograms per meter squared) with serum insulin levels ≥104 pmol/L (≥14.5 μU/mL) but <215.3 pmol/L (<30 μU/mL) and ≥215.3 pmol/L (≥30 μU/mL) and serum glucose levels ≥5.8 mmol/L (≥105 mg/dL) but <7.8 mmol/L (<140 mg/dL) remained independent predictors of serum insulin concentrations (P<.001 for each) whether or not all or only those with less than a 25% disparity in the mean value of the duplicate specimens were included in the analysis. Intracellular potassium and magnesium levels were associated with higher serum insulin concentrations (P<.001 for each) and lower serum glucose values (F<.01 for each).

**Multivariate Analysis**

Two multivariate regression equations were run: one that evaluated the effects of body mass index and serum insulin levels, and one that evaluated the effects of blood pressure-lowering properties, but also for the top quartile of body mass index (data not shown). Again, the only group to change significantly were the nine participants in the top quartile of body mass index randomized to chlorothalidone, in whom 44% had insulin levels ≥104 pmol/L (≥14.5 μU/mL) at baseline and 89% after randomization (P<.05) and 11% had insulin levels ≥215.3 pmol/L (≥30 μU/mL) at baseline and 22% after randomization. Because of the small number of participants in this analysis, our results should be repeated in other studies before their clinical significance is determined.

**Serum Insulin and Glucose Levels in Relation to Serum and Intracellular Electrolyte Levels**

Table 3 presents data showing the association between serum and intracellular potassium and magnesium levels and serum insulin and glucose levels after 2 months of randomized treatment combining participants from all groups. The tabled data are displayed by quartile ranks for comparative purposes. However, the regression equations were run using continuous independent variables. Both intracellular potassium and magnesium were associated with higher serum insulin concentrations (P<.001 for each) and lower serum glucose values (P<.01 for each).

**Discussion**

Thiazide diuretics are commonly prescribed antihypertensive agents; hydrochlorothiazide alone accounts for approximately one quarter of all antihypertensive prescriptions in the United States. The 1993 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends hydrochlorothiazide and β-blockers as first-choice agents "unless they are contraindicated or unacceptable," because they are the only classes of drugs that have been shown in long-term controlled clinical trials to reduce cardiovascular morbidity and mortality. Other experts disagree with this recommendation. Weber and Laragh argue that "the thinking physician will choose antihypertensive drugs not only for their blood pressure-lowering properties, but also for..."
TABLE 3. Association of Intracellular and Serum Potassium and Magnesium Levels With Insulin and Glucose Values After Randomized Treatment

<table>
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<tr>
<th>Quartile</th>
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| **Intracellular potassium,**
| mmol/mg of protein | | | | | | | | | | | | | | |
| 1 | 375.4 | 4.9 | 0.3 | .9† | 39 | 105.5 | 12.2 | <.001‡ |
| 2 | 484.1 | 4.7 | 0.4 | | 39 | 101.2 | 11.5 | |
| 3 | 553.1 | 5.2 | 0.4 | | 39 | 136.3 | 20.8 | |
| 4 | 664.6 | 5.2 | 0.4 | | 40 | 221 | 45.2 | |

| **Intracellular magnesium,**
| mmol/mg of protein | | | | | | | | | | | | | | |
| 1 | 29.2 | 4.9 | 0.3 | .80 | 40 | 107.6 | 12.9 | <.001 |
| 2 | 33.5 | 5.2 | 0.5 | | 42 | 122.7 | 16.5 | |
| 3 | 36.1 | 5.1 | 0.4 | | 39 | 147.8 | 18.7 | |
| 4 | 40.7 | 4.7 | 0.1 | | 42 | 202.3 | 43.8 | |

| **Serum potassium,**
| mmol/L | | | | | | | | | | | | | | |
| 1 | 3.2 | 4.8 | 0.2 | <.01 | 50 | 141.3 | 12.9 | .95 |
| 2 | 3.7 | 4.7 | 0.2 | | 51 | 182.2 | 36.6 | |
| 3 | 3.9 | 5.3 | 0.3 | | 50 | 170 | 48.8 | |
| 4 | 4.4 | 6.1 | 0.5 | | 53 | 132.7 | 17.9 | |

| **Serum magnesium,**
| mmol/L | | | | | | | | | | | | | | |
| 1 | 0.74 | 5.9 | 0.4 | <.01 | 51 | 187.3 | 45.9 | .6 |
| 2 | 0.82 | 5.4 | 0.4 | | 52 | 152.8 | 31.6 | |
| 3 | 0.86 | 4.8 | 0.2 | | 49 | 106.2 | 11.5 | |
| 4 | 0.91 | 4.8 | 0.2 | | 52 | 177.2 | 38.7 | |

*Intracellular values reflect exclusion of data where duplicate samples varied from mean by more than 25%.
†From regression of glucose on electrolyte level.
‡From regression of insulin on electrolyte level.

Their effects on other critical intermediate cardiovascular, metabolic, and renal endpoints . . . [and that] the inferred benefits of the newer agents should not be ignored." Given the 20 to 30 million people in the United States taking a thiazide diuretic, it is important to determine which of these hypertensive individuals are at increased risk for metabolic abnormalities including increases in serum glucose and insulin that might have an adverse effect on CHD risk.

**Thiazides and Serum Glucose and Insulin**

Some nonrandomized (in terms of assignment to diuretics) studies have found an association between thiazide diuretics and hyperglycemia, and others have not. In the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial, 2.9% of diuretic-treated men developed glucose intolerance over 45 months of treatment, representing an excess incidence of diabetes in the diuretic group of 6 per 1000 patient years. In a nonrandomized study of 34 hypertensive individuals treated with thiazides, mean fasting blood glucose increased over 14 years, and withdrawal of thiazides at the end of this time resulted in decreases of blood glucose. Investigators in the San Antonio Heart Study found that the 8-year incidence of NIDDM was positively associated with hypertension but not with thiazide or /3-blocker use, although they noted that they lacked information on the duration of antihypertensive agent use or whether participants changed medications from baseline. In a case-control study of New Jersey Medicaid enrollees, investigators did not find an association between thiazide use and initiation of diabetic treatment. Our findings in a randomized controlled trial are in agreement with studies that have found limited effects of hydrochlorothiazide on serum glucose and insulin metabolism, whether or not participants received potassium or potassium- and magnesium-conserving treatment.
Treatment with chlorthalidone raised glucose and insulin concentrations. To the best of our knowledge, only one previous study has examined the effect of chlorthalidone on insulin sensitivity; participants receiving chlorthalidone who became hyperlipidemic also became more insulin resistant.38 These results should be interpreted with caution because baseline insulin levels were lowest in the chlorthalidone group, and thus the change after randomized therapy might represent a chance finding. However, if this finding is repeated in other studies, it suggests that chlorthalidone should be used cautiously in hypertensive individuals at high risk of diabetes such as those with a family history of diabetes or high-risk ethnic groups such as blacks or Hispanics.

Effects of Obesity

We found a strong association between body mass index and serum insulin levels and to a lesser degree between body mass index and serum glucose levels. When the effects of hydrochlorothiazide on serum insulin were investigated based on body mass index, increasing body mass index appeared to result in a greater effect of thiazide treatment on serum insulin levels. However, although our findings reached statistical significance ($P=.04$) when all participants randomized to hydrochlorothiazide were pooled, because of the multiple comparisons made our results should be interpreted with caution until they are repeated in other studies. The effects of chlorthalidone on serum insulin and glucose levels did not appear to be potentiated by increasing body mass index, but our analysis is limited by a lack of power, with only 28 participants randomized to this antihypertensive agent.

Intracellular Potassium and Magnesium and Serum Insulin

Higher mononuclear cell potassium and magnesium levels were each associated with higher serum insulin concentrations. Resnick and colleagues39 used $^{31}$P-nuclear magnetic resonance spectroscopy to assess erythrocyte-free magnesium levels in 20 normotensive and 20 hypertensive subjects off diuretics for at least 6 months. Erythrocyte-free magnesium levels were reduced in the hypertensive subjects, were inversely related to diastolic and systolic blood pressures, and were also inversely related to the insulin response to a 100-g glucose load. Our study differs from their study in that our participants were fasting and were on thiazide diuretics at the time of study and we used nucleated cells for our intracellular determinations. Mononuclear cell magnesium and potassium are better indicators of total body magnesium and potassium stores than serum or plasma levels.35,36 Additionally, mononuclear cell magnesium and potassium are more accurate reflections of skeletal and cardiac muscle magnesium and potassium than erythrocyte levels of these electrolytes.36,37 Erythrocytes are less active than mononuclear cells, and there is evidence that they respond less to acute changes in cation fluxes.36 One animal study found that decreased insulin secretion is associated with magnesium deficiency.39 Our finding that there is a direct relation between mononuclear magnesium levels and serum insulin levels is consistent with this observation. Additional studies are needed to replicate our findings and explore their clinical significance.

Other Considerations

To our knowledge, the 202 participants who completed our study and who had serum available at both baseline and after treatment represent the largest randomized trial of the effects of several diuretic combinations on serum glucose and insulin levels. However, our study still has a limited ability to detect small differences in serum glucose and insulin levels between randomized groups. Our findings pertain to 2 months of treatment with 50 mg/d hydrochlorothiazide or chlorthalidone, and other doses and durations of treatment might have different effects. Additionally, our findings may not be generalizable to other populations of hypertensive patients. We studied older men (average age, 61 years), who might be more prone to developing insulin and glucose abnormalities as a consequence of thiazide treatment than women or younger men.

Diabetic patients might be more likely to have a serious deterioration of serum glucose and insulin levels with diuretic use. In 23 patients with NIDDM, treatment with 12.5 to 25 mg hydrochlorothiazide was associated with increased hemoglobin A1c levels,40 whereas a retrospective analysis of 759 diabetics with severe insulin-dependent diabetes and extensive vascular disease found a strong positive association between diuretic use and subsequent total and CHD mortality.41 In the latter study, the relative odds for cardiovascular mortality compared with normotensive subjects were 1.5 for untreated hypertensive individuals, 2.1 for hypertensive individuals given antihypertensive agents other than diuretics, 3.2 for hypertensive individuals given diuretics plus other antihypertensive agents, and 5.7 for hypertensive individuals given diuretics alone. Although the conclusions from this study are limited because information on diuretic dosage, blood pressure levels, electrolyte levels, and the presence of left ventricular hypertrophy is missing, the results suggest that patients with diabetes should be treated with other agents, such as angiotensin-converting enzyme inhibitors, which appear to slow the rate of progression of renal disease,42,43 until more conclusive evidence is available.

Conclusions

In many hypertensive individuals, chlorthalidone increases glucose and insulin serum levels, whereas administration of hydrochlorothiazide with or without potassium- and/or magnesium-conserving strategies does not. Obesity is associated with increased serum insulin, and our results suggest that obese individuals are more sensitive to the adverse effects of hydrochlorothiazide on insulin metabolism.

Based on our findings, we feel that hydrochlorothiazide remains an effective and inexpensive treatment for most hypertensive individuals and it should not be excluded from consideration for use because of fear of precipitating diabetes. In hypertensive individuals at risk of diabetes (eg, blacks, Hispanics, or patients with a family history of diabetes) and in obese individuals, glucose and insulin concentrations should be monitored carefully after hydrochlorothiazide is started, or an alternative agent should be chosen. Chlorthalidone should be used with caution or avoided in these indi-
iduals because equally effective blood pressure-lowering treatment is available.

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