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Hypertension. 2008;52:1009-1011; originally published online November 3, 2008;
doi: 10.1161/HYPERTENSIONAHA.108.120923
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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Mechanistic Insights into Diuretic-Induced Insulin Resistance

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The incidence of diabetes mellitus and hypertension continues to rise worldwide. The proportion of patients with hypertension at risk for developing diabetes mellitus is also growing secondary to aging and increased obesity rates. Several guidelines recommend thiazide diuretics as either first-line or add-on antihypertensive therapy to achieve blood pressure goals. Concern over negative metabolic effects associated with thiazide diuretics, however, dates back >3 decades. A substantial fraction of patients with hypertension have additional cardiovascular risk factors, and many have elevated fasting glucose and are at risk for developing diabetes mellitus. Impaired fasting glucose itself increases the risk for cardiovascular events.

Any medication that worsens insulin sensitivity, ie, thiazide diuretics or most β-blockers will hasten the development of diabetes mellitus in those with impaired fasting glucose. Large observational studies demonstrate that thiazide diuretics and most β-blockers increase the incidence of new-onset diabetes mellitus compared with renin-angiotensin system (RAS) blockers or calcium channel blockers. To further support this observation, a network-based meta-analysis of hypertensive agents showed that RAS blockers were the agents least likely to increase risk of diabetes mellitus compared with placebo.

The mechanism traditionally associated with this increased risk of diuretic-associated diabetes mellitus is a reduction in serum potassium. A meta-analysis of 59 studies involving 83 thiazide diuretic treatment arms found a significant correlation between the degree of diuretic-induced hypokalemia and an increase in plasma glucose. Moreover, there is evidence that prevention of hypokalemia with K+ supplementation or potassium-sparing agents lessens the degree to which plasma glucose is increased consequent to diuretic therapy. The mechanism of this glucose increase by diuretics may relate to insulin secretion. Mechanisms related to insulin release were reviewed recently, and it was noted that hyperkalemia stimulates insulin secretion and induces cellular uptake of potassium. This suggests that low plasma potassium could impair insulin secretion and thereby increase plasma glucose. Ironically, the significant hypokalemia associated with hyperaldosteronism is not associated with hyperglycemia.

Given this background, combining an agent that reduces potassium loss, ie, an RAS blocker with a thiazide diuretic, should reduce the risk of new-onset diabetes mellitus. Unfortunately, the Study of Trandolapril/Verapamil SR and Insulin Resistance failed to support this hypothesis. It demonstrated a 4-fold increase in diabetes mellitus at 1 year in comparison with a fixed-dose combination of an RAS blocker with a calcium channel blocker. This result was not attributable to differences in serum potassium between groups, because serum potassium values were >4.0 mEq/L in both groups. Thus, mechanisms other than changes in potassium may be operative to worsen glycemic control and are summarized elsewhere.

One mechanism proposed for the prevention of worsening glycemic control by RAS blockers is their peroxisome proliferator-activated receptor-γ stimulating effects; however, this was not observed in this or any other trial, because candesartan had a neutral effect on glucose. Moreover, the peroxisome proliferator-activated receptor-γ stimulating effect observed by some RAS blockers appears relevant only in animal models or at a cellular level.

The current study by Eriksson et al provides a potentially novel mechanism by which diuretics worsen insulin resistance. Twenty-six obese, hypertensive subjects were randomly assigned to candesartan, hydrochlorothiazide (HCTZ), or placebo (in random sequence), each for 12 weeks, using a 3-way crossover design. Insulin sensitivity and secretion, hepatic fat accumulation, inflammatory markers, and the ratio of subcutaneous:visceral abdominal fat were measured. Insulin sensitivity was assessed using a hyperinsulinemic, euglycemic clamp. Significant reductions in insulin sensitivity were present with HCTZ compared with candesartan. Serum potassium levels were within the normal range in all of the groups but 0.3 mEq/L lower among those randomly assigned to HCTZ. The authors reported that differences in potassium level be-

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DOI: 10.1161/HYPERTENSIONAHA.108.120923

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tween groups did not correlate with changes in insulin sensitivity. The epidemiological data, however, suggest that the risk for new-onset diabetes mellitus is increased if the serum potassium levels fall below 3.5 mEq/L; levels in the current study were well above this value.

Perhaps the most interesting finding in this study was the increase in hepatic fat content after treatment with HCTZ; this fat increase correlated with the magnitude of insulin sensitivity decrease. Insulin secretion was not affected by HCTZ or candesartan, despite older studies implying decreased insulin secretion with HCTZ as the mechanism for worsened metabolic control.

Given this new information, an additional mechanism to explain why thiazide diuretics worsen insulin resistance needs consideration. Before we embrace this concept, however, one needs to ask why this occurred. The increased shift of fat in liver, with resultant relative increases in visceral adiposity, is an intriguing perspective of this study. Hepatic fat accumulation is associated with insulin resistance, at the level of liver and skeletal muscle. The changes in content of visceral and hepatic fat could contribute to worsening of insulin sensitivity, but which occurs first? Is it possible that decreased insulin sensitivity and elevated insulin levels promote hepatic fat storage and visceral fat accumulation? In the Mechanisms for the Diabetes Preventing Effect of Candesartan Study, there was some correlation ($r^2=0.26$; $P=0.04$) between the increased hepatic fat content and the observed decrease in insulin sensitivity.

Other possible mechanisms that contributed to decreases in insulin sensitivity include increased inflammatory response or oxidative stress with diuretics, resulting in altered adipocyte activity. Inflammatory markers, such as high-sensitivity C-reactive protein and serum amyloid A, were higher in the diuretic group compared with the other groups. Changes in adiponectin levels may have also contributed to this shift in fat; however, adiponectin levels were not different between groups. Thus, there is no clear reason why this shift in fat occurred with HCTZ, but, if confirmed, this would provide another reason for the higher risk of new-onset diabetes.

Apart from the cost and inconvenience of new medications now required to treat the diabetes mellitus, the main concern is whether the cardiovascular risk–reduction that diuretics confer is lost in this subgroup of obese older patients who prematurely develop diabetes mellitus. Three posthoc analyses of large cardiovascular outcome trials evaluated whether the development of new-onset diabetes mellitus predicted a higher cardiovascular event rate. The results of 2 these analyses demonstrated no significant increase in risk, whereas another showed that those who developed diabetes mellitus had an intermediate cardiovascular risk less than those with diabetes mellitus but higher than those who did not develop diabetes mellitus. These analyses have major limitations, however, not the least of which is that they are posthoc, and most people in the analysis were not obese. There is, however, one ongoing trial that will address this issue and is due to be completed by 2010.

In short, thiazide diuretics are associated with decreased insulin sensitivity over a relatively short time period in obese subjects with impaired fasting glucose. The mechanisms by which this occurs appear to be multifactorial. The current study provides new data to help us understand the interaction between thiazide diuretics and the adipocyte. This information, coupled with the results of a large multicentered cardiovascular outcome study that favors RAS blockade combined with a calcium channel blocker rather than a diuretic, may provide an option other than diuretics as initial agents in high-risk patients. Nevertheless, more detailed mechanistic studies are needed to explain further why insulin resistance is worsened with thiazide diuretics.

Disclosures

None.

References


