Thiazide diuretics such as HCTZ more often cause hyperglycemia (or) chlorthalidone than other diuretics

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Abstract

Background: Antihypertensive drugs including thiazide diuretics, beta blockers (BB), calcium channel blockers (CCB), reninangiotensin inhibitors or vasodilators produce elevated blood glucose (hyperglycemia) (>70-99 mg/dL). Hyperglycemia is more common and severe with thiazide diuretics than with BB, CCB, ACEI or ARB drugs. Questions have been raised about the mechanism and risk of drug-induced hyperglycemia.

Method: We present here four patients treated with diuretics who developed hyperglycemia - fasting blood glucose (FBG) > 126 mg/ dL (7 mmol/L) diagnostic of diabetes. Three patients had hypertension and one, congestive heart failure (CHF). Three patients had no diabetes, one gave 8 to 10 year history of diabetes. One patient received no diuretic therapy and his glucose level was normal with insulin and oral hypoglycemic agent treatment. Subsequently, he became hypertensive and was treated with a thiazide diuretic but no antidiabetic agents. He then developed new-onset diabetes.

Results: All patients showed hyperglycemia above FBG criteria for diabetes. 2-hour postprandial blood glucose (2hPPG) was not diagnostic of diabetes in three patients. Two patients were prescribed antidiabetic therapy which was stopped with no worsening of hyperglycemia although diuretic therapy continued. In two patients diuretic was discontinued. Hyperglycemia abated in one, while in the other, hyperglycemia worsened requiring Glargine insulin.

Conclusion: Hyperglycemia is common in patients with hypertension or CHF treated with a thiazide diuretic alone or in combination with other diuretics. Although by definition the term new-onset diabetes may be used to connote hyperglycemia, in reality diabetes induced by diuretics is not diabetes as 2hPPG does not usually exceed 200 mg/dL (11.1 mmol/L), and patients show no evidence of any vascular complications. It may be more appropriate to define elevated glucose associated with diuretic "hyperglycemia" rather than new-onset diabetes. The real issue is that use of thiazide diuretics is imperative in blood pressure control especially in resistant hypertension. Even with new-onset diabetes, thiazide diuretics are commonly found to be safe, reducing risk of stroke, heart attack, and renal failure characteristic of uncontrolled hypertension. Therefore, risks of new-onset diabetes, induced by diuretic therapy, will be difficult to ascertain because of hypertension for which thiazide diuretic is widely used.

keywords: hyperglycemia, diuretics, diabetes.

Background

Diabetes is a major cardiovascular risk factor, but drug-induced new-onset diabetes may not have clinical significance and should not be a major determinant when choosing a treatment for hypertension if the medication is necessary to reduce blood pressure[1]. A study found no difference in the number of patients who developed diabetes with different antihypertensive drugs, including diuretics and beta blockers as shown in Figure 1 [2].

Figure 1: Risk of hyperglycemia in patients receiving antihypertensive drugs. ACE – angiotensin converting enzyme; ORs-odds ratios; CIs-confidence intervals. Adapted from Gurwitz J.H. et al. Ann Intern Med 1993; 118: 273-278 [2].

Figure 1 demonstrates that all antihypertensive drugs may produce hyperglycemia although the risk of hyperglycemia varies. In the ALLHAT study, chlorthalidone treated patients achieved the same primary end point results – fatal and nonfatal infarcts – as amldipine or Lisinopril treated subjects despite the fact that an increase in serum glucose of 3 to 5 mg/dL and new-onset diabetes was more frequent in the diuretic-based treatment groups. The investigators concluded that “there was no advantage to the use of Lisinopril compared with a diuretic despite the difference in new-onset diabetes”. The use of alpha blockers does not increase serum glucose; but in the ALLHAT study, cardiovascular events were more frequent with an alpha blocker compared with a diuretic [3].

A group of investigators from Italy studied the outcome of new-onset diabetes in treated hypertensive subjects compared to those with previously known diabetes. They found that subjects in whom diabetes developed were exposed to diuretics, calcium channel blockers, and angiotensin converting enzyme inhibitors (ACEI) more frequently than those in whom diabetes did not develop as shown in Figure 2 [4].
The purpose of this communication is to present a few patients who were diagnosed to have developed diabetes during treatment of hypertension who were then placed on anti-diabetic therapy. Withdrawal of anti-diabetic therapy and treatment with potassium supplements did not result in worsening of hyperglycemia or appearance of overt diabetes.

In addition, a patient is presented to demonstrate that diuretic-induced hyperglycemia may occasionally lead to overt diabetes requiring insulin therapy.

**Methods and Results**

Overt diabetes is defined by a 2-hour post-load plasma glucose (2 hPPG) concentration of ≥ 200 mg/dL (11.1 mmol/L) [5]. Hyperglycemia or new-onset diabetes has not been clearly defined. However, in this study hyperglycemia is defined by FBG above 126 mg/dL (7 mmol/L).

Patient #1 – A 67 year old African American male was referred by a primary care physician and seen by the authors (AKM) in the office in November of 2011 for renal insufficiency. He gave history of hypertension for a long time and diabetes for nine months. He is a farm worker and is very active. Daily medication at the time of first visit consisted of hydrochlorothiazide (HCTZ) 25 mg, glimepiride 2 mg, Lisinopril 40 mg, pravastatin 80 mg, amlodipine 10 mg, metoprolol 100 mg, and allopurinol 300 mg all PO daily. During this visit he had a pulse of 66 beats/min and sitting and upright blood pressures (BP) were 130/90 mmHg. Otherwise his physical examination was normal. The only available laboratory data at this visit was decreased estimated glomerular filtration rate (eGFR) of 42 mL/min (N =60 ml/min). Action at this office visit included discontinuation of Lisinopril, increase of allopurinol to 10 mg a.m. and 5 mg p.m. to improve BP control, and decrease of allopurinol 150 mg (due to decreased kidney function), and decrease of pravastatin to 40 mg PO daily. Fasting and 2-h basic metabolic panel (BMP), glycosylated hemoglobin (HbA1c) and serum insulin levels were ordered. At his next visit, two weeks later, FBG was 102 mg/dL and 2 hPPG was 139 mg/dL. Both of these levels were normal. Serum creatinine (mg/dL) and eGFR (ml/ min) for the corresponding periods were 1.73/42 and 1.66/44 respectively. The 2hPP serum insulin level was 126.5 μU/L. At this time, he was advised to discontinue glimepiride, switch HCTZ to chlorthalidone 25 mg daily, increase amlodipine to 10 mg twice daily, and potassium chloride 20 mEq daily was added. At his third visit, six weeks later, his glucose levels for both FBG and 2 hPPG were increased. He returned to the office in late March of 2012 with a laboratory done March 1, 2012. He is no longer taking glimepiride but taking thiazide diuretic chlorthalidone 25 mg/day to keep hypertension under control. His sitting and upright BP were 120/80 mmHg. FBG and 2 hPPG decreased to 130 mg/dL and 152 mg/dL, respectively compared to those in the previous visit even though he was no longer taking the glimepiride.
He floridly responded to Glargine insulin with regression of hyperglycemia. He feels well and maintains normal blood glucose levels (FBG and 2hPP) with 10 units of glargine insulin twice daily.

**Discussion**

This study presents four patients who were treated with thiazide diuretic and developed hyperglycemia. Two patients were treated with oral hypoglycemic agents and one with insulin detemir. Discontinuation of thiazide diuretic resulted in restoration of normoglycemia and termination of oral hypoglycemic agents. Diabetes in insulin treated patient (Patient #2) could not be documented after discontinuation of insulin. Authors observations indicate that hyperglycemia of variable severity is common in hypertensive patients treated with diuretics, mainly thiazide diuretics. However, unlike other authors, these authors have demonstrated that hyperglycemia is reversible upon discontinuation of the diuretic as it is shown clearly in patient #3. However, a patients' glucose level may not decrease upon discontinuation of the diuretic as in patient #4.

This patient who has developed overt diabetes, requiring insulin therapy, raises an important question: does diuretic induced hyperglycemia lead to overt diabetes? To that effect other authors have asked the question “are antihypertensive agents simply unmasking or masking diabetes” [6]? Intracellular potassium deficiency even with near normal serum potassium, is an important determining factor for hyperglycemia induced by diuretic therapy, and correction of hypokalemia using potassium supplements attenuates hyperglycemia [7].

Low serum potassium has been considered an important mechanism in the pathogenesis of diuretic induced hyperglycemia by these and other authors [6,7]. It is important to understand that serum potassium does not necessarily correlate with intracellular potassium stores. Therefore serum potassium may be normal but intracellular potassium deficit still persists and hence may attenuate endogenous insulin release and cause hyperglycemia. Since it is difficult to measure intracellular potassium, we have to depend on serum potassium as an index of intracellular potassium. In patient #4 for example, serum potassium levels varied between 4.2 and 4.4 mmol/L from 2007 to 2011 during continuous potassium supplementation and use of triamterene along with HCTZ. He still developed sustained hyperglycemia with time leading to overt diabetes and required insulin therapy to control glucose levels. A pearl of wisdom came from this patient where it was observed that control of persistent hyperglycemia with insulin therapy, markedly decreased his shortness of breath and he no longer requires oxygen therapy. He is more lively than before. To that effect, it is important to seek out mechanisms other than hypokalemia alone to explain hyperglycemia. As such, other authors have identified HbA1c (odd ratio 4.21 per 1% increment) as baseline predictor of diabetes [8]. The findings in our patient #4 concur with the previous observation. HbA1c in patient #4 increased from baseline 6.6% in 2007 to 9.8% in 2011 when he developed overt diabetes.

The problem of predicting cardiovascular or renal risk associated with drug-induced hyperglycemia still remains. There are several reasons for that: 1. Diuretic, especially thiazide diuretic, is an essential therapy in hypertension and 2. Hypertension in and of itself is associated with much greater cardiovascular and renal risks thus making it difficult to distinguish them from those caused by diuretic therapy. 3. Most studies are post hoc findings and were not adequately powered to assess the association between diuretic therapy and new-onset diabetes [9]. 4. New-onset diabetes was defined differently in different studies [9]. Further, comparing antihypertensive drug classes is difficult owing to differing study designs [10].

**Conclusion**

It is evident from all previous studies and our own observations that use of diuretics in the treatment of hypertension or CHF gives rise to hyperglycemia. Thiazide diuretics such as HCTZ or chlorothalidone more often cause hyperglycemia than other diuretics. Severity of hyperglycemia varies but generally does not exceed 200 mg/dL (> 11 mmol/L) to call this condition established diabetes by definition.
However, no prospective or long-term follow up studies are available to determine that diuretics merely cause hyperglycemia or unmask diabetes. Thus for now, diuretic-induced hyperglycemia is caused by volume and potassium depletion and treatment with potassium or reduction of the dose of diuretics reduce blood glucose levels to near normal or normal levels. However, there are exceptions to this dictum. As such occasional patients with use of multiple diuretics may give rise to symptomatic diabetes requiring insulin therapy. Except for that, no microvascular or macrovascular complications, unique for untreated diabetes, have been observed in diuretic-induced hyperglycemia.

References

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