Hypokalemia, Glucose Intolerance, and Hyperinsulinemia During Diuretic Therapy

Frida L. Plavinik, Cibele I.S. Rodrigues, Maria Teresa Zanella, and Artur B. Ribeiro

Hypokalemia and glucose intolerance may result from diuretic therapy. Increases in plasma insulin and glucose levels have been observed in thiazide-treated hypertensive patients and have been attributed to a diminished insulin sensitivity induced by diuretic therapy. To investigate the effects of hypokalemia on glucose tolerance and insulin secretion, we studied 21 essential and nine diabetic hypertensive patients after 4 weeks of placebo and after 4 weeks of chlorthalidone therapy (25 mg/day). Plasma glucose and insulin levels were measured for a 3-hour period after a 75-g glucose oral dose. Hypokalemia developed in seven of the essential hypertensive patients (HK group), whereas only one diabetic patient had decreased plasma potassium levels to below 3.5 meq/l. The results obtained in the HK group after chlorthalidone showed that plasma glucose and insulin values increased after the oral glucose load to levels significantly higher than those observed after placebo. In contrast, the patient who remained normokalemic after chlorthalidone did not show any change in plasma insulin and glucose levels during glucose tolerance testing. These results show that diuretic therapy may induce hyperglycemia and hyperinsulinemia and suggest that potassium depletion is involved in the increase in insulin resistance that has been demonstrated during thiazide therapy. (Hypertension 1992;19[suppl II]:II-26–II-29)

The thiazide diuretics are currently the most widely used initial therapy in essential hypertensive patients, and their adverse effects on glucose homeostasis are well documented.1,2 They are known to impair glucose tolerance in nondiabetic humans and have been involved in the progression from impaired glucose tolerance to overt diabetes.3 Several mechanisms have been proposed to explain the impairment in carbohydrate metabolism during thiazide therapy. Hypokalemia has been implicated in the deterioration of glycemic control during thiazide therapy, because adequate potassium supplementation has been shown to restore glucose tolerance to pretreatment levels.4,5

More recently, some reports have demonstrated that the increases in plasma glucose levels consequent to diuretic therapy during glucose tolerance tests are associated with increases in plasma insulin values.6,7 These observations suggest a decreased tissue sensitivity to insulin as the causative factor of thiazide-induced glucose intolerance. However, a role for potassium depletion in the development of a diuretic-related impairment in peripheral glucose uptake and hyperinsulinemia has not been established.

The aim of this study was to investigate the relations among glucose intolerance, hypokalemia, and hyperinsulinemia in diuretic-treated essential and diabetic hypertensive patients.

Methods

Twenty-one hypertensive patients (five men, 16 women; aged 30–68 years) and nine diabetic patients (two men, seven women; aged 43–68 years) were included in this study. All were mildly hypertensive, with diastolic blood pressure ranging from 95 to 105 mm Hg after at least 2 weeks without any antihypertensive medication. Patients were recruited from the Hypertension Clinic, Escola Paulista de Medicina, and none of the secondary causes of hypertension was clinically present. However, tests to exclude such possibilities were not performed routinely, except that serum potassium and creatinine concentrations were within normal limits in all individuals. The protocol was approved by the Medical Ethics Committee of the Hospital São Paulo, and informed consent was obtained from all individuals.

The protocol of study comprised a 4-week placebo period and a 4-week period of active therapy with 25 mg/day chlorthalidone. Before and after chlorthalidone therapy, blood samples were collected for determination of plasma potassium and creatinine and for glycosylated hemoglobin. Systolic and diastolic blood pressures were measured, and an oral glucose tolerance test was also performed, both before and
TABLE 1. Effects of 4 Weeks Placebo Administration and Chlorthalidone Therapy (25 mg/day)

<table>
<thead>
<tr>
<th>Groups and therapy</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>Plasma potassium (meq/l)</th>
<th>Creatinine (mg/dl)</th>
<th>Glycosylated hemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension (NK group) (n=14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>142±0</td>
<td>96±4</td>
<td>4.4±0.4</td>
<td>0.9±0.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>128±8*</td>
<td>86±6†</td>
<td>4.1±0.4</td>
<td>0.8±0.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Essential hypertension (HK group) (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>149±13</td>
<td>98±4</td>
<td>4.6±0.8</td>
<td>0.8±0.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>125±7*</td>
<td>87±3*</td>
<td>3.4±0.5*</td>
<td>0.9±0.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Diabetes and hypertension (n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>147±15</td>
<td>95±6</td>
<td>4.3±0.3</td>
<td>1.0±0.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>131±14†</td>
<td>85±6*</td>
<td>4.0±0.4†</td>
<td>1.0±0.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Values are mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; NK, normokalemic hypertensive patients; HK, hypokalemic hypertensive patients.

*p<0.01, †p<0.05 vs. placebo.

after 4 weeks of active treatment. The glucose tolerance test was performed after an overnight fast with 75 g of oral glucose, and blood samples for plasma glucose were collected every 30 minutes during 2 hours. Plasma insulin levels were determined before and 2 hours after the oral glucose overload.

Plasma insulin levels were measured by radioimmunoassay, and glycosylated hemoglobin was estimated using an affinity chromatographic method; serum creatinine levels were measured according to the method of Jaffe. Plasma glucose and potassium levels were measured by routine methods.

Statistical analysis was done using the Student's paired t test to compare values obtained before and after chlorthalidone therapy. The correlation coefficient of Pearson was calculated to test the relations between plasma potassium and plasma insulin or glycemic levels.

Results

Chlorthalidone, 25 mg/day for 4 weeks, induced a fall in plasma potassium levels in all 21 essential hypertensive patients and in five of the nine diabetic hypertensive patients studied. The mean fall in plasma potassium of 0.7±0.6 meq/l observed in the essential hypertensive patients was greater than the value of 0.3±0.1 meq/l observed in the diabetic patients.

When the decreases in plasma potassium level were considered, the upper quartile of the values observed in the essential hypertensive patients was defined by the value 0.9 meq/l. When we considered the plasma potassium levels achieved after 4 weeks of chlorthalidone therapy, the value 3.4 meq/l limited the lower quartile of all values. The group of essential hypertensive patients thus was divided into two subgroups. The hypokalemic subgroup (HK group) comprised seven patients who showed a fall in plasma potassium equal to or more than 0.9 meq/l and/or plasma potassium values equal to or less than 3.4 meq/l. The remaining 14 normokalemic essential hypertensive patients were included in the NK group. Only one patient in the diabetic hypertensive group decreased plasma potassium value to 3.4 meq/l, so this group was not subdivided.

The antihypertensive effect of chlorthalidone was statistically significant in the three groups studied, whereas no significant changes were observed in plasma creatinine or glycosylated hemoglobin, as shown in Table 1. After placebo administration, plasma potassium levels did not differ in the three groups studied, and after chlorthalidone, the decrease in plasma potassium levels observed in the NK group did not reach statistical significance as occurred in the other two groups.

FIGURE 1. Line graphs show plasma glucose levels before and after 75 g oral glucose load, after placebo, and after chlorthalidone therapy in patients who developed hypokalemia (HK), in normokalemic hypertensive patients (NK), and in diabetic patients. Mean values±SEM are shown. *p<0.01 vs. placebo.
Changes in plasma glucose levels during glucose tolerance testing are depicted in Figure 1. During placebo administration, the increases in plasma glucose levels induced by oral glucose load did not differ in the two subgroups of hypertensive patients and reached levels that were clearly lower than those observed in the diabetic group. During chlorthalidone administration, the plasma glucose levels observed after glucose load in the HK group increased markedly, reaching values higher than those observed during the placebo period and approaching the values detected in the diabetic patients. In contrast, plasma glucose levels after glucose load did not change significantly with chlorthalidone in the HK and diabetic groups.

At the end of the placebo period, plasma insulin levels did not differ in the three groups studied, both before and after oral glucose load, as shown in Figure 2. In contrast, during chlorthalidone therapy, marked changes were observed in plasma glucose levels only in the HK group, associated with pronounced increases in plasma insulin levels, both in the basal condition and after 2 hours of glucose load. Chlorthalidone therapy did not induce any change in plasma insulin or glucose levels in the diabetic and NK groups. Although glucose intolerance and hyperinsulinemia were observed in the group of patients that showed the more pronounced falls in plasma potassium levels, considering all the essential hypertensive patients after chlorthalidone, no significant correlations were found between plasma potassium and insulin values ($r = -0.31; p > 0.1$) or between plasma potassium and glycemic levels ($r = -0.24; p > 0.1$).

**Discussion**

The results presented confirm previous studies showing that deterioration in glucose tolerance during diuretic therapy is related to the fall in serum potassium levels. Many different mechanisms may explain the impairment in carbohydrate metabolism during diuretic-induced hypokalemia. Perhaps the best documented is the reduction in insulin secretion caused by potassium depletion. Gorden et al examined patients with abnormal glucose tolerance and hypokalemia resulting from other causes than diuretic therapy and confirmed a deficient insulin response to oral glucose load in the hypokalemic state. They also observed that the decreases in insulin secretion, consequent to potassium depletion, were largely due to a reduction in the insulin component with full biological activity, whereas little change was detected in the biologically less active proinsulin-like component. This raises the possibility that the proportions of insulin and proinsulin components in the total amount of insulin released from beta cells may be influenced by plasma potassium levels. In the hypokalemic state, a diminution in active insulin components could contribute to the impairment in glucose tolerance. In contrast, other studies have suggested that thiazide may inhibit directly insulin release from beta cells or impair tissue sensitivity to insulin. The reasons for these discrepant findings regarding the mechanism involved in the reduction of glucose tolerance during diuretic therapy are not clear.

Contrasting with the studies showing a reduction in insulin secretion during diuretic therapy, the results of the present study show pronounced increases in plasma insulin levels associated with hypokalemia and glucose intolerance in essential hypertensive patients.

In the last few years, a considerable number of studies have demonstrated glucose intolerance, insulin resistance, and hyperinsulinemia in nonobese essential hypertensive patients. The results presented here provide some evidence that diuretic-induced hypokalemia may accentuate these abnormalities in glucose and insulin metabolism, as also shown in other studies. These findings suggest that an increased resistance to insulin action may be the major factor underlying thiazide-induced glucose intolerance. Indeed, euglycemic hyperinsulinemic clamp experiments in humans have demonstrated that the mechanism involved in diuretic-induced hyperinsulinemia in glucose intolerance is a decrease in peripheral insulin sensitivity. The results of our study raise the possibility that potassium depletion aggravates the defect in the ability of insulin to stimulate glucose uptake in hypertensive patients.

Although insulin may stimulate the flux of potassium into the cells, it is unlikely that insulin resistance and hyperinsulinemia, consequent to chlorthalidone therapy, were the cause of the potassium fall in the hypokalemic group. The fact that potassium supplementation has been shown to correct the abnormality in glucose tolerance caused by diuretic therapy suggests that potassium repletion may restore insulin sensitivity to pretreatment levels. The observations of Tourniaire et al support this hypothesis. Using a euglycemic hyperinsulinemic clamp procedure, these authors demonstrated a diminished...
insulin sensitivity in type II diabetic patients with chronic hypokalemia secondary to a selective renal tubulopathy. After successful correction of plasma potassium levels with indomethacin or spironolactone, the indexes of insulin sensitivity returned to normal values. However, in our study, no significant correlations were found between serum potassium and glycemic or insulin values after chlorthalidone therapy. Despite this, a possibility exists that the diuretic-induced decreases in insulin sensitivity do not depend on the hypokalemia itself but on the degree of potassium deficiency in skeletal muscle, the chief target of insulin action.

After 4 weeks of chlorthalidone therapy, no changes in plasma insulin levels or glucose tolerance were observed in essential hypertensive and diabetic patients who showed variations in plasma potassium levels within the normal range. We have also observed that hypokalemia during chlorthalidone therapy was less frequent in diabetic patients. Some studies in humans have indicated that one cause of the fall in plasma potassium levels during diuretic therapy is the movement of potassium into the cells due to alkalosis, resulting from hydrogen ion excretion. In diabetic patients, however, hyperglycemia and reduced flux of glucose into the cells appear to limit the influx of potassium through the cell membranes,17 and this may reduce the chances of hypokalemia.

Although normokalemic patients in this study did not show any significant changes in glycemic control after 4 weeks of diuretic therapy, we cannot exclude the possibility of a deterioration in glucose tolerance after prolonged diuretic therapy. After 11 months of hydrochlorothiazide therapy in a group of hypertensive patients, Pollare et al17 found increases in insulin resistance that could not be attributed to the small changes observed in plasma potassium levels.

In conclusion, evidence has been presented demonstrating that chlorthalidone-induced hypokalemia results in hyperinsulinemia and glucose intolerance. These alterations may be the reflection of an impairment in peripheral insulin sensitivity by potassium depletion. However, our results do not permit the exclusion of an alteration in insulin secretion, leading to a high proportion of a less biologically active component in the total amount of insulin released in the circulation. Further studies are needed to clarify the exact mechanism mediating chlorthalidone-induced hyperinsulinemia.
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