Etiological Factors in Thiazide-induced or Aggravated Diabetes Mellitus

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SUMMARY

Nine patients with diabetes mellitus and three normal controls were treated for one week with hydrochlorothiazide (150 mg. per day), and certain effects on carbohydrate metabolism were observed. Evidence presented in this study confirms the thiazide-induced carbohydrate intolerance. Tests of insulin reserve (serum ILA response to glucose), response to insulin, insulin binding, urinary steroid excretion, serum potassium, serum nonesterified fatty acids, and serum amylase failed to reveal any abnormality related to the carbohydrate intolerance. There was reduction of the whole blood glutathione levels in six of seven subjects. DIABETES *14*:132-36, March 1965.

It is now established that the administration of thiazides to patients with diabetes mellitus may further impair their carbohydrate tolerance and make the management of the diabetic state more difficult.[1-3] This effect on carbohydrate metabolism was reported first in 1959,[4-6] and these preliminary observations were later substantiated by several case reports of patients whose diabetes was either aggravated,[7-9] or precipitated,[10] by the administration of thiazides. Because of the limited number of reports, however, it was generally felt that the hyperglycemic effect was an unusual complication of therapy.

Prospective studies, however, in both normals and diabetics demonstrated the deterioration of carbohydrate tolerance to be relatively common.[1-3,11,12]

The purpose of this study is to investigate certain mechanisms which might account for the carbohydrate intolerance produced by thiazides.

MATERIALS AND METHODS

Observations were made in nine mild adult onset diabetic and three nondiabetic, ambulatory, asymptomatic, adult males hospitalized at the Birmingham Veterans Administration Hospital. The diabetic patients had been treated with diet only. During the time of study all patients received a daily diet of 2,500 calories (250 gm. carbohydrate, 125 gm. protein, and 111 gm. of fat). The study was divided into a five-day control and a seven-day therapy period. On the first two days of the control period, determinations were made of the serum potassium, uric acid, amylase, urea nitrogen and twenty-four-hour urinary excretion of 17-hydroxycorticoids and 17-ketosteroids. On day three, a two-hour oral glucose tolerance test, (30 gm. of glucose per square meter of body surface) was performed and serum insulin-like activity, using the rat epididymal fat pad,[13] was determined on each sample. A beef insulin tolerance test* was performed on day four and an oral tolbutamide tolerance test[14] on day five.

Following the oral tolbutamide test, each patient was given 50 mg. of hydrochlorothiazide,† without potassium supplement, three times a day for the next seven days. Four days after therapy was begun the same blood chemical tests and twenty-four hour urinary steroids were repeated. The glucose tolerance test, beef insulin, and oral tolbutamide tests were repeated on the fifth, sixth, and seventh days respectively.

Three additional patients with diabetes mellitus were studied to determine the effect of thiazide therapy on bound and free insulin.[15,16]

RESULTS

All twelve patients tolerated hydrochlorothiazide without difficulty. There was no significant alteration in body weight, hematocrit, WBC, or liver function tests during the study. The mean values for serum potassium, uric acid, amylase, and blood urea nitrogen are presented in table 1. The mean serum potassium fell 0.4 mEq./L. (range plus 1 to minus 1.2 mEq./L.), and the mean serum uric acid rose 0.5 mg. per cent (range plus 2.6 to minus 1.2 mg. per cent), during the administration of hydrochlorothiazide. There was a slight rise in the mean blood urea nitrogen in all patients during therapy. No consistent changes in serum amylase

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*Crystalline Beef Insulin (0.1 U. per kilogram) was injected intravenously to each patient in the fasting state. Blood samples are drawn 10, 20, 30, 40, 50, and 60 min. after the injection of the insulin.

†Administered as 50 mg. Hydrodiuril tablets.

TABLE 1

Mean values obtained in patients before and during hydrochlorothiazide therapy

Patient	Serum potassium (mEq./L.)		Uric acid (mg./100 ml.)		Serum amylase Russell units		Urea blood nitrogen (mg./100 ml.)		Urinary 17-OHCS (mg./24 hrs.)		Urinary 17-KS (mg./24 hrs.)	
	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
Diabetics (Mean of 6 pts.)	4.4	4.0	5.1	5.6	56	57	18	23	9.7	9.7	12.9	11.2
Normals (Mean of 3 pts.)	4.3	3.7	4.4	4.3	67	50	18	23	10.0	10.0	14.3	9.6

TABLE 2

Whole blood reduced glutathione* levels obtained in patients before and during thiazide therapy

Patient	Fasting		Half hour		One hour		Two hours	
	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
Diabetics (Mean of 4 pts.)	27.5	24.7	32.8	24.1	27.1	25.2	29.0	25.4
Normals (Mean of 3 pts.)	23.9	20.1	24.4	19.4	26.5	19.2	22.4	17.9

*Expressed as mg./100 ml. during glucose tolerance test.

were observed.

The urinary excretion of 17-hydroxycorticoids and 17-ketosteroids[17-19] and the serum levels of potassium, uric acid, amylase and urea nitrogen for each period are shown in table 1. There was no change in these values before or during thiazide therapy.

Whole blood was analyzed for reduced glutathione[20] content on four diabetic and three nondiabetic patients during the glucose tolerance tests both before and during thiazide therapy. The results of these determinations are presented in table 2. In six of these seven patients, a slight but consistent fall in reduced glutathione during thiazide therapy was observed.

Fasting nonesterified fatty acid (NEFA) levels[21] were determined in six patients before and during therapy. The mean fasting levels in the control and in the diabetic patients were 573 mEq./L. before therapy and 625 and 677 mEq./L. respectively during therapy.

The mean values for blood glucose during two-hour glucose tolerance tests performed before and during therapy are shown in figure 1. It is apparent that there is no difference in the response to glucose loading among the three nondiabetic patients before or during thiazide therapy. There is a striking difference, however, among the patients with diabetes mellitus. Increase in hyperglycemia occurred throughout the entire test and was most marked ninety and 120 minutes after the glucose load was administered. The differences at these two times are statistically significant at the 0.05 and 0.01 level respectively.

The mean values for serum insulin-like activity obtained during the glucose tolerance tests are presented in figure 2. Insulin-like activity among the diabetics was unchanged during thiazide therapy. However, there is some blunting of the peak response among the nondiabetic controls. Because of the small number of patients, this minimal change should be interpreted with caution.

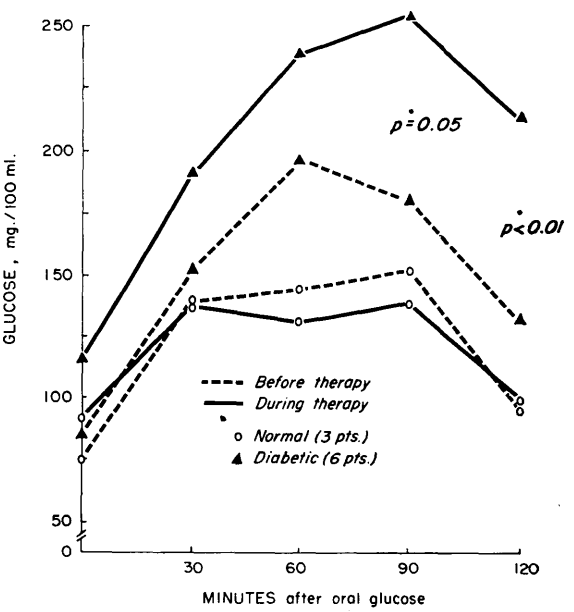

FIG. 1. Glucose tolerance tests: Mean values in patients before and during thiazide therapy.

The response of the three controls and six diabetic patients to crystalline beef insulin is shown in figure 3. The blunted response seen initially in the diabetics is

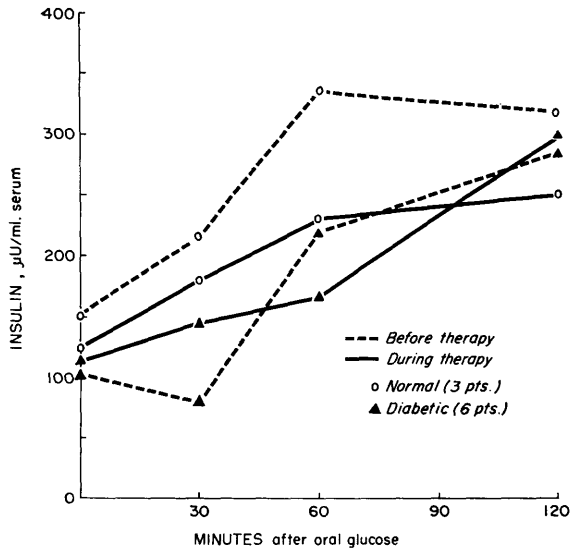

FIG. 2. Serum insulin-like activity: Mean values in patients before and during thiazide therapy.

not altered during the administration of thiazides. There is no significant difference in the response of the control patients to beef insulin before or during thiazide administration.

The diabetic patients had the expected abnormal response to oral tolbutamide during both phases of the study (figure 4). The controls on the other hand responded normally on both occasions.

In three additional patients with diabetes mellitus, free and bound serum insulin activity were determined[15,16] during the course of a glucose tolerance test. These studies were performed before and on the fifth day of hydrochlorothiazide therapy (table 3). No significant changes in either free or bound insulin were noted.

DISCUSSION

In five of the six diabetic patients the hyperglycemic effect of a glucose load was increased during the administration of hydrochlorothiazide. In no case was the increased hyperglycemia associated with symptoms of uncontrolled diabetes, however. Thus many patients who may exhibit only this biochemical abnormality may be overlooked in clinical practice.

In the present study the possible mechanisms considered by which thiazides may alter carbohydrate metabolism included: (a) direct or indirect toxic effect on the islet cells of the pancreas; (b) decreased sensitivity to insulin; (c) decreased secretion of insulin; (d) increased binding of insulin; or (e) a secondary effect resulting from other biochemical alterations that frequently accompany thiazide treatment,

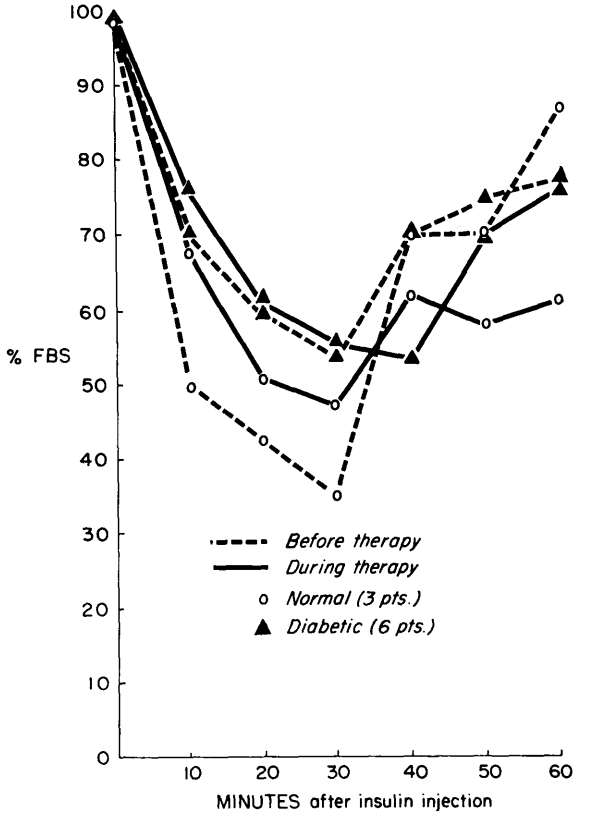

FIG. 3. Insulin tolerance tests: Mean values in patients before and during thiazide therapy.

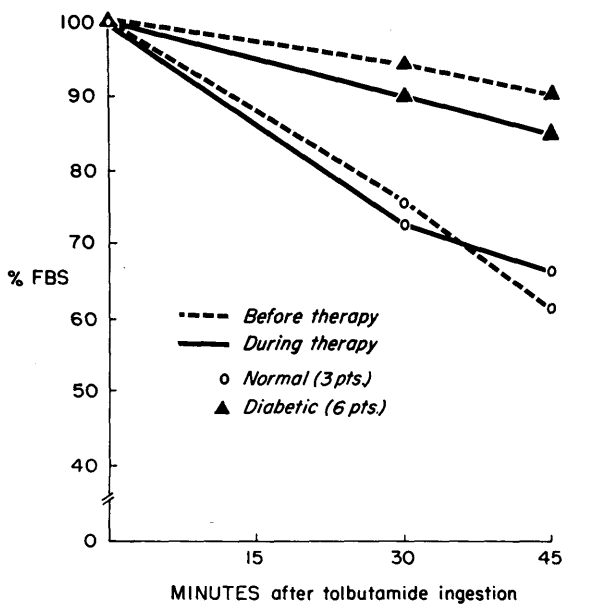

FIG. 4. Oral tolbutamide tests: Mean values in patients before and during thiazide therapy.

TABLE 3

Free and bound serum insulin-like activity*

Serum ILA (μU./ml.)	Fasting		Half hour		One hour		Two hours	
	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
Free	316	336	378	408	456	505	509	665
Bound	64	94	59	59	51	63	63	88
Blood glucose (mg./100 ml.)	74	80	160	162	169	187	143	175

*Mean values during GTT for three patients.

i.e., hyperuricemia, hypokalemia, etc.

A. *Direct or indirect toxic effect*

Several cases of acute pancreatitis have been reported in patients receiving thiazides.[22] Cornish et al. demonstrated a small increase in serum amylase in ten of twenty patients during therapy with chlorothiazide.[23] None of these values exceeded 230 Somogyi units, and in no instance was there evidence of pancreatitis. In the nine patients of the present study, even this mild elevation in serum amylase was not observed (table 1).

Cornish[23] also found that 7 per cent of 300 rats treated with chlorothiazide developed diffuse inflammatory lesions in the pancreas. No abnormalities were observed in any of the islet cells; however, Shanklin reported a case of pancreatic fibrosis associated with thiazide therapy but without pathologic changes in the beta cells.[24] Accordingly, there is some evidence to suggest that thiazides may have a toxic effect on pancreatic acinar tissue but none to suggest that there is adverse effect on islet cells.

B. *Decreased sensitivity to insulin*

The response to crystalline beef insulin was examined in both diabetic and control patients. The diabetic patients responded similarly both before and during thiazide therapy (figure 3). The control patients had a normal response on both occasions.

Although the response to exogenous insulin appears to be unaltered during hydrochlorothiazide therapy, the presence of peripheral antagonists cannot be definitely ruled out. Increased concentration of adrenocorticosteroids could interefere with the action of insulin. No difference in the urinary excretion of either 17-hydroxycorticoids or 17-ketosteroids was observed during hydrochlorothiazide therapy (table 1). This observation is in agreement with that of Shapiro et al.[2]

Randle et al.[25] have recently suggested that the insensitivity to insulin exhibited by some diabetics is due to the release of increased amounts of fatty acids and the increased levels of nonesterified fatty acids (NEFA) in the serum. Nonesterified fatty acid levels were determined in six of our patients. There was no significant difference in the serum values obtained before and during thiazide therapy.

C. *Decreased secretion of insulin*

Samaan et al. described four patients who developed diabetes during the administration of diazoxide. In all of the patients there was decreased insulin-like activity levels during hyperglycemia, and this activity gradually returned towards normal after the discontinuation of the drug and return of normoglycemia.[26] In the present study no effects of thiazide on serum insulin-like activity were seen (figure 2).

The nondiabetic patients responded normally to the oral tolbutamide test during thiazide therapy (figure 4). This response suggests that there has been no depletion of insulin reserve during therapy.

D. *Increased binding of insulin*

Antoniades et al. have demonstrated that serum insulin is present in both the free (active) and bound (inactive) form.[27] It is possible that the thiazides may increase the amounts of bound insulin and thus reduce the amount of free (active) insulin, although the total serum insulin remains unchanged. There was no significant change, however, in the concentration of complexed insulin in the three diabetic patients studied (table 3).

E. *Secondary to other biochemical alterations*

Hyperuricemia occurs in many patients receiving thiazides, and there appears to be an increased prevalence of hyperglycemia in patients with hyperuricemia.[28,29] It has been postulated that uric acid, which is structurally similar to alloxan, may have an alloxan-like effect on the beta cells and that the diabetogenic effect of both uric acid and alloxan can be enhanced by lowering the whole blood concentration of reduced glutathione.[30-35]

With this in mind blood was analyzed for reduced glutathione content on four diabetic and three nondiabetic patients before and during thiazide therapy. The results of these determinations are presented in table 2. In six of these seven patients there is a slight but consistent fall in reduced glutathione during thia-

zide therapy. Glutathione changes occurred in both the normals and diabetics, however the uric acid increase occurred only in one of the three normals, and his glucose tolerance test during therapy became more abnormal than before therapy in that the two-hour blood sugar value rose from 117 to 130 mg. per 100 ml. The number of patients studied and the short duration of therapy preclude concluding a definite cause and effect, but this relationship warrants further exploration.

Reduction in serum potassium frequently accompanies thiazide administration. However, no consistent change in serum potassium concentration and carbohydrate tolerance has been observed in other studies[1,2] and did not occur in the patients we evaluated.

That thiazides may induce carbohydrate intolerance in many patients is well established. The exact mechanism remains in doubt and may be multifactorial.

ACKNOWLEDGMENT

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