Plasma Renin Activity in Juvenile Diabetes Mellitus and Effect of Diazoxide

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SUMMARY

Low plasma renin activity (PRA) has been reported in patients with long-term diabetes mellitus complicated by hypertension and nephropathy.[4] We have assayed PRA in twelve normal subjects and in eight age- and sex-matched juvenile diabetics of greater than twelve years' duration without hypertension and nephropathy under control conditions and following stimulation with diazoxide. During control conditions PRA did not decrease with time in the diabetics as it did in the normals. Following diazoxide infusion, PRA increased in both groups, and although the levels were often higher in diabetics than in normals, the mean differences were not statistically significant. The findings are consistent with the suggestion that PRA is normal or possibly elevated in clinically uncomplicated insulin-dependent diabetes mellitus and decreases with establishment of hypertension and nephropathy. DIABETES *24*:833-35, **September, 1975.**

Hypertension is commonly associated with diabetes mellitus.[1,2] The onset usually parallels the appearance of proteinuria. About 20 per cent of diabetics of twenty years' duration are hypertensive at a time when proteinuria is often manifest, and the incidence of hypertension along with proteinuria increases to 50 per cent in those surviving thirty-five years after the onset of diabetes.[3] Although the role of the renin-angiotensin system has been examined extensively in hypertension, only a few investigators have studied its role in the hypertension of diabetics. Recently, Christlieb[4] suggested that there is a suppression of plasma renin activity (PRA) in patients with long-term diabetes mellitus who have evidence of renal disease and hypertension, as well as in alloxan-diabetic rats. In the present study we measured PRA and its stimulation after diazoxide[5] in a small group of juvenile diabetic subjects without clinically evident renal disease, vascular complications, or hypertension. The aim was to determine the status of renin activity prior to clinical appearance of hypertension but probably during the pathogenetic process. The findings indicate that PRA is normal or possibly elevated in uncomplicated long-standing diabetes mellitus.

MATERIALS AND METHODS

Twelve normal subjects (six males and six females) in the age range of twenty-one to thirty years (mean twenty-five years) and eight juvenile diabetic patients (five females and three males) in the age range of twenty-one to thirty-five years (mean twenty-six years) were studied. CBC, urinalysis, SMA-12, serum sodium, potassium, creatinine, ECG, and x-ray of the chest were normal in both groups. The patients and the normal subjects were normotensive (BP range 100-130 systolic, 65-85 mm. mercury diastolic). Mean BP for control subjects and diabetic patients was 110/68 and 110/74, respectively. Normal subjects were on weight-maintaining diets and diabetics were consuming an "unmeasured diet."[6] Both groups were on an ad libitum sodium intake. None of the diabetics had clinical evidence of macroangiopathy. Mean duration of diabetes was 18.5 years (range twelve to thirty years); all patients required insulin for control. After an overnight fast, patients and normal subjects rested supine for at least two hours, during which several

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control readings of pulse and blood pressure were obtained. Diazoxide, 5 mg. per kilogram, was injected rapidly intravenously as a solution containing 15 mg. per milliliter, and blood samples were obtained at 0 (basal), 90, and 180 minutes for measurement of PRA utilizing a radioimmunoassay of angiotensin I,[7] plasma cortisol,[8] and plasma glucose.[9] A control test was performed with a similar 20-ml. volume of normal saline on another day. The subjects remained supine throughout both procedures. Insulin administration was delayed until after the test procedure was completed in diabetic subjects. Administration of normal saline or diazoxide was randomized without knowledge of the patients. Informed consent was obtained from all subjects. Student's *t* test for paired or unpaired data was used to define the significance of the difference between means within a group or between the two groups respectively.

RESULTS

PRA, figure 1. During the control infusion, PRA decreased significantly at 90 and 180 minutes in the control subjects but not in the diabetics. Following diazoxide infusion, PRA increased significantly in both groups. Although the mean levels of PRA were higher in diabetics than in the normals under control conditions and following diazoxide infusions, differences did not achieve statistical significance at any point.

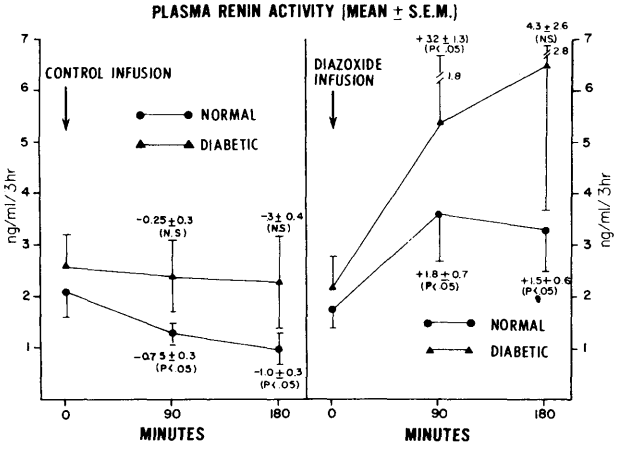

FIG. 1 PRA obtained after control and diazoxide infusions. The arrows indicate the time of injection, and the figures indicate mean change of PRA from the baseline.

Cortisol, figure 2. There were no consistent significant differences in cortisol levels between the two groups. However, the mean values were higher in the diabetics, and on the control day at basal time the

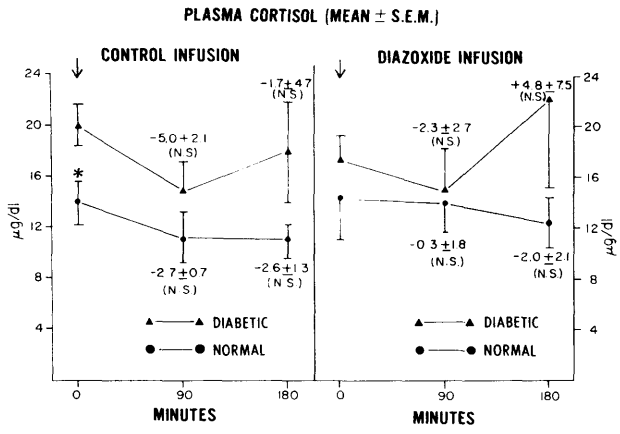

FIG. 2. Plasma cortisol levels obtained after control and diazoxide infusions. The arrows indicate the time of injection, and the figures indicate mean change from baseline levels. Asterisks indicate significant differences ($P < 0.05$) between the two groups.

mean difference was statistically significant ($P < 0.05$).

Glucose, figure 3. As expected, plasma glucose concentration was higher among diabetics at all intervals in the control experiment as well as in response to diazoxide. After diazoxide, mean plasma glucose ± S.E. increased significantly ($P < 0.01$) in the normals from 82.2 ± 2.7 to 96.6 ± 2.6 at 90 minutes and to 94.5 ± 2.6 at 180 minutes, whereas there were no significant changes among the diabetics, the levels

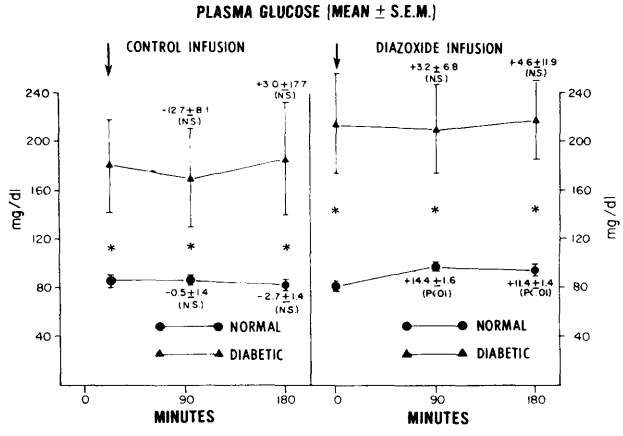

FIG. 3. Plasma glucose levels obtained after control and diazoxide infusion. The arrows indicate the time of injection, and the figures indicate mean change from baseline levels. Asterisks indicate significant differences between the two groups. ($P < 0.05$)

being 214 ± 37.9 at 0 minute, 210.7 ± 35.8 at 90 minutes, and 218.6 ± 30.6 at 180 minutes.

DISCUSSION

The present study revealed that PRA levels were

not significantly different between the normal and diabetic groups before and after diazoxide stimulation. There was a suggestion, however, that levels may be slightly higher in patients with diabetes of the type studied, since the mean levels were greater than normal. Furthermore, in the control study PRA declined significantly from 9 a.m. to 12 noon in the normal group, consistent with a normal diurnal variation,[10] but did not change in the diabetics. The finding of normal to questionably high PRA in diabetics is at variance with the reports of Christlieb[4] and Roginsky et al.,[11] who reported low PRA in diabetes mellitus. The studies, however, were not comparable. Both Christlieb[4] and Roginsky[11] investigated patients with coexisting hypertension and renal disease, whereas patients with these complications were excluded from our study. Thus, it is likely, as mentioned by Christlieb, that PRA remains normal or is even elevated during the development of diabetic vascular complications and then decreases in the advanced stages as the hypertension and nephropathy are clinically established.[4]

It was believed important in this study to measure circulating cortisol concentration after endogenous stimulation of angiotensin for two reasons: First, exogenous infusion of angiotensin II has been reported to suppress cortisol production,[12] though physiologic amounts had no effect in the dog, sheep, or man.[13] Second, the level of cortisol may serve as an index of stress. In regard to these points, the rise in PRA after diazoxide was not associated with a decrease in plasma cortisol concentration in either study group, indicating that small fluctuations of endogenous angiotensin do not affect cortisol secretion. It was of interest that the plasma cortisol levels were significantly higher in the diabetics than in the normals at one point, suggestive of a greater stress response in the former. Prior measurements of plasma cortisol in nonacidotic, nonhypoglycemic diabetics have not produced consistent results,[14-16] which also suggests that stress may be a variable influence.

Finally, the fact that diazoxide administration resulted in an elevation of circulating glucose concentration in the normals but not in the presumably insulinopenic diabetics is consistent with the observation that the drug produces this effect by inhibition of insulin secretion.[17]

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