

Aldosterone Responsiveness in Patients with Diabetes Mellitus

A. Richard Christlieb, M.D., Antoine Kaldany, M.D.,
John A. D'Elia, M.D., and Gordon H. Williams, M.D., Boston

SUMMARY

Plasma aldosterone (PA) and plasma renin activity (PRA) were determined in 44 diabetics, of whom nine were normotensive but not nephropathic (group 1), 10 were hypertensive but not nephropathic (group 2), and 25 were hypertensive and nephropathic (group 3); they were kept in balance on a diet composed of 10 to 20 mEq. of sodium (Na) and 100 mEq. of potassium (K). Supine PA in group 1 was 38 ± 7 ng. per deciliter, whereas in normals it was 24 ± 2 ng. per deciliter ($P < 0.05$); beyond that, neither supine nor upright PA or PRA differed significantly from normal in groups 1 and 2. By contrast, in group 3, supine PA was 13 ± 1 ng. per deciliter and PRA 2.0 ± 0.2 ng./ml. and upright PA was 39 ± 7 ng. per deciliter and PRA 3.8 ± 0.5 ng./ml., all significantly lower than those in the other groups ($P < 0.01$). Nine patients, one in group 1 and eight in group 3, had low supine and upright PA and PRA; four had hyperkalemia. An additional nine patients in group 3 had low upright PA, with normal or low PRA; two had hyperkalemia. Of the 18 patients with low upright PA, K correlated with glucose ($R = 0.46$, $P < 0.05$). These results suggest (1) the renin-aldosterone system generally responds normally in diabetics without nephropathy but responds subnormally when nephropathy is present, (2) hyporeninemic hypoaldosteronism is frequent in diabetics with nephropathy but may occur in the absence of clinical nephropathy, and (3) hyperkalemia in some diabetic patients may be secondary to hypoaldosteronemia and hyperglycemia. *DIABETES* 27:732-37, July, 1978.

Alterations in the renin-angiotensin-aldosterone system in diabetic patients have been documented. Both plasma renin activity (PRA) and plasma aldosterone (PA) are elevated significantly in diabetic ketoacidosis, in which plasma volume is severely de-

From the Joslin Clinic and Elliott P. Joslin Research Laboratory Divisions of the Joslin Diabetes Foundation, the Departments of Medicine, New England Deaconess and Peter Bent Brigham Hospitals, and Harvard Medical School, Boston, Massachusetts.

Address reprint requests to Dr. Christlieb at the Joslin Clinic, One Joslin Place, Boston, Massachusetts 02215.

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pleted.¹ Decreased or poorly stimulated PRA has been observed in diabetic patients with nephropathy and hypertension,² orthostatic hypotension,³ and peripheral neuropathy.⁴ When studied, aldosterone was also decreased in patients with these complications.⁴ Further, about 25 per cent of the reported patients with hypoaldosteronism also have diabetes mellitus.⁵ In the majority of these patients, PRA is low. In two diabetic patients, defective biosynthesis of aldosterone and, possibly, of renin has been observed.⁵ However, most studies have examined only patients with significant complications of their diabetes.

It is the purpose of this report to define aldosterone responsiveness in relation to PRA in diabetic subjects with and without hypertension and nephropathy and to assess the relationships among aldosterone, blood glucose, and serum potassium.

Experimental subjects. Forty-four diabetic subjects were studied while hospitalized at the New England Deaconess Hospital. Table 1 is an outline of the clinical characteristics of these patients. Nine of them had no hypertension and no clinical evidence of nephropathy (group 1), 10 had hypertension but not nephropathy (group 2), and 25 had both hypertension and nephropathy, defined as proteinuria with excretion of 2 gm. or more daily (group 3). Twenty-four of these 25 patients with nephropathy had evidence of retinopathy with microaneurysms and/or neovascularization. With the exception of two patients in group 2 (one treated with diet plus acetohexamide and one with diet alone), all were receiving insulin. Appropriate studies, including 17-hydroxycorticosteroids, metanephrines, intravenous pyelography, and renal vein renin activities, were performed to rule out surgically treatable causes for the hypertension when indicated clinically.

TABLE 1
Clinical characteristics

	Normotension		Hypertension	
	No nephropathy (group 1)	P	No nephropathy (group 2)	Nephropathy (group 3)
Sex	6 M, 3 F		7 M, 3 F	18 M, 7 F
Age (yr.)	47 ± 4		39 ± 4	37 ± 2
Duration of diabetes (yr.)	25 ± 2	<0.005	13 ± 2	19 ± 1
Retinopathy (no. patients)	5		4	24
Neuropathy (no. patients)	5		3	9
Blood pressure (mm. Hg)				
Systolic	123 ± 5	<0.001	161 ± 6	172 ± 4
Diastolic	73 ± 3	<0.001	97 ± 2	102 ± 2
Mean	90 ± 3	<0.001	118 ± 3	126 ± 2
Proteinuria (gm./day)	0		0	5.7 ± 0.7
Creatinine (mg.%)	1.0 ± 0.1		1.1 ± 0.1	3.7 ± 0.5
BUN (mg.%)	22 ± 1		18 ± 1	49 ± 5
Hematocrit (%)	45 ± 2		43 ± 1	36 ± 1
Cholesterol (mg.%)	193 ± 12		215 ± 12	234 ± 14
Serum albumin (mg.%)	4.6 ± 0.1	<0.02	4.1 ± 0.1	3.5 ± 0.1

MATERIALS AND METHODS

Informed consent for these studies was obtained from normotensive subjects. The following studies were performed on hypertensive patients as part of their evaluation. Antihypertensive medications were discontinued on the day before the protocol began. In seven patients (all in group 3), pre-existing diuretic therapy was continued. The patients were maintained on a diet consisting of 10 to 20 mEq. of sodium (Na) and 100 mEq. of potassium (K) daily for four days. On the second day of this diet, each received furosemide, 40 mg. orally, in the morning and at noon. On the fourth day, serum electrolytes were determined and a 24-hour urine collection was made for analysis of Na, K, creatinine, and protein. Plasma (EDTA) was obtained at 8 a.m., after the patient had remained supine overnight, and again at noon, after the patient had been upright for four hours, for analysis of plasma renin activity,¹ plasma aldosterone,⁶ and plasma cortisol.⁶ The results of the plasma renin activity test in these patients have been reported previously.²

Mean blood pressure was defined as diastolic plus 1/3 (systolic minus diastolic) blood pressure. Because

TABLE 2
Urinary electrolytes

Group	24-Hour urinary	
	Na (mEq./day)	K (mEq./day)
Group 1	21 ± 4	54 ± 8
Group 2	23 ± 4	53 ± 5
Group 3	21 ± 3	47 ± 7

each of two experimental groups were compared only with the control group, statistical comparison between mean values was made by student's *t*-test. Relationships between variables were analyzed by Pearson's correlation method.⁷

RESULTS

Mean daily urinary Na and K excretion on the study day did not differ significantly among the groups (table 2). Because of edema, diuretic therapy (furosemide, 40 to 120 mg. daily) was continued throughout the study in seven patients of group 3 (numbers 19-25 in table 3). Mean Na excretion was 80 ± 13 mEq. and mean K excretion 78 ± 7 mEq. daily in these patients. Therefore their results are not included in table 2. Because the renin-aldosterone system should be stimulated by this diuretic therapy, these patients are included in the other analyses of data.

Group mean plasma cortisol values were normal, consistent with intact function of the pituitary-adrenal axis (table 3).

Individual and group supine and upright PRA and PA are given in table 3. In normal subjects who were in balance on a diet containing 10 mEq. Na and 100 mEq. K, supine PRA was 4.7 ± 4.1 ng./ml. (\bar{x} ± S.E.M.) (16 subjects, mean age 33 ± 3 years, eight males and eight females), upright PRA was 13.3 ± 2.3 ng./ml. (10 subjects, mean age 39 ± 3 years, four males and six females), supine PA was 24 ± 2 ng. per deciliter (range 10 to 40), and upright PA 74 ± 7 (range 45 to 130) (40 subjects, mean age 41 ± 4

TABLE 3

Serum electrolytes, PRA, plasma aldosterone, and plasma cortisol in individual patients

Group	Subject	Serum creatinine (mg./dl.)	Na (mEq./L.)	Serum		PRA (ng./ml.)		Plasma aldosterone (ng./dl.)		Plasma cortisol (μ g./dl.)	
				K (mEq./L.)	glucose (mg./dl.)	Supine	Upright	Supine	Upright	8 a.m.	Noon
Group 1	1	1.6	139	4.1	164	6.3	11.1	50.8	81.7	16.4	15.1
	2	1.0	136	4.2	109	4.6	18.7	22.2	57.6	12.6	16.0
	3	0.9	136	4.2	257	2.9	7.5	33.3	68.7	21.4	19.8
	4	—	140	4.1	71	12.5	22.0	34.3	50.2	22.9	16.8
	5	1.0	139	4.2	254	2.5	11.4	—	49.7	21.5	—
	6	1.1	134	5.3	218	12.3	21.7	50.2	79.3	20.6	13.8
	7	0.9	134	4.6	196	3.6	13.1	75.3	109.9	17.5	13.1
	8	1.1	136	5.3	313	1.9	2.1	4.6	12.7	2.7	3.0
	9	0.8	140	4.7	234	5.9	8.0	36.7	169.9	11.7	—
	Mean	1.0	137	4.5	202	5.8	12.8	38.4	75.5	16.4	13.9
S.E.M.	± 0.1	± 1	± 0.2	± 25	± 1.3	± 2.2	± 7.4	± 14.8	± 2.2	± 2.0	
Group 2	1	1.1	141	4.0	266	4.7	7.0	17.1	45.4	8.3	—
	2	0.9	136	4.5	191	5.4	7.6	39.1	47.3	23.4	14.3
	3	1.0	139	4.2	89	10.8	17.5	32.2	41.9	20.8	9.3
	4	1.0	142	4.8	175	5.8	7.1	15.3	55.8	21.9	12.0
	5	0.9	141	4.3	202	4.3	6.2	28.6	62.2	21.1	13.9
	6	0.9	146	4.0	175	0	1.6	11.0	41.1	40.1	29.1
	7	0.9	139	3.4	140	1.6	5.0	21.8	56.5	22.3	17.6
	8	1.3	136	4.8	177	5.9	9.6	12.2	92.2	17.8	15.1
	9	1.7	141	3.6	112	5.3	9.8	17.7	43.0	16.0	11.5
	10	1.2	138	3.9	122	6.2	14.9	30.4	170.0	15.3	11.1
Mean	1.1	140	4.2	165	5.0	8.6	22.5	65.5	20.7	14.9	
S.E.M.	± 0.1	± 1	± 0.1	± 16	± 0.9	± 1.5	± 3.0	± 12.6	± 2.6	± 2.0	
Group 3	1	2.1	139	4.2	158	1.5	2.8	20.6	75.6	15.1	13.2
	2	10.1	130	4.7	322	0.9	1.6	11.8	18.6	14.7	10.8
	3	2.0	138	5.2	280	1.4	2.2	3.8	23.2	10.5	5.0
	4	0.8	138	4.5	126	1.2	6.2	16.0	20.4	—	10.7
	5	1.0	139	4.5	228	2.0	4.6	22.6	59.3	20.0	17.6
	6	1.0	136	4.9	136	1.0	2.2	8.6	12.4	16.9	15.4
	7	4.5	132	5.0	174	3.5	4.4	10.4	140.6	21.8	7.9
	8	2.1	141	4.1	85	3.2	4.4	12.1	32.1	17.9	7.7
	9	1.4	134	6.0	81	1.6	0.8	4.7	3.8	—	8.6
	10	1.9	137	4.9	472	0.1	1.5	5.8	10.4	16.4	14.3
	11	1.7	139	4.9	230	3.4	3.9	20.6	40.3	19.5	7.8
	12	2.8	134	4.2	101	2.0	6.2	13.0	31.0	13.5	7.3
	13	7.9	137	5.6	298	2.2	1.6	34.7	32.2	13.3	13.0
	14	1.3	139	3.9	98	—	6.5	11.3	28.3	—	15.3
	15	2.0	141	4.6	210	3.0	3.8	14.5	51.2	18.4	14.3
	16	5.1	138	5.1	211	1.2	1.3	14.1	13.1	11.9	10.8
	17	8.3	139	5.0	155	2.0	2.8	15.9	51.0	8.0	4.3
	18	6.7	143	4.1	64	2.6	4.2	6.4	30.6	17.1	16.2
	19*	1.5	135	4.9	278	0.5	0.8	9.1	29.0	21.4	20.6
	20*	4.1	140	4.3	107	2.9	8.2	10.7	36.2	10.1	6.5
	21*	1.9	133	4.9	96	2.8	5.8	8.4	62.5	14.5	13.6
	22*	2.0	138	3.7	300	3.5	7.3	15.9	71.9	24.0	19.9
	23*	1.5	134	4.6	114	3.0	8.6	14.7	62.2	22.9	10.7
	24*	7.9	136	5.6	277	0	0.8	8.1	26.3	11.2	8.5
	25*	5.4	140	4.6	131	1.6	1.8	3.9	6.3	10.1	3.1
Mean	3.5	137	4.7	189	2.0	3.8	12.7	38.7	15.9	11.3	
S.E.M.	± 0.5	± 1	± 0.1	± 20	± 0.2	± 0.5	± 1.4	± 5.9	± 1.0	± 0.9	

*Diuretic therapy maintained throughout study.

years, 24 males and 16 females). Mean values in diabetics without hypertension or nephropathy did not differ significantly from those of the normal subjects with the exception of the supine PA, which was elevated at 38 ng. per deciliter ($P < 0.05$).

Comparing group 2 with group 1 diabetics, mean supine and upright PRA and PA were decreased, but only the supine PA met statistical significance ($P < 0.05$).

When compared with group 1 diabetics, those in

group 3 (those with hypertension and nephropathy) had significantly lower supine PRA and PA ($P < 0.001$), upright PRA ($P < 0.001$), and upright PA ($P < 0.01$). In this group, upright PRA correlated with upright PA ($r = 0.41$, $P < 0.05$). No significant correlation was observed between supine PRA and PA, between serum K and supine or upright PA, or between serum creatinine and supine or upright PRA or PA.

In each group, upright posture was associated with a parallel increase in PRA and PA. To evaluate indirectly the relative responsiveness of the adrenal cortex to angiotensin II⁸ among the groups, the increment in PA from supine to upright posture was divided by the postural increment in PRA. Mean ratios were 16.1 ± 8.1 in group 1, 13.9 ± 2.9 in group 2, and 26.4 ± 7 in group 3 ($P = \text{N.S.}$)

Nine patients had low PA in both the supine and upright positions. In patient 8 (group 1), low PA was associated with a low PRA and an elevated serum K of 5.3 mEq. per liter. Subsequently, serum K ranged between 5.2 and 6.4. Forty-five minutes after adrenocorticotropin (Cortrosyn, 25 U. intravenously), PA increased from a baseline of 8.4 ng. per deciliter to only 10 ng. per deciliter, with plasma cortisol increasing from 3 to 12 μg . per deciliter.

Of the eight patients in group 3 with low supine and upright PA (patients 3, 6, 9, 10, 18, 19, 24, and 25), each had low supine PRA, with blunted responses to upright posture. Only three had serum K above the normal range. Mean serum K for these eight patients was 5.0 ± 0.2 mEq. per liter compared with 4.5 ± 0.2 in seven patients in this group with normal supine and upright PA and 4.6 ± 0.2 in nine patients with normal supine and low upright PA ($P = \text{N.S.}$).

The effect of insulin, assessed indirectly by the level of blood glucose (mean of fasting, 11 a.m., and 3 p.m. determinations on the study day), on serum K was evaluated. In patients with normal aldosterone concentrations in groups 1 and 2, no significant correlation was observed between glucose and K. In group 3, glucose did not correlate significantly with K in patients with both low supine-and-upright PA ($r = 0.15$). When the patients with low supine-and-upright PA were combined with those with low upright PA only, the correlation was significant ($r = 0.46$, $P < 0.05$).

No significant correlations were observed between glucose and either PRA or PA in any group.

DISCUSSION

The major stimulus for aldosterone secretion when volume or dietary Na intake is changed in normal subjects is the renin-angiotensin system.⁹ In the current study, responsiveness of PA to the stimulus of Na restriction and Na restriction with upright posture was determined in three groups of patients with diabetes mellitus. In each group, PRA and PA increased when changing from supine to upright posture, suggesting that, under these conditions, aldosterone release is controlled by the renin-angiotensin system.

Differences in the responsiveness of PRA and PA were observed among the groups. In general, diabetics without nephropathy, whether hypertensive or not, had normal PRA and PA in response to the stimulus of Na depletion and to upright posture. One non-hypertensive patient, however, with no clinical evidence of nephropathy, had low PRA and PA despite the stimuli of Na depletion and upright posture and, later, adrenocorticotropin. This suggests that hyporeninemic hypoaldosteronism can be present in diabetics without diabetic nephropathy.

The diabetics with nephropathy, each of whom was hypertensive, had PRA and PA that were significantly lower in both supine and upright positions than those in either normal subjects or the other diabetic groups. Because angiotensin infusions were not performed, it is impossible to be confident that the low PA is entirely secondary to a primary decrease in renin and angiotensin. Defective aldosterone biosynthesis has been observed in diabetics previously.⁵ The relative increase in PA compared with PRA with assumption of upright posture,⁸ although higher than in the other groups, was not significantly higher statistically. This suggests that the primary control of PA may still be mediated through PRA in these patients.

Eight of these patients had values of both supine and upright PA that were below the normal range. These patients clearly have hyporeninemic hypoaldosteronism, since all had low PRA. Nine other patients had normal supine but low upright PA, with PRA ranging between low and low normal. This group also, by definition, had hypoaldosteronism, which may be hyporeninemic or possibly secondary to defective aldosterone synthesis.

There was no significant difference in mean serum K between patients with and without poorly responsive aldosterone. The combined roles of insulin and aldosterone in regulating serum K have recently been

emphasized.¹⁰ Of the 18 patients reported here with evidence of hypoaldosteronism, only six had hyperkalemia at the time of the study. Were it not for other compensatory mechanisms to regulate serum K, patients with hypoaldosteronism would all be expected to have hyperkalemia. Several studies have indicated that insulin may be needed to assist in the maintenance of potassium homeostasis.¹¹⁻¹³ Further indirect evidence supporting this concept derives from the observation that in the patients with hypoaldosteronism, serum K correlated significantly with the concentration of blood glucose. This emphasizes the importance of good diabetic control in maintaining both normoglycemia and normokalemia in such patients.

The mechanisms responsible for hypertension in the diabetic population remain undefined. It is clear from this report that excessive production of aldosterone is not a cause. In the absence of clinical renal disease, it is probable that much of the hypertension is essential hypertension. In that hypertension is encountered more frequently in diabetic than in nondiabetic subjects, factors associated with the diabetic state may be operative.

In diabetics with clinical renal disease, the onset of hypertension frequently coincides with the onset of proteinuria¹⁴ and is accompanied by low renin and low aldosterone. There is data to suggest that four mechanisms, either individually or collectively, could be responsible for the decreased PRA. First, hyalinization of the afferent arteriole could block renin release from the juxtaglomerular cells to the circulation¹⁵ or juxtaglomerular cells themselves could become hyalinized.¹⁶ Second, there may be decreased catecholamine stimulation of renin release. Decreased circulating levels of catecholamines have been observed in diabetic neuropathy.¹⁷ In one diabetic with neuropathy and orthostatic hypotension with low PRA, however, norepinephrine infusions failed to increase the PRA.³ Third, diabetics with nephropathy have elevated levels of a high molecular weight biologically inactive form of renin, "big renin" or "prorenin."¹⁸ Enzymatic defects may be present in patients with diabetic nephropathy that prevent the synthesis of renin from prorenin. Fourth, decreased free water clearance in patients with compromised renal function and hyperosmolarity secondary to hyperglycemia could result in increased extracellular fluid and blood volume. In alloxan-treated diabetic rats, the blood volume is clearly elevated and associated with decreased PRA.¹⁹ In diabetic patients with hyperglycemia, the blood volume may be ele-

vated compared with that when the same patient is normoglycemic.¹ This hypervolemia, together with increased peripheral vascular resistance secondary to renal arteriolar hyalinization, could explain this hypertension and the associated decrease in PRA and PA.

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