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Sodium, renin, aldosterone, catecholamines, and blood pressure in diabetes mellitus

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Sodium, renin, aldosterone, catecholamines, and blood pressure in diabetes mellitus. Interrelations among plasma renin activity (PRA), aldosterone and cortisol levels, blood volume, exchangeable sodium, urinary catecholamines, and blood pressure were studied in 35 normal subjects and 60 age-matched non-azotemic patients with diabetes mellitus (60% with hypertension, 15% with orthostatic hypotension). Basal PRA, plasma aldosterone, cortisol, blood volume, plasma potassium, and urinary electrolytes were comparable in diabetic and normal subjects. Diabetic patients, however, had a 10% increase in body sodium ($P < 0.01$), and 8% of them showed normal postural PRA responses and subnormal aldosterone responses; 22% had subnormal PRA and normal aldosterone responses, and 17% had subnormal responses of PRA and aldosterone. Non-PRA-related aldosterone responses could not be explained by ACTH or electrolytes. Orthostatic decreases in blood pressure correlated ($P < 0.01$) with both catecholamine excretion and basal PRA. This suggests that in diabetes mellitus, body sodium is increased. Basal PRA and plasma aldosterone are usually normal, but their postural responses are frequently impaired. Absent aldosterone responses, despite normal PRA responsiveness, may reflect an adrenal abnormality or an ineffective form of renin. Marked postural aldosterone stimulation, unrelated to PRA, ACTH, or electrolytes, points to a potent unknown factor in aldosterone control. Low levels of free peripheral catecholamines and PRA may be complementary factors contributing to postural hypotension.

Sodium, rénine, aldostérone, catécholamines et pression artérielle dans le diabète sucré. Les inter-relations entre l'activité rénine plasmatique (PRA), les concentrations d'aldostérone et de cortisol, le volume sanguin, le sodium échangeable, les catécholamines urinaires et la pression artérielle ont été étudiées chez 35 sujets normaux et 60 malades atteints de diabète, sans insuffisance rénale et dont les âges étaient appariés (60% avaient une hypertension et 15% une hypotension orthostatique). La PRA de base, l'aldostérone et le cortisol plasmatiques, le volume sanguin, le potassium plasmatique et les électrolytes urinaires étaient comparables chez les diabétiques et les sujets normaux. Les malades diabétiques, cependant, ont une augmentation de 10% de leur sodium corporel ($P < 0,01$). Huit pour cent d'entre eux ont une réponse posturale de PRA normale et une réponse de l'aldostérone inférieure à la normale, 22% ont une reponse de PRA inférieure à la normale et une reponse de l'aldosterone normale, et 17% ont des réponses de PRA et de l'aldostérone inférieures à la normale. Les réponses de l'aldostérone sans rapport avec PRA ne peuvent pas être expliquées par l'ACTH ou les électrolytes. Les diminutions de la pression artérielle liées à l'orthostatisme sont correlées ($P < 0,01$) à la fois avec l'excrétion de catécholamines et la PRA de base. Ceci suggère qu'au cours du diabète le sodium corporel est augmenté. La PRA et l'aldostérone de base sont souvent normales mais leur réponse posturale est souvent modifiée. L'absence de réponse de l'aldostérone malgré une réponse normale de PRA peut traduire une anomalie surrénale ou une forme de rénine inefficace. Une stimulation posturale importante de l'aldostérone non expliquée par la PRA, l'ACTH ou les électrolytes oriente vers un facteur inconnu mais puissant du contrôle de la sécrétion d'aldostérone. Des concentrations basses de catécholamines libres et une PRA basse peuvent être des facteurs complémentaires qui participent à l'hypotension posturale.

Diabetes mellitus is frequently accompanied by hypertension [1] and may be associated with orthostatic hypotension [2]. Relatively little, however, is known about major blood pressure-regulating factors such as the catecholamines, the renin-angiotensin-aldosterone system, and the body sodium-volume state in patients with diabetes mellitus. Plasma levels of total catecholamines were studied in a group of long-term diabetics with normal or elevated blood pressure and were found to be reduced in patients with neuropathy and normal in those without neuropathy [3]. Regarding renin-aldosterone activity, we previously noted an association between diabetes mellitus and the syndrome of hyporeninemic hypoaldosteronism [4, 5]. Moreover, some recent studies have suggested that plasma renin activity is normal in uncomplicated diabetes mellitus, but may be low in diabetic patients with nephropathy, orthostatic hypotension, or hypertension [1, 6-8].

Theoretically, changes in plasma renin or aldosterone levels occurring in a diabetic patient could be related directly to an aspect of the underlying metabolic disorder; or they could develop as a consequence of associated alterations in the body sodium-volume state [9], the function of the sympathetic system [10], the activity of the pituitary-adrenal axis [11], the blood pressure [12, 13], or renal structural

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changes [5, 6, 14]. Furthermore, disturbances in the balance between the three former factors could lead to abnormalities in blood pressure regulation. Therefore, the present study was undertaken to systematically analyze the interrelations among plasma renin, aldosterone and cortisol levels, blood volume and exchangeable body sodium, urinary catecholamine excretion rates and blood pressure in a large population of patients with clinically stable diabetes mellitus. Possible alterations in these components were delineated by comparing the diabetic patients, all of whom were non-azotemic, with age-matched normal control subjects.

Methods

Sixty patients with diabetes mellitus and 35 age-matched normal volunteers were studied. They were stratified into three age-groups, and diabetic and normal subjects were age-matched. The young groups (25 to 39 yr) included 10 diabetic patients (6 males and 4 females) and 10 normal subjects (6 males and 4 females). The middle-aged groups (40 to 59 yr) consisted of 22 patients (10 males and 12 females) and 11 normal subjects (5 males and 6 females). The elderly groups (60 to 70 yr) comprised 28 diabetic patients (12 males and 16 females) and 14 normal subjects (5 males and 9 females).

The diagnosis of diabetes mellitus was established by standard laboratory methods. All patients were followed regularly in the Diabetes Clinic at the Medical Policlinic, University of Berne, and all were studied, similarly to the control subjects, in the same institution. None of the patients showed clinical or laboratory evidence of congestive heart failure, edema, or renal failure, and their metabolic state was good or fairly well controlled at the time of the study. The control subjects were healthy persons with a blood pressure of $\leq$ 140/90 mm Hg and without signs of heart or kidney disease or other disorders.

Antihypertensive drugs and diuretics were discontinued at least 14 days before the study; the dose of insulin or hypoglycemic drugs, and carbohydrate intake were not altered. Patients were instructed not to add salt to their food, starting at least five days prior to the test.

Following the oral administration of approximately 60 μCi of radioactive sodium (^{24}Na) between 8:00 and 8:30 A.M., a 24-hr urine was collected for the determination of ^{23}Na, ^{24}Na, potassium, creatinine, and catecholamine excretion rates. During the last hour of the 24-hr period, the subjects remained recumbent; at the end of this equilibration period, blood pressure and pulse rate were determined, and venous blood samples were collected from an indwelling cannula for determination of plasma ^{23}Na, ^{24}Na, potassium, and creatinine concentrations, blood glucose level, and plasma renin activity (PRA), aldosterone and cortisol concentrations. Immediately thereafter, plasma volume was determined in the supine position, using a contralateral vein for the injection of 20 μCi of human serum albumin radioactively labeled with iodine-131 (^{131}I-HSA). Subjects then changed from the supine to upright posture, and measurements of blood pressure, pulse rate, and plasma sodium, potassium, PRA and plasma aldosterone and cortisol levels were repeated following one hour of ambulation.

Blood pressure was measured using standard pressure cuff and sphygmomanometer. The pressure at the disappearance of the Korotkoff sounds was considered as the diastolic pressure. Each blood pressure reading was the mean of three recordings. The mean pressure was calculated as the sum of the diastolic and one-third of the pulse pressure.

Plasma and urinary sodium and potassium concentrations were determined by a flame photometer (Instrumentation Laboratory). Exchangeable body sodium and plasma volume were measured by the isotope dilution technique, using ^{24}Na and ^{131}I-HSA, respectively, and blood volume was calculated based on the measurement of ^{131}I activity in whole blood and corrected for large vessel hematocrit; the standardized techniques in this laboratory have been described previously [15, 16]. Exchangeable sodium, and plasma or blood volumes were expressed as mEq/kg of lean body mass (LBM) and ml/kg of LBM, respectively; LBM was estimated using the leanness index (body height^3/weight) of Nicholson and Zilva [17]. PRA and plasma aldosterone concentration were measured by radioimmunoassay [18, 19]; plasma cortisol, by competitive protein binding assay [20]; and urinary catecholamines, by the method of Bertler, Carlsson, and Rosengren [21]. The "volume-renin-product" was obtained by multiplying blood volume computed for LBM with the natural logarithm of PRA (expressed in ng/liter/min) to avoid negative logarithms; the "sodium-renin-product" was derived in a similar way [13, 15]. Blood glucose was determined by the hexokinase method; plasma creatinine levels, by a Greiner Analyzer; and plasma albumin, by the bromocresol green method [22].

An unpaired data *t* test was used for data comparison between patients and control subjects, or between age-groups or other subgroups of patients or controls. A paired data *t* test was applied for data comparison between the supine and upright postures. In our previous studies, absolute plasma renin

and aldosterone levels and urinary catecholamine excretion rates were found to be abnormally distributed, with an approximately normal distribution following logarithmic transformation [13, 15, 16, 23]. Therefore, natural logarithms of these values were utilized for all statistical calculations involving a *t* test or linear regression analysis.

Results

Clinical characteristics of the diabetic study population (Table 1). Considering all diabetic patients together, we found that the mean duration of this disease was 10.2 yr; 50% of the patients were treated with insulin; 60% had hypertension (supine blood pressure, > 140/90 mm Hg; and/or mean pressure, > 107 mm Hg); 15% exhibited persistent (1-hr) orthostatic decreases in blood pressure exceeding 40 mm Hg systolic and 20 mm Hg diastolic, and/or 27 mm Hg mean blood pressure; 42% had retinopathy; 37% showed neuropathy; and 15% had peripheral occlusive arterial disease. Moreover, 28% of the patients had nephropathy, as evidenced by proteinuria and/or a mild reduction in GFR which was measured by the constant infusion clearance technique using ethylene diamine tetraacetate labeled with chromium-51 [24], although plasma creatinine concentrations were normal in all patients studied (≤ 1.3 mg/100 ml). Mean blood glucose concentration, measured approximately one hour after a light breakfast with minimal fluid intake (1 cup), was 207 mg/100 ml. Considering the three age-groups individually, we found that the known duration of diabetes and the prevalence of diabetic retinopathy, neuropathy, and occlusive arterial disease were highest in the young patients, while hypertension was more prevalent in the elderly patients, and orthostatic hypotension and nephropathy were about equally distributed.

Blood pressure and pulse rate (Fig. 1). The mean supine blood pressure and pulse rate were significantly higher in the middle-aged and elderly patients with diabetes than in the age-matched control groups

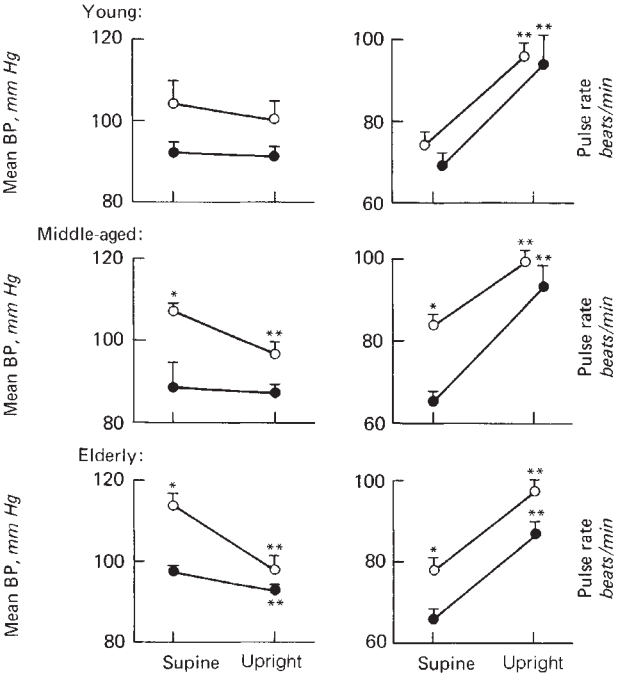

Fig. 1. *Blood pressure and pulse rate in age-matched normal subjects and diabetic patients. One asterisk* (*) depicts a significant difference between diabetic and normal subjects ($P < 0.02$); *two asterisks* (**) indicate a significant orthostatic change ($P < 0.025$). The *closed circles* (•) denote values for normal subjects; the *open circles* (○), diabetic patients. All values represent the mean ± SEM.

Table 1. General characteristics of the diabetic study population[a]

		Age groups		
	All patients (N = 60)	Young (N = 10)	Middle-aged (N = 22)	Elderly (N = 28)
Age, *yr*	54.6 ± 13.1	32.0 ± 4.6[b]	50.8 ± 6.5[b]	65.6 ± 3.0[b]
Duration of diabetes, *yr*	10.2 ± 8.4	14.8 ± 9.7	10.8 ± 9.0	8.1 ± 6.8
Blood glucose, *mg/100 ml*	206.8 ± 98.9	233.4 ± 91.6	218.0 ± 101.3	188.4 ± 99.4
Plasma creatinine, *mg/100 ml*	0.94 ± 0.30	0.94 ± 0.24	0.83 ± 0.20	1.03 ± 0.37
Insulin therapy, %	50	100	55	29
Prevalence of complications, %				
Hypertension[c]	60	50	55	68
Orthostatic hypotension[d]	15	20	9	18
Retinopathy	42	70	50	25
Neuropathy	37	50	41	29
Nephropathy	28	33	32	25
Peripheral occlusive arterial disease	15	30	14	11

[a] All values denote the mean ± SEM.
[b] Values in normal control subjects are: young group, 32.0 ± 4.9 yr; middle-aged group, 48.0 ± 6.6 yr; elderly group, 65.5 ± 3.0 yr.
[c] Supine blood pressure, > 140/90 mm Hg; and/or supine mean blood pressure, > 107 mm Hg.
[d] Blood pressure fall of > 40 mm Hg systolic and > 20 mm Hg diastolic and/or > 27 mm Hg mean, measured after one hour of ambulation.

($P < 0.05$); a similar, although statistically insignificant, tendency was also noted in the young diabetics. When measured following one hour of ambulation, a significant ($P < 0.025$) orthostatic decrease in mean blood pressure was observed in the elderly normal subjects and in the middle-aged and elderly diabetic patients; thus, mean upright blood pressure was still higher in the diabetic patients than in the age-matched control subjects, but this was significant for the middle-aged groups only ($P < 0.05$). Pulse rates showed a postural rise in each study group ($P < 0.025$), and magnitude of this did not differ significantly between the normal and diabetic subjects.

Body fluid-electrolyte status (Table 2). Regardless of their age, the diabetic patients had a lower mean concentration of plasma sodium ($P < 0.005$) and a higher exchangeable body sodium ($P < 0.05$) than normal subjects had. Body sodium was comparable in patients with or without insulin therapy (48.4 ± 3.5 vs. 50.0 ± 5.5 mEq/kg of LBM). Plasma potassium, urinary sodium and potassium excretion, plasma and blood volumes, and hematocrit did not differ significantly between the two populations. Except for a tendency of plasma potassium to increase with aging in the diabetic patients ($P < 0.05$), there were no age-related variations in the fluid-electrolyte status of the patients or normal subjects.

The mean serum albumin concentration was significantly lower in the patients with diabetes than that in the normal subjects (4.19 ± 0.37 vs. 4.35 ± 0.33 g/100 ml; $P < 0.02$).

Plasma renin activity, aldosterone and cortisol levels, and urinary catecholamines. In both diabetic patients and normal subjects, PRA decreased with aging (Table 3). In the diabetic patients, the supine PRA correlated significantly with the urinary noradrenaline excretion rate ($r = 0.28$; $P < 0.05$), but not with any of the other measured parameters; no such correlation was found in normal subjects. Upright PRA did not correlate with other measured parameters.

In the normal subjects, plasma aldosterone levels also tended to be lower in the elderly than in the young age-group; no age-related decrease of plasma aldosterone levels, however, was noted in the diabetic patients (Table 3). Furthermore, except for a significantly lower mean upright plasma aldosterone level in the young diabetic patients, as compared to that in young normal subjects ($P < 0.02$), mean supine and upright PRA or plasma aldosterone levels did not differ significantly between age-matched diabetic patients and normal subjects.

Plasma cortisol levels showed no significant age-dependent variations and were also comparable in the normal subjects and diabetic patients (Table 3). While urinary noradrenaline and total catecholamine excretion rates showed no significant variations with aging in the diabetic patients, adrenaline excretion was significantly lower in the elderly than it was in the young patients ($P < 0.05$). Urinary catecholamines, however, also did not differ significantly between age-matched normal subjects and diabetic patients.

Postural responsiveness of plasma renin and aldosterone. When compared with the normal subjects, the diabetic patients analyzed as one group showed a significant reduction in mean postural PRA responsiveness ($P < 0.005$), while mean increases in plasma aldosterone were not significantly impaired. In 95% of a population of 60 normal subjects [16], the PRA and plasma aldosterone levels obtained in the supine position were increased by at least 40% after one

Table 2. Plasma and urinary sodium and potassium concentrations, exchangeable body sodium concentrations, plasma and blood volumes, and hematocrit in patients with diabetes mellitus and age-matched normal subjects[a]

	Plasma sodium *mEq/liter*	Plasma potassium *mEq/liter*	Urinary sodium *mEq/24 hr*	Urinary potassium *mEq/24 hr* *hr*	Hematocrit %	Exchangeable sodium *mEq/kg LBM*[b]	Plasma volume *ml/kg LBM*[b]	Blood volume *ml/kg LBM*[b]	Leanness index
Normal subjects									
Young ($N = 10$)	141.4 ± 2.2	3.88 ± 0.18	124 ± 62	72 ± 20	43.6 ± 4.0	44.4 ± 4.1	42.5 ± 6.8	74.7 ± 10.8	0.0823 ± 0.0062
Middle-aged ($N = 11$)	140.6 ± 1.3	4.11 ± 0.37	138 ± 46	63 ± 13	43.1 ± 4.4	44.9 ± 4.1	41.6 ± 6.6	73.2 ± 10.7	0.0735 ± 0.0092
Elderly ($N = 14$)	141.8 ± 1.4	4.07 ± 0.34	125 ± 77	58 ± 18	43.0 ± 3.9	44.4 ± 3.4	42.6 ± 5.0	72.9 ± 9.6	0.0706 ± 0.0122
Diabetes patients									
Young ($N = 10$)	137.3 ± 2.5[c]	3.70 ± 0.36	140 ± 37	62 ± 15	43.0 ± 3.9	48.4 ± 3.3[d]	40.6 ± 5.8	67.7 ± 8.2	0.0791 ± 0.0151
Middle-aged ($N = 22$)	136.8 ± 2.6[c]	4.04 ± 0.34[e]	160 ± 79	80 ± 32	42.3 ± 4.8	48.0 ± 4.1[d]	39.0 ± 9.5	71.3 ± 13.0	0.0604 ± 0.0124
Elderly ($N = 28$)	138.1 ± 3.0[c]	4.08 ± 0.32[e]	149 ± 60	68 ± 21	42.5 ± 3.9	49.5 ± 5.4[c]	43.2 ± 6.0	77.4 ± 7.4[e]	0.0620 ± 0.0100

[a] All values denote the mean ± SD.
[b] LBM = lean body mass.
[c] $P < 0.005$ vs. age-matched normal subjects.
[d] $P < 0.05$ vs. age-matched normal subjects.
[e] $P < 0.05$ vs. young diabetic patients.

Table 3. Plasma renin activity (PRA), aldosterone and cortisol levels, and urinary catecholamines in normal subjects and in patients with diabetes mellitus, stratified by age[a]

	PRA *ng/ml/hr*		Aldosterone *ng/100 ml*		Cortisol *μg/100 ml*		Catecholamines *μg/g of creatinine*		
	Supine position	Upright position	Supine position	Upright position	Supine position	Upright position	Adrenaline	Noradrenaline	Total catecholamines
Young									
Normal (N = 10)	2.20 ± 1.36	6.29 ± 5.28	7.2 ± 5.5	27.1 ± 16.5	12.1 ± 4.4	10.9 ± 3.6	4.1 ± 2.4	29.2 ± 16.6	33.3 ± 16.2
Diabetes (N = 10)	2.55 ± 1.66	4.11 ± 1.62	6.7 ± 4.0	11.9 ± 11.5[b]	11.0 ± 4.6	10.8 ± 7.2	4.6 ± 3.6	23.2 ± 15.3	28.1 ± 17.5
Middle-aged									
Normal (N = 11)	1.52 ± 0.80	3.69 ± 2.16	4.5 ± 1.5	13.3 ± 5.9	11.9 ± 4.9	10.0 ± 5.2	4.6 ± 6.1	30.0 ± 15.2	34.5 ± 16.1
Diabetes (N = 22)	1.89 ± 1.24	3.64 ± 2.62	4.5 ± 2.3	16.1 ± 9.0	9.7 ± 3.8	10.3 ± 4.2	2.8 ± 3.3	30.1 ± 17.2	32.9 ± 17.1
Elderly									
Normal (N = 14)	1.00 ± 0.47	2.66 ± 1.85[c]	4.4 ± 1.2	14.7 ± 4.5[c]	8.8 ± 3.9	13.5 ± 7.4	2.4 ± 3.1	31.1 ± 13.3	33.6 ± 15.7
Diabetes (N = 28)	1.30 ± 0.91[c,d]	2.22 ± 1.79[c,d]	5.3 ± 3.6	12.7 ± 9.5	11.0 ± 5.3	9.1 ± 3.2	2.0 ± 3.1[c]	27.5 ± 18.1	29.5 ± 18.7

[a] Values represent the mean ± SD.
[b] $P < 0.02$ vs. age-matched normal subjects.
[c] $P < 0.05$ vs. young subjects or patients.
[d] $P < 0.05$ vs. middle-aged diabetes patients.

hour of ambulation. Using this increase as the normal postural responsiveness, we have found that the patients with diabetes mellitus show four different response patterns (Fig. 2). Of the 59 patients in whom the effects of posture were studied, 31 patients (53%) exhibited normal renin and aldosterone responses; in this group of patients, PRA increased 144 ± (SEM) 16%, and the plasma aldosterone level rose 319 ± 45%, as compared to 165 ± 20% and 273 ± 34%, respectively, in normal subjects. Five (8%) of the diabetic patients showed a normal PRA response and a subnormal aldosterone response (93 ± 34% and −3 ± 13%, respectively). Thirteen patients (22%) had a subnormal PRA response and a normal aldosterone response (16 ± 3 and 298 ± 82%). Finally, 10 patients (17%) had subnormal postural responses of both PRA and plasma aldosterone levels (7 ± 7 and 5 ± 7%).

Both patient-subgroups with a normal postural aldosterone response showed a significant orthostatic fall in blood pressure (Fig. 2). In contrast, no significant orthostatic variations in blood pressure were noted in the two patient-subgroups with a blunted aldosterone response or in the normal subjects. Postural changes in mean plasma cortisol were insignificant in both normal subjects and patient-subgroups.

When comparing other clinical or laboratory features among diabetic renin-responders or aldosterone-responders and non-responders (Table 4), no significant differences were apparent regarding the age of the patients, the prevalence of hypertension, orthostatic hypotension, retinopathy, neuropathy or nephropathy, the use of insulin or oral antidiabetic agents, blood glucose concentrations, or exchangeable sodium, blood volume, plasma or urinary electrolytes, or catecholamine excretion rates.

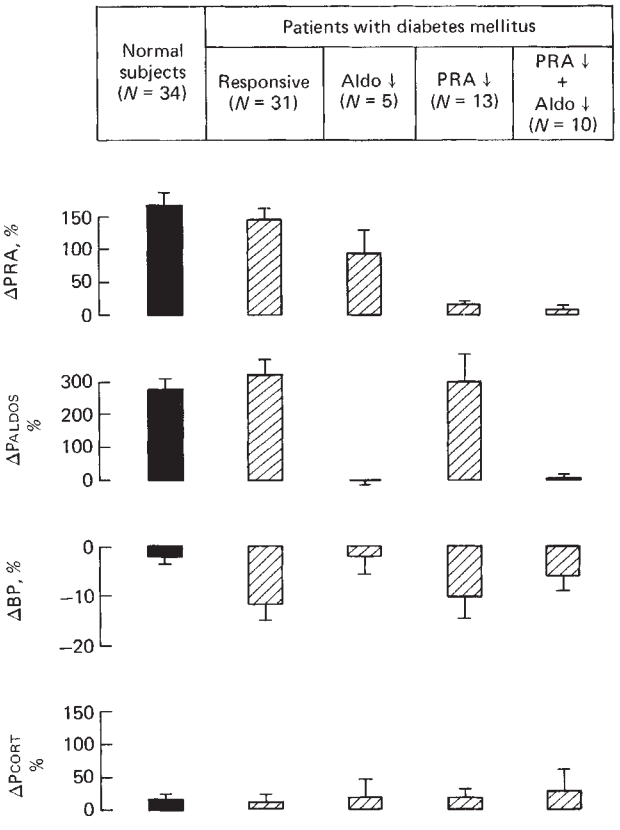

Fig. 2. *Postural plasma renin and aldosterone responses in normal and diabetic subjects (mean ± SEM).* Abbreviations used are: PRA, plasma renin activity; PALDO, plasma aldosterone level; BP, blood pressure; PCORT, plasma cortisol level.

Relationship between blood pressure and various parameters. Supine mean blood pressure was 93 ± 7 mm Hg in the normal subjects, 96 ± 8 mm Hg in the 24 patients with a normal blood pressure, and 119 ± 9 mm Hg in the 36 patients with hypertension. When compared with the diabetic patients with a normal

Table 4. Comparison of various clinical and laboratory parameters between diabetic patients with normal postural renin or aldosterone responses and non-responses

	Renin		Aldosterone	
	Responders (N = 36)	Non-responders (N = 23)	Responders (N = 44)	Non-responders (N = 15)
Mean age, *yr*	55.0 ± 12.0	55.1 ± 13.7	56.0 ± 12.3	52.3 ± 13.7
Hypertension, *% afflicted*	58	61	59	66
Orthostatic blood pressure fall, *% afflicted*	11	17	16	7
Retinopathy, *% afflicted*	42	35	40	33
Neuropathy, *% afflicted*	33	35	34	33
Nephropathy, *% afflicted*	25	30	30	20
Insulin, *% treated*	50	43	50	53
Oral antidiabetic agents, *% treated*	33	35	39	27
Blood glucose, *mg/100 ml*	213.6 ± 94.9	188.1 ± 99.6	210.2 ± 95.2	193.4 ± 113.4
Exchangeable sodium, *mEq/kg of LBM*	48.0 ± 4.3	49.9 ± 5.1	48.7 ± 5.1	48.2 ± 3.1
Blood volume, *ml/kg of LBM*	69.3 ± 11.5	75.6 ± 7.8	71.5 ± 11.2	72.1 ± 8.9
Urinary sodium excretion, *mEq/24 hr*	147.7 ± 62.2	159.7 ± 69.2	146.0 ± 66.2	171.3 ± 57.6
Plasma sodium, *mEq/liter*	137.5 ± 3.0	137.4 ± 2.4	137.3 ± 2.9	137.5 ± 2.4
Plasma potassium, *mEq/liter*	3.98 ± 0.35	4.05 ± 0.37	4.03 ± 0.34	3.99 ± 0.28
Urinary adrenaline, *μg/g of creatinine*	2.2 ± 3.3	3.8 ± 3.4	2.8 ± 3.4	3.0 ± 3.5
Urinary noradrenaline, *μg/g of creatinine*	27.3 ± 18.3	28.8 ± 15.9	27.6 ± 17.5	29.4 ± 16.8
Urinary total catecholamines, *μg/g of creatinine*	29.4 ± 18.7	32.6 ± 17.1	30.4 ± 17.6	32.3 ± 18.6

blood pressure, those with hypertension had a greater mean orthostatic decrease in mean blood pressure (18.3 vs. 3.8 mm Hg; $P < 0.01$), and they tended to have a slightly lower mean upright PRA (2.46 ± 1.72 vs. 3.76 ± 2.55 ng/ml/hr; $P < 0.05$). Mean age, heart rate, supine PRA, supine and upright plasma aldosterone levels, plasma potassium and sodium concentrations, exchangeable sodium and blood volume, the products of the natural logarithm of PRA and exchangeable sodium or blood volume [13, 15], and urinary sodium or catecholamine excretion rates did not differ significantly among these groups.

Linear regression analysis of supine mean blood pressure on the various measured parameters was performed. In normal subjects, blood pressure correlated positively, although weakly, with noradrenaline excretion rate ($r = 0.40$; $P < 0.02$), but not with any of the other parameters. In the diabetic patients, blood pressure correlated inversely, but also weakly, with basal PRA ($r = -0.29$; $P < 0.05$) but not with postural renin responses or any other study parameter.

Comparison between diabetic patients without and those with orthostatic hypotension revealed that the latter group tended to have higher exchangeable body sodium concentrations and lower supine and upright PRA levels ($P < 0.05$); mean age, supine heart rate, plasma aldosterone level, blood volume, and urinary sodium excretion did not differ significantly among these groups (Table 5). In addition, the patients without orthostatic hypotension showed a significant postural increase in pulse rate ($P < 0.025$), while those with orthostatic hypotension did not. The patients with orthostatic hypotension also tended to excrete less noradrenaline than the normal subjects did ($P < 0.05$).

Linear regression analysis in the diabetic patients revealed significant correlations between orthostatic changes in blood pressure and noradrenaline ($r = 0.29$; $P < 0.05$) or total catecholamine excretion rates ($r = 0.35$; $P < 0.01$) or basal PRA ($r = 0.54$; $P < 0.001$) (Fig. 3), but not between postural variations in blood pressure and the associated changes in PRA ($r = 0.06$).

Discussion

This comparative analysis of various vasoactive factors in 60 patients with stable non-azotemic diabetes mellitus and age-matched normal subjects demonstrated several abnormalities in the diabetic population. These included a significant increase in the concentration of exchangeable body sodium ($P < 0.01$), an impaired postural responsiveness of plasma renin and/or aldosterone levels in 47% of the patients, and a tendency for low basal PRA values and urinary noradrenaline excretion rates ($P < 0.05$) in those patients who had orthostatic hypotension.

The finding of a 9.5% increase in the mean concentration of exchangeable sodium in our diabetic study population probably represents a real abnormality in body composition and is not related to differences in age or body habitus [13, 16, 17]. Several factors may cause sodium retention in patients with diabetes mellitus. Since none of our patients had renal or heart failure, edema, or increased plasma aldosterone levels, the excess concentration of body sodium could

Table 5. Comparison of findings in normal subjects and patients with or without orthostatic hypotension[a]

	Normal subjects (N = 35)	Patients with diabetes mellitus	
		No orthostatic BP ↓ [b] (N = 51)	Orthostatic BP ↓ [b] (N = 9)
Age, *yr*	50.4 ± 14.8	54.4 ± 12.8	55.3 ± 15.4
Mean blood pressure, *mm Hg*			
supine	93.3 ± 6.8	109.1 ± 13.9[c]	114.9 ± 16.0[c]
upright	90.9 ± 6.7	102.5 ± 10.7[c]	68.7 ± 19.2[c]
Heart rate, *beats/min*			
supine	68.3 ± 8.2	79.6 ± 14.4[c]	80.3 ± 18.5[c]
upright	91.1 ± 17.1	98.7 ± 15.2[c]	92.9 ± 12.8
Plasma renin activity, *ng/ml/hr*			
supine	1.51 ± 1.00	1.85 ± 1.27	1.03 ± 0.97[c,d]
upright	4.06 ± 3.55	3.25 ± 2.27	1.72 ± 1.40[c,d]
Plasma aldosterone, *ng/100 ml*			
supine	5.2 ± 3.3	5.4 ± 3.4	4.38 ± 2.8
upright	17.9 ± 11.4	13.7 ± 9.1[c]	15.2 ± 13.5
Exchangeable sodium, *mEq/kg of LBM*	44.6 ± 3.7	48.0 ± 3.6[c]	52.7 ± 7.4[c,d]
Blood volume, *ml/kg of LBM*	73.5 ± 10.0	70.9 ± 9.7	74.8 ± 14.2
Urinary adrenaline, *μg/g of creatinine*	3.5 ± 4.4	3.0 ± 3.5	1.4 ± 1.5
Urinary noradrenaline, *μg/g of creatinine*	30.3 ± 14.2	29.2 ± 17.8	19.7 ± 10.4[c]
Urinary sodium, *mEq/24 hr*	131.9 ± 60.5	157.2 ± 65.2	119.9 ± 51.5

[a] All values represent the mean ± SD.
[b] BP ↓ represents orthostatic decrease of blood pressure exceeding 40 mm Hg systolic and 20 mm Hg diastolic, and/or 27 mm Hg mean pressure.
[c] $P < 0.05$ vs. normal subjects.
[d] $P < 0.05$ vs. patients without postural hypotension.

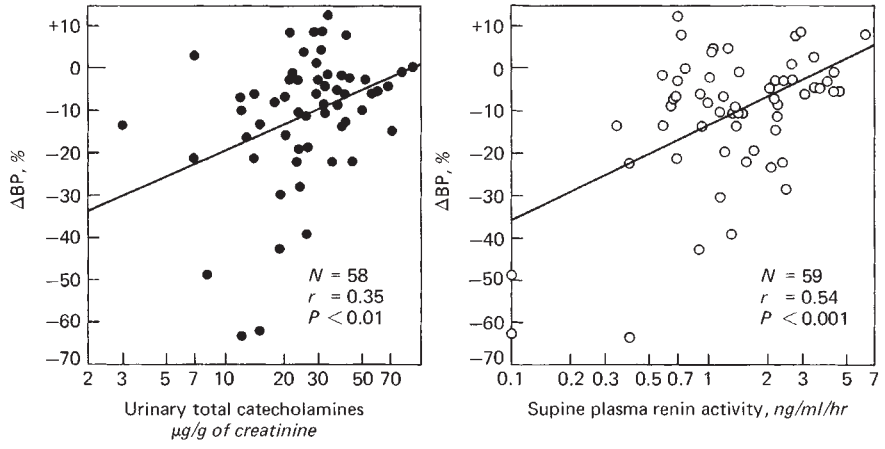

Fig. 3. *Relationships between orthostatic changes in blood pressure and noradrenaline excretion rate or basal plasma renin activity in patients with diabetes mellitus.*

not be explained by one of these mechanisms [15, 25, 26]. Insulin given acutely to patients with poorly controlled diabetes is known to contribute to sodium retention [27]. Exchangeable sodium, however, was comparable in the 47% of our patients who chronically received insulin and in the 53% who did not (48.4 ± 3.5 vs. 50.0 ± 5.5 mEq/kg of LBM). Yet another factor which may influence the body sodium-fluid state is the serum protein concentration. Our diabetic patients had a lower concentration of serum albumin than that of the normal subjects (4.19 ± 0.37 [SD] vs. 4.35 ± 0.33 g/100 ml; $P < 0.02$), as has been reported by others [28]. Thus, it is conceivable that a reduction in plasma oncotic pressure could initially

lead to a shift of fluid from the intravascular to the extravascular space; the deficit in circulatory volume would, in turn, result in a finite degree of renal sodium retention, thus establishing a new steady-state with increased extracellular sodium and fluid volume and normal blood volume.

In previous studies of the renin-angiotensin system in diabetes mellitus, basal plasma renin levels and/or renin responsiveness to stimuli were described as being normal in uncomplicated diabetes mellitus [1, 7] or in diabetes complicated by retinopathy [29], while low values were reported in alloxan-diabetic rats [1], diabetic patients with nephropathy [1, 6], orthostatic hypotension [6] or hypertension [8], or unselected diabetics [30]. Since the activity of the renin-angiotensin-aldosterone system is normally age-dependent [16, 23], evaluation of this factor was included in the present study. Age-related decreases in supine and upright PRA levels were noted in both normal and diabetic subjects, while plasma aldosterone levels showed a similar tendency in normal subjects but not in patients with diabetes mellitus. Moreover, taking the age of the patients into account, we have found that basal plasma renin and aldosterone levels were comparable in the diabetic and normal subjects.

In contrast, the mean orthostatic rise in PRA was significantly lowered in the diabetic patients (88 vs. 165%; $P < 0.001$), and the individual postural increases in level of PRA and plasma aldosterone were subnormal in 39 and 25% of patients, respectively. Moreover, based on their plasma renin and aldosterone responses, the diabetic population could be stratified into four subgroups. Fifty-three percent showed normal renin and aldosterone responses, 8% had a normal renin response and a subnormal aldosterone response, 22% had an impaired renin response and a normal aldosterone response, and 17% exhibited subnormal responses of both renin and aldosterone.

The diminished PRA responsiveness in some of our patients did not occur preferentially in patients with diabetic complications such as retinopathy, nephropathy manifested by impaired glomerular filtration rate or proteinuria, or orthostatic hypotension, as reported by others [1, 6, 29]. This disturbance in renin metabolism was also not related to several factors known to inhibit renin release, including aging [16, 23], overhydration [9, 23], hyperkalemia [31], or hypertension [12, 13, 23]. The diminished postural PRA responses, however, could reflect certain other abnormalities known to be associated with diabetes mellitus, such as impaired adrenergic activity [3, 10, 32-34] or hyalinosis of the glomerular arterioles with destruction of the juxtaglomerular apparatus [14, 35]. The finding of comparable 24-hr catecholamine excretion rates in our patients with normal or impaired renin-responsiveness does not exclude a role of the former factor, since orthostatic changes in plasma catecholamines were not assessed. On the other hand, afferent arteriolar sclerosis is an early event which may precede the clinical signs of diabetic nephropathy [36]. Thus, hyalinization of renin-producing cells or receptor sites may well have contributed to diminished renin responsiveness in our diabetic patients, regardless of the presence or absence of impaired renal function or proteinuria.

Postural dissociation of plasma renin and aldosterone levels was noted in 30% of our diabetic patients. The failure of plasma aldosterone levels to increase with upright posture, despite a normal rise in PRA in some patients, could be related either to an adrenal biosynthetic abnormality or an ineffective form of circulating renin. Based on the lack of clinical signs of adrenal dysfunction, the normal basal plasma aldosterone, cortisol and electrolyte levels, there was no evidence for adrenocortical insufficiency. A relatively inactive precursor of renin, termed "big renin," however, has recently been identified in plasma and kidney extracts of some patients with diabetic nephropathy [37]. Moreover, in two such patients "big renin" replaced 50 to 100% of normal circulating renin, and this was associated with aldosterone deficiency [40].

The normal postural plasma aldosterone responses, despite blunted or absent renin responsiveness in another sizeable subgroup of our diabetic patients, could not be explained by several known aldosterone-regulating mechanisms such as variations in concentrations of plasma potassium or sodium, or the level of ACTH as judged by plasma cortisol concentrations. Since angiotensin levels and adrenal sensitivity to angiotensin were not actually measured, the renin-angiotensin system cannot be dismissed with certainty as a regulator of aldosterone release in these patients. The finding of marked postural falls in blood pressure in our diabetic patients, as well as in anephric subjects [39] or patients with dysautonomia [40] in whom similarly unexplained orthostatic aldosterone stimulation occurred, however, suggests that a decrease in systemic pressure may be an additional stimulus, triggering an aldosterone-secretory response via mediators other than renin, potassium, sodium, or ACTH.

When evaluated in the supine position, 60% of our diabetic patients had hypertension. In this study population, no positive correlations were observed

among blood pressure and major blood pressure-regulating factors, such as PRA, circulatory volume, concentration of exchangeable sodium, or catecholamine excretion rates, singly or in combination. Others found also no relationship between blood pressure and circulating total catecholamines [3]. Furthermore, the normal or even low activity of the sympathetic and renin-angiotensin systems suggests that they are probably not of primary importance in the maintenance of hypertension associated with diabetes mellitus. On the other hand, it appears possible that the increased concentration of body sodium may have contributed to the hypertension in our patients. The lack of a significant blood pressure-sodium relationship is not against this, but could reflect marked variability in the vascular sensitivity to sodium and/or an important complementary role of other factors not delineated in this study [15, 26].

Nine (15%) of our diabetic patients had marked orthostatic hypotension. The mechanisms controlling postural blood pressure homeostasis are very complex, including neural, hemodynamic, fluid-electrolyte, and, possibly, circulating pressor factors, such as catecholamines and angiotensin II [41]. Body fluid volume depletion did not appear to contribute to the orthostatic hypotension in our patients, since their blood volumes were normal, and their mean concentration of exchangeable sodium tended to be even higher than that in the patients with normal postural blood pressure regulation ($P < 0.05$). Orthostatic hypotension in diabetic patients is usually associated with impaired function of the afferent (parasympathetic) and/or efferent (sympathetic) limb of the autonomic reflex arch [2, 42, 43], and low serum activities of dopamine beta-hydroxylase were reported [33]. The previous observation of an association among postural decreases in blood pressure and impaired responsiveness of PRA to upright posture [6] was not confirmed in the present study, although the lack of an exaggerated orthostatic renin-response in our patients with orthostatic hypotension may be considered inappropriate [44]. In this diabetic study population, postural changes in blood pressure correlated directly with basal PRA ($r = 0.54$; $P < 0.001$) and total catechlolamine excretion rate ($r = 0.35$; $P < 0.05$), and patients with orthostatic hypotension tended to have decreases in both circulating renin and noradrenaline excretion ($P < 0.05$). A retrospective analysis of another study indicates that the 12 anephric patients who had no functioning renin-angiotensin system were more prone to orthostatic decreases in blood pressure than the 17 non-nephrectomized hemodialysis patients with normal to high PRA (14.3 ± 3.9 [SEM] vs. 1.2 ± 2.8%; $P < 0.01$) [39, 45]. The latter data support the conclusion that low activity of the renin-angiotensin system may be a factor complementing autonomic insufficiency in the pathogenesis of diabetic orthostatic hypotension.

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