Relationship Between Autonomic Neuropathy, 24-h Blood Pressure Profile, and Nephropathy in Normotensive IDDM Patients

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OBJECTIVE — To evaluate the relationship between autonomic neuropathy, nephropathy, and 24-h blood pressure (BP) pattern in insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — We studied 30 normotensive IDDM patients without overt nephropathy, divided into two groups and matched for age, duration of diabetes, and HbA_1, according to the presence of cardiovascular autonomic neuropathy. We simultaneously measured 24-h BP and urinary albumin excretion rate (UAE) on urine collections timed overnight and at 2-h intervals during the day.

RESULTS — Mean day and night systolic and diastolic BP values did not significantly differ between the groups. Mean night albuminuria was significantly higher in patients with autonomic neuropathy than in those without (61.4 ± 104.6 [mean ± SD] vs. 16 ± 25.2 μg/min, $P < 0.04$). The percentages day-night changes in systolic BP, diastolic BP, and UAE were significantly lower in neuropathic patients (systolic BP: 2.4 ± 7.7 vs. 9.6 ± 4.2%, $P < 0.001$; diastolic BP: 8.4 ± 6.9 vs. 15.5 ± 5.4%, $P < 0.002$; UAE: −8 ± 99.4 vs. 49.3 ± 29.4%, $P < 0.02$) and were inversely related to autonomic score, index of autonomic neuropathy degree ($r = -0.54$, $P < 0.002$; $r = -0.58$, $P < 0.001$; and $r = -0.53$, $P < 0.005$, respectively). In patients with autonomic neuropathy, 2-h day periods and day and night UAE were more strongly related, respectively, to mean 2-h day periods ($r = 0.58$, $P < 0.0001$), day systolic BP ($r = 0.67$, $P < 0.04$), and night systolic BP ($r = 0.69$, $P < 0.04$) than in patients without autonomic neuropathy (2-h day periods: $r = 0.32$, $P < 0.001$; day: $r = 0.37$, NS; night: $r = 0.35$, NS).

CONCLUSIONS — Autonomic neuropathy in IDDM patients is associated with reduced nocturnal falls in BP and UAE and with a stronger relationship of UAE to systolic BP. We suggest a pathogenetic role of autonomic neuropathy in the development of diabetic nephropathy through changes in nocturnal glomerular function and by enhanced kidney vulnerability to hemodynamic effects of BP.

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IDDM, insulin-dependent diabetes mellitus; BP, blood pressure; ABPM, ambulatory 24-h blood-pressure monitoring; UAE, urinary albumin excretion.

Clinical and epidemiological studies have shown an association between autonomic neuropathy and nephropathy in insulin-dependent diabetes mellitus (IDDM) (1–4). This finding is of prognostic interest, because both of these diabetic complications are associated with a higher mortality rate (5–9).

A pathogenetic significance of the association between diabetic neuropathy and nephropathy has been proposed preliminarily by some authors (4,10,11) and supported by the knowledge of a rich innervation of the kidney and of a neural control of renal function (12–16). Moreover, abnormalities in kidney function have also been described in conditions of autonomic failure other than diabetic neuropathy (17,18).

The pathogenesis of diabetic nephropathy is not wholly understood, and the temporal link between hypertension and nephropathy is still under debate. Ambulatory 24-h blood-pressure monitoring (ABPM) has been proved to be a useful tool for recording blood pressure (BP). Compared to casual BP, ABPM is both more strongly related to target organ damage of hypertension and to albuminuria and more sensitive in detecting an early increase in BP load in diabetic patients (19–21). Moreover, ABPM has allowed us to detect in diabetic patients unsuspected abnormalities of the BP circadian rhythm and to relate them to autonomic (22–24) or renal dysfunction (21,25). More information on the relationship between autonomic neuropathy, BP, and nephropathy might lead to a better pathogenetic understanding of hemodynamic changes of diabetic nephropathy.

We performed this study to evaluate in normotensive IDDM patients without clinical nephropathy the relationship between autonomic neuropathy, nephropathy assessed by albuminuria, and the 24-h BP pattern.

RESEARCH DESIGN AND METHODS

— Thirty subjects with IDDM participated in the study. Informed

Table 1—*Clinical parameters and cardiovascular reflex tests of IDDM patients without and with autonomic neuropathy (AN)*

IDDM patients	Without AN	With AN	*P* value
n	18	12	
Age (years)	39.3 ± 8.9	41.5 ± 12.7	NS
Sex (M/F)	9/9	7/5	NS
Diabetes duration (years)	16 ± 9.1	18.5 ± 8.2	NS
Body mass index (kg/m^2)	23.1 ± 2.7	22.9 ± 3.5	NS
Insulin (U/day)	43.2 ± 14	39.4 ± 12.5	NS
HbA_1 (%)	8.2 ± 1.8	9.2 ± 1.9	NS
Serum creatinine (μM)	73.2 ± 20.9	73.1 ± 20.9	NS
Retinopathy (absent/background/ proliferative)	11/6/1	4/6/2	NS
Casual systolic BP (mmHg)	116.16 ± 13.84	114.66 ± 13.73	NS
Casual diastolic BP (mmHg)	72.11 ± 5.63	72.27 ± 10.36	NS
Deep breathing (breaths/min)	22.19 ± 7.37	7.68 ± 7.23	0.0001
Lying to standing	1.15 ± 0.10	0.97 ± 0.05	0.0001
Valsalva ratio	1.46 ± 0.35	1.21 ± 0.2	0.02
Postural hypotension (mmHg)	3.62 ± 7.27	17.85 ± 14.18	0.001
Autonomic score	0.67 ± 0.69	4.75 ± 1.66	0.0001

Data are means ± SD.

consent was obtained from all participants. They were consecutively recruited from the diabetic clinic of the University of Rome Tor Vergata. Inclusion criteria were <60 years of age; values of casual BP in the normal range according to World Health Organization criteria (≤140/90 mmHg); and the absence of macroalbuminuria (urinary albumin excretion (UAE) ≥200 μg/min), urinary infection, and any clinically relevant acute or chronic disease other than diabetes, especially if it affected renal, respiratory, or cardiovascular function. No subject was taking any drug other than insulin. Sixteen were men and 14 were women. Age (mean ± SD) was 40.2 ± 10.4 years (range 23–59). Duration of diabetes was 17 ± 8.7 years (range 1–38). HbA_1 was 8.6 ± 1.7%, measured with chromatography (reference range 5–8%). Creatininemia was 73.2 ± 20.6 μM. Nonproliferative retinopathy was present in 12 patients and proliferative retinopathy in 3 patients.

Diabetic patients were compared to a control group of 29 age-matched normal subjects (21 men and 8 women, 42.8 ± 11.1 years of age) for 24-h BP monitoring.

Autonomic function was explored by deep breathing, lying to standing, Valsalva maneuver, and postural hypotension tests, performed and evaluated according to standard procedures (26). To quantify the combined results from the tests, an autonomic score was calculated from the sum of scores given for each of the four tests (0 for a normal result, 1 for a borderline result, and 2 for an abnormal result) (27). This score ranged from 0 to 8. Patients with at least one abnormal cardiovascular test were considered to have autonomic neuropathy, and those with less than one positive test were considered to be free of neuropathy. In more detail, 18 patients had all normal tests or one or two borderline results with an autonomic score of 0–2, 5 patients had one abnormal test and one borderline test with an autonomic score of 3, and 7 patients had more than two abnormal tests with an autonomic score of 5–7. Clinical data and cardiovascular tests of diabetic patients with and without autonomic neuropathy are given in Table 1. No significant difference in any clinical parameter was found.

Noninvasive ABPM was performed using an oscillometric recorder (SpaceLabs 90202, Redmond, WA), a device of proven accuracy, satisfying the validation requirements for ABPM systems (28). The device was programmed to measure BP every 20 min for 24 h. Recordings were started between 0800 and 0900. Patients were hospitalized; they were free to move in the hospital area during the monitoring and were requested to comply with hospital routines and to record their activities and the time of waking up and going to bed. BP recordings were automatically edited and then visually screened for artefactual readings (29). Systolic and diastolic BP measurements were averaged for each hour, for 2-h intervals during the day, and for the day (0800–2200) and the night (2200–0800) periods. In addition, the percentage change in BP from day to night (Δ day-night BP) was calculated as: (day BP − night BP) × 100/day BP. The same evaluation was performed in the group of control subjects.

Albumin concentration was measured by a double antibody radioimmunoassay (Albumin RIA 100, Pharmacia, Uppsala, Sweden) on urine collections timed overnight and at 2-h intervals during the day. Samples were simultaneous to 24-h BP monitoring and were stored at −20°C until the test procedure. The detection limit of assay was ≤0.4 mg/L, and interassay coefficients of variation ranged from 3–7%. UAE was calculated for each 2-h period during the day, for the day (0800–2200) and the night (2200–0800) periods, and for the 24-h period. In addition, the percentage change in UAE from day to night (Δ day-night UAE) was calculated as: (day UAE − night UAE) × 100/day UAE. Similarly, 24-h, day, night, and Δ day-night urine volumes were measured.

Statistical analysis

Data are expressed as means ± SD, unless specified differently. Unpaired Student's *t*

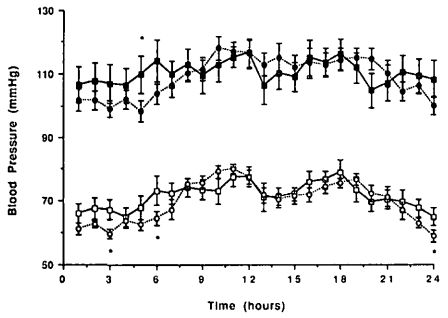

Figure 1—*Mean hourly systolic (●, ■) and diastolic (○, ⊡) BP in IDDM patients without autonomic neuropathy (●, ○) and with autonomic neuropathy (■, ⊡). The x-axis indicates clock hours from 0100 to 2400. Values are means ± SE. *P < 0.05 between the groups for systolic and diastolic BP.*

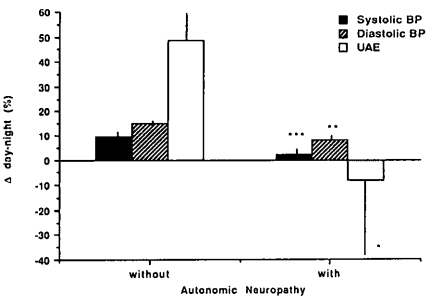

Figure 2—*The Δ day-night in systolic BP, diastolic BP, and UAE in IDDM patients without and with autonomic neuropathy. Values are means ± SE. *P < 0.02, **P < 0.002, ***P < 0.001 among the groups.*

test was used to compare diabetic patients to control subjects and diabetic patients with neuropathy to those without. Linear regression analysis was used to relate different variables. All statistical analyses were done using the program StatView II (Abacus Concepts, Berkeley, CA) on a Macintosh IIci computer. A value of $P < 0.05$ was considered significant.

RESULTS— Control subjects displayed a clear decrease in BP during the night hours and an increase that started at about 0700 and peaked at about 1100. Diabetic patients compared with control subjects showed a trend to lower mean hourly BP during the day, with a significant difference in systolic BP at 0800 ($P < 0.02$), 0900 ($P < 0.01$), and 1300 ($P < 0.02$) and in diastolic BP at 0900 ($P < 0.02$), 1300 ($P < 0.04$), and 2000 ($P < 0.03$). Figure 1 shows 24-h profiles of mean hourly systolic and diastolic BP in diabetic subjects with and without neuropathy. Diabetic patients with neuropathy compared with those without showed significantly higher systolic BP at 0500 and higher diastolic BP at 0300, 0600, and 2400.

No differences were seen in average 24-h and day and night systolic and diastolic BP between diabetic patients and control subjects (Table 2), whereas Δ day-night systolic BP was significantly reduced in diabetic subjects ($P < 0.002$). When considering diabetic subjects with and without neuropathy separately, we observed that only those with neuropathy displayed significant lower Δ day-night systolic BP in comparison with control subjects ($P < 0.0001$). In addition, diabetic patients with neuropathy showed significant reductions in Δ day-night systolic and diastolic BP when compared with diabetic patients without neuropathy ($P < 0.001$ and $P < 0.002$, respectively) (Fig. 2).

That the abnormal 24-h pattern of BP in IDDM patients could depend on the presence of autonomic neuropathy was also indicated by the fact that Δ day-night systolic and diastolic BP was inversely related to the autonomic score ($r = -0.54$, $P < 0.002$ and $r = -0.58$, $P < 0.001$, respectively) and to postural hypotension ($r = -0.58$, $P < 0.001$ and $r = -0.53$, $P < 0.005$, respectively). In other words, the abnormality in day-night variation of BP was related to the degree of autonomic cardiovascular impairment and in particular to postural hypotension.

Of the diabetic patients, 21 had a 24-h UAE ≤20 μg/min (normoalbuminuria) and 9 had a UAE between 20 and 200 μg/min (microalbuminuria). In the group of 18 diabetic patients without autonomic neuropathy, 5 patients had microalbuminuria (28%), and in the group of diabetic patients with autonomic neuropathy 4 patients had microalbuminuria (33%). Mean values of night UAE were slightly higher in neuropathic subjects than in non-neuropathic patients ($P < 0.04$). In addition, Δ day-night UAE was significantly lower in patients with autonomic neuropathy compared with diabetic subjects without neuropathy ($P <$

Table 2—*Average 24-h, day, and night values of systolic and diastolic BP, and average Δ day-night systolic and diastolic BP in control subjects, in all IDDM patients and in IDDM patients without and with autonomic neuropathy (AN)*

		IDDM patients		
	Control subjects	All	Without AN	With AN
n	29	30	18	12
Systolic BP				
24-h (mmHg)	112.04 ± 10.10	109.84 ± 13.02	109.49 ± 11.42	110.37 ± 15.65
day (mmHg)	117.87 ± 10.59	113.14 ± 13.35	114.26 ± 12.38	111.45 ± 15.08
night (mmHg)	104.52 ± 10.36	105.43 ± 14.03	103.14 ± 10.77	108.87 ± 17.84
Δ day-night (%)	11.30 ± 4.62	6.70 ± 6.76*	9.58 ± 4.22†	2.37 ± 7.68‡
Diastolic BP				
24-h (mmHg)	72.06 ± 6.69	70.54 ± 7.69	70.10 ± 6.78	71.20 ± 9.17
day (mmHg)	76.60 ± 6.69	74.50 ± 7.85	74.93 ± 6.87	73.84 ± 9.41
night (mmHg)	66.31 ± 7.00	65.06 ± 8.31	63.28 ± 6.90	67.73 ± 9.76
Δ day-night (%)	13.54 ± 6.00	12.67 ± 6.90	15.50 ± 5.39§	8.43 ± 6.93‖

Data are means ± SD. *$P < 0.002$ vs. control subjects; †$P < 0.001$ vs. IDDM patients with AN; ‡$P < 0.0001$ vs. control subjects; §$P < 0.002$ vs. IDDM patients with AN; ‖$P < 0.01$ vs. control subjects.

Table 3—*Average 24-h, day, night, and Δ day-night UAE and urine volume in IDDM patients without and with autonomic neuropathy (AN)*

	IDDM patients		
	Without AN	With AN	*P* value
n	18	12	
UAE			
24-h (μg/min)	22.03 ± 37.50	50.40 ± 75.34	NS
day (μg/min)	26.33 ± 46.16	53.55 ± 76.68	NS
night (μg/min)	16.04 ± 25.24	61.41 ± 104.56	0.04
Δ day-night (%)	49.29 ± 29.37	−7.98 ± 99.41	0.02
Urine volume			
24-h (ml)	1581.11 ± 479.89	1863.5 ± 455.79	NS
day (ml)	1000.52 ± 345.21	1055.83 ± 545.72	NS
night (ml)	626.11 ± 351.77	932 ± 285.80	0.01
Δ day-night (%)	34.86 ± 43.27	−31.50 ± 93.19	0.01

Data are means ± SD.

0.02) (Table 3 and Fig. 2). Moreover, Δ day-night UAE was inversely related to the autonomic score ($r = -0.53$, $P < 0.005$) and to postural hypotension ($r = -0.39$, $P < 0.05$), and positively related to Δ day-night systolic BP ($r = 0.45$, $P < 0.02$).

The 2-h day periods UAE, day UAE, and night UAE were found to be more strongly related to average synchronous 2-h day periods systolic and diastolic BP ($r = 0.58$, $P < 0.0001$ and $r = 0.51$, $P < 0.0001$), day systolic and diastolic BP ($r = 0.67$, $P < 0.02$ and $r = 0.68$, $P < 0.02$), and night systolic and diastolic BP ($r = 0.69$, $P < 0.04$ and $r = 0.64$, NS) in neuropathic patients than in diabetic subjects without neuropathy (systolic BP: 2-h day: $r = 0.32$, $P < 0.001$; day: $r = 0.37$, NS; night: $r = 0.35$, NS; diastolic BP: 2-h day: $r = 0.36$, $P < 0.0001$; day: $r = 0.44$, NS; night: $r = 0.54$, $P < 0.02$). The slopes of the regression lines between UAE and systolic BP of 2-h day periods were 3.09 for neuropathic and 0.98 for non-neuropathic subjects, with a significant difference between them ($P < 0.001$), as evaluated by the method of comparison of regression lines (Fig. 3).

As shown in Table 3, night urine volume was significantly greater and Δ day-night urine volume was significantly smaller in patients with neuropathy than in those without ($P < 0.01$ for both). The Δ day-night volume was related to autonomic score ($r = -0.59$, $P < 0.001$), to postural hypotension ($r = -0.44$, $P < 0.02$), to Δ day-night systolic BP ($r = 0.57$, $P < 0.002$), and to Δ day-night UAE ($r = 0.68$, $P < 0.0001$).

CONCLUSIONS— Twenty-four-hour BP monitoring has shown an altered profile in normotensive IDDM patients compared with control subjects. This abnormality seems to be related to the presence of autonomic neuropathy, because diabetic subjects with cardiovascular autonomic neuropathy display a blunted nocturnal BP fall in comparison with those without autonomic neuropathy, and the day-night change in BP is related to the degree of cardiovascular reflex test impairment and, in particular, to the postural hypotension test.

A decrease in nocturnal BP fall or higher nocturnal BP has been observed in IDDM patients with different degrees of diabetic nephropathy (21,25). Whether diabetic nephropathy itself or an associated autonomic dysfunction was responsible for the altered circadian pattern was not fully explored in those studies. In this study, none of the diabetic patients was hypertensive or macroalbuminuric, and the percentage of microalbuminuric patients was not different among diabetic subjects with and those without autonomic neuropathy. Thus, the abnormality in BP profile in neuropathic patients is probably not attributable to hypertension or diabetic nephropathy, but it is possibly dependent on autonomic dysfunction, according to previous reports on patients with autonomic failure (30) and diabetic autonomic neuropathy (22–24). Moreover, in diabetic patients with autonomic neuropathy, the normal circadian rhythm of sympathovagal interaction is lost, with a blunted vagal increase and a sympathetic relative prevalence during the night (31). Finally, we have found in diabetic patients a clear correlation between the decrease in nocturnal BP fall and the prevalence of sympathetic tone at night (32).

In this study, diabetic patients

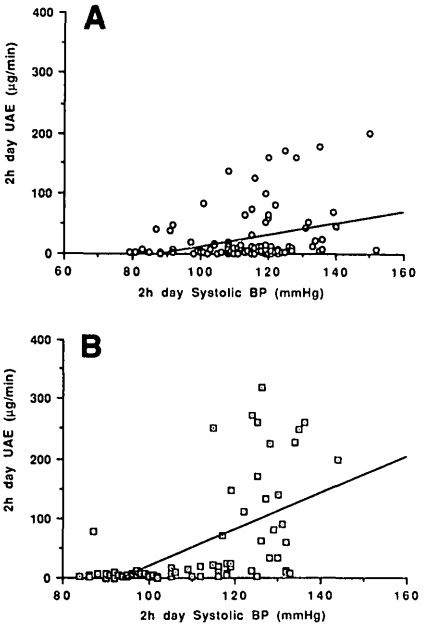

Figure 3—*Correlation between 2-h day periods for UAE and systolic BP in IDDM patients without (A) and with autonomic neuropathy (B). The slopes between UAE and BP are significantly different for the two groups (P < 0.001), being steeper in patients with neuropathy. A: r = 0.32, P < 0.001. B: r = 0.58, P < 0.0001.*

with autonomic neuropathy displayed night UAE values slightly but significantly higher and a day-night change in UAE significantly lower than those in diabetic subjects without neuropathy. A clinical association between neuropathy and nephropathy in diabetes has been documented in some studies (1–4,33). So far, only a few studies have suggested a pathogenetic relationship between these two diabetic complications, starting with the report of an increase in renal flow in IDDM patients with autonomic neuropathy (34). Some evidence of a neural regulatory function of kidney exists. After renal nerve stimulation in rats, vascular resistances increase, with a consequent reduction in both renal blood flow and glomerular filtration rate, and proximal water and sodium reabsorption is enhanced. However, although diuretic and natriuretic effects of denervation show up well in experimental conditions, hemodynamic consequences of renal denervation are less clear (13,15,16). On the other hand, observations in human autonomic dysfunction fit well with a possible pathogenetic significance of the association between autonomic neuropathy and nephropathy. Excessive nocturnal diuresis and natriuresis have been described both in nondiabetic autonomic failure (17) and in diabetic autonomic neuropathy (35). Higher nocturnal UAE and nocturnal sodium excretion rates have been reported in neuropathic insulin-treated patients and have been attributed to a derangement of nocturnal renal hemodynamics and glomerulotubular balance (11). Finally, in a 10-year prospective study, glomerular filtration rate decreased more than expected in IDDM patients with autonomic neuropathy (36). Decrements in intraglomerular pressure during the day and increments at night were the hypothesized connecting link between autonomic neuropathy and the deterioration in glomerular filtration rate.

In this study, compared with non-neuropathic diabetic subjects, patients with neuropathy displayed a lower nocturnal fall of UAE that is correlated to the degree of autonomic neuropathy. In the same patients, an altered circadian pattern of BP also occurs. The correlation between the day-night change in systolic BP and changes in UAE and urine volume might be interpreted as reflecting some possible causal connection. That is, a reduced fall in BP during the night might be responsible for increased nocturnal urine output and albuminuria. Nevertheless, because the day-night changes in BP, UAE, and urine volume are strongly related to the degree of autonomic impairment, the possibility that autonomic neuropathy acts directly on all three parameters exists, e.g., by blunting the night BP fall, by increasing renal blood flow and glomerular filtration rate, and by impairing the tubular water and sodium reabsorption. According to this line of reasoning, the relationship between the altered day-night patterns of BP, UAE, and urine volume would be secondary, at least in part, to the widespread influence of autonomic neuropathy. The relationship of these day-night patterns to the postural hypotension test might further involve the dysfunction of reflex postural adjustments, as previously suggested (35).

This study brings out another interesting aspect, that of the relationship between BP and nephropathy. As in essential hypertension (37,38), in IDDM patients, as well, a positive correlation between albuminuria and BP levels has been described (39,40). Night UAE has been found to be related to day and night systolic BP in a group of normo- and microalbuminuric IDDM patients (25) and, in another study, in microalbuminuric patients to 24-h and day diastolic BP and to night systolic BP (21). No assessment of autonomic function was made in these studies. In this study, for the first time, BP and UAE have been evaluated simultaneously over the whole 24-h period and related to autonomic neuropathy. This approach has allowed us to find that in neuropathic patients 2-h day periods and day and night UAE are more strongly related to mean 2-h day, day, and night systolic BP, respectively, than in patients without neuropathy. In other words, for a certain value of systolic BP, neuropathic patients would have higher UAE than non-neuropathic patients. Two interpretations for this finding are possible. The simpler explanation is that neuropathic patients could have a more advanced nephropathy compared with patients without neuropathy and that, in patients with more developed nephropathy, BP could be more effective on albumin excretion. There were, however, no significant differences in 24-h UAE between diabetic patients with and diabetic patients without autonomic neuropathy, and the small number of microalbuminuric patients was equally distributed between them. In addition, in the study by Hansen et al. (25), the relationship between UAE and BP was similar in micro- and normoalbuminuric patients. Nevertheless, because we did not perform more sensitive assessment of renal function in this study, we cannot exclude a different degree of nephropathy between the two groups of diabetic patients. The second possible explanation comes from and supports the suggestion of a pathogenetic relationship between diabetic neuropathy and nephropathy. The loss of nervous control of renal function might make the kidneys more vulnerable to the hemodynamic effects of systemic BP. This could be a result of the deprivation of compensative mechanisms, under autonomic nervous system control, active on the glomerular hemodynamics. In a recent study, Krolewski et al. (41) pointed out that autonomic neuropathy may be a strong risk factor for early-onset proliferative retinopathy, suggesting a possible role for autonomic neuropathy in the development of retinal blood flow abnormalities. In a similar way, hemodynamic changes could follow autonomic denervation in the kidney and favor the development and/or progression of nephropathy.

In conclusion, autonomic neuropathy in IDDM patients is associated with a reduced nocturnal fall in BP and in UAE and with a stronger relationship of

UAE to systolic BP. These findings might shed light on the known association between diabetic neuropathy and nephropathy. We suggest a pathogenetic role of autonomic neuropathy in the development of diabetic nephropathy through changes in nocturnal glomerular function and by enhancement of kidney vulnerability to the hemodynamic effects of BP.

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