Altered blood pressure profile, autonomic neuropathy and nephropathy in insulin-dependent diabetic patients

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To evaluate the relationship between autonomic neuropathy (AN) and nephropathy we measured 24-h blood pressure (BP) and overnight urinary albumin excretion (UAE) in 38 patients with insulin dependent diabetes mellitus (IDDM). Autonomic function was evaluated by the heart rate response to deep breathing, Valsalva maneuver, heart rate at rest and BP variation with posture. Sympathetic cutaneous reflex was also tested in both inferior and superior limbs. Patients with mean day diastolic BP (DDBP) < 90 mmHg without AN (N = 15) compared to 12 normal controls had similar BP values, but compared to those with DDBP ≤ 90 mmHg and AN (N = 12) they had lower night diastolic BP (NDBP) (66 ± 4.8 vs 72 ± 8.8 mmHg; p < 0.05) and UAE (9.8 ± 2.3 vs 107.2 ± 3.5 μg/min; p < 0.001). No difference in DDBP was observed between these two diabetic groups (80 ± 3.9 vs 83 ± 6.1 mmHg). Of the 11 patients with DDBP > 90 mmHg, only three were free of AN and only two of the eight with AN where free of diabetic nephropathy. The percentage day/night changes in systolic BP were lower in patients with AN (13 vs 7.9%; p < 0.05) and were inversely related to autonomic score, used as an index of the degree of autonomic dysfunction (r = −0.48; p < 0.01) and to UAE (r = −0.39; p < 0.05). Furthermore, UAE correlated with autonomic score (r = 0.69; p < 0.0001) and with NDBP (r = 0.44; p < 0.01). Our results show that AN in IDDM patients is associated with a reduced nocturnal fall in BP and suggest a pathogenic role of autonomic dysfunction in the development of diabetic nephropathy, possibly favoring both BP elevation during the night and increases in intraglomerular pressure.

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The pathogenesis of diabetic nephropathy in patients with insulin-dependent diabetes mellitus (IDDM) appears closely related to the development of hypertension (1). However, it is currently unknown whether early elevations in blood pressure (BP) are a primary factor in the development of diabetic nephropathy. The subclinical stage of nephropathy characterized by microalbuminuria has been shown to precede hypertension (2) or to develop in parallel with increasing BP (3, 4).

Clinical studies using 24-h ambulatory BP monitoring (ABPM) have shown blunted physiological nocturnal falls in BP in normotensive IDDM with microalbuminuria (5, 6). The fact that the reduced nocturnal fall in BP in IDDM is also associated with autonomic neuropathy (AN) (7, 8) raises the possibility that autonomic dysfunction may contribute to the development of diabetic nephropathy through changes in BP profile. In addition, clinical and epidemiological studies have shown an association between autonomic neuropathy and nephropathy in IDDM (9–11) and diabetic nephropathy appears as one of the main causes of death in patients with AN (12). The concept that AN may be related to the development of diabetic nephropathy is also supported by the fact that changes in autonomic nervous function may alter renal hemodynamics (13).

The aim of the present study was to evaluate in normotensive and hypertensive IDDM patients the relationship between AN and nephropathy.

Patients and methods

Thirty-eight patients with IDDM and 19-age matched normal controls participated in the study. Patients were recruited from the diabetes clinics of Escola Paulista de Medicina (São Paulo, Brazil). Control subjects were healthy, non-diabetic, normotensive individuals as determined by history and physical examination. The study was approved by the institutional ethical committee and informed consent was obtained from all participants. The patients were insulin dependent under 60 years of age, with the age at onset of diabetes before 35 years and with diabetes mellitus for at least 5 years.
All patients were prone to ketosis and had in the past at least one episode of ketoacidosis. All of them had serum creatinine below 1.5 mg/dl and none had urinary infection or any relevant disease other diabetes affecting the renal, respiratory or cardiovascular system. Thirteen were men and 25 were women. Age was 32.3 ± 10.3 years (mean ± sd), ranging from 16 to 55 years. Duration of diabetes were 14.9 ± 6.6 years, ranging from 5 to 38 years. Non-proliferative retinopathy was present in 17 patients and proliferative retinopathy in 10 patients. None of them had diastolic BP higher than 105 mmHg. All antihypertensive agents were withdrawn 15 days prior to the evaluation and no medication other than insulin was administered during this period. All patients were under a two-dose NPH insulin regimen, with a complimentary dose of regular insulin when necessary. The first dose was given in the morning, before breakfast, and the other in the afternoon, before dinner. Before clinical and laboratory evaluation, patients were oriented to improve their glycemic control when necessary so that their blood glucose would reach values below 200 mg/dl. The control group included 19 normal subjects (13 women and 6 men) 30.4 ± 8.6 years of age, ranging from 17 to 53 years.

Tests for autonomic nervous system evaluation included heart rate at rest, heart rate response to deep breathing, Valsalva maneuver and the BP variation from supine to upright posture (postural hypotension). All these tests were performed and evaluated according to standard procedures included in the Consensus Statement Report and Recommendations of the San Antonio Conference (14, 15). Sympathetic cutaneous reflex was tested both in the superior and in the inferior limbs according to procedures described previously (16).

The result obtained in each test for each patient was compared with the result obtained in the control group. For each test, values out of the range between the mean value for the control group ± 2 sd were considered abnormal. Each abnormal test received the score 1 when the result obtained was in the range between the mean ± 3 sd of the control group and received score 2 when the result was out of this range. Patients with sympathetic cutaneous reflex absent only in the inferior limbs received score 1, while patients with this reflex absent in both superior and inferior limbs received score 2. Normal tests received score 0. The degree of AN was quantified through an autonomic score that was calculated from the sum of scores given for each of the five tests. This score ranged from 0 to 10. Patients presenting an autonomic score ≥ 2 were considered to have AN. Eighteen patients had all normal tests or one abnormal test with an autonomic score of 1 (total score 0–1); four had two abnormal tests, each one with an autonomic score of 1 (total score 2); four had two abnormal tests, one with an autonomic score of 1 and another with a score of 2 (total score 3) and 12 had three or more abnormal tests (total score 3–8). Clinical data and cardiovascular tests of the control group and of diabetic patients with and without AN are shown in Table 1.

During the periods of ambulatory 24-h blood pressure monitoring (ABPM), all subjects pursued their normal daily activities. They were advised not to rest in bed or to exercise during the day so that their daily activities would not differ roughly among patients. Blood pressure measurements were obtained every 15 min between 0600 and 2300 h and every 20 min between 2300 and 0600 h, using an oscillometric AMBP recorder (SpaceLabs 90202, Redmond, WA) in the non-dominant arm. Patients were requested to record

**Table 1. Neurological evaluation in control group and in IDDM patients with and without autonomic neuropathy (AN).**

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Without AN</th>
<th>With AN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (HR) at rest (bpm)</td>
<td>69 ± 10.1</td>
<td>78 ± 11.8**</td>
<td>92 ± 10.2**</td>
</tr>
<tr>
<td>HR response to deep breathing (bpm)</td>
<td>23 ± 5.8</td>
<td>21 ± 9.6</td>
<td>7.9 ± 6.4**</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.49 ± 0.21</td>
<td>1.53 ± 0.33</td>
<td>1.30 ± 0.31</td>
</tr>
<tr>
<td>Δ BP on standing 1/5 min (mmHg)</td>
<td>-4.1 ± 4.1/3.5 ± 4.3</td>
<td>-1.3 ± 6.8/0.8 ± 7.8</td>
<td>-13.7 ± 15.5**</td>
</tr>
<tr>
<td>Sympathetic cutaneous reflex absent (superior/ inferior limbs)</td>
<td>0/0</td>
<td>1/3</td>
<td>4/10</td>
</tr>
</tbody>
</table>

*Significance: *p < 0.05 and **p < 0.01 vs controls; *p < 0.05 and ** p < 0.01 vs IDDM without AN.
their activities and the time of waking up and going to bed. Systolic and diastolic BP measurements were averaged for the waking period (day BP) and for the sleep period (night BP), based on patients' records. The percentage change in BP (Δ BP) from the waking hours to sleep period was calculated as:

\[ ΔBP = (day \text{ BP} - night \text{ BP}) \times 100/\text{day BP}. \]

The same evaluation was performed in 12 normal controls.

Albumin urinary excretion (UAE) was measured by ELISA (16) on 12-h overnight urine samples and each result was the mean of three samples collected on three different occasions. These samples were collected within a period of 2 or 3 weeks and patients with diabetic nephropathy had at least two of three samples with UAE > 20 µg/min.

Blood samples were obtained after an overnight fasting for blood glucose, serum creatinine and glycosylated hemoglobin (HbA1) determinations.

Statistical analysis

Data are expressed as means ± sd. Albumin excretion rates were logarithmically transformed (log10) to achieve a near-normal distribution. These data are presented as the geometric mean multiplied or divided by the tolerance factor (= antilog to sd of log10 transformation). Unpaired Student's t-test or the Mann–Whitney U-test were used where appropriate for testing differences between subgroups of patients with and without AN. Analysis of variance (ANOVA) was used when more than two groups were compared. Correlation between variables was tested by calculating Pearson or Spearman correlation coefficients where appropriate. Chi-squared and Fisher tests were used to test the association between variables.

Results

Table 1 shows the cardiovascular reflex tests in the control group in two subgroups of diabetic divided according to the presence or absence of AN, while the general characteristics of these two groups of diabetic patients are shown in Table 2. There were no significant differences between patients with and without AN with respect to age, sex distribution, disease duration, body mass index and mean insulin dose. However, the presence of diabetic AN was associated with higher levels of HbA1, urinary albumin excretion, serum creatinine and with a higher proportion of patients with proliferative diabetic retinopathy.

Data from the 24-hour BP profile for the control and diabetic groups are shown in Table 3. Over the entire period of 24 h, mean systolic and diastolic BP were higher in diabetic patients with AN than in patients without AN or in the control group, while no differences in BP values were observed between the control group and the diabetic group without AN. During the sleep period both controls and diabetic patients without AN showed a smaller fall in BP while diabetic patients with AN showed a marked reduced fall in BP. Furthermore, the differences between the day and night systolic and diastolic BP were inversely related to the autonomic scores (rs = −0.50; p < 0.002 and rs = −0.48; p < 0.003).

In our group of IDDM patients some evidence points to an association between AN and nephropathy. The presence of diabetic nephropathy (UAE > 20 µg/min) was found in four (22%) out of the 18 patients without AN and in 17 (85%) of the 20 diabetics with AN (chi squared test, p < 0.001). Furthermore, the UAE was not only related to night diastolic BP (r = 0.44; p < 0.02) but also showed a positive correlation with the autonomic score (rs = 0.69; p < 0.0001), as depicted in Fig. 1, and a negative correlation with the systolic and diastolic day BP–night BP (rs = −0.40; p < 0.02 and rs = −0.34; p < 0.04).

When the BP values are considered, the presence of AN was found in eight (73%) of the 11 hypertensive patients (24 h diastolic BP < 90 mmHg) and in 12 (44%) of the 27 normotensives (24 h diastolic BP < 90 mmHg). In the hypertensive group, only one of the three patients without AN had macroalbuminuria (UAE ≥ 200 µg/min), while seven of the eight with AN had increased UAE, three with microalbuminuria (UAE > 20 µg/min and < 200 µg/min) and four with macroalbuminuria. Because of the small number of patients, the association between AN and nephropathy in this group did not reach statistical significance, while in the normotensive group it became more evident. Three (20%) of the 15 normotensive patients without AN were microalbuminuric, while 10 (83%) of the 12 patients with AN had high levels of UAE (Fisher test; p < 0.01), seven with microalbuminuria and three with macroalbuminuria.

To further evaluate the relationship between AN and nephropathy, independently of the presence of established hypertension, we compared the patients with
Table 3. Average 24-h, day, night and Δ day – night values of systolic and diastolic blood pressure (BP) in control subjects and in IDDM patients with and without autonomic neuropathy (AN)*.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Without AN</th>
<th>With AN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h (mmHg)</td>
<td>117 ± 6.4</td>
<td>124 ± 14.0</td>
<td>136 ± 15.2***#</td>
</tr>
<tr>
<td>Day (mmHg)</td>
<td>119 ± 6.2</td>
<td>130 ± 11.3</td>
<td>138 ± 15.1***#</td>
</tr>
<tr>
<td>Night (mmHg)</td>
<td>104 ± 6.5</td>
<td>113 ± 9.8</td>
<td>127 ± 16.1***###</td>
</tr>
<tr>
<td>ΔDay – night (%)</td>
<td>12.9 ± 2.6</td>
<td>13.0 ± 5.4</td>
<td>7.9 ± 6.6*</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h (mmHg)</td>
<td>74 ± 4.1</td>
<td>78 ± 10.2</td>
<td>88 ± 11.4***#</td>
</tr>
<tr>
<td>Day (mmHg)</td>
<td>77 ± 7.9</td>
<td>83 ± 7.2</td>
<td>91 ± 11.5***#</td>
</tr>
<tr>
<td>Night (mmHg)</td>
<td>61 ± 2.4</td>
<td>68 ± 6.6</td>
<td>79 ± 12.1***###</td>
</tr>
<tr>
<td>ΔDay – night (%)</td>
<td>20.6 ± 3.1</td>
<td>17.8 ± 5.9</td>
<td>13.2 ± 7.1**</td>
</tr>
</tbody>
</table>

*Significance: *p < 0.05, **p < 0.01 and ***p < 0.001 vs controls; #p < 0.05, ##p < 0.01 and ###p < 0.001 vs IDDM without AN.

(N = 12) and without AN (N = 15) in the group with DDBP ≤ 90 mmHg. The two subgroups did not differ with respect to sex distribution, age, diabetes duration, body mass index, insulin dose or serum creatinine. Compared to patients without AN, those with AN showed higher levels of HbA1c (6.1 ± 1.3 vs 8.1 ± 2.7; p < 0.05) and UAE (9.8 ± 2.4 vs 107 ± 4.1). We also analysed patients with less severe AN. Among those 12 normotensives with AN, we found six with one or two abnormal neurological tests (automatic score 2–4). All these six patients had increased UAE, four of them with values above 70 µg/min. In contrast, only three out of 15 patients without AN (autonomic score 0–1) showed increases in urinary albumin excretion, all of them with values below 70 µg/min (Fisher test; p < 0.02).

As shown in Table 4, no differences were seen in average 24 h day and night systolic and day diastolic BP between normotensive diabetic patients with and without AN, whereas night diastolic BP was significantly increased in patients with AN. The differences between the day and night systolic and diastolic BP also tended to be reduced in patients with AN, but the differences did not achieve statistical significance.

Discussion

The present study shows that signs of AN are associated with nephropathy in IDDM patients. Some clinical and epidemiological studies have also documented the association between these two complications of diabetes (9–11). Our results confirm previous observations that an abnormal BP pattern during sleep occurs in diabetic patients with AN (5–7, 18, 19). The blunted nocturnal fall in BP observed in IDDM patients seems to be dependent on the presence of AN because diabetic patients with normal cardiovascular reflex tests and control subjects displayed similar day/night BP variations. This abnormality in BP profile in neuropathic patients is probably not attributable to hypertension because it was also observed in normotensive diabetic patients with AN. Furthermore the magnitude of the BP fall during sleep was related to the autonomic score, considered as an index of the degree of cardiovascular reflex impairment. In diabetics with AN, signs of sympathetic nerve failure often co-exist with a prevalence of sympathetic tone during the night, due to a blunted vagal activity during sleep (20). The decrease in nocturnal BP fall in diabetic neuropathic patients has been related to this nocturnal sympathetic relative prevalence (21). A decreased BP fall during sleep has been described in IDDM patients with different degrees of diabetic nephropathy (22). In our study, as shown previously by others, this abnormality was found not only in patients with high levels of BP (18) but also in
normotensive microalbuminuric patients (5, 6). Because the occurrence of microalbuminuria reflects the presence of incipient diabetic nephropathy, it is apparent that in IDDM there is an early association between BP dysregulation during sleep and renal lesion. Because evidence exists indicating that AN may be responsible for the altered circadian BP pattern, it is possible that elevated BP during sleep may have a role in the development of diabetic nephropathy. In our study the findings that UAE was related to autonomic score, to diabetic BP during the night and inversely related to the values of day/night BP changes are compatible with a pathogenic relationship between AN and nephropathy. The concept that sympathetic nerve dysfunction may participate in the mechanism of renal lesion is supported by the knowledge that decreased sympathetic nerve activity causes vasodilatation of the preglomerular vessels in the kidney (23). This may favor increases in renal flow and the transmission of the systemic BP to the glomeruli. During the day, decrements in intraglomerular pressure due to sympathetic failure would alternate with increments at night, when the blunted fall in BP results in higher nocturnal blood pressure levels, even in normotensive patients. This would explain the higher nocturnal UAE and nocturnal sodium excretion rates that have been described in diabetic neuropathic patients (24). This renal hemodynamic mechanism has been proposed as the connecting link between AN and the more progressive rate of deterioration in glomerular function in IDDM with AN (25).

In this study, normotensive diabetic patients with AN showed higher diastolic BP at night and higher nocturnal UAE than patients without AN, while day diastolic blood values were not different in these two groups. This could be simply attributable to the fact that patients with AN could have more advanced nephropathy than patients without AN. Although this hypothesis cannot be ruled out, another explanation exists. This considers the possibility of a causal connection between diabetic neuropathy and nephropathy. By blunting the night BP fall, and favoring increases in renal blood flow and intraglomerular pressure at night, the autonomic dysfunction could be the mechanism responsible for the increases in night blood pressure and UAE. Studies in normotensive IDDM patients by Spallone et al. (6) suggest that for a certain value of systolic BP, diabetes with AN would have a higher UAE than diabetics without AN. The possible explanation for this observation considers that the loss of nervous control of renal function would make the kidney more vulnerable to the hemodynamic effects of systemic BP. In keeping with this, the presence of signs of AN predicts a deterioration in the glomerular filtration rate (25).

Diabetic nephropathy is associated with raised arterial blood pressure (1, 2). Because a small increase in BP is an early finding in patients with incipient nephropathy with microalbuminuria (4) and bearing in mind that effective antihypertensive therapy reduces the rate of decline in renal function (26), elevated BP has been thought to promote diabetic nephropathy. Studies examining the chronological and epidemiological relationship between hypertension and diabetic nephropathy have raised the possibility that hypertension may precede or occur very early in the course of renal disease. Nevertheless, it has been considered also that increases in arterial pressure in IDDM patients may
result from renal damage and the question of whether elevation of BP actually precedes or is concomitant with the appearance of incipient nephropathy (1, 2) is currently unsettled. Because the majority of our normotensive patients with autonomic neuropathy were micro- or macroalbuminuric, an altered renal mechanism as a cause of the altered BP profile in these patients should also be considered. Spallone et al. (6), however, could not attribute the blunted nocturnal fall in BP observed in neuropathic patients to the presence of nephropathy. In their study the percentage of microalbuminuric patients was not different among diabetic subjects with and without AN. In addition, the findings reported by Lurbe et al. (5), that some subjects without microalbuminuria already had an abnormal BP pattern during sleep, also suggest a mechanism of BP dysregulation unrelated to renal impairment. Finally it is also possible that these events are concomitant and share an unknown causative factor. In any event, BP dysregulation is present in the early course of diabetic nephropathy and the results of this study bring out the aspect that this early BP abnormality may not be detected through casual BP measurements. Thus, further studies are needed to show whether the loss of the physiological nocturnal fall in BP, detected during ambulatory BP monitoring, is a sensitive marker indicative of the presence of AN and, in this way, useful to detect IDDM normoalbuminuric patients prone to develop diabetic nephropathy.

In conclusion, in IDDM patients, AN and nephropathy are strongly associated. The blunted fall in BP during sleep seems to be related to the presence of AN. This abnormality results in the maintenance of higher BP values at night that, in association with impaired autoregulation of glomerular function, may theoretically contribute to the development of diabetic nephropathy.

References


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