Autonomic Neuropathy Predicts Deterioration in Glomerular Filtration Rate in Patients With IDDM

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OBJECTIVE — To evaluate whether autonomic neuropathy predicts deterioration in glomerular filtration rate in IDDM patients.

RESEARCH DESIGN AND METHODS — A prospective study in which 35 IDDM patients have been followed for 10–11 yr. Autonomic nerve function tests included heart-rate reactions to deep breathing (expiration-to-inspiration ratio) and to tilt (acceleration and brake indexes). GFR was evaluated by the ^{51}Cr-EDTA plasma clearance method.

RESULTS — At entry to the study, no significant differences were noted in age (39 ± 2 [mean ± SE] vs. 42 ± 4 yr), duration of diabetes (20 ± 3 vs. 23 ± 4 yr), supine blood pressures (120/79 ± 3/2 mmHg vs. 121/78 ± 6/3 mmHg), and GFR (113 ± 6 vs. 107 ± 3 ml · min^{-1} · 1.73 m^{-2}) between 20 patients with and 15 without autonomic neuropathy (age-corrected criteria). After 10–11 yr, GFR had decreased significantly (22 ± 4 ml · min^{-1} · 1.73 m^{-2}, $P < 0.001$) in patients with autonomic neuropathy but not (8 ± 5 ml · min^{-1} · 1.73 m^{-2}, NS) in patients without. In keeping with this, GFR decreased more than expected (difference in GFR/expected decrease in GFR) in patients with autonomic neuropathy, compared with those without (4.46 ± 0.98 vs. 0.48 ± 0.73, $P < 0.005$).

CONCLUSIONS — Autonomic neuropathy predicts future deterioration in GFR in IDDM patients.

Autonomic neuropathy is a serious complication of diabetes associated with a high mortality (1). The increased mortality is not attributed solely to sudden death, a feature of autonomic neuropathy (2); in a previous study, half of the deaths in diabetic patients with autonomic neuropathy were attributable to diabetic nephropathy (1). The concomitant occurrence of nephropathy and autonomic neuropathy has been believed to reflect the severity of diabetes—and not causality. In 1985, however, we reported that GFR seemed to deteriorate more than expected in diabetic patients with autonomic neuropathy (3). This report of a putative association between autonomic neuropathy and diabetic nephropathy, as also later suggested by others (4–6), was founded on a 5- to 7-yr period of prospective observation on a cohort of patients with IDDM (7,8). The patients have now been followed for 10–11 yr, and the results are presented here. The major aim of this prospective study was to establish whether signs of autonomic neuropathy predict deterioration in GFR in IDDM patients.

RESEARCH DESIGN AND METHODS

— In the first study, 52 IDDM patients (24 women) were examined (20–72 yr of age, mean 43 yr; duration of diabetes 5–49 yr, mean 23 yr) (7). The 52 patients were invited to a second examination 5–7 yr after the first: 41 agreed to participate in the evaluation of autonomic nerve function (8), and 43 in the evaluation of kidney function (3). Five of the original patients had died before the second study; 2 suddenly (one with autonomic neuropathy), 2 of uremia (both with autonomic neuropathy), and 1 of myocardial infarction (with autonomic neuropathy). At 5–6 yr after the second study, all surviving patients (another patient had died from myocardial infarction and another of unclear cardiovascular cause, both with autonomic neuropathy) were invited to a third study, and 38 accepted. Complete examinations in all three studies were lacking in 3 of 38 patients. Accordingly, 35 patients (14 women) were evaluated three times with regard to autonomic nerve and kidney functions in the 10–11 yr prospective study.

Autonomic nerve function was

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; GFR, GLOMERULAR FILTRATION RATE; E/I RATIO, EXPIRATION/INSPIRATION RATIO; HPLC, HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY; ANOVA, ANALYSIS OF VARIANCE; BP, BLOOD PRESSURE; sBP, SYSTOLIC BLOOD PRESSURE; dBP, DIASTOLIC BLOOD PRESSURE.

Table 1—*GFR, BPs, and R-R intervals (heart-rate frequency) in diabetic patients with and without autonomic neuropathy*

	Autonomic neuropathy		*P* value between groups
	Without	With	
n	15	20	
GFR (ml · min^{-1} · 1.73 m^{-2})			
First study	107 ± 3	113 ± 6	NS
Second study	111 ± 5	106 ± 5	NS
Third study	100 ± 6	92 ± 5*	NS
Supine BPs (mmHg)			
First study	121/78 ± 6/3	120/79 ± 3/2	NS
Second study	135†/82 ± 4/2	141‡/88§ ± 3/2	NS
Third study	144‖/81 ± 4/2	147/84 ± 5/2	NS
R-R intervals (s)			
First study	0.840 ± 0.031	0.749 ± 0.025	$P < 0.05$
Second study	0.777 ± 0.024	0.751 ± 0.024	NS
Third study	0.809 ± 0.024	0.770 ± 0.022	NS

Data are means ± SE.
*$P < 0.01$ compared with the second study.
†$P < 0.02$ compared with the first study.
‡$P < 0.005$ compared with the first study.
§$P < 0.01$ compared with the first study.
‖$P < 0.05$ compared with the second study.

evaluated by the heart rate reactions to deep breathing (E/I ratio, mean R-R interval during expiration/mean R-R interval during inspiration) (9) and to a fast 90° tilt (acceleration and brake indexes) (10). The immediate heart-rate reaction to a fast (2-s) 90° head-up tilt features an immediate acceleration followed by a transient deceleration (10). The immediate changes in heart rate are evaluated by the acceleration index, [(A − B)/A] × 100, where A = mean R-R interval 1 min before tilt and B = shortest R-R interval before the deceleration, and the brake index, [(C − B)/A] × 100, where C = longest R-R interval after B during the deceleration, as described previously (10). BPs were recorded in supine position 4 min before tilt and then every minute after. Autonomic neuropathy was defined as at least one autonomic neuropathy index 1.5 SD below the age-related reference value (i.e., Z scores were used to match for the influence of age on autonomic nerve test results) for the E/I ratio, acceleration index, and/or the brake index (11,12). Reference material for BPs was 56 healthy subjects (16–59 yr of age, mean 40 yr) (13).

GFR was evaluated by the ^{51}Cr-EDTA plasma clearance method (14). A decrease in GFR >0.4 ml · min^{-1} · yr^{-1} in patients 20–50 yr old and >1 ml · min^{-1} · yr^{-1} in patients >50 yr old was considered as a decrease greater than normally expected (15), and this was expressed as a GFR deterioration index (difference in GFR between the first and the third study/expected decrease in GFR between the first and the third study); an index value of 1 indicates that GFR had decreased as expected. The first and the second study were conducted in 1976–1978 and 1982–1983, respectively, before the concept of microalbuminuria as a predictor of diabetic nephropathy was introduced (16) and, therefore, microalbuminuria was not assessed in these studies. In the third study, however, albuminuria was determined in some (24 of 35) patients in whom the frequency of microalbuminuria (30–300 mg albumin/24 h) (17) could be assessed. To evaluate metabolic control, HbA_{1c} was determined in the second (isoelectric focusing) (18) and the third (HPLC) (19) study; no HbA_{1c} assay was available in the first study.

Statistical analysis

Friedman's test was used in intragroup ANOVA and when significant Wilcoxon's paired test was used. In intergroup analysis, the Kruskal-Wallis test was used for ANOVA and when the significant Mann-Whitney *U* test was applied. Spearman's rank correlation test was used for determination of *r* values, and the χ^2 test with contingency correction when differences in frequency was compared. Multiple and stepwise regression was conducted, and, as in all tests, the StatView II software version 1.03 (Abacus, Berkley, CA) was used. All tests were two-tailed and $P < 0.05$ was considered significant. Data are presented as means ± SE.

RESULTS — In the first and the second study, 20 (6 women) patients demonstrated autonomic neuropathy on both occasions; 15 patients had concordant abnormal E/I ratios, 4 concordant abnormal acceleration indexes, and 9 concordant abnormal brake indexes. In the first study, no significant differences were observed in age (39 ± 2 vs. 42 ± 4 yr), duration of diabetes (20 ± 3 vs. 23 ± 4 yr), and GFR (Table 1) between patients with and without autonomic neuropathy; low GFR (<80% of expected values) (15) was shown in 1 patient with and 1 patient without autonomic neuropathy. In the first study, 1 patient without autonomic neuropathy (on a β-blocker), and in the second study, 3 patients with (1 on a β-blocker and a diuretic, 2 on diuretics only) and 2 without (1 on a β-blocker, 1 on a diuretic) autonomic neuropathy were treated for hypertension.

During the 10–11 yr, patients with autonomic neuropathy showed a significant decrease (22 ± 4 ml · min^{-1} ·

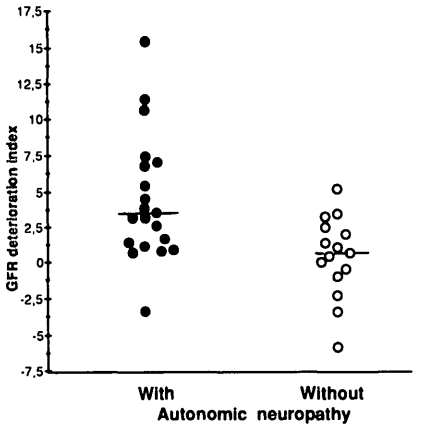

Figure 1—*GFR deterioration index in patients with (n = 20, ●) and without (n = 15, ○) autonomic neuropathy, prospectively followed for 10–11 yr. An index >1 indicates that GFR deteriorates greater than expected. Horizontal line indicates median.*

1.73 m^{-2}, $P < 0.001$) in GFR that essentially occurred between the second and third study (Table 1) while GFR did not change (8 ± 5 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, NS) in the 15 patients without autonomic neuropathy. In keeping with this, GFR decreased significantly more (greater than fourfold) than expected (Fig. 1) in patients with autonomic neuropathy, compared with patients without (GFR deterioration index 4.46 ± 0.98 vs. 0.48 ± 0.73, $P < 0.005$). The brake index (first study) correlated with GFR in the second ($r = 0.41$, $P < 0.02$) and in the third study ($r = 0.54$, $P < 0.005$), with the difference in GFR between the first and the third study ($r = -0.43$, $P < 0.02$), and with the GFR deterioration index ($r = -0.37$, $P < 0.05$).

No significant differences in supine BPs were observed between patients with and without autonomic neuropathy in the first study (Table 1). Moreover, BPs increased during the 10–11 yr to about the same extent in patients with and without autonomic neuropathy, although the increase seemed to be established earlier (second study) in patients with autonomic neuropathy. Even though the tendency was for a higher prevalence in patients with autonomic neuropathy in the third study, the frequency of patients treated for hypertension did not differ significantly between patients with and without autonomic neuropathy (first study: 0 of 20 vs. 1 of 15; second study: 3 of 20 vs. 2 of 15; third study: 9 of 20 vs. 3 of 15). In the third study, as in the first and second, β-blockers and diuretics were the major antihypertensive agents used in the patients. Only 3 patients (all with autonomic neuropathy) had other kinds of treatment; 1 was treated with an angiotensin converting enzyme inhibitor, and 2 were on calcium-channel blockers. During the years, metabolic control (HbA_{1c}) did not differ significantly between patients with and without autonomic neuropathy (second study: 10.8 ± 0.4 and 10.3 ± 0.4% [isoelectric focusing; reference values 5.1–7.5%]; third study: 7.69 ± 0.27 and 7.67 ± 0.37% [HPLC, reference values 4.0–5.3%]). Albuminuria was assessed in 24 patients (16 with autonomic neuropathy) in the third study; 5 of 16 patients with and 0 of 8 without autonomic neuropathy demonstrated macroalbuminuria (>300 mg/24 h), 6 of 16 patients with and 3 of 8 without autonomic neuropathy displayed microalbuminuria (30–300 mg/24 h) and 5 of 16 patients with and 5 of 8 without lacked albuminuria (<30 mg/24 h).

In the first study, the immediate (Δ 0–1 min) sBP fell significantly after tilt in patients with autonomic neuropathy compared with control subjects (−7 ± 3 vs. 1 ± 1 mmHg, $P < 0.01$). In addition to this, the immediate (Δ 0–1 min) dBP increased significantly less both in patients with (2 ± 2 mmHg; $P < 0.02$) and without (2 ± 1 mmHg, $P < 0.02$) autonomic neuropathy compared with control subjects (6 ± 1 mmHg) after tilt. The Δ 0–1 min dBP after tilt (first study) correlated with GFR in the second ($r = -0.51$, $P < 0.005$) and in the third ($r = -0.37$, $P < 0.05$) study in all patients and Δ 0–1 min sBP after tilt (first study) correlated with GFR in the third study ($r = -0.55$, $P < 0.05$) in patients with autonomic neuropathy. No significant correlations were seen between the brake index and Δ 0–1 min sBP and dBP. Using multiple and stepwise regression, the brake index (first study), and not the Δ 0–1 min sBP and dBP (first study), correlated with GFR (third study).

To evaluate the consistency of autonomic nerve function, the age-corrected values for the three different autonomic indexes were compared in the three studies. Autonomic nerve function did not change significantly in patients with autonomic neuropathy whereas the acceleration ($P < 0.05$) and brake index ($P < 0.05$) decreased slightly (Friedman's test) in patients without autonomic neuropathy (Table 2). Hence, differences in autonomic nerve indexes between patients with and without autonomic neuropathy became less evident with time. In fact, only the brake index constantly displayed significant differences between the two patient groups during the 10–11 yr of observation.

CONCLUSIONS— Our prospective study demonstrated that signs of autonomic neuropathy predicted deterioration in GFR in IDDM patients. Note that the association between autonomic neuropathy and deterioration in GFR was unrelated to age, duration of diabetes, and supine BPs. Disturbed sBP and dBP reactions to tilt in the first study correlated, however, with GFR in the third study and, therefore, sympathetic nerve failure may be a factor behind the deterioration in GFR. This study confirms that autonomic neuropathy may contribute to the development of diabetic nephropathy (3–6). If autonomic neuropathy is involved in deterioration of GFR, possible mechanisms need to be discussed.

Autonomic neuropathy has at least two components—parasympathetic and sympathetic neuropathy. Although parasympathetic neuropathy might be a

Table 2—*Autonomic neuropathy indexes (age-corrected values) in patients with and without autonomic neuropathy*

	Autonomic neuropathy		*P* value
	Without	With	between groups
n	15	20	
E/I ratio (SD)			
First study	−1.11 ± 0.18	−1.90 ± 0.22	<0.01
Second study	−1.12 ± 0.14	−1.71 ± 0.15	NS
Third study	−1.06 ± 0.17	−1.67 ± 0.14	NS
Acceleration index (SD)			
First study	0.03 ± 0.19	−0.87 ± 0.22	<0.005
Second study	−0.87 ± 0.26*	−1.48 ± 0.17	NS
Third study	−0.63 ± 0.27	−1.20 ± 0.19	NS
Brake index (SD)			
First study	−0.07 ± 0.26	−1.62 ± 0.18	<0.001
Second study	−0.59 ± 0.24	−1.35 ± 0.29	<0.01
Third study	−0.66 ± 0.23	−1.27 ± 0.13	<0.02

Data are means ± SE. SD indicates age-corrected values (Z score) expressed in SDs.
*$P < 0.02$ compared with the first study.

primary event (20), as also indicated by the increased heart rate in our patients with autonomic neuropathy, recent studies have shown that sympathetic neuropathy may develop not only in parallel with (21) but also before parasympathetic neuropathy (22,23). The indexes of autonomic neuropathy in this study evaluated parasympathetic as well as sympathetic neuropathy. The E/I ratio (heart-rate reaction to deep breathing), a test of parasympathetic neuropathy (9), was unrelated to alterations in GFR. Hence, parasympathetic neuropathy seems to be of less importance for kidney function than sympathetic nerve dysfunction. Low brake indexes, measuring disturbances in the transient deceleration of the heart after tilt, were clearly associated, however, with deteriorations in GFR. Disturbed brake function is related to sympathetic nerve failure as shown from impaired responses of plasma catecholamines to exercise (24) and increased norepinephrine efflux rate from thrombocytes (25) in IDDM patients with abnormal brake indexes. Therefore, in agreement with found correlation between orthostatic BP falls and decreases in GFR, sympathetic dysfunction seemed to be associated with impairment in GFR. We speculate that slight postural BP falls during daily activities have an adverse effect on GFR.

The concept that sympathetic nerve failure was related to deterioration in GFR is supported by previous morphological findings; renal glomeruli and tubulus are innervated by sympathetic nerves only (26). Further evidence for the importance of sympathetic nerves for kidney function can be provided. Sympathetic denervation increases renal sodium excretion (27), decreased sympathetic nerve activity decreases renal vascular resistance (28), and increased sympathetic nerve activity constricts preglomerular vessels in the kidneys (29). Recently, Mølgaard et al. reported an association between disturbed parasympathetic nerve function and diabetic nephropathy (30). This does not argue against an association between sympathetic neuropathy and renal dysfunction: sympathetic nerve function was not evaluated in that study. In our study, the majority of patients (15 of 20) with autonomic neuropathy showed signs of parasympathetic neuropathy (abnormal E/I ratios) but, despite this, only sympathetic nerve dysfunction (abnormal brake function and impaired BP reactions to tilt) was related to deterioration in GFR. Coexisting sympathetic neuropathy in patients with parasympathetic neuropathy most likely explains Mølgaard's observation.

The dissociation between orthostatic BPs and brake indexes with regard to end-point GFR, after correlation and regression analysis, indicates that postural BP falls, a bad prognostic sign in diabetic patients (5,17,31), not is the only factor behind deteriorations in GFR. Instead, abnormal BP regulation might be involved. Ambulatory 24-h BP recordings have shown that BPs during the night do not decrease (32–34) in diabetic patients with autonomic neuropathy. Accordingly, patients with diabetic autonomic neuropathy will have a higher intraglomerular pressure at night compared with patients without autonomic neuropathy. The connection between alterations in renal function and abnormal cardiovascular reflexes would then be analogous to reported associations between autonomic neuropathy and cardiac dysfunction (35). Interestingly, the excretion of sodium (4,36) and albumin (4) is increased at night in diabetic patients with autonomic neuropathy, which fits well with the concept of increased nocturnal intraglomerular pressure in diabetic autonomic neuropathy and also with the increased renal sodium excretion in the experimental situation (27). In this context, it has to be clarified that kidney functions in the patients in general were normal; only 2 patients in the first study and 3 patients in the second study showed a low GFR (<80% of the expected value [15]). Cardiovascular autonomic dysfunction as reported in diabetic patients with overt kidney failure (37–38) cannot explain our findings.

Both overt diabetic nephropathy featuring persistent albuminuria (>300 mg/24 h) with a relentless decline in GFR

(39) and incipient nephropathy with microalbuminuria (16,40) are associated with raised arterial BP. Because a small increase in BP is an early finding in patients with microalbuminuria (41) and antihypertensive treatment in diabetic nephropathy inhibits progression of nephropathy (42–44), elevated BPs have been thought to promote diabetic nephropathy. The recent finding, however, that angiotensin-converting enzyme inhibitor treatment postpones nephropathy in normotensive IDDM patients with microalbuminuria (45) raises the issue that elevated systemic BPs in the initial phase of nephropathy are unrelated to progression of nephropathy. In fact, it has been difficult to connect deterioration in kidney function to arterial pressure (46). In keeping with this, improvement in glycemic control but not in BP levels prevented deterioration in GFR in diabetic patients; actually elevations in BPs occurred in parallel with deterioration in GFR (47). The lack of predictive value of supine BPs with regard to deterioration in GFR in our study is therefore not surprising. Local factors in the kidneys (48) may operate, but our study argues for a role for autonomic neuropathy in the pathogenesis of diabetic nephropathy. Although, angiotensin-converting enzyme inhibition prevents nerve dysfunction in experimental diabetes (49) and arteriovenous shunts, closed by ephedrine when localized to the legs in diabetic patients with autonomic neuropathy (50), have been found in the juxtamedullary cortex of human kidney (51), our study cannot establish how autonomic neuropathy impairs GFR. Nevertheless, the hypothesis that decrements in intraglomerular pressure during day time and increments in intraglomerular pressure at night time are the connecting links between autonomic neuropathy and progressive deteriorations in GFR is plausible.

If autonomic neuropathy contributes to the development of diabetic nephropathy, it does not exclude that other factors are important. Familiar clustering of cardiovascular disease (52), whether or not related to abnormalities in red cell sodium-lithium countertransport (53,54), could still be operating as an augmenting factor.

This study gave us the opportunity to test the consistency of autonomic nerve function tests when the duration of diabetes increases. As recently shown by Sampson et al. (5), abnormal autonomic nerve function was remarkably constant and consistent. Our study, as well as Sampson et al.'s (5), indicate that autonomic nerve damage may occur early in diabetes and that further deterioration is rare. In fact, slight deteriorations in autonomic nerve function was only shown in patients without autonomic neuropathy. The prognosis regarding mortality could not be appropriately assessed in our study because of the limited number of patients studied. According to Ewing et al. (1), however, we found the mortality to be essentially confined to patients with autonomic neuropathy. The prognosis versus life was less severe than in Ewing et al.'s (1) study, on the other hand, and more in agreement with Sampson et al.'s experience (5). Nevertheless, our prospective study, as well as the studies of Ewing and Sampson et al.—until now the only major prospective studies of autonomic neuropathy reported—demonstrate that autonomic neuropathy is a serious condition in diabetic patients.

In conclusion, autonomic neuropathy predicts deteriorations in GFR. Future studies will show whether autonomic nerve function tests have the clinical utility to identify individuals at risk for deteriorations in GFR.

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