Autonomic Symptoms and Diabetic Neuropathy

A population-based study

PHILLIP A. LOW, MD
LISA M. BENRUD-LARSON, PHD
DAVID M. SLETTEN
TONETTE L. OPFER-GEHRKING
STEPHEN D. WEIGAND, MS
PETER C. O'BRIEN, PHD
GUILLERMO A. SUAREZ, MD
PETER J. DYCK, MD

OBJECTIVE — The prevalence of autonomic symptoms and deficits in certain systems is known, but a comprehensive autonomic symptom profile in diabetes is not available. We aimed to estimate this using a laboratory evaluation of autonomic function and a validated self-report measure of autonomic symptoms in patients and matched control subjects from the population-based Rochester Diabetic Neuropathy Study.

RESEARCH DESIGN AND METHODS — Participants included 231 patients with diabetes (type 1, $n = 83$; type 2, $n = 148$) and 245 healthy age-matched control subjects. We assessed symptoms using a validated self-report instrument (Autonomic Symptom Profile) and evaluated the severity and distribution of autonomic deficits (cardiovagal, sudomotor, adrenergic) with the objective, laboratory-based Composite Autonomic Severity Score (CASS).

RESULTS — Autonomic symptoms were present more commonly in type 1 than in type 2 diabetes, with symptoms of orthostatic intolerance, secretomotor, urinary control, diarrhea, and sleep disturbance and pupillomotor, vasomotor, and erectile dysfunction significantly increased over healthy control subjects in type 2 diabetic patients. The prevalence of autonomic impairment was 54% in type 1 and 73% in type 2 diabetic patients. Severity of autonomic failure was mild overall (mean CASS 2.3; maximum 10), with orthostatic hypotension occurring in 8.4 and 7.4% of type 1 and 2 diabetic patients, respectively. Fourteen percent of patients had a CASS ≥5, indicating moderate to severe generalized autonomic failure. The correlation of symptoms with autonomic deficits (CASS) was better in type 1 than type 2 diabetic subjects and was weak overall.

CONCLUSIONS — These findings indicate that autonomic symptoms and deficits are common in diabetes, but mild in severity, and that the correlation between symptom scores and deficits is overall weak in mild diabetic neuropathy, emphasizing the need to separately evaluate autonomic symptoms.

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Peripheral neuropathy is a common complication of diabetes. Dyck et al. (1) reported a neuropathy prevalence of 66% in type 1 and 59% in type 2 diabetes in the Rochester, Minnesota, population. Autonomic fiber involvement can occur as a component part of the neuropathy or in isolation. The "prevalence" of autonomic neuropathy, based on autonomic testing, is reported to be between 7.7 and 90% (2), but the 16 studies reviewed generally were not population based. There is information on the prevalence of autonomic symptoms affecting specific regions such as the gastrointestinal tract (3–5) and erectile dysfunction (6), but information is lacking on a comprehensive evaluation using a validated symptom profile (7,8). We have, therefore, undertaken a laboratory evaluation of autonomic function (cardiovagal, adrenergic, sudomotor) and related that to findings from a validated, comprehensive self-report instrument to evaluate autonomic symptoms (7,8) in patients and matched control subjects in the population-based Rochester Diabetic Neuropathy Study.

RESEARCH DESIGN AND METHODS

— Potential study participants were identified from a database of patients enrolled in the Rochester Diabetic Neuropathy Study (9) and recruited via mail. At the prevalence date (1 July 1986), all known patients with diabetes in Rochester, Minnesota, were invited to participate in a cross-sectional and longitudinal study of the prevalence, incidence, course, and risk factors for complications in diabetes (1,10). The participating cohort is representative of diabetic patients mainly of Northern European extraction. As part of the Rochester Diabetic Neuropathy Study, patients complete general medical and neurological evaluations and a full autonomic reflex laboratory evaluation annually. Patients enrolled in the Rochester Diabetic Neuropathy Study who had not completed the self-report Autonomic Symptom Profile (ASP) (see MEASURES) within 2 years before the start of the study were contacted via mail ($n = 204$) and asked to participate in the study. Inclusion/exclusion criteria and demographics of this cohort have been fully described (1,10,11). Of the 204 patients contacted by mail, 18 (9%) were either deceased or too ill to participate. One hundred seventy-six patients (86%) returned a completed ASP. An additional 55 patients in the Rochester Diabetic Neuropathy Study had completed an ASP during a visit to the Mayo Clinic, resulting in a final sample size of 231. Participants completed the ASP within 6 months of their last autonomic reflex laboratory evaluation. The study protocol was approved by the Mayo

From the Mayo Clinic, Rochester, Minnesota.
Address correspondence and reprint requests to Phillip A. Low, MD, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: low@mayo.edu.
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Abbreviations: ASP, Autonomic Symptom Profile; CASS, Composite Autonomic Severity Score.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Demographic and clinical characteristics of patients with type 1 and type 2 diabetes*

	Type 1 diabetes*	Type 2 diabetes*
n	83	148
Sex (women)	53%	45%
Race (white)	100%	98%
Age (years)	50.9 ± 14.7	64.1 ± 11.7†
Weight (kg)	79.8 ± 17.0	93.8 ± 22.6†
BMI (kg/m^2)	27.9 ± 6.0	33.4 ± 7.5†
Duration of diabetes (years)	24.3 ± 11.1	15.3 ± 8.6
HbA_{1c} (%)	7.4 ± 1.0	7.2 ± 0.9

Data are mean ± SD unless otherwise indicated. *Group sizes vary due to missing data in some domains. †$P < 0.01$

Clinic Institutional Review Board, and data were collected between 1999 and 2001.

The sample of healthy control subjects on which the ASP normative data are based consisted of 245 participants drawn from the population-based Rochester Diabetic Neuropathy Study normal control subjects to ensure comparable age and sex distribution. The demographics of this cohort have been fully described (12).

Measures

ASP. The ASP is a self-report instrument of 169 questions designed to provide an index of autonomic symptom severity (7,8). It yields one total score reflecting overall severity of autonomic symptoms and 11 weighted subscale scores that assess severity of symptoms within the following domains: orthostatic intolerance, syncope, sexual failure (men only), bladder dysfunction, diarrhea, constipation, upper gastrointestinal symptoms, secretomotor dysfunction, sleep dysfunction, vasomotor symptoms, and pupillomotor symptoms. The total score is calculated by summing the individual scale scores. ASP scores have been shown to correlate with objective indexes of autonomic function (7,8). Our group recently calculated norms for the ASP based on a sample of 245 healthy control subjects (see RESULTS) who completed the ASP between April 1993 and April 2001.

Composite Autonomic Severity Score. As part of the Rochester Diabetic Neuropathy Study, participants had undergone a standard autonomic reflex screen at the Mayo Clinic Autonomic Reflex Laboratory. This test evaluates the severity and distribution of postganglionic sudomotor, adrenergic, and cardiovagal function (13). Sympathetic postganglionic cholinergic function is assessed using the quantitative sudomotor axon-reflex test, which quantitatively evaluates the postganglionic sympathetic sudomotor axon at the forearm and three lower extremity sites. Sympathetic adrenergic function is assessed by beat-to-beat blood pressure and heart rate responses to head-up tilt and the Valsalva maneuver. Cardiovagal function is evaluated by the heart rate responses to deep breathing and the Valsalva maneuver. Results are compared with a normative database of 557 normal subjects (14). Based on the results of the autonomic reflex screen, a 10-point Composite Autonomic Severity Score (CASS) is generated that corrects for the confounding effects of age and sex (13). The 10-point total CASS score is divided into three subscales: adrenergic (range 0–4), sudomotor (0–3), and cardiovagal (0–3). Generally, a total CASS score ≤3 indicates no or mild autonomic failure, scores from 4 to 6 indicate moderate autonomic failure, and scores from 7 to 10 indicate severe autonomic failure (13,14). Orthostatic hypotension was defined as a fall in systolic blood pressure ≥30 mmHg at 1 min of head-up tilt, which corresponds to ≥97.5 percentile of control subjects (14).

Data analysis

Before analyzing the data collected from the diabetic sample, we transformed participants' raw scores on several of the ASP domains to standardized scores based on a sample of 245 healthy control subjects who completed the ASP between April 1993 and April 2001. We used the methodology of Dyck et al. (11) for calculating standardized scores. Briefly, this method uses least squares regression modeling among control subjects to determine whether the mean and the variability about the mean of the variable for which standardized values are desired (e.g., ASP domain scores) change with the level of one or more covariates. The covariates of interest for the ASP were age, sex, race (white versus nonwhite), height, and weight. The standardized scores for each domain score control for the covariates that demonstrated a significant relationship with that domain (e.g., if urinary scores depended on age, but not height, weight, or sex, only age is accounted for in the final standardized score). The standardized scores have a Gaussian distribution with a mean of 0.00 ± 1.00. Consequently, the value can be interpreted as the number of standard deviations above or below the mean of healthy control subjects. Due to a preponderance of zero values among the original healthy control sample, three ASP domains were unsuitable for standardized scores: upper gastrointestinal symptoms, vasomotor, and syncope. Consequently, any analyses on these domains were conducted with raw scores instead of standardized scores. Group comparisons among patients with type 1 and type 2 diabetes and control subjects on the ASP domain scores were conducted with one-way analysis of variance tests when standardized scores were available and with Kruskal-Wallis when raw scores were used. When indicated, post hoc pairwise comparisons were made with Tukey's Honestly Significant Different Test or Mann-Whitney *U* tests and Bonferroni corrections. Mann-Whitney *U* tests evaluated differences between patients with type 1 and type 2 diabetes on the CASS, and comparisons of percentages between groups were made using χ^2 tests. Associations between the ASP domains and the CASS were evaluated using Spearman correlations.

RESULTS

The diabetes sample (n = 231) was 99% white, was 52% male, and had a mean age of 59.4 ± 14.3 years. Table 1 presents a breakdown of demographic and clinical characteristics by type of diabetes. Patients with type 2 diabetes were significantly older than those with type 1 diabetes ($P < 0.001$) and had significantly greater body weight ($P < 0.001$). Patients with type 1 diabetes had been living with diabetes significantly longer than those with type 2 diabetes ($P < 0.001$). Sex and race distributions did not differ significantly between the

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Table 2—*Mean scores on autonomic symptom profile domains*

ASP domain	Type 1 diabetes*	Type 2 diabetes*	Healthy control subjects*
Orthostatic intolerance†	0.13	0.30	0.08‡
Secretomotor†	0.46	0.68	0.08‡§
Urinary†	0.14‡	0.44§	0.07‡
Diarrhea†	−0.02‡	0.40§	0.07‡
Constipation†	0.13	0.28	0.08
Sleep†	0.27	0.38	0.07‡
Pupillomotor†	1.01	1.20	0.69‡§
Male sexual failure†	1.00	0.76	−0.02‡§
Vasomotor‖	0.82 ± 1.91	0.98 ± 1.98	0.40 ± 1.34‡
Upper gastrointestinal symptoms‖	0.36 ± 1.06	0.48 ± 0.94	0.18 ± 0.72‡
Syncope‖	0.36 ± 2.36	0.38 ± 1.95	0.08 ± 0.57

Data are mean ± SD unless otherwise indicated. *Group sizes vary due to missing data in some domains. †Standardized scores. ‡Significantly different from type 2 group ($P < 0.05$). §Significantly different from type 1 group ($P < 0.05$). ‖Raw scores (maximum possible vasomotor score 10; maximum possible upper gastrointestinal score 10; maximum possible syncope score 20).

two groups. The sample of healthy control subjects on which the ASP normative data are based consisted of 245 participants (45% male, 92% white) with a mean age of 50.4 years.

Table 2 presents mean scores on the 11 ASP domains. Scores are expressed as standardized scores when available (for eight domains, see DATA ANALYSIS and table legends) and otherwise as raw scores and standard deviations. Patients with type 1 diabetes differed from control subjects on only 3 of the 11 domains: secretomotor function, pupillomotor function, and sexual failure (men only). Patients with type 2 diabetes tended to have slightly higher scores on the ASP than those with type 1 diabetes and differed significantly from control subjects on 9 of the 11 ASP domains. Overall, the patients with diabetes did not achieve highly elevated scores on the ASP, suggesting only limited autonomic dysfunction in this group.

Prevalence of autonomic neuropathy

Autonomic neuropathy, defined as a minimum score of 1 in at least two of the three CASS domains (cardiovagal, sudomotor, adrenergic) or a minimum score of 2 in one domain, was present in 54% of type 1 and 73% of type 2 patients ($P < 0.01$) (Table 3). The prevalence of autonomic neuropathy in this study is very similar to the reported prevalence of diabetic peripheral neuropathy (66% in type 1; 59% in type 2) (1). The mean sudomotor (0.69; maximum 3), cardiovagal (0.84; maximum 3), and adrenergic (0.75; maximum 4) CASS scores and a total CASS score of 2.27 (maximum 10) indicate that the patients on average had mild autonomic failure (8). The distribution of scores was skewed toward the lower scores. However, there was a subset of patients with generalized autonomic failure (Fig. 1) comprising 14% who had CASS ≥5 ($N = 33$ [$n = 9$ type 1 diabetic, $n = 24$ type 2 diabetic patients]), which was indicative of moderate to severe generalized autonomic failure. Seven (8.4%) type 1 diabetic patients and 11 (7.4%) type 2 diabetic patients had orthostatic hypotension.

Group comparisons: type 1 versus type 2 diabetes

Results revealed only limited differences in autonomic function between patients with type 1 and type 2 diabetes. On the ASP, participants with type 2 diabetes had significantly higher scores on the diarrhea ($P = 0.001$) and urinary ($P = 0.03$) domains compared with participants with type 1 diabetes (Table 2). Participants with type 2 diabetes also received significantly higher scores on the CASS cardiovagal scale (type 1 mean 0.84; type 2 mean 1.24; $P = 0.005$) than participants with type 1 diabetes. In addition, those with type 2 diabetes were significantly more likely to have a diabetic autonomic neuropathy, as indicated by a CASS total score ≥2 ($P = 0.006$), than those with type 1 diabetes (Table 3).

Relationship between CASS and ASP

Table 4 presents the Spearman correlations between CASS and ASP scores for the type 1 and type 2 diabetic groups. As shown, the pattern of correlations differed somewhat between groups. Among the type 1 patients, the most significant relationships were among CASS and secretomotor, urinary, sleep, and pupillomotor symptoms. In contrast, there were virtually no significant relationships between the CASS and the ASP in patients with type 2 diabetes. Correlations that are significantly different between patients with type 1 and type 2 diabetes are presented in bold.

CONCLUSIONS — This study was undertaken to address the question of the prevalence of autonomic symptoms in patients with diabetes and to relate these findings to autonomic deficits. The present study is unique in that we use a comprehensive validated instrument, the ASP, consisting of 169 questions in 11 domains and relate the findings to a comprehensive battery of autonomic tests (CASS). Previously reported prevalences (e.g., 3–6) were either not true prevalences because the studies were not pop-

Table 3—*Percentage of patients with scores of 0, 1, and ≥2 on the CASS*

CASS scale	Range	Type 1 diabetes* Score = 0	Type 1 diabetes* Score = 1	Type 1 diabetes* Score ≥2	Type 2 diabetes* Score = 0	Type 2 diabetes* Score = 1	Type 2 diabetes* Score ≥2
Sudomotor	0–3	49%	38%	13%	38%	40%	22%
Cardiovagal	0–3	48%	25%	27%	28%	28%	44%
Adrenergic	0–4	50%	34%	16%	52%	32%	16%
Total	0–10	24%	22%	54%	9%	18%	73%
Presence of neuropathy (CASS total ≥2)			54%		73%†		
n			68			134	

*Group sizes smaller due to missing data; †$P < 0.01$.

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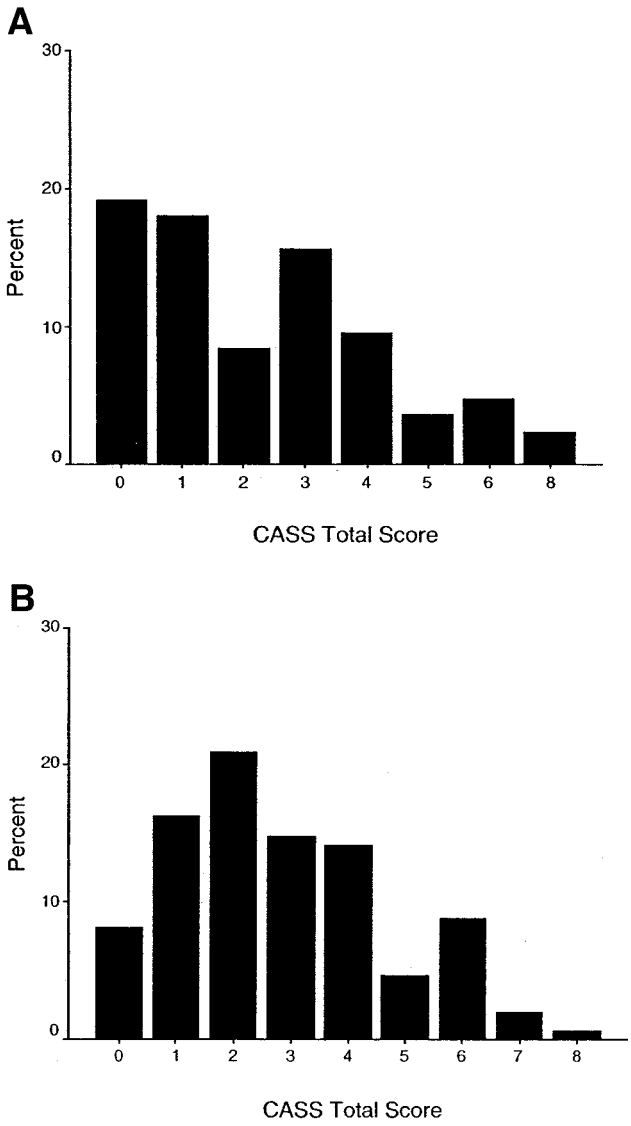

Figure 1—*A: Distribution of CASS total scores for patients with type 1 diabetes,* n = *68. B: Distribution of CASS total scores for patients with type 2 diabetes,* n = *134.*

ulation based or were confined to a limited region or system. Other investigators have focused on defining the presence of autonomic deficits, usually impairment of heart rate variation (15–17).

The ratio of type 1 to type 2 diabetic patients in this population is somewhat larger than usually reported for white patients. This is mainly due to the use of the National Diabetes Data Group criteria for diabetes (milder type 2 diabetic patients being excluded) and use of strict criteria for type 1 diabetes (C-peptide response to glucagon infusion (10). Some patients who fulfill American Diabetes Association criteria for type 2 diabetes would not have been included here. The other possibility of selection bias is unlikely because all known individuals with diabetes were contacted and all volunteers participated. By the criteria of comorbidity and for individuals <75 years old, a significant difference was not found between volunteers and nonvolunteers.

Autonomic function tests have been an integral component of the Rochester Diabetic Neuropathy Study. Autonomic impairment has been one criterion in the composite diagnosis of neuropathy (10,11). Earlier publications addressed the issue of prevalence of symptomatic visceral autonomic neuropathy and orthostatic hypotension but did not address the prevalence of autonomic neuropathy (1). The present finding of orthostatic hypotension in 8.4 and 7.4% of type 1 and type 2 diabetes, respectively, is quite consistent with earlier reports from this population (1). We used the criterion of 30 mmHg systolic blood pressure since the 97.5 percentile fall in blood pressure for our normal subjects was 29 mmHg (14). If we were to use the consensus criterion of 20 mmHg, the corresponding percentages of OH for type 1 and type 2 diabetes would be higher at 22.9% (n = 19) and 16.2% (n = 24), respectively. Only 14% of patients had a CASS ≥5, emphasizing the mildness of autonomic involvement in the majority of patients. The similar percentages for peripheral neuropathy and autonomic neuropathy emphasize the fact that autonomic neuropathy is an integral part of most cases of peripheral neuropathy (1).

Apart from patient selection, prevalence depends on the end points selected to define the presence of neuropathy. Autonomic testing needs to be sufficiently sensitive to detect the presence of dysautonomia (18). It needs to be specific enough to ensure the deficits are truly due to involvement of autonomic nerves. The battery of tests also needs to be sufficiently comprehensive to define the severity and distribution of autonomic failure over a range of autonomic functions. Our selection of tests was made to provide a comprehensive evaluation of sudomotor, adrenergic, and cardiovagal functions (18). We used CASS scoring instead of percentiles for a number of reasons. Although we have a large normative database of 557 normal subjects aged 10–85 years (14,19) and have percentiles for the majority of tests, there are a number of practical limitations. First, the distribution of results was not normal for all tests. Second, providing percentiles (and normal deviates) for each test results in an unmanageable number of indexes. For instance, quantitative sudomotor axon-reflex test alone has four sites and, therefore, four sets of values. Third, adrenergic deficits are defined according to changes in blood pressure in response to head-up tilt and the Valsalva maneuver. The number of parameters evaluated in beat-to-beat arterial waveform is large, and difficulties in quantitating these variables render the percentile approach impractical. CASS values define deficits that are corrected for age and sex (14,19). A score of 1 indicates a score that is between the 1st percentile and a loss of up to 25%

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Table 4—*Spearman correlations between ASP domain scores and CASS scores for patients with type 1 and type 2 diabetes**

	CASS scales			
ASP domains	Sudomotor	Cardiovagal	Adrenergic	Total
Orthostatic intolerance	−0.03 ≈ 0.07†	0.08 ≈ 0.00	0.03 ≈ −0.17	0.04 ≈ −0.03
Secretomotor	0.32 ≈ 0.03‡	0.24 ≈ 0.06	0.40 > 0.04§	0.37 > 0.05§
Urinary	0.21 ≈ 0.00	0.24 ≈ 0.12†	0.32 > −0.05§	0.37 > 0.05§
Diarrhea	0.11 ≈ −0.03	0.20 ≈ 0.02	−0.07 ≈ −0.18‡	0.08 ≈ −0.09
Constipation	0.17 ≈ 0.00	0.28 ≈ 0.14‡	0.11 ≈ 0.12	0.22 ≈ 0.12
Sleep	0.22 ≈ 0.03	0.35 > 0.01§	0.27 ≈ −0.04‡	0.41 >> −0.04§
Pupillomotor	0.35 > −0.03§	0.30 > −0.12§	0.13 ≈ −0.06	0.35 >> −0.09§
Male sexual failure	−0.04 ≈ −0.04	0.06 ≈ 0.07	0.12 ≈ −0.21	0.06 ≈ −0.16
Vasomotor	0.10 ≈ −0.04	0.01 ≈ 0.07	0.11 ≈ 0.08	0.07 ≈ 0.06
Upper gastrointestinal symptoms	0.04 ≈ 0.02	0.28 ≈ 0.11‡	0.13 ≈ −0.09	0.19 ≈ 0.01
Syncope	−0.18 ≈ −0.05	0.03 ≈ −0.23§	−0.17 ≈ −0.12	−0.12 ≈ −0.19‡

*Group sizes for individual correlations vary due to missing data in some domains; †correlation for type 1 group listed first in each cell, followed by correlation for type 2 group; ‡correlation significantly different from zero at the 0.05 level; §correlation significantly different from zero at the 0.01 level. ≈, correlation between CASS domain and ASP domain not significantly different for type 1 and type 2 groups; >, correlation between CASS domain and ASP domain is significantly different for type 1 and type 2 groups at the 0.05 level; >>, correlation between CASS domain and ASP domain is significantly different for type 1 and type 2 groups at the 0.01 level.

of function. Scores of 2 and 3 describe increasing deficits (13). We selected a score of 2 for diagnosis of neuropathy. This criterion indicates mild abnormalities in two of three autonomic domains or moderate impairment in one domain. Could our selection of criteria have resulted in a larger prevalence? Most other investigators have defined diabetic autonomic neuropathy based on tests of cardiovagal function, sometimes supplemented by detection of orthostatic hypotension. The criteria we adopt for cardiovagal function is more conservative than most criteria adopted by other investigators. Our autonomic screen does incorporate sensitive tests of postganglionic sudomotor and adrenergic function so that it is possible (and indeed likely based on CASS scores) that the high prevalence could be due to abnormalities detected in areas beyond cardiovagal function. This prevalence estimate is appropriate because autonomic impairment extends beyond cardiovagal impairment. If autonomic neuropathy were defined by cardiovagal testing alone and the criterion was CASS cardiovagal ≥1, prevalence of autonomic neuropathy would be 48.6 and 70.5% for type 1 and type 2 diabetes, respectively. If the criterion were CASS cardiovagal ≥2, prevalence would be 25.0 and 44.0% for type 1 and type 2 diabetes, respectively. If the criterion were CASS total ≥5, prevalence would be 14%. Although the agreement between cardiovagal function and other autonomic domains are reported to be good (2,20), most of the reports have been biased by overrepresentation of advanced cases. Even in the autonomic laboratory, one in six patients will have involvement of one autonomic system without involvement of cardiovagal function (20). In a population-based setting in which mild autonomic impairment predominates, the agreement among autonomic domains is quite poor (11). The mean CASS of <3 indicates that on average, the patient in this study had mild autonomic impairment (13).

Autonomic symptoms among the diabetic sample were significantly increased over control subjects, especially in patients with type 2 diabetes, in whom 9 of the 11 symptom domains on the ASP were significantly increased over control subjects. These symptoms are in clinically relevant domains. For instance, orthostatic intolerance symptoms detect symptoms of cerebral hypoperfusion on standing alone or after meals, exercise, or with additional heat stress. The secretomotor domain included symptoms characteristic of thermoregulatory impairment such as heat intolerance, changes in general and specific areas of body sweating, and dry eyes and mouth. Urinary domain focuses on symptoms of impaired voiding or control. Upper and lower gastrointestinal symptoms (diarrhea, constipation) evaluates gastroparesis (bloating/nausea/vomiting) as well as constipation and diarrhea. The pupillomotor domain measures symptoms such as difficulty focusing, photophobia, and blurring in an attempt to detect impaired neural control of the pupils.

The generally low ASP scores in the present study and the generally weak correlation between these scores and the CASS contrasts with our earlier report of higher scores and higher correlations (8). The close correlation of symptoms of orthostatic intolerance and CASS in neurogenic orthostatic hypotension (8) contrasts with the present lack of correlation in diabetic subjects. However, the differences are more apparent than real. The earlier study was made up of equal groups of patients with neuropathy (mean CASS 3.1; $n = 33$), neurogenic orthostatic hypotension (mean CASS 6.9; $n = 39$), and control subjects ($n = 41$). The significant increase in symptoms for all domains was seen in the neurogenic orthostatic hypotension group with generalized autonomic failure, whereas the level of significant increases in symptoms in the neuropathy group and both diabetic groups were very similar. With the generally higher prevalence of symptoms in patients with type 2 diabetes, the higher CASS scores in this group are expected. The correlations between CASS and symptoms are of the same order as observed previously for neuropathy patients (8). The robust relationship between symptoms of orthostatic intolerance and CASS in our earlier study likely relates to the fact that all patients with neurogenic orthostatic hypotension (comprising one-third of all cases) had orthostatic hypotension, whereas <9% of patients with

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type 1 or type 2 diabetes had orthostatic hypotension. What is surprising in the present study is the lack of correlation between symptoms and deficits in patients with type 2 diabetes. We have no explanation for that. The present study does emphasize the need to evaluate symptoms in addition to autonomic deficits.

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References

1. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, Wilson DM, O'Brien PC, Melton LJ III: The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology* 43:817–824, 1993
2. Vinik AI, Maser RE, Mitchell BD, Freeman R: Diabetic autonomic neuropathy. *Diabetes Care* 26:1553–1579, 2003
3. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M: Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 161: 1989–1996, 2001
4. Maleki D, Locke GR 3rd, Camilleri M, Zinsmeister AR, Yawn BP, Leibson C, Melton LJ 3rd: Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 160:2808–2816, 2000
5. Icks A, Haastert B, Rathmann W, Wareham N: Prevalence of gastrointestinal symptoms in patients with type 2 diabetes: a population-based study. *Arch Intern Med* 162:1067–1069, 2002
6. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinaly JB: Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 151:54–61, 1994
7. Suarez GA, Opfer-Gehrking TL, Fealey RD, Offord KP, Atkinson EJ, O'Brien PC, Low PA: Autonomic symptom profile (ASP): a new questionnaire for assessment of autonomic symptoms. *Clin Auton Res* 5:324, 1995
8. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA: The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. *Neurology* 52:523–528, 1999
9. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC: Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. *Neurology* 49:229–239, 1997
10. Dyck PJ, Kratz KM, Lehman KA, Karnes JL, Melton LJ III, O'Brien PC, Litchy WJ, Windebank AJ, Smith BE, Low PA: The Rochester Diabetic Neuropathy Study: design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests. *Neurology* 41:799–807, 1991
11. Dyck PJ, Karnes JL, O'Brien PC, Litchy WJ, Low PA, Melton LJ III: The Rochester Diabetic Neuropathy Study: reassessment of tests and criteria for diagnosis and staged severity. *Neurology* 42:1164–1170, 1992
12. Dyck PJ, Litchy WJ, Lehman KA, Hokanson JL, Low PA, O'Brien PC: Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. *Neurology* 45:1115–1121, 1995
13. Low PA: Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc* 68:748–752, 1993
14. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM: Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. *Muscle Nerve* 20:1561–1568, 1997
15. Neil HA, Thompson AV, John S, McCarthy ST, Mann JI: Diabetic autonomic neuropathy: the prevalence of impaired heart rate variability in a geographically defined population. *Diabet Med* 6:20–24, 1989
16. Shaw JE, Zimmer PZ, Gries FA, Ziegler D: Epidemiology of diabetic neuropathy. In *Textbook of Diabetic Neuropathy*. Gries FA, Cameron NE, Low PA, Ziegler D, Eds. New York, Thieme, 2002, p. 64–82
17. Maser RE, Pfeifer MA, Dorman JS, Kuller LH, Becker DJ, Orchard TJ: Diabetic autonomic neuropathy and cardiovascular risk: Pittsburgh Epidemiology of Diabetes Complications Study III. *Arch Intern Med* 150:1218–1222, 1990
18. Low PA: Autonomic nervous system function. *J Clin Neurophysiol* 10:14–27, 1993
19. Denq JC, O'Brien PC, Low PA: Normative data on phases of the Valsalva maneuver. *J Clin Neurophysiol* 15:535–540, 1998
20. Low PA, Zimmerman BR, Dyck PJ: Comparison of distal sympathetic with vagal function in diabetic neuropathy. *Muscle Nerve* 9:592–596, 1986

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