

Noninvasive Evaluation of Neural Impairment in Subjects With Impaired Glucose Tolerance

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The frequency and intensity of neuropathy symptoms were evaluated by the Neuropathy Total Symptom Score (4). Sensory function was assessed by a Neurometer R device (Baltimore, Maryland), Medoc device (Ramat Yishay, Israel), calibrated 128-Hz tuning fork, and Semmes-Weinstein monofilament. Current perception threshold (CPT) was measured at the median and peroneal nerves (digital branches) by the Neurometer at three different frequencies (2 kHz, 250 Hz, and 5 Hz) assessing large myelinated, small myelinated and small unmyelinated sensory fiber function, respectively (5). Cold and heat detection thresholds were assessed by a thermal sensory analyzer (TSA-II), and vibration perception threshold (VPT) was evaluated by a vibratory sensory analyzer (VSA-3000) on the Medoc device. Plantar pressure was measured by dynamic pedobarography.

Cardiovascular autonomic neuropathy was detected by standard cardiovascular reflex tests: heart rate responses to deep breathing and standing (30/15 ratio) and the Valsalva maneuver (Valsalva ratio), assessing mainly parasympathetic function; and blood pressure responses to standing and sustained handgrip, assessing mainly sympathetic function (6). Heart rate variability (HRV) was characterized by the triangular index (HRVti). The HRVti is an estimate of overall HRV, being a time domain measure of HRV. HRVti is presented as a conversion of the R-R intervals into a geometric pattern and is calculated by dividing the integral of the density distribution by the maximum of the density distribution. The HRVti is considered the most reliable single measure of HRV.

Data are expressed as means \pm SD for normally distributed data and as median (interquartile range) for non-normally distributed data. The latter variables were log transformed to adjust for skewness. For comparison between groups, either χ^2 tests, two sample *t* tests, or Mann-Whitney *U* tests were used as required. To take into account the difference in BMI, multiple logistic regression (categorical

OBJECTIVE — To evaluate neural dysfunction in subjects with impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — For this study, 46 subjects with IGT and 45 healthy volunteers underwent detailed neurological assessment. Cardiovascular autonomic function was assessed by standard cardiovascular reflex tests, and heart rate variability was characterized by the triangle index. Sensory nerve function was assessed using Neurometer (for current perception threshold) and Medoc devices. Peak plantar pressure was measured by dynamic pedobarography, and symptoms were graded using the neuropathy total symptom score.

RESULTS — Subjects with IGT had significantly greater abnormalities detected by four of five cardiovascular reflex tests and greater heart rate variability characterized by the triangle index. They had a higher frequency of both hyperesthesia and hypoesthesia as detected by current perception threshold testing at 5 Hz, as well as increased heat detection thresholds.

CONCLUSIONS — This study provides evidence that subclinical neural dysfunction is present in subjects with IGT and can be detected noninvasively. Cardiovascular autonomic neuropathy may contribute to increased cardiovascular risk in IGT subjects.

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Several prospective studies have documented a positive association between A1C values and specific microvascular complications, including neuropathy (1). The relationship, however, between impaired glucose tolerance (IGT) and neuropathy is less clear. There are only limited and conflicting data supporting increases in neuropathy with IGT (2,3). The aim of our study was a comprehensive evaluation of neural dysfunction in IGT subjects.

RESEARCH DESIGN AND METHODS — IGT was diagnosed based on a 75-g oral glucose tolerance test according to World Health Organization

criteria (fasting blood glucose <6.0 mmol/l and 120-min value 7.8–11.0 mmol/l). Subjects with isolated IGT from our outpatient clinic ($n = 46$) and age- and sex-matched healthy volunteers with normal glucose tolerance ($n = 45$) were assessed (IGT vs. healthy volunteers: male/female, 21/25 vs. 18/27, $P = \text{NS}$; mean \pm SD age, 53.0 \pm 11.1 vs. 55.8 \pm 11.4 years, $P = \text{NS}$; fasting plasma glucose, 5.40 \pm 0.57 vs. 4.70 \pm 0.50 mmol/l, $P < 0.0001$; 120-min plasma glucose, 8.61 \pm 1.01 vs. 4.90 \pm 0.45 mmol/l, $P < 0.0001$; A1C, 5.97 \pm 0.38 vs. 4.99 \pm 0.45%, $P < 0.0001$ [further data available in online appendix Table

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Table 1—Comparison of noninvasive measurements of neural function between the IGT and the healthy control group

	Reference values	Subjects with IGT (n = 46)	Control subjects (n = 45)	P	P adjusted for BMI
Cold detection threshold (degrees Celsius)	26				
Upper limb		30.00 (1.60)	30.20 (0.70)	0.411	0.444
Lower limb		29.00 (3.08)	27.80 (1.60)	0.028	0.059
Heat detection threshold (degrees Celsius)	44				
Upper limb		34.35 (3.28)	33.70 (1.20)	0.003	0.002
Lower limb		37.59 ± 4.35	35.54 ± 1.63	0.005	0.007
VPT (Hz)	1.87–4.06				
Upper limb		0.62 (0.88)	0.35 (0.26)	0.001	0.005
Lower limb		4.25 (13.28)	2.45 (6.10)	0.007	0.251
Rydel-Seiffer tuning fork	≥5	8.0 (1.0)	8.0 (1.0)	0.147	0.104
Peak plantar pressure (Pa)	≤60	52.47 ± 14.15	44.5 ± 7.53	0.002	0.0001
Beat-to-beat variation (bpm)	≥15	10.00 (4.5)	18.0 (5.0)	0.0001	0.0001
Postural heart rate change (30:15 ratio)	≥1.04	1.18 (0.11)	1.15 (0.12)	0.385	0.182
Valsalva ratio	≥1.21	1.25 (0.15)	1.36 (0.34)	0.0001	0.0001
Postural systolic blood pressure changes (mmHg)	<10	0 (10)	0 (0)	0.0001	0.0001
Diastolic blood pressure elevation during sustained handgrip (mmHg)	>16	20 (9)*	22 (10)	0.045	0.008
Triangle index	37 ± 15	26.0 (9.3)	40.00 (13.0)	0.0001	0.0001

Data are means ± SD or median (interquartile range). Between-group differences are reported according to two-sample *t* tests or Mann-Whitney *U* tests as indicated. BMI-adjusted *P* values determined by multiple linear regression after transformation of the outcomes. *Lower ranks.

outcomes) and multiple linear regression (continuous outcomes) were used with the actual parameter as the outcome and BMI and IGT/control group as predictors. $P \leq 0.05$ was considered significant. All analyses were performed using SPSS version 14.0. The study protocol was approved by the local ethics committee and all subjects gave written informed consent.

RESULTS — Mild-to-moderate symptoms of neuropathy were present only in the IGT group (5 of 41 vs. 0 of 45, $P = 0.0056$). Both hyperesthesia (7 of 35 vs. 0 of 44, $P = 0.005$), a recognized phenomenon in early neuropathy, and hypoesthesia (5 of 37 vs. 0 of 44, $P = 0.024$), usually seen in later stages of neuropathy, were detected by Neurometer CPT testing at 5 Hz in more IGT subjects than healthy volunteers. These differences, however, lost significance after BMI adjustment.

Compared with healthy volunteers, heat detection thresholds in IGT subjects were increased in both upper and lower limbs, whereas a significant increase in cold detection threshold was found in lower limbs only (Table 1). Significant differences were found between the IGT and control groups in VPT in both upper and lower limbs, but there were no significant differences between the two groups with tuning fork

assessment. Peak plantar pressure was significantly higher in IGT subjects, and significant differences were found between IGT and control subjects in four of five classic cardiovascular reflex tests and HRVti. BMI adjustment had only minor effects on the outcomes except for a loss of significance of cold detection threshold and VPT.

CONCLUSIONS — There remains considerable controversy regarding the relationship between IGT and neuropathy. While observational studies have shown an increased prevalence of IGT among subjects with idiopathic neuropathy (7), there are limited data concerning the prevalence of neuropathy in IGT. The few studies performed have shown mixed results (2,3). Part of the explanation for this may lie in the design of these studies and the disparate methods used to assess neuropathy (8).

This study shows that neural impairment in IGT subjects is mainly subclinical, asymptomatic, and characterized by small-fiber neuropathy and mild impairment of cardiovascular autonomic function. Many population-based studies of IGT have used methods that predominantly detect large-fiber dysfunction, and it is therefore not surprising that they failed to pick up the subtle changes present in IGT.

Assessment of both CPT at 5 Hz and heat detection threshold seems to detect small-fiber neuropathy among IGT subjects. Using the gold-standard punch skin biopsy, altered morphology and small-fiber neuropathy was previously identified in IGT; in that study, IGT subjects had only small-fiber neuropathy, whereas diabetic patients had more extensive damage, involving both large and small nerve fibers (9). However, skin biopsy is clearly not a technique that can be used as a widespread diagnostic tool. Our results indicate that noninvasive assessment may serve as an alternative in order to detect neuropathy in IGT. However, simple and popular noninvasive tests such as the tuning fork and monofilaments, which assess mainly large-fiber function, did not detect neuropathy in the IGT subjects.

Recently, traditional markers of macrovascular disease, such as hypertension, obesity, and hyperlipidemia, have also emerged as risk factors for diabetic neuropathy (1). These are widely prevalent in IGT and may therefore be equally important in the pathogenesis of neuropathy in IGT. Because we found only increased BMI among IGT subjects and no differences in other cardiovascular risk factors and because the group differences were robust for BMI adjustment, it is likely that hyperglycemia per

se may be the reason for neuropathy in the IGT subjects.

Autonomic neuropathy, altered cardiac vagal response in particular, is a common early feature of diabetes (10). Overall, there are limited data on autonomic dysfunction in IGT. However, this study shows that subjects with IGT have subtle but detectable changes in autonomic function, and subjects with IGT have an increased risk of cardiovascular death (11). Cardiovascular autonomic neuropathy, although asymptomatic and mild in nature, may in part be responsible for this increased risk.

In conclusion, this study has demonstrated that subclinical small-fiber neuropathy and autonomic neuropathy are commonly present in IGT subjects. Clinical trials are required to study whether these early losses of nerve function, associated with one of the most devastating complications of diabetes, can be halted or reversed by glycemic or cardiovascular risk reduction.

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