Altered C-Fiber Function as an Indicator of Early Peripheral Neuropathy in Individuals With Impaired Glucose Tolerance

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OBJECTIVE — This study explored the importance of glycemic burden compared with features of the metabolic syndrome in the pathogenesis of diabetic neuropathy by comparing C-fiber function in people with type 1 diabetes to that in people with impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — The axon reflex–elicited flare areas (LDIflares) were measured with a laser Doppler imager (LDI) in age-, height-, and BMI-matched groups with IGT ($n = 14$) and type 1 diabetes ($n = 16$) and in healthy control subjects ($n = 16$).

RESULTS — The flare area was reduced in the IGT group compared with the control (2.78 ± 1.1 vs. 5.23 ± 1.7 cm^2, $P = 0.0001$) and type 1 diabetic (5.16 ± 2.3 cm^2, $P = 0.002$) groups, whereas the flare area was similar in the type 1 diabetic and control groups.

CONCLUSIONS — This technique suggests that small-fiber neuropathy is a feature of IGT. The absence of similar small-fiber neuropathy in those with longstanding type 1 diabetes suggests that glycemia may not be the major determinant of small-fiber neuropathy in IGT.

Diabetes Care 33:174–176, 2010

Small nerve fibers are lost early in the natural history of type 2 diabetes (1–3). A recent study of individuals with idiopathic neuropathy, but normal glucose tolerance, found the majority had features of the metabolic syndrome (4). Given that small-fiber neuropathy is apparent in pre-diabetic and insulin resistant states, the relative importance of hyperglycemia per se, as opposed to other metabolic factors, is unclear. Indeed, recent studies have shown associations between neuropathy and traditional cardiovascular risk factors such as BMI and lipids in pre- and established diabetes (5,6).

This study explored the importance of glycemic burden versus metabolic factors in the pathogenesis of diabetic small-fiber neuropathy by using the axon reflex–elicited flare area (LDIflare) technique to assess C-fiber function in subjects with impaired glucose tolerance (IGT) and type 1 diabetes with minimum or no microvascular complications, the latter representing individuals with a high glycemic burden without significant neural microangiopathy. The LDIflare technique measures the area of neurogenic vasodilatation induced by heat with a laser Doppler imager (LDI) (Moor Instruments, Devon, U.K.). The test has good reproducibility and correlates with nerve fiber density (1,7).

RESEARCH DESIGN AND METHODS

— LDIflares were measured in age-, height-, and BMI-matched groups of type 1 diabetic ($n = 16$), IGT ($n = 14$), and healthy control ($n = 16$) subjects. The latter groups were confirmed by an oral glucose tolerance test. Those with type 1 diabetes presented with a typical history or ketoacidosis and were treated with insulin from diagnosis. Subjects with ankle brachial pressure indexes of <0.8 were excluded. Subjects were assessed for metabolic syndrome using the International Diabetes Federation criteria (8).

Assessment of the LDIflare

After 20 min acclimatizing in a temperature-controlled room (25 ± 1°C), the neurogenic flare was induced by heating a 1-cm diameter area on the dorsum of the foot to 44°C for 20 min. The area was scanned using the imager, and the flare area was identified (with a hyperemic response >300 PU) and measured. Additionally, the maximum hyperemia (LDImax) in the skin immediately beneath the heater was measured using the imager. Unlike the flare, LDImax is mediated by nonneurogenic means and reflects maximum microvascular hyperemia (1). In all subjects clinical neuropathy was excluded using the neuropathy disability scale (9); vibration perception thresholds (neurothesiometer); and quantitative sensory testing of warming, cooling, and vibration perception (Computer Aided Sensory Evaluator IV).

Statistical analysis

LDIflare and LDImax were expressed as means ± SD. The means were compared sequentially with ANOVA and then with Student *t* tests. Variables were correlated using Pearson coefficient. With coefficients of variation (CVs) for LDIflare and LDImax conservatively estimated at 20% (actual CVs: LDIflare, 13%; LDImax, 6%), a prestudy power calculation suggested 16 participants per group would detect a 20% difference with 80% power.

RESULTS

— Group characteristics and results are summarized in Table 1. The LDIflare was significantly lower in the IGT compared with the control (2.78 ± 1.1 vs. 5.23 ± 1.7 cm^2, $P = 0.0001$) and type 1 diabetic (5.16 ± 2.3 cm^2, $P = 0.002$) groups. In contrast, the LDIflares of the type 1 diabetic and control groups were not different. LDImax was reduced

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Received 19 January 2009 and accepted 2 August 2009.
DOI: 10.2337/dc09-0101

See accompanying editorial, p. 207.

Table 1 —*Summary of results for IGT, diabetic, and control groups*

	Control subjects	Type 1 diabetic subjects	IGT subjects
n	16	16	14
Age (years)	50 ± 8	46 ± 7	50 ± 5
Sex			
Male	6 (40)	8 (50)	9 (64)
Female	10 (60)	8 (50)	5 (36)
2-h glucose (mmol/l)	4.8 ± 0.94	—	9.1 ± 1.0
BMI (kg/m^2)	27 ± 5	27 ± 4	31 ± 7
Waist circumference (cm)	88 ± 11†	87 ± 20*	103 ± 16
Blood pressure (mmHg)	124/75 ± 14/9	129/71 ± 19/9	124/70 ± 15/11
Lipid-lowering therapy	0 (0)	8 (50)	4 (29)
Total cholesterol (mmol/l)	5.44 ± 1.3	4.80 ± 1.0	5.61 ± 1.0
HDL cholesterol (mmol/l)	1.59 ± 0.3*	1.71 ± 0.3†	1.30 ± 0.4
LDL cholesterol (mmol/l)	3.26 ± 0.9	2.74 ± 1.0	3.26 ± 1.3
Triglycerides (mmol/l)	1.26 ± 0.4§	0.84 ± 0.4‖	1.97 ± 0.6
Metabolic syndrome	0 (0)	1 (6)	10 (71)
Neuropathy Disability Scale score (0–10)	1	1	0
Vibration perception threshold (V)	7 ± 4	8 ± 4	7 ± 4
Vibration sensation (JND)	16 ± 3	17 ± 5	16 ± 3
Cooling sensation (JND)	10 ± 3	10 ± 4	11 ± 6
Warming sensation (JND)	18 ± 3	19 ± 3	19 ± 4
LDIflare (cm^2)	5.23 ± 1.7‖	5.16 ± 2.3§	2.78 ± 1.1
LDImax (PU)	550 ± 86	489 ± 90	504 ± 78

Data are means ± SD or *n* (%) unless otherwise indicated. All groups not significantly different unless marked: *$P < 0.05$ vs. IGT; †$P < 0.01$ vs. IGT; §$P = 0.002$ vs. IGT; ‖$P = 0.0001$ vs. IGT. JND, just noticeable difference.

in the type 1 diabetic but not in the IGT group. There was no correlation between LDImax and LDIflare either within groups or when combined. The relatively favorable lipid profile in the diabetic group may be related to greater use of lipid-lowering therapy. In the combined IGT and healthy control groups, fasting triglycerides ($r = -0.39$; $P = 0.044$) and 2-h glucose ($r = -0.48$; $P = 0.0066$) were inversely correlated with LDIflare.

CONCLUSIONS — This study has yielded several important findings. First, the LDIflare technique detects early small-fiber dysfunction when conventional tests, including Computer Aided Sensory Evaluator IV, are normal. The potential for earlier detection and the noninvasive nature of the method are advantages over existing techniques such as skin biopsy, particularly when repeated measurements are required.

Second, the detection of small-fiber dysfunction in the feet in the IGT group is consistent with other studies but is novel in that functional rather than structural integrity was examined (10–12). Given that functional defects may precede structural changes and are more likely to be reversible, the method may be particularly valuable in assessing interventions to prevent or delay progress of neuropathy. Further studies comparing LDIflare technique with other functional tests such as cardiac autonomic function and the newer structural techniques, intraepidermal and corneal nerve fiber density, would help determine its relative value.

Third, small-fiber dysfunction in the IGT group contrasts with the apparent normality in the type 1 diabetic subjects. The latter group was unusual, being relatively free from complications, but this was necessary to exclude endoneural microangiopathy, which itself is associated with neuropathy (13). It is possible that other tests such as cardiac autonomic function may have been abnormal in this group. The difference in small-fiber function between these two groups suggests factors other than hyperglycemia are implicated in the development of small-fiber dysfunction. The significant association with certain features of the metabolic syndrome, namely 2-h glucose and triglyceride levels, suggests a common metabolic link. Further studies would be required to confirm these suggestions.

The flare, although dependent on intact small fibers, requires sufficient microvascular vasodilatation for it to be detected by the imager. This was so in all subjects, demonstrated by the LDImax measurements. In this context, the absence of any correlation between LDImax and LDIflare measurements confirms that they reflect different parameters. Additionally, LDIflare was undiminished in the type 1 diabetic group despite, as expected from our previous study, a reduction in their LDImax (14). LDImax is believed to reflect endothelial function (15), and impaired endoneurial function is implicated in the development of neuropathy (13). However, that LDImax did not correlate with small-fiber function might indicate that endothelial dysfunction only affects neural function at more advanced stages when there is significant microangiopathy.

In summary, the LDIflare technique has adequate sensitivity to detect early small-fiber dysfunction. The presence of small-fiber dysfunction in those with IGT and not in those with long-duration type 1 diabetes in the absence of significant microvascular disease suggests that factors other than hyperglycemia contribute to small-fiber dysfunction in those with IGT.

Acknowledgments — No potential conflicts of interest relevant to this article were reported.

We thank the Medical Research Council Epidemiology Unit, Cambridge, U.K., and the Princess of Wales Hospital, Ely, U.K., for logistical support and help with subject recruitment.

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