EDITORIAL (SEE GREEN ET AL., P. 174)

Neuropathy of Impaired Glucose Tolerance and Its Measurement

Impaired glucose tolerance (IGT) was originally shown in the prospective Whitehall Study (1) to carry an increased risk of large-vessel disease only. Whether or not IGT may also confer an increased risk for microvascular complications is not clear. Although microalbuminuria has been shown to be increased in those with IGT compared with control subjects (2), the incidence of retinopathy (IGT 6.7% vs. NGT 5.8%) (3) and moderate neuropathy (IGT 5.7% vs. NGT 2.8%) (4) have been found to be similar.

Nevertheless, it has been proposed that IGT may cause neuropathy (5). However, little is new in clinical medicine; over 40 years ago Ellenberg (see ref. 5) suggested that neuropathy may indeed occur in pre-diabetes, although it is interesting that the interpretation was that factors other than hyperglycemia may cause the neuropathy. The recent resurgence of interest in IGT neuropathy is based on four separate studies of patients with idiopathic small-fiber neuropathy, where the prevalence of IGT was found to be 34–35.6%, three times the prevalence in age-matched control subjects (5). We believe the interpretation of these studies has significant limitations because the populations studied were selected for the presence of idiopathic small-fiber neuropathy, rather than IGT. Furthermore, as pointed out by Dyck et al. (6) in a critical review, the association between IGT and neuropathy remains to be confirmed in an ongoing prospective study. Added to this the relationship between the metabolic syndrome, and its component constituents, to IGT neuropathy has come under scrutiny. Thus in an earlier study, whereas 32% of patients with chronic idiopathic axonal polyneuropathy compared with 14% of control subjects had IGT, insulin resistance did not differ between the two groups; after adjustment for BMI, age, and sex, only triglycerides were found to be significantly higher in those with neuropathy (7). This association has been confirmed recently in 219 patients with idiopathic peripheral neuropathy compared with 175 diabetic patients without neuropathy (8). The prevalence of metabolic syndrome was comparable in normoglycemic and IGT patients with neuropathy; however, compared with diabetic subjects without neuropathy, the normoglycemic neuropathy patients had comparable obesity and hypertension but significantly higher total cholesterol, LDL cholesterol, and triglycerides, with lower HDL cholesterol (8). This association between the development of neuropathy and features of the metabolic syndrome has previously been shown in those with type 1 diabetes (9) and more recently in a nerve biopsy study in relation to triglycerides in those with type 2 diabetes (10).

Two population-based studies have assessed the prevalence of neuropathy in IGT: the San Luis Valley (USA) (11) and the MONICA/KORA Augsburg (Germany) studies (12). Using differing diagnostic criteria, the results of these two epidemiologic surveys are remarkably similar, with neuropathy present in 11–13% of IGT and 26–28% of diabetic subjects but also in 4–8% of the nondiabetic control populations. Although resetting the diagnostic criteria for IGT may be considered unrealistic, a recent analysis has shown no evidence of a clear and consistent glycemic threshold for the presence or incidence of retinopathy across three different populations, suggesting that the criteria even for diagnosing diabetes may need reassessment (13).

If we are to undertake a similar analysis for neuropathy, the challenge is going to be in relation to the tests used to define nerve damage. In the San Luis Valley study a combination of symptoms, neurological deficits, and vibration perception threshold was used (11), whereas in the German study a combination of the Michigan Neuropathy Screening Instrument, a symptom, and brief neurological examination was used (12); both studies are weighted toward large-fiber dysfunction. It has been suggested that future studies to address IGT neuropathy should assess neuropathic clinical signs and symptoms, electrophysiologic tests, specialized sensation and autonomic tests, and perhaps also intraepidermal nerve fibers (IENFs) (6). However, in a recent study, quantitative sudomotor axon-reflex test responses were significantly impaired in those with IGT compared with control subjects, indicative of early distal small-fiber neuropathy (14). Similarly, although nerve conduction studies and cardiac autonomic function tests were normal, the amplitudes of the sympathetic skin responses were lower in IGT patients (15). Moreover, in 46 subjects with IGT, an abnormality in four of five cardiovascular reflex tests, a greater heart rate variability, and increased heat detection thresholds have been shown recently (16). Studies quantifying IENFs also demonstrate that the earliest damage in those with IGT is to the small fibers (17). Indeed, these data are supported by studies in those with early diabetic neuropathy, where despite normal electrophysiology and quantitative sensory testing, a significant reduction in IENF density (IENFD) has been demonstrated (18,19). Thus, designing a longitudinal study, such as that of Dyck et al. (6), will require detailed metabolic and physical phenotyping, particularly in relation to the end points selected to define neuropathy.

As stated above, the body of evidence has suggested a predominance of involvement of small nerve fibers in the neuropathy of IGT, although some preliminary evidence also supports involvement of large nerve fibers (20). Nevertheless, skin biopsies have been proposed to assess early small-fiber damage (21); indeed, a small study quantifying IENFD has already shown that dietary management together with an exercise program can result in improvement in IENFD and painful symptoms in those with IGT neuropathy (22). However, punch skin biopsies are still invasive and can cause some discomfort; a noninvasive alternative would therefore be preferable, particularly for longitudinal studies. Two such alternatives exist: First, the technique of corneal confocal microscopy enables the direct visualization of small corneal nerve fibers in vivo, has been shown to detect small-fiber damage earlier than IENFD in skin biopsies on the dorsum of the foot (23), and detects nerve repair within 6 months of pancreas transplantation (24). Second, Krishnan and Rayman (25) pre-

viously described an abnormal axon reflex–elicited flare area (LDIflare) test and a test of C-fiber function, and Krishnan, Rayman, and colleagues (26) showed that these tests are abnormal despite preserved dermal nerve fiber density. In the current issue of *Diabetes Care*, Krishnan, Rayman, and colleagues (27) demonstrate a significant reduction in the LDIflare test without abnormalities in quantitative sensory testing or maximum hyperemia (LDImax) in subjects with IGT. These findings contrast with a previous study that demonstrated a significant reduction in LDImax in a larger group of patients with IGT (28). It also raises issues regarding the validity of the LDIflare regarding whether it specifically measures C- nociceptive fiber function. From a physiological perspective, thermal (25,26) and pharmacological (29,30) stimuli have consistently induced a nerve axon reflex; moreover, local anesthesia has been shown to reduce both the thermal- (25) and acetylcholine- (29) but not sodium nitroprusside – (30) mediated response by ~70%. Hence, one can conclude that the nerve axon reflex depends principally but not exclusively on the function of C-nociceptive fibers and therefore can be used as a surrogate measure of small-fiber damage.

In conclusion, neuropathic changes predominantly affecting small fibers appear to occur more commonly in those with IGT than in the normal population, and ongoing prospective studies should provide confirmation of these initial observations. If confirmed, an internationally agreed definition as to what constitutes IGT neuropathy is required, and the noninvasive techniques of corneal confocal microscopy and LDIflare may be useful in assessing longitudinal cohorts and potential pharmacological interventions for what is often a painful condition.

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