Value of the Oral Glucose Tolerance Test in the Evaluation of Chronic Idiopathic Axonal Polyneuropathy

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Background: An underlying cause is found in only 7% to 30% of patients with chronic idiopathic axonal polyneuropathy (CIAP). Diabetes mellitus, inherited disorders, toxin exposure, and primary amyloidosis are the most common identified causes of sensory neuropathies affecting both large and small myelinated fibers. Undiagnosed impaired fasting glucose metabolism has been associated with CIAP at a higher frequency rate than in the general population. This increased prevalence rate was identified using the 2-hour oral glucose tolerance test (2h-OGTT) and a previous version of the American Diabetes Association (ADA) guidelines.

Objectives: To determine the prevalence of abnormal fasting glucose metabolism in patients with CIAP and to compare the value of determining fasting plasma glucose levels using revised (2003) ADA criteria with the 2h-OGTT for predicting abnormal fasting glucose metabolism.

Patients: In this 24-month retrospective study, 100 consecutive patients were identified with no known cause for CIAP, including diabetes mellitus, between January 2003 and January 2005. All had both a fasting plasma glucose test and a 2h-OGTT in addition to a complete neurological examination. Neurophysiological studies, computer-assisted sensory examination, and quantitative sudomotor axonal reflex testing were used to classify CIAP into subtypes according to nerve fiber involvement.

Results: The prevalence of undiagnosed abnormal fasting glucose metabolism was found to be nearly 2-fold higher (62%) in patients with CIAP than in similar age-matched general population groups (33%). Using the 2003 revised ADA criteria, 39 patients (39%) had abnormal fasting plasma glucose metabolism (36 with impaired fasting glucose, 3 with diabetes mellitus), while the 2h-OGTT provided an even higher diagnostic rate of 62% (62 patients; \(P < 0.001\)) of impaired fasting glucose metabolism (38 with impaired glucose tolerance, 24 with diabetes mellitus). The abnormal glucose metabolism rates were found to be similar across the 3 subtypes (sensorimotor, pure sensory, and small-fiber neuropathy) of CIAP (\(P = 0.60, 0.72, \text{ and } 0.61\)).

Conclusions: This study adds to emerging evidence that abnormal glucose metabolism may be a risk factor for CIAP. Even with revised (2003) ADA criteria, the 2h-OGTT provides additional diagnostic information to the health care professional in the evaluation of CIAP. Subtypes of CIAP are equally likely to have abnormal glucose metabolism.

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The symptoms of “burning feet” and other unpleasant distal lower limb sensory complaints in middle and late adulthood are hallmarks of painful sensory polyneuropathy, which is the most commonly encountered neuropathy in clinical practice. Such patients typically present with a slowly progressive predominantly sensory or sensorimotor neuropathy with or without pain and electrophysiological evidence of a distal length-dependent axonal process.

When no underlying cause can be identified despite extensive laboratory investigations, these neuropathies are referred to as chronic idiopathic axonal polyneuropathy (CIAP). An underlying cause is found in only 7% to 30% of such patients. The diagnostic yield of determining an underlying cause falls lower than

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10% in patients with normal findings on electrodagnostic studies in whom small-fiber involvement is suspected. Diabetes mellitus (DM), inherited disorders, toxin exposure, and primary amyloidosis are among the most common identified causes of sensory neuropathies affecting both large and small myelinated fibers.

Intriguingly, recent studies have suggested that patients presenting with CIAP have nearly a 2-fold higher frequency of un-
diagnosed DM and impaired fasting glucose (IFG) (56%-68%) using the 2-hour oral glucose tolerance test (2h-OGTT) than does the age-matched general population.5-10

The Centers for Disease Control and Prevention (CDC) estimated that 33% of the US population older than 60 years met criteria for either diagnosed or undiagnosed DM or IFG.10 Within this group with abnormal fasting glucose metabolism, approximately 15% had DM and an additional 15% had IFG, with no sex difference. These prevalence rates were based on fasting plasma glucose values that have since been revised downward in 2003 by the American Diabetes Association (ADA). These revised guidelines lowered the definition of IFG (ie, plasma glucose level >100 but <126 mg/dL).11

The studies implicating undiagnosed abnormal fasting glucose metabolism with CIAP had used the 2h-OGTT to detect impaired fasting glucose metabolism and the former ADA criteria for IFG (110-125 mg/dL), raising the question whether there was still value to using the 2h-OGTT when evaluating patients presenting with CIAP. Furthermore, the findings suggest impaired glucose tolerance (IGT) was linked more frequently to small-fiber neuropathies (SFNs).5-9 Emerging evidence is, however, mixed; a study by Hughes et al12 using nonblood relatives as control subjects suggested that triglyceride and environmental toxins, but not abnormal glucose metabolism, are significant risk factors for CIAP.

This study seeks to examine the prevalence of undiagnosed abnormal fasting glucose metabolism using 2003 ADA criteria compared with the 2h-OGTT in patients presenting to a tertiary neuromuscular clinic with distal sensory complaints where no cause had been found, including DM. The current study aims to provide further insight as to whether abnormal glucose metabolism selectively affects certain populations of nerve fibers (sensorimotor, sensory, and/or SFNs).

**METHODS**

Five hundred sixty-two medical records were reviewed according to predetermined criteria to identify patients with neuropathic symptoms but no known cause for their neuropathy. One hundred consecutive patients were identified with symptoms suggesting idiopathic neuropathy, all of whom had previously been screened for DM. These patients presented during 2 years (January 2003-January 2005) to Mayo Clinic Arizona and were evaluated in the Neurology Department by 1 of us (E.P.B., B.E.S., C.H.S., or M.A.R.). One hundred patients met the inclusion criteria of (1) a documented history of positive sensory complaints more than 3 months in duration, with or without neuropathic pain; (2) a detailed neurological examination including the Neuropathy Impairment Score (NIS);13 (3) a fasting, nonfasting state 2h-OGTT using a 75-g oral D-glucose (dextrose) load; (4) nerve conduction studies; and (5) a diagnosis of CIAP.

Patients were excluded who had documented evidence for a known cause of chronic axonal polyneuropathy, such as (1) presence of a family history of neuropathy and “hammer” or “claw” toe deformities; (2) documentation of a toxic or pharmacological exposure or coexisting medical conditions associated with neuropathy such as chronic alcoholism; metabolic disturbances; DM; hypothyroidism; and autoimmune conditions such as connective tissue diseases, including sicca syndrome, malignancies, or human immunodeficiency virus or other active infections (Lyme disease, Hansen disease, hepatitis C); (3) general weakness except for distal leg muscle weakness; (4) abnormal results on complete blood cell count, electrolyte levels, liver function studies, vitamin B12 levels, thyrotropin levels, and serum protein electrophoresis with serum immunofixation. Human immunodeficiency virus testing was not routinely performed in this low-risk population, and nerve conduction studies excluded features of demyelination.

Procedures for the 2h-OGTT required fasting after mid-night, obtaining a baseline fasting glucose level, and administration of the oral glucose load within a 5-minute period. Blood specimens to determine plasma glucose level were subsequently drawn at 120 minutes, timed from the beginning of the glucose load. Patients were established as having IFG if the venous plasma glucose level was greater than 126 mg/dL or having IGT if the 120-minute venous plasma glucose value fell between 140 and 200 mg/dL. Criteria for new-onset DM were a fasting plasma glucose level greater than 126 mg/dL or 120-minute venous plasma glucose level greater than 200 mg/dL on the OGTT.11

Nerve conduction studies included the ulnar/hypotenar motor (wrist and elbow) and peroneal (fibular/extensor digitorum brevis motor (ankle and knee) nerve conduction studies as well as median and sural sensory nerve conduction studies performed by standard methods.14

Concentric-needle electromyography (EMG) of distal leg muscles (anterior tibialis and gastrocnemius) was performed. Electrophysiological results were recorded as normal or compatible with axonal sensorimotor or sensory polyneuropathy.15

 Quantitative sudomotor axon reflex testing (QSART) assesses a cutaneous axon reflex mediated by postganglionic sympathetic sudomotor axons and is helpful in detecting small-fiber involvement. Abnormal QSART results were defined as reduced sweat production or 30% or greater reduction of sweat production compared with controls.16

 Quantitative sensory testing (QST) was performed using the CASE-IV computerized sensory testing system.17 Assessments included vibratory detection threshold of the dorsal surface of the great toe as well as cooling detection threshold and heat pain visual analog scales on the dorsum of the foot.17

 According to clinical, neurophysiologic data and QST and QSART responses, each patient was classified into 1 of 3 subtypes of CIAP: (1) CIAP-sensorimotor (CIAP-SM) subtype patients had sensorimotor symptoms and signs supported by abnormal results on motor conduction studies and denervation in anterior tibial and gastrocnemius muscles. (2) CIAP-sensory (CIAP-S) subtype patients had sensory symptoms and distal impairment for vibration sense, light touch, and pin-prick associated with distal loss of reflexes but preserved motor function. Reduced to absent sural sensory nerve action potentials were found but results of motor conduction studies and needle EMG of distal leg muscles were normal. (3) Small-fiber neuropathy subtype patients were classified into “probable” or “possible” subtypes. Both groups had positive sensory symptoms and clinical findings limited to sensory impairment but normal results on nerve conduction studies and needle EMG. Patients were classified as having probable SFN if small-fiber involvement could be confirmed by abnormal QST results (elvated cooling detection thresholds or supersensitivities on heat pain visual analog scales), abnormal QSART responses, or both.16,17 Patients with similar complaints and findings but normal QST and QSART studies were defined as having possible SFN.

Recorded medical record data included demographic information (age, sex, race), body mass index (calculated as weight in kilograms divided by the square of height in meters), posi-
tive complaints of altered sensation and pain, duration of symp-
toms, neurologic deficits summarized by the NIS, responses to
nerve conduction studies (sural nerve sensory amplitude, ve-
locity), EMG, QST results (vibratory detection threshold, cool-
ing detection threshold, and supersensitivity to heat-pain vi-
rial analog scales), QSART responses (proximal leg, distal leg,
and foot), fasting blood glucose level, 2h-OGTT results, and
serum triglyceride levels.

STATISTICAL ANALYSIS

The McNemar test was used to compare the abnormal glucose me-
tabolism rates of fasting and 2-hour glucose tolerance. The QSART
responses were compared among the 3 groups of CIAP (CIAP-
SM, CIAP-S, and SFN). A 1-way analysis of variance was used to
assess statistical significance. The $\chi^2$ test was used to compare
categorical variables and a t test was used to compare categorical
and continuous variables. In all cases, a $P$ value of .05 was con-
sidered to be statistically significant. All tests were 2-sided, and
95% confidence intervals were generated where appropriate.

RESULTS

Sixty women and 40 men with CIAP met inclusion cri-
teria. Using the 2003 revised ADA criteria, 39 patients
(39%) had abnormal fasting plasma glucose metabolism
(36 with IFG, 3 with DM). When using the 2h-
OGTT, an even higher association with abnormal fast-
ing glucose metabolism (62%; 62 patients) was found in
patients with CIAP (38 with IGT, 24 with DM). The dif-
ference between rates was significant ($P<.001$ (Table 1).

At presentation, age was a predictor for DM ($P = .002$;
mean age was 65 years for patients with IGT and 70.4
years for patients with DM. The mean body mass index
for all groups was similar (28.4 for patients with normal
glucose metabolism, 30.6 for patients with IGT, and 30.3
for patients with DM). Mean duration of symptoms was
50.2 months for patients with IGT and 57.8 months for
patients with DM. Clinical findings using the NIS re-
vealed mild deficits in all groups (Table 2). All pa-
tients reported sensory complaints (numbness or tin-
gling). Neuropathic pain was higher among patients with
abnormal glucose metabolism (88%) than with normal
 glucose metabolism (76%) ($P = .52$).

Neurophysiologic studies showed reduced sural sen-
sory nerve action potential amplitude (IGT, 5.7; DM, 3.6;
$P = .16$) in patients with newly discovered DM.

Using the neurologic examination, EMG, nerve con-
duction studies, QST, and QSART, patients were classi-
fied by CIAP subtype and their frequency of abnormal
glucose metabolism compared (Table 3). Forty-two had
CIAP-SM, 15 had CIAP-S, 37 had SFN, and 6 had nor-
mal test results and were classified as possible SFN. Thirty-
seven patients had IGT (CIAP-SM, 42%; CIAP-S, 13%;
and SFN, 42%), and 24 had newly diagnosed DM (CIAP-
SM, 50%; CIAP-S, 21%; and SFN, 29%) by 2h-OGTT. The

Table 1. Frequencies of Identifying Abnormal Glucose Metabolism in CIAP by 2h-OGTT and Fasting Plasma Glucose Level Using Revised ADA Criteria

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose Level (n = 100)</th>
<th>2-h OGTT (n = 100)</th>
<th>$P$ Value</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal glucose metabolism</td>
<td></td>
<td></td>
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<tr>
<td>IFG</td>
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<td></td>
<td></td>
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<tr>
<td>DM</td>
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<tr>
<td>Normal glucose metabolism</td>
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<td>Abnormal glucose metabolism</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IFG</td>
<td></td>
<td></td>
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<tr>
<td>DM</td>
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</tbody>
</table>

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; CIAP, chronic idiopathic axonal polyneuropathy; DM, diabetes mellitus; IFG, impaired fasting glucose; 2h-OGTT, 2-hour oral glucose tolerance test.
*Values are expressed as number (percentage) or number of patients unless otherwise indicated.

Table 2. Features of 100 Patients With CIAP Grouped According to Glucose Metabolism by 2h-OGTT

<table>
<thead>
<tr>
<th>Patients With Normal Glucose Metabolism (n = 38)</th>
<th>Patients With IGT (n = 38)</th>
<th>Patients With DM (n = 24)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.9</td>
<td>65.0</td>
<td>70.4</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (37)</td>
<td>18 (47)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (63)</td>
<td>20 (52)</td>
<td>16 (66)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.4</td>
<td>30.6</td>
<td>30.3</td>
</tr>
<tr>
<td>Duration of symptoms, mo</td>
<td>49.0</td>
<td>50.2</td>
<td>57.8</td>
</tr>
<tr>
<td>Neuropathic pain, No. (%)</td>
<td>29 (76)</td>
<td>32 (84)</td>
<td>21 (88)</td>
</tr>
<tr>
<td>NIS$^{13}$</td>
<td>7.5</td>
<td>8.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Sural, amplitude</td>
<td>5.6</td>
<td>5.7</td>
<td>3.6 (n = 23)</td>
</tr>
</tbody>
</table>

Abbreviations: CIAP, chronic idiopathic axonal polyneuropathy; DM, diabetes mellitus; IGT, impaired glucose tolerance; NIS, Neuropathy Impairment Score; 2h-OGTT, 2-hour oral glucose tolerance test.
*Values are expressed as mean unless otherwise indicated.

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3 conditions (normal glucose metabolism, IGT, and DM) were found in all groups of CIAP with similar frequency (CIAP-SM, \( P = 0.60 \); CIAP-S, \( P = 0.72 \); SFN, \( P = 0.61 \)).

Among 74 patients with CIAP, QSART responses were abnormal in 43% (16/37) of those with SFN. The QST results were abnormal (eg, elevated cooling detection threshold or supersensitivity to heat-pain visual analog scales) in 51% (19/37) of patients with SFN. Six patients with symptoms of SFN had both normal QST and QSART responses.

### Table 3. Frequency of Abnormal Glucose Metabolism in CIAP Subgroups by 2h-OGTT*

<table>
<thead>
<tr>
<th>CIAP Subgroup</th>
<th>Normal Glucose Metabolism (n = 33)</th>
<th>IGT (n = 37)</th>
<th>DM (n = 24)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIAP-SM</td>
<td>14 (37)</td>
<td>16 (42)</td>
<td>12 (50)</td>
<td>0.60</td>
</tr>
<tr>
<td>CIAP-S</td>
<td>5 (13)</td>
<td>5 (13)</td>
<td>5 (21)</td>
<td>0.72</td>
</tr>
<tr>
<td>SFN</td>
<td>14 (37)</td>
<td>16 (42)</td>
<td>7 (29)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*The 6 patients classified as having possible SFN were not included in this analysis.

Abnormal glucose metabolism was found at nearly a 2-fold higher rate (62%) in patients with CIAP when compared with CDC–published, general age-matched population prevalence rates (33%) in adults 60 years and older.\(^5\)\(^-\)\(^11\) Using the CDC rates provides a control population that supports the conclusions of previously published data that IGT and IFG may be risk factors for the development of CIAP.\(^5\)\(^-\)\(^10\)

Although the 2003 ADA criteria for IFG increases the number of patients identified as having IFG (39%), the 2h-OGTT still had a higher diagnostic yield for the detection of abnormal glucose metabolism (62%) in patients with CIAP. This is similar to a recent study by Smith and Singleton,\(^19\) which found that the 2h-OGTT had the highest diagnostic yield (61%) and was more sensitive than other measures of testing glucose metabolism in patients with CIAP. The 2h-OGTT is of considerable value in the diagnostic workup of CIAP.\(^19\) The 2h-OGTT is often avoided by busy health care professionals, perhaps because of the inconveniences posed by the testing procedure. The fasting plasma glucose level alone does not always identify patients with IGT and neither does the 2h-OGTT always detect patients with impaired glucose metabolism. Both tests are, however, useful to detect hyperglycemia and the consequences of disordered glucose metabolism.\(^11\) The ADA diagnostic criteria identified IGT as a risk factor for cardiovascular disease independent of frank DM, while the consensus of the International Diabetes Foundation of the United Kingdom acknowledged that both IGT and IFG represent risk factors and risk markers for DM and coronary artery disease.\(^20\) All-cause mortality has been observed to be higher in subjects with IGT but normal fasting glucose blood levels.\(^21\) The current findings provide additional support that peripheral nerve dysfunction may predate development of frank DM.\(^6\)\(^-\)\(^9\)

Identifying patients with impaired glucose metabolism provides the opportunity for more aggressive management of the risks associated with hyperglycemia. Lifestyle changes such as diet control and exercise have been shown in recent preliminary studies to not only correct the metabolic abnormality but also to reduce neuropathic pain.\(^22\)\(^,\)\(^23\)

The current study found that age was a predictor for both impaired fasting glucose metabolism and bona fide DM (IGT, 63.0 years; DM, 70.4 years; \( P < 0.01 \)). Body mass index was found to be elevated for both the normal and abnormal glucose metabolism groups (28.4 vs 30.3; \( P = 0.19 \)). This is similar to previous studies.\(^5\)\(^-\)\(^9\) The duration of both painful and nonpainful symptoms ranged from 50.2 months in IGT to 57.8 months in DM, both slightly longer than previously reported.\(^5\)\(^-\)\(^9\) Conventional thinking among diabetologists is that diabetic polyneuropathies are the result of prolonged hyperglycemia.\(^24\) Like previous studies, this investigation supports the hypothesis that distal axonal polyneuropathies may occur in much earlier stages of abnormal glucose metabolism than previously thought.\(^25\) Recent studies suggest that the neuropathy associated with IGT may be milder than neuropathies traditionally associated with DM and may be the earliest detectable sign of abnormal glucose metabolism.\(^25\) While the neuropathic deficits were mild (mean NIS across all groups, 8.2), all patients had sensory symptoms and 82% had complaints of neuropathic pain. Unlike the findings of Singleton et al,\(^9\) who found painful symptoms more common in patients with CIAP associated with IGT, this study found neuropathic pain across the spectrum of CIAP and abnormal glucose metabolism (Table 2).

The current study found the frequency of abnormality in QSART results to be lower than previously reported in SFNs. Lacomis\(^1\) found the predictive value of QSART studies to range from 60% to 80% in SFNs. Among patients with painful CIAP, Periquet et al\(^13\) found abnormal QSART responses in 72% and in 43% of patients with SFN. The abnormal QSART responses in our study patients were less frequent than previously reported.\(^16\) When QSART re-
sponses were combined with QST results, 86% of our patients with SFN had abnormalities in either 1 or both test outcomes. Abnormal glucose metabolism was found across the spectrum of CIAP without any increase across subtypes. This differs from previous studies that found that IGT associated more often with SFN. Singleton et al\(^8\) found that EMG findings were less severe in patients with IGT and more confined to sensory fibers than in patients with DM. Sumner et al\(^9\), using skin biopsy with epidermal nerve fiber studies, suggested that patients with IGT had less severe neuropathy with preferential small-fiber involvement than patients with frank DM.

This retrospective analysis of patients with CIAP adds to the increasing body of evidence that shows a higher prevalence of abnormal fasting glucose metabolism in patients with CIAP in comparison with an age-matched US population. Thus, IFG or IGT may be risk factors for the development of CIAP. The use of the 2h-OGTT is still of greater value than the revised fasting plasma glucose values to detect impaired glucose metabolism in patients with chronic neuropathies of unknown cause. Additional studies with age-matched case-control subjects are warranted before definite causal relationships between peripheral nerve dysfunction and abnormal glucose metabolism can be fully accepted.

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