

# Treatment-Induced Diabetic Neuropathy: A Reversible Painful Autonomic Neuropathy

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**Objective:** To describe the natural history, clinical, neurophysiological, and histological features, and outcomes of diabetic patients presenting with acute painful neuropathy associated with glycemic control, also referred to as *insulin neuritis*.

**Methods:** Sixteen subjects presenting with acute painful neuropathy had neurological and retinal examinations, laboratory studies, autonomic testing, and pain assessments over 18 months. Eight subjects had skin biopsies for evaluation of intraepidermal nerve fiber density.

**Results:** All subjects developed severe pain within 8 weeks of intensive glucose control. There was a high prevalence of autonomic cardiovascular, gastrointestinal, genitourinary, and sudomotor symptoms in all subjects. Orthostatic hypotension and parasympathetic dysfunction were seen in 69% of subjects. Retinopathy worsened in all subjects. Reduced intraepidermal nerve fiber density (IENFD) was seen in all tested subjects. After 18 months of glycemic control, there were substantial improvements in pain, autonomic symptoms, autonomic test results, and IENFD. Greater improvements were seen after 18 months in type 1 versus type 2 diabetic subjects in autonomic symptoms (cardiovascular  $p < 0.01$ ; gastrointestinal  $p < 0.01$ ; genitourinary  $p < 0.01$ ) and autonomic function tests ( $p < 0.01$ , sympathetic and parasympathetic function tests).

**Interpretation:** Treatment-induced neuropathy is characterized by acute, severe pain, peripheral nerve degeneration, and autonomic dysfunction after intensive glycemic control. The neuropathy occurred in parallel with worsening diabetic retinopathy, suggesting a common underlying pathophysiological mechanism. Clinical features and objective measures of small myelinated and unmyelinated nerve fibers can improve in these diabetic patients despite a prolonged history of poor glucose control, with greater improvement seen in patients with type 1 diabetes.

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Although chronic neuropathic pain occurs frequently in diabetic patients, acute severe neuropathic pain is rarely encountered. Several different acute painful syndromes occur:

Pain may appear shortly after the initiation of intensive glycemic control, sometimes referred to as *insulin neuritis* or treatment-induced neuropathy.<sup>1–3</sup> Characteristically, the painful neuropathy is preceded by rapid glycaemic control.

Additional cases present in association with severe weight loss with or without a change in glycemic control, a disorder referred to as *diabetic neuropathic cachexia*.<sup>4–6</sup> The weight loss in these patients is unintentional.

Pain may also present with intentional weight loss unrelated to changes in glucose control, a condition called *diabetic anorexia*.<sup>7</sup>

Rarely, an acute painful neuropathy may present with no apparent underlying cause.<sup>8–11</sup>

Treatment-induced neuropathy was first described by Caravati in 1933. He reported a diabetic woman with numbness, tingling, and shooting pains in the lower extremities that appeared 4 weeks after the initiation of insulin.<sup>1</sup> The pain increased despite the use of analgesics and sedatives, but resolved within 3 days of stopping insulin concurrent with severe hyperglycemia. Further at-

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tempts at insulin use resulted in similar levels of pain. He called the condition *insulin neuritis*.<sup>1</sup>

Recent reports have described treatment-induced neuropathy in individuals with type 1 and type 2 diabetes treated with oral hypoglycemic agents or with insulin. Pretreatment glycosylated hemoglobin (A1C) is typically high and glycemic control rapid. Pain, the most prominent symptom of treatment-induced neuropathy, may occur distally in a length-dependent fashion or be more generalized and involve proximal sites including the trunk.<sup>2-4</sup>

Reports of treatment-induced neuropathy have been predominantly small observational case studies with variable follow-up.<sup>2-5,12,13</sup> In this article, we report a cohort of 16 patients with the sudden onset of pain, autonomic dysfunction, and microvascular complications after rapid glycemic control without associated weight loss. We provide the largest case series and first detailed report of autonomic testing, autonomic symptoms, intraepidermal nerve fiber density, concomitant microvascular complications, and longitudinal follow-up of patients with treatment-induced neuropathy.

## Patients and Methods

This study was approved by the institutional review board of Beth Israel Deaconess Medical Center. Sixteen cases of acute painful neuropathy were referred to our diabetic neuropathy clinic over 4 years after rapid and sustained glycemic control and were followed prospectively for 18 months or more. All patients underwent a standard battery of autonomic tests within 3 months of the onset of pain, with repeated autonomic testing 18 months later ( $\pm 4$  weeks). Subjects underwent detailed neurologic examinations approximately every 3 months, with pain scores measured at each visit. Selected patients underwent skin biopsy evaluation of intraepidermal nerve fiber density (IENFD). All subjects were evaluated for routine screening tests, including complete blood count, erythrocyte sedimentation rate, thyroid function tests, serum B12, comprehensive metabolic panel (including renal and hepatic function), and serum and urine protein electrophoresis. Subjects had yearly (or more frequent) retinal examinations and spot urine tests for microalbuminuria as part of their routine care. All subjects had A1C scores monitored every 3 months.

### Physical Examination

The physical examination findings were quantified with the neuropathy impairment score in the lower limb (NIS-LL) (see Supplementary Table 1 for details).<sup>14</sup>

### Pain Scores

Subjects ( $n = 16$ ) rated their pain on an 11-point Likert scale at every neurologic examination (every 3 months); a score of 0 denoted no pain, and a score of 10 denoted the worst pain imaginable. Subjects were treated with medications to reduce neuropathic pain, including anticonvulsants, antidepressants, and

opioids, alone or in combination. Pain scores were measured while subjects were on medication.

### Autonomic Testing

Subjects ( $n = 16$ ) had tests of cardiovascular parasympathetic function (the heart rate response to a Valsalva maneuver and deep respiration) and cardiovascular sympathetic function (the blood pressure response to tilt-table testing at 60° and a Valsalva maneuver). Patients had continuous electrocardiographic monitoring, continuous beat-to-beat blood pressure recordings, and manual blood pressure measurements every minute during tilt-table testing.

### Autonomic Questionnaires

Subjects ( $n = 16$ ) completed a detailed questionnaire addressing autonomic symptoms related to cardiovascular, gastrointestinal, genitourinary, vasomotor, and sudomotor dysfunction at the time of autonomic testing. Autonomic symptoms were rated on an 11-point scale (where 0 = no symptoms and 10 = severe symptoms). For determination of symptom prevalence, a symptom was considered clinically significant if score was  $>2$ .

### Skin Biopsy Evaluation of IENFD

Subjects ( $n = 10$ ) underwent 3mm punch skin biopsies at the lateral aspect of the distal leg, distal thigh, and proximal thigh within 5 months of the onset of pain and in 3 subjects 1 year later at the distal leg adjacent to the original biopsy sites using standard techniques.<sup>15</sup> Specimens were fixed and stained with PGP 9.5 (ubiquitin hydrolase, Chemicon, Temecula, CA). All patients underwent IENFD counting by a blinded technician. Results were expressed as a linear density (number of fibers per millimeter).<sup>16</sup>

### Statistics

The group data are presented as mean  $\pm$  standard deviation. Autonomic test results were analyzed using analysis of variance and Student *t* test where applicable. A *p* value  $<0.05$  was considered significant. All analyses were performed using Systat 11 (Systat software, SPSS, Richmond CA).

## Results

The complete demographic data for all 16 subjects is shown in Supplementary Table 1. Nine subjects had type 1 diabetes (7 female; mean age, 25 years), and 7 had type 2 diabetes (2 female; mean age, 47 years). None of the subjects had other abnormal laboratory values suggestive of other causes of neuropathy (mild anemia was seen in 4/7 of the female type 1 diabetic subjects). Vitamin B12 levels ranged from 632 to  $>2,000$ pg/ml. Compared with subjects with type 2 diabetes, subjects with type 1 diabetes had higher baseline A1C scores ( $15.5 \pm 1.3\%$  vs  $13.0 \pm 0.8\%$ ,  $p < 0.01$ ) and lower A1C scores after treatment ( $6.4 \pm 0.6\%$  vs  $7.5 \pm 0.7\%$ ,  $p < 0.01$ ). Subjects with type 1 diabetes also had lower blood pressure

(116/74  $\pm$  5/3mmHg vs 139/86  $\pm$  7/5mmHg,  $p < 0.01$ ) and lower cholesterol levels (168  $\pm$  11mg/dl vs 213  $\pm$  24mg/dl,  $p < 0.01$ ) at baseline.

All 7 female subjects with type 1 diabetes had a remote history of diabetic anorexia (intentionally withholding insulin for weight loss). The average duration of diabetic anorexia prior to the development of painful neuropathy was 5.6 years (range, 3–9 years), but there was no change in weight for an average of 1.8 years (range, 6 months to 4 years) prior to the onset of pain. One male subject, with type 2 diabetes and an A1C of 12.1%, intentionally lost 21lb. in 2 months by restricting himself to a 500-calorie per day diet to avoid taking oral hypoglycemic medications. His average daily blood glucose dropped from approximately 402mg/dl to 126mg/dl within a week of this dietary restriction. He noted tingling 4 weeks after starting his diet, and pain 2 weeks later. The male subjects with type 1 diabetes and all subjects with type 2 diabetes had historically poor glucose control due to treatment noncompliance. All patients reported a specific life event that caused them to rapidly improve glycemic control. Examples include death of a close friend or family member from diabetes, or personal hospitalization from a diabetes-related complication.

Physical examinations, quantified by NIS-LL scores, are reported in Supplementary Table 1. All subjects had normal motor strength examinations. The initial NIS-LL scores for individuals with type 2 diabetes were higher than those with type 1 diabetes (NIS-LL 10.5  $\pm$  2.2 for type 2, 5.1  $\pm$  1.4 for type 1,  $p < 0.001$ ). One year later, there were no significant changes in NIS-LL scores in either group (NIS-LL 10.8  $\pm$  1.9 for type 2, 5.3  $\pm$  1.3 for type 1,  $p < 0.001$ ). Reduced pain and thermal sensation were seen in 100% of subjects in the distal legs. All subjects reported severe 10/10 pain within 6 to 8 weeks of the onset of glucose control, independent of diabetes type. Most (81% of subjects) reported pain in a stocking and glove distribution (67% with type 1 and 100% with type 2). Three (19%) subjects, all with type 1 diabetes, reported more diffuse pain all over their bodies.

The A1C values and corresponding pain scores from each visit are shown in Figure 1. Despite maximal medical therapy, typically involving 2 to 3 drugs in combination, subjects still reported average pain scores of 7 to 9/10 (therapeutic regimen reported in Supplementary Table 1). The average duration of time required for a 50% reduction in pain (on maximal therapy) was 15 months, with a range of 12 to 28 months. In all cases, pain medications had been unchanged for several months prior to pain reduction. Hyperalgesia and allodynia was present in 57% of subjects (78% with type 1 and 29% with type 2).

Hyperalgesia alone was seen in 1 patient with type 1 diabetes and 1 patient with type 2 diabetes. Allodynia was not seen without hyperalgesia in these subjects.

There was a high prevalence of cardiovascular, gastrointestinal, genitourinary, and sudomotor symptoms in all subjects (clinically meaningful responses defined as  $>2$  on questionnaire; summarized in Fig 2). Orthostatic symptoms were the most common, with lightheadedness seen in 69%, dizziness in 75%, presyncope in 52%, and syncope in 31%. Symptoms of gastrointestinal dysfunction were also common: nausea in 69%, vomiting in 56%, diarrhea in 50%, loss of appetite in 43%, and early satiety in 43%. Erectile dysfunction was seen in 86% of male subjects. All autonomic symptoms were worse in type 1 diabetes patients. Most symptoms improved after 18 months in subjects with type 1 diabetes, but little change was noted in those with type 2 diabetes (see Fig 2).

There was a high prevalence of sympathetic and parasympathetic autonomic dysfunction (defined by age- and sex-derived normative values). Regarding parasympathetic function, abnormal heart rate response to deep breathing was present in 69%, abnormal expiratory to inspiratory ratio in 62%, and abnormal Valsalva ratio in 56%. Regarding sympathetic function, orthostatic hypotension (defined as systolic blood pressure fall of  $>20$ mmHg within 3 minutes of standing or upright tilt<sup>17</sup>) was present in 69% of individuals. All autonomic abnormalities were more frequent and more severe in patients with type 1 diabetes. Autonomic test results are summarized in Supplementary Table 2.

Eighteen months later there was a substantial reduction in the prevalence of autonomic dysfunction. Regarding parasympathetic function, abnormal heart rate response to deep breathing was present in 48%, abnormal expiratory to inspiratory ratio in 19%, and an abnormal Valsalva ratio in 43%. Regarding sympathetic function, orthostatic hypotension was present in 31%. Results are shown in Supplementary Figure 1 and Supplementary Table 2.

Skin biopsies revealed abnormal or borderline nerve fiber densities at the distal leg in all 8 tested subjects. Large nerve-fiber swellings were noted at the distal leg in all tested subjects, with some small and medium size nerve fiber swellings noted at the distal thigh in 5/8 subjects. More diffuse patterns of large nerve fiber swellings, at all biopsy sites, were noted in 2 patients (1 and 4) who reported diffuse non-length-dependent pain. Intraepidermal nerve fiber density data are shown in Supplementary Table 3 and Supplementary Figure 2. The 3 individuals with skin biopsies repeated 1 year later had increased nerve fiber densities at the distal leg.

Retinal examination worsened in all patients within

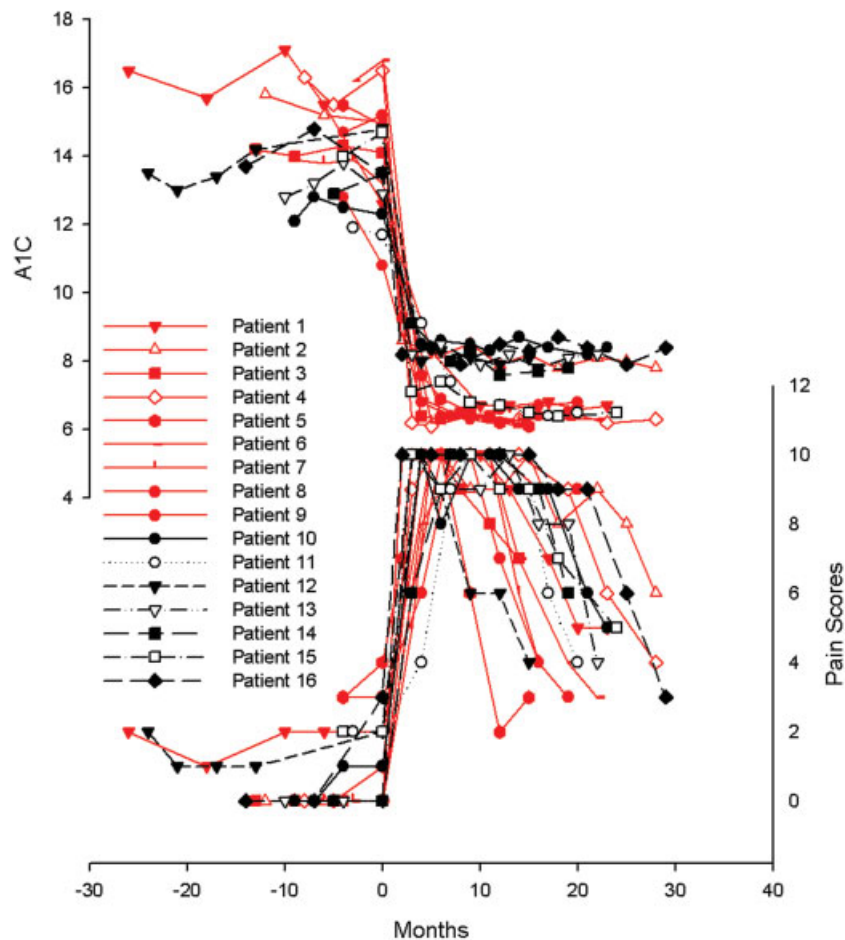


FIGURE 1: The upper portion of the graph reveals the glycosylated hemoglobin (A1C) scores over time, and the lower portion of the graph reveals neuropathic pain scores at the same visits. Patient numbers correspond to the data shown in Supplementary Tables 1 to 3. Red lines represent those with type 1 diabetes; black lines represent those with type 2 diabetes. The pain relief that occurred after 1 year was not associated with any pharmaceutical intervention. All pain medications had been stable for >6 months at the time of pain improvement (detailed in supplementary Table 1). [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

1 year after the onset of glycemic control. At baseline, 9/16 subjects had no retinopathy, and 7/16 had nonproliferative retinopathy (3 mild, 2 moderate, and 2 severe). After 6 months of sustained glycemic control, 0/16 subjects had no retinopathy, 8/16 had nonproliferative retinopathy (2 moderate and 6 severe), and 8/16 had severe proliferative retinopathy. The presence of microalbuminuria was detected in 8/16 individuals at baseline and 13/16 patients 1 year later.

## Discussion

We report the largest case series and first detailed analysis of autonomic symptoms, autonomic testing, cutaneous innervation, accompanying microvascular complications, and longitudinal follow-up of patients with the acute onset of neuropathy associated with glycemic control. Our data show that treatment-induced neuropathy is a reversible disorder characterized by severe pain, autonomic dys-

function, and unmyelinated nerve fiber damage after rapid and sustained glucose regulation in individuals with historically poor glycemic control. All subjects reported an improvement in pain after many months of continued glucose control, and those with type 1 diabetes in particular had improved autonomic symptoms, autonomic testing, and nerve fiber density. The data suggest diffuse damage to the unmyelinated and lightly myelinated nerve fibers that is temporally related to the rapid improvement in glucose control. Furthermore, there was parallel worsening of diabetic retinopathy, also a microvascular complication of diabetes, suggesting a possible common underlying pathophysiology.

The pain in our cohort differed from that observed in subjects with the generalized painful polyneuropathy associated with diabetes. First, pain was more severe and more refractory to therapeutic interventions; the pain was rated 10 on a scale of 10 by all subjects despite treatment

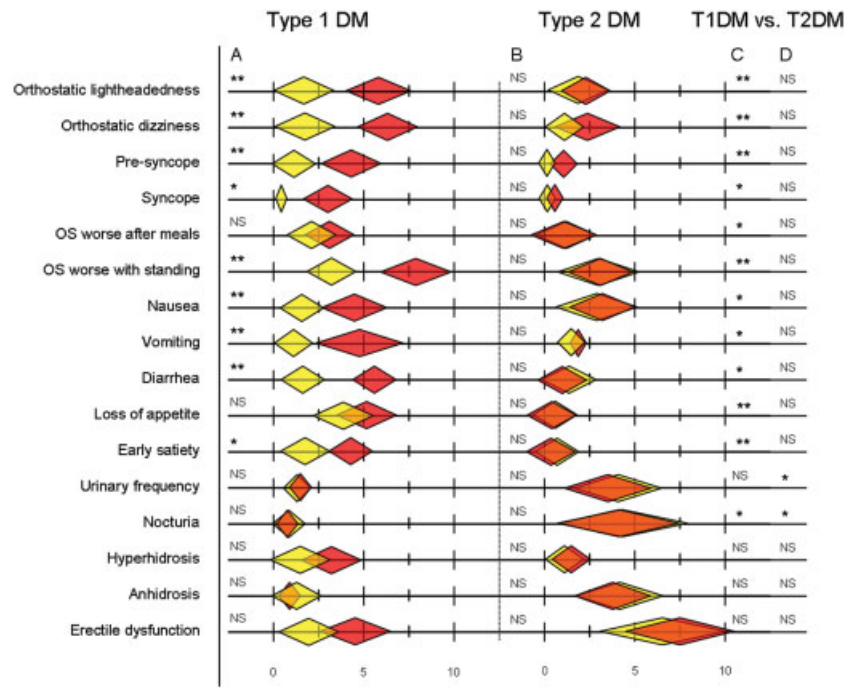


FIGURE 2: Autonomic symptoms were rated using a modified Likert scale where 0 = no symptoms and 10 = worst possible symptoms. The graph reveals the mean and standard deviation of the questionnaire scores at baseline (shown in red) and 18 months later (shown in yellow). The questionnaire was administered at the time of autonomic testing; clinically meaningful scores are >2. Results of baseline versus 18-month tests for type 1 diabetes (column A) and type 2 diabetes (column B), baseline comparisons of type 1 versus type 2 diabetes (column C), and 18-month comparisons of type1 versus type 2 diabetes (column D) are shown. All results include 9 subjects with type 1 diabetes and 7 subjects with type 2 diabetes, except erectile dysfunction, which was limited to male subjects (2 individuals with type 1 diabetes and 5 with type 2). DM = diabetes mellitus; NS = not significant; OS = orthostatic symptoms. \**p* < 0.005; \*\**p* < 0.001. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

with multiple medications. Second, all subjects had the onset of pain within 6 weeks of rapid glucose control. Third, although the pain was symmetric and length dependent in the majority of patients, 1/3 of the type 1 diabetic patients reported generalized pain; proximal and/or generalized pain has been previously reported in this disorder.<sup>3,5,18,19</sup> Fourth, evoked pain—hyperalgesia and allodynia—was present in 60% of subjects (80% of type 1 subjects and 40% of type 2 patients), a greater prevalence than in distal symmetric polyneuropathy.<sup>20</sup> Finally, pain was self-limited in all subjects.

Unlike many reports of acute painful neuropathy,<sup>2,3,13</sup> none of the individuals in our cohort had diabetic neuropathic cachexia. Only 1 of our subjects, a male patient with type 2 diabetes, intentionally dieting to improve glycemic control, reported substantial weight loss. All 7 of the women with type 1 diabetes had a remote history of diabetic anorexia. These women intentionally withheld insulin (in most cases in adolescence) to induce weight loss. The weight loss preceded the onset of acute painful neuropathy by at least 6 months and an average of almost 6 years. Prior reports of diabetic anorexia have noted pain onset with weight loss, but in our subjects there were no

reports of weight loss with pain. In all cases, weight remained stable until resumption of insulin use and consequent weight gain.<sup>7</sup> Furthermore, in contrast to reports of diabetic neuropathic cachexia<sup>5</sup> and other reports of treatment-induced neuropathy,<sup>4</sup> where symptoms peaked at the nadir of weight loss and resolved with weight gain, pain developed in these women after the weight gain. Although it is not likely that the diabetic anorexia was a direct precipitant of the acute painful neuropathy, it is possible that it created a predisposition to later nerve injury.

All individuals with treatment-induced neuropathy had evidence of autonomic dysfunction on testing and exhibited symptoms of autonomic impairment that were more prevalent and more severe than in patients with generalized diabetic peripheral neuropathy.<sup>21</sup> For example, 69% of our cohort had systolic blood pressure falls >20mmHg (78% of type 1 and 43% of type 2). In comparison, in the Rochester population-based study of generalized neuropathy, blood pressure falls of >20mmHg were present in 22.9% of type 1 and 16.2% of type 2 patients. In our cohort, even after 18 months, 31% of patients had blood pressure falls of >20mmHg (22% with type 1 and 43% with type 2).

Symptoms of autonomic dysfunction were more prevalent and more severe in subjects with type 1 diabetes, particularly with respect to symptoms of orthostatic intolerance and gastrointestinal function. Urinary frequency, nocturia, and anhidrosis were reported more frequently in individuals with type 2 diabetes, although it is unclear if this increase is due to differences in age and gender.

All subjects also had worsening of their retinopathy within 1 year of rigorous control. This observation is consistent with prior reports of unanticipated worsening of retinopathy in individuals with type 1 and type 2 diabetes that occurred shortly after the initiation of intensive treatment with insulin. The risk of early worsening retinopathy increases with each percentage point decrease in A1C.<sup>22</sup> The cause of the early worsening of retinopathy is not known. Cytokines and trophic factors, including the mitogenic cytokine, vascular endothelial growth factor, insulin growth factor, interleukin (IL)-6, IL-8, and tumor necrosis factor- $\alpha$ , have been implicated in the pathogenesis of diabetic retinopathy. It is hypothesized that upregulation of these cytokines and trophic factors associated with intensive glycemic control is responsible for the early worsening of retinopathy.<sup>23–25</sup>

Similarly, the underlying pathophysiology of this acute treatment-induced neuropathy is not known. Proposed mechanisms include the development of epineurial arteriovenous shunting causing endoneurial ischemia,<sup>2</sup> apoptosis due to sudden glucose deprivation,<sup>26</sup> recurrent hypoglycemia resulting in microvascular neuronal damage,<sup>27,28</sup> ectopic pain from regenerating nerve fibers,<sup>19</sup> ectopic firing of regenerating axon sprouts<sup>19</sup> (most likely due to channel or receptor upregulation), and insulin-induced reduction in endoneurial oxygen tension due to opening of arteriovenous shunts.<sup>2</sup> Nerves of streptozotocin-induced diabetic rats appear resistant to this hypoxic effect of insulin, but with control of hyperglycemia this susceptibility reappears.<sup>29</sup> A direct relationship to hypoglycemia seems unlikely; hypoglycemic neuropathy preferentially involves the motor nerves.<sup>30</sup> Although the possibility of a nutritional deficiency has been raised when treatment-induced neuropathy occurs in association with weight loss, the absence of weight loss in our subjects makes that etiology unlikely.

We and others have recently observed an increase in proinflammatory cytokines in association with experimental hypoglycemia.<sup>31,32</sup> Elevated cytokine levels, including IL-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$ , have been associated with painful neuropathy.<sup>33–35</sup> We have also observed impaired autonomic function after experimental hypoglycemia.<sup>36</sup> Thus, acute treatment-induced neuropathy and worsening of retinopathy after intensive glycemic control may have a common underlying pathophysiological mech-

anism that involves upregulation of proinflammatory cytokines. Recent data suggest that activation of microglia with subsequent cytokine production may underlie both the pathogenesis of worsening retinopathy after intensive glycemic therapy and treatment-induced neuropathy.<sup>37,38</sup> Microglial activation is present in human and preclinical models of diabetic retinopathy, and in preclinical models of neuropathic pain in which microglial activation with subsequent upregulation of cytokines and chemokines contributes to the development and maintenance of neuropathic pain.<sup>39,40</sup> Taken together these data suggest an additional hypoglycemia-related pathophysiological mechanism and provide potential targets for therapeutic intervention.

Sural nerve biopsies have been reported in 8 patients in 4 different studies, with results revealing variable loss of myelinated fibers, acute axonal degeneration, and some clusters of regenerating myelinated fibers,<sup>4–6,13</sup> findings similar to other published data on sural nerve pathology in diabetes.<sup>41,42</sup> There are no reports of a follow-up biopsy in these acute painful neuropathy subjects.

Of the 8 subjects in our study with skin biopsies, all had borderline or abnormal nerve fiber densities at the distal leg. Morphologic abnormalities, including large swellings on small nerve fibers, were seen in several individuals (see Supplementary Fig 2). The decreased IENFD at proximal sites tended to be seen in those with more widespread distribution of pain, but not in all cases. Those individuals with proximal pain who had normal IENFD at the distal and proximal thighs did have more prominent nerve fiber swellings. We and others have reported that large nerve fiber swellings are associated with a decline in IENFD.<sup>15,43</sup> However, those subjects with large swellings who had biopsies repeated 1 year later did not have a reduction in IENFD and did not have morphologic abnormalities. These data suggest that if the stimulus for nerve damage is removed, nerve fiber swellings need not necessarily portend a decline in IENFD.<sup>44,45</sup>

The cases in this report highlight that symptoms, signs, and objective measures of small myelinated and unmyelinated nerve fibers can improve in patients with a prolonged history of very poor glucose control. After 18 months of improved glucose control, there were improvements in pain, symptoms and tests of autonomic function, and IENFD. The improvements in individuals with type 2 diabetes were not as marked as in those with type 1 diabetes. There are several factors that may explain the differences between these groups. Specifically, individuals with type 1 diabetes were younger, had fewer comorbid medical conditions such as hyperlipidemia and hypertension, known risk factors for diabetic polyneuropathy,<sup>46</sup> and ultimately had better glucose control (A1C average of 6.3) compared with those with type 2 diabetes (A1C av-

erage of 8.1). Nevertheless, even in the patients with type 2 diabetes pain improved substantially. We suggest that *treatment-induced neuropathy* more accurately encompasses the disorder than the historic term *insulin neuritis*.

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## Potential Conflicts of Interest

Roy Freeman has been a paid consultant for Pfizer and Eli Lilly.

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