Acute Improvement in Intraoperative EMG During Common Fibular Nerve Decompression in Patients with Symptomatic Diabetic Sensorimotor Peripheral Neuropathy: EMG and Clinical Attribute Interrelations

Dwayne S. Yamasaki[1] D. Scott Nickerson[2] James C. Anderson[3]

[1] Department of Research & Development, Enso Medical Technologies, Inc., Jacksonville, Florida, United States
[2] P.O. Box 278, Big Horn, Wyoming, United States
[3] Anderson Center for Nerve Pain, Fort Collins, Colorado, United States

Address for correspondence J.C. Anderson, DPM, Anderson Center for Nerve Pain, 1355 Riverside Avenue, Fort Collins, CO 80524, United States (e-mail: jafootdoc@email.com).

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Abstract

Study Aims Electromyographic (EMG) recordings of the fibularis longus and tibialis anterior muscles were performed intraoperatively during nerve decompression (ND) of the common fibular nerve (CFN) in patients with symptomatic diabetic sensorimotor peripheral neuropathy. Patient demographics and clinical attributes were compared against changes in EMG after ND and analyzed for possible correlations.

Methods Intraoperative changes in CFN EMG were analyzed for correlations against sex, age, body mass index (BMI), hemoglobin A1c (A1c), and type and duration of diabetes.

Results Statistically significant changes were found between EMG changes and patient attributes, but no individual correlations were established. Significant EMG improvement was observed for both men and women ($p < 0.0001$ and $p < 0.05$, respectively), age groups (4th decade: $p < 0.05$; 5th decade: $p < 0.05$; 6th decade: $p < 0.01$; 7th decade: $p < 0.005$), diabetes duration (0–9 years: $p = 0.002$; 10–19 years: $p = 0.002$; 20–29 years: $p = 0.03$), and for type 1 and 2 diabetes (type 1: $p < 0.005$; type 2: $p < 0.001$). EMG improvement was greater in patients with the highest BMI levels (30–34.9: $p = 0.014$; 35–39.9: $p = 0.013$; > 39.9: $p = 0.043$), and highest A1c levels ($> 6.4\%$; $p < 0.0001$).

Conclusion Although long-term clinical studies are needed, these results provide insight into which patients might benefit most from this surgery. These results also suggest that surgical ND can produce an acute improvement in nerve function for both men and women, for people with type 1 and 2 diabetes, and across a wide range of ages, BMI, A1c levels, and disease duration.

Keywords

- diabetic sensorimotor peripheral neuropathy
- common peroneal nerve decompression
- motor evoked potentials
- acute objective functional improvement

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Introduction

In a previous retrospective study,[1] we reported the results of intraoperative nerve recordings during surgical common fibular nerve (CFN) decompression. In that report, 46 legs were treated in 40 patients, 82.6% of the legs showed increased electromyographic (EMG) amplitudes, 44 of 60 fibularis longus (FL) and tibialis anterior (TA) muscles (73.3%) showed improved EMG signals, and the average EMG improvement was 73.6%. Improved visual analog scale (VAS) scores were also shown for pain, burning, numbness, tingling, weakness, and balance. In this article we report the same EMG data across the range of patients' clinical parameters and demographic data. This analytic approach provides initial insights on appropriate patient selection, the degree to which patient characteristics and comorbidities affect the intraoperative change in nerve function, and which patients might benefit most from this procedure.

Materials and Methods

This retrospective analysis was performed on data collected during procedures conducted by J.C.A. at the Anderson Center for Nerve Pain. The protocol was approved by the Poudre Valley Health System institutional review board, and consent for the surgery was obtained from each of the subjects in the study. Forty consecutive diabetic sensorimotor peripheral neuropathy (DSPN) patients who underwent CFN decompression surgery with intraoperative nerve monitoring from June 6, 2007, to April 13, 2011, were included in the study. Indications for nerve decompression (ND) surgery were patients with diabetes on standard medical care with painful neuropathy unrelieved by pharmacologics, adequate circulation based on pedal pulses and capillary refill time, an abnormal neurologic sensibility examination, and a positive Tinel's percussion sign on the CFN at the fibular neck suggesting entrapment. Patient screening, surgical procedure, and intraoperative monitoring were all performed as described previously.[1]

In that report, EMG data were collected from 60 muscles (FL: $n = 31$; TA: $n = 29$) innervated by the CFN minutes before and within minutes after decompression of the CFN.

Statistical Procedures

The pre- and post-release EMG amplitude values (Pre and Post, respectively) for each of the 60 measured muscles were compared using the *t* test to determine statistical significance. Values are expressed as mean ± SD in the text and mean ± SEM in the figures. The *t* tests (paired, one tailed) were used to determine significance in changes of EMG signals to decompression (i.e., same samples Pre versus Post treatment, where an improvement was being evaluated). The effect of CFN decompression on EMG was expressed two ways: $Normalized\ EMG\ Response = \frac{Post}{Pre}$ and $Percent\ EMG\ Change = \left(\frac{Post-Pre}{Pre}\right) \times 100$. Asterisks were used to indicate statistical significance ($p < 0.05$).

Scatterplots were used to look for correlations in Pre versus Post EMG values, and EMG changes versus patient demographic and clinical data. Regression statistics analysis was performed on the scatterplot regression lines to determine R^2 and significance for slope, y-intercept, and F-significance.

EMG odds ratio analyses were performed for EMG responses against patient data to determine possible trends and correlations such as EMG improvement in patients with low versus high body mass index (BMI) or hemoglobin A1c, diabetes mellitus type 1 (DM1) versus DM2, patient age, diabetes duration, and sex.

Results

In the previous report we demonstrated EMG improvement in 82.6% of the treated legs and 73.3% of the monitored muscles, with an average EMG improvement of 73.6%.[1] The extent and significance of the immediate EMG responses (as an index to the nerve's response to decompression) were then analyzed to see if there were correlations of the neuromuscular responses to patient demographic and clinical data.

Sex

When the EMG values were grouped by sex, the significance in improvement was maintained (►**Fig. 1**). Mean EMG amplitudes for men increased from 3,018 ± 2,675 μV to 5,906 ± 4,236 μV ($p = 6.8^{-5}$) and from 3,015 ± 2,860 μV to 4,473 ± 4,156 μV ($p = 0.0472$) for female patients, reflecting increases of 95.7% and 48.4%, respectively. Improvements in the men were more striking than those in women, but a *t* test (not shown) showed the difference in improvements was not significant ($p = 0.19$).

Age

Subject ages ranged from 44 to 83 years, so it was of interest to determine if age was a factor in EMG response. Patient ages were grouped by decade and compared using the *t* test (paired, one tailed). Significant improvement was seen in each age group except the oldest (►**Fig. 2**). Although not significant, EMG improvements were seen in this 8th decade as well (Pre: 2,246 ± 1,989 μV; Post: 2,993 ± 3,718 μV; 33.3% improvement). Three of the eight muscles in this group

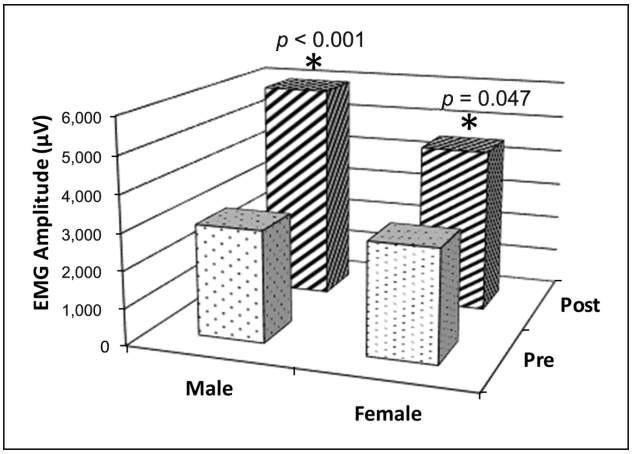

Fig. 1 Significant increases in electromyographic (EMG) amplitude were seen in both male and female patients.

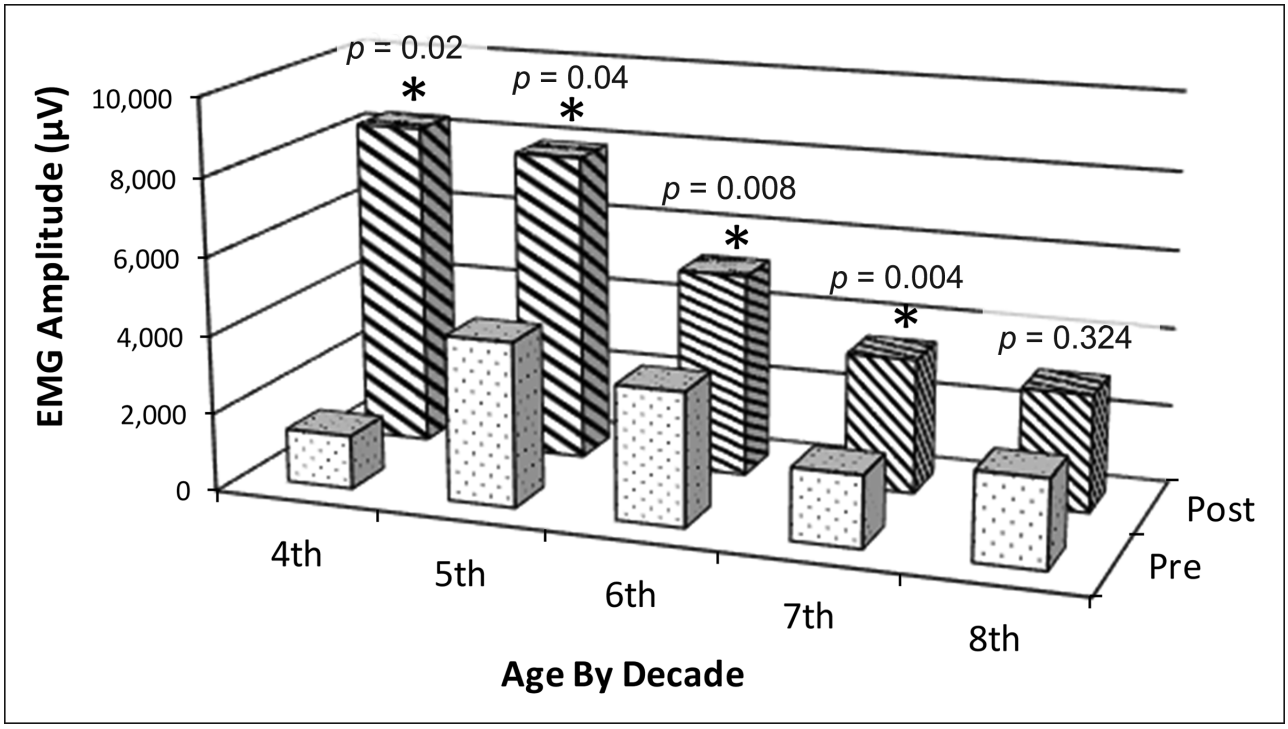

Fig. 2 Effect of age on common fibular nerve response to nerve decompression. Significant improvement in electromyographic (EMG) amplitude was noted for all age groups except the oldest (significance indicated by asterisks). The number of muscles in each age group by decade were 4th: $n = 4$; 5th: $n = 8$; 6th: $n = 32$; 7th: $n = 8$; and 8th: $n = 8$.

improved with an average change of 381.6%; five muscles declined with an average change of − 77.48%. ►**Table 1** lists the EMG results for each age group and the percentage of muscles that improved in each group. We tested whether there was a correlation using a scatterplot of normalized EMG response over patient age. However, the scatterplots (data not shown), similar to the graph in ►**Fig. 4b**, showed no correlation. We also performed an odds ratio analysis comparing each age group against every other age group, and no greater likelihood of good outcome for any decade group was found.

Diabetes Duration

The range of diabetes duration in the study was 1 to 62 years (mean: 12.1 ± 9.9 years). The durations were parsed by decades. A single patient in the 30- to 39-year-old group with a 79.1% EMG improvement (Pre: 3,258 μV; Post: 5,836 μV) was included in the 3rd decade group (20–30 years). An unexpected result emerged. Significant improvements in intraoperative EMG were seen in each of the decades for which there was more than one sample. In the seventh decade, there was only one muscle measured, and even that muscle improved (62 years: 11.3% improved EMG; ►**Table 2** and ►**Fig. 3**). The preoperative EMG values dropped with disease duration, as did the absolute postoperative EMG values. However, the percentage change increased with disease duration out to the 3rd decade (77.6%, 89.2%, and 138.1%, respectively). Details of the results are shown in ►**Table 2**. A scatterplot analysis was used to look for correlations between the normalized EMG response and diabetes duration (i.e., normalized EMG response over disease duration; data not shown). The regression slope was close to zero (− 0.01; $p = 0.64$), suggesting no change and specifically no decrease in the effectiveness of the surgery with increasing duration of the disease out to 30 years.

Table 1 Electromyographic response to nerve decompression in patients grouped by age in decades

Age, decade	n[a]	Mean Pre EMG, μV	Mean Post EMG, μV	EMG improvement, %	Showing improvement, %
4th	4	1,369 ± 909	8,352 ± 4,838	510.3	100.0
5th	8	4,212 ± 3,759	7,896 ± 5,367	87.4	75.0
6th	32	3,413 ± 2,845	5,193 ± 3,955	52.1	78.1
7th	8	1,829 ± 1,658	3,446 ± 2,335	88.4	75.0
8th	8	2,246 ± 1,989	2,993 ± 3,718	33.3	37.5

Abbreviation: EMG, electromyography.
[a]Number of muscles measured (fibularis longus and tibialis anterior) not number of patients.

Table 2 Electromyographic response to nerve decompression and duration of diabetes

Disease duration, y	Muscles tested, *n*	Mean Pre EMG, μV	Mean Post EMG, μV	EMG improvement, %
0–9	19	3,844 ± 3,718	6,829 ± 4,711	77.6
10–19	24	2,864 ± 2,023	5,420 ± 3,832	89.2
20–30	7	1,652 ± 1,256	3,933 ± 3,144	138.1
60–69	1	4,553	5,068	11.3

Abbreviation: EMG, electromyography; ND, nerve decompression.

Body Mass Index

Patient EMG results were parsed into five groups based on the World Health Organization's BMI classification.[2] None of the patients fell into the underweight range (< 18.50), so that category was omitted. The data could have been parsed into the three remaining main groups (normal, overweight, and obese), but the three subclasses of obesity were included to see if a correlation existed in spite of reducing the sample size for each group (►**Table 3**). There was a positive relationship between EMG response and BMI (►**Fig. 4a**). Improvement was seen at each level but was significant only in the obese ranges. Interestingly, ►**Table 3** shows that EMG percentage change increased with each BMI level, with the highest percentage change in the severely obese group (class III) in spite of the low sample size ($n = 6$). These results suggest a relationship between EMG improvement and BMI level; however, a scatterplot of normalized EMG response over BMI did not show significance (►**Fig. 4b**). The regression had a slight positive slope of 0.06, but the regression line was not significant (p values of 0.13 and 0.17 for slope and y-intercept, respectively, and an F-significance of 0.13).

Hemoglobin A1c Levels

Patients were parsed into three A1c levels: normal (4–5.6%), prediabetic (5.7–6.4%), and diabetic (> 6.4).[3] The results showed improved EMG responses in all three groups but were significant only in the diabetic level (►**Fig. 5**). As with BMI and diabetes duration, improvements were seen in all A1c levels, although they were only significant at diabetic levels, suggesting a correlation of EMG response with inadequacy of glucose control. However, a scatterplot of normalized EMG response over A1c levels did not show a significant correlation (not shown). The EMG values per A1c levels are shown in ►**Table 4**. Although only those with the highest A1c levels showed significant improvement in EMG, each of the groups showed impressive improvements (normal: 63.0%; prediabetic: 47.0%; diabetic: 104.9%).

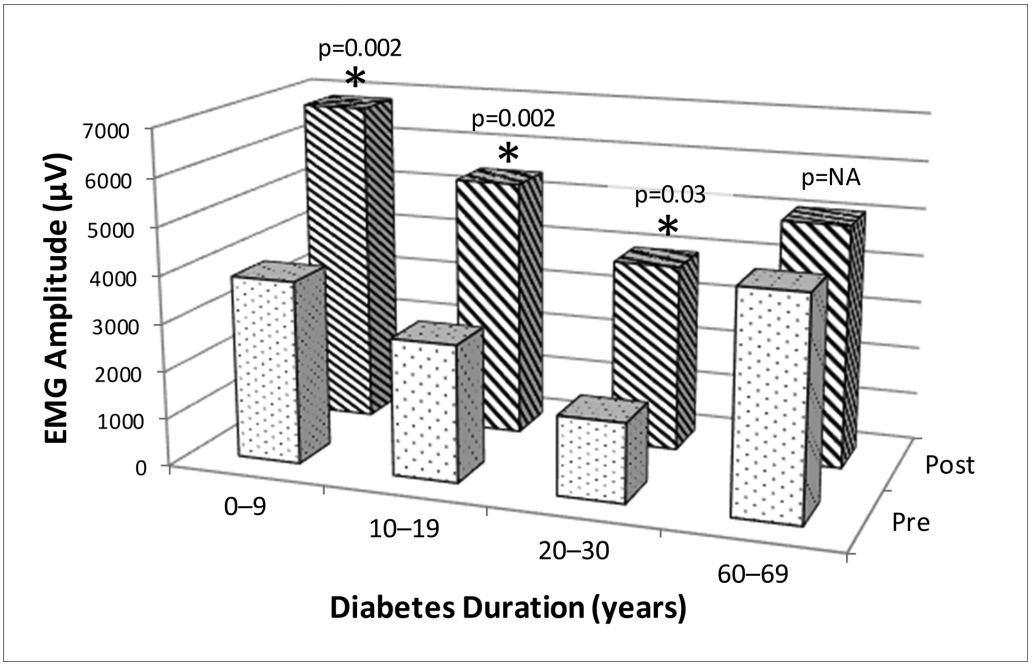

Fig. 3 Interaction between electromyographic (EMG) response and duration of diabetes in years. Significant improvement in EMG was seen out to the 3rd decade of the disease (20–30 years). There was one muscle in one patient who had the disease for 62 years. Although a *t* test could not be run, the EMG amplitude increased by 11.3% (Pre: 4553 μV; Post: 5068 μV) in this patient. The only patient with a 30-year duration was included in the 3rd decade group.

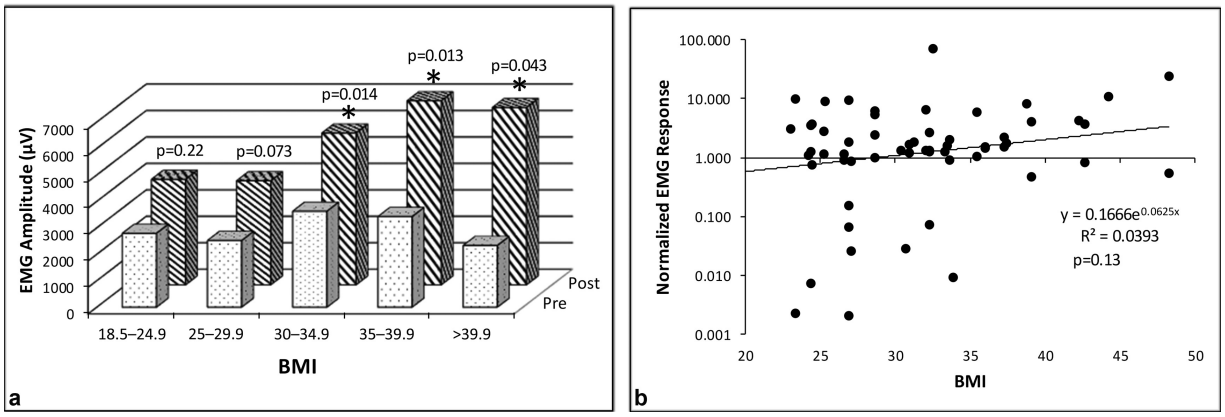

Fig. 4 Correlation between electromyographic (EMG) response and body mass index (BMI). (**a**) The BMI levels are based on the World Health Organization classification (normal, overweight, obese class I, II, and III). Significant EMG improvement was seen only in the obese ranges. Further, the EMG percentage change increased with each BMI level (►**Table 3**). (**b**) Normalized EMG response (Post EMG/Pre EMG) for each muscle plotted over BMI level. The exponential regression suggests a positive relationship, but the fit ($R^2 = 0.04$) and slope were not significant ($p = 0.13$).

Type 1 versus Type 2 Diabetes

The surgery resulted in statistically significant improvement in EMG in patients with either DM1 or DM2 (►**Fig. 6**). Although the Post decompression EMG values were nearly identical for DM1 and DM2 patients (DM1 Post: 5,222 ± 3,197 μV; DM2 Post: 5,268 ± 4,407 μV), there was a greater percentage improvement in the DM1 group (331.9% vs. 159.8%). To evaluate possible correlations or explanations for the greater improvement in the DM1 subjects, a comparison was made between the DM type, disease duration, BMI, and A1c versus the EMG responses (►**Table 5**) because these were the attributes that showed trends.

As expected, patients with DM1 had the disease significantly longer than those with DM2 by the time of the surgery (22.3 ± 16.0 years and 9.9 ± 6.5 years, respectively; $p = 0.02$; ►**Fig. 7b**), and the percentage change of EMG response was significantly greater for DM1 patients (►**Fig. 7a** and ►**Table 5**). This is consistent with the diabetes duration results that showed a positive trend with percentage EMG improvement and duration out to 30 years (►**Table 2**). The BMI analysis showed increasing improvement in EMG with increasing BMI values (►**Table 3**). This conflicts with the DM type results because DM1 patients have lower BMI values than DM2. There also was a significant difference in A1c values (DM1: 8.01 ± 0.84; DM2: 6.70 ± 1.09). Although interesting, these results do not provide insight into why DM1 improvements are greater. Knowing the relative importance of each of these parameters would be helpful in patient selection and is treated in the next section.

Potential Predictors of Neuromuscular Improvement

In an attempt to identify possible predictors of improved EMG after ND and their relative importance, a multivariate regression analysis was undertaken for BMI, A1c, DM type, and diabetes duration. This analysis assesses multiple factors and determines if they account for the variance in normalized EMG, either as a group or individually. The overall regression model was significant: $F(4,40) = 3.09$; $p = < 0.05$; $R^2 = 0.236$. As a group, these four factors did predict 23.6% of the variance in normalized EMG ($R^2 = 0.236$). Individually, both BMI ($p = 0.010$) and DM type ($p = 0.046$) were significant predictors of normalized EMG variance, whereas duration of diabetes ($p = 0.095$) and preoperative A1c ($p = 0.62$) were not significant. ►**Figs. 4a** and **7a** combined with this analysis indicate that DM1 and increasing BMI values in the obese ranges are the significant individual predictors of improved neuromuscular function.

Discussion

To our knowledge, this is the first study showing significant intraoperative EMG improvement within minutes of the ND in patients with diabetic neuropathy with nerve entrapment. We want to emphasize that the study results make

Table 3 Electromyographic amplitude and body mass index levels

WHO classification	BMI level	Muscles tested, *n*	Mean Pre EMG, μV	Mean Post EMG, μV	EMG change, %
Normal	18.5–24.9	11	2,791 ± 2,538	3,988 ± 3,714	42.9
Overweight	25–29.9	16	2,521 ± 2,839	3,937 ± 4,157	56.1
Obese class I	30–34.9	17	3,628 ± 2,956	5,738 ± 4,455	58.2
Obese class II	35–39.9	10	3,427 ± 2,978	6,962 ± 4,555	103.1
Obese class III	> 39.9	6	2,334 ± 2,117	6,706 ± 3,478	187.3

Abbreviations: BMI, body mass index; EMG, electromyography; WHO, World Health Organization.

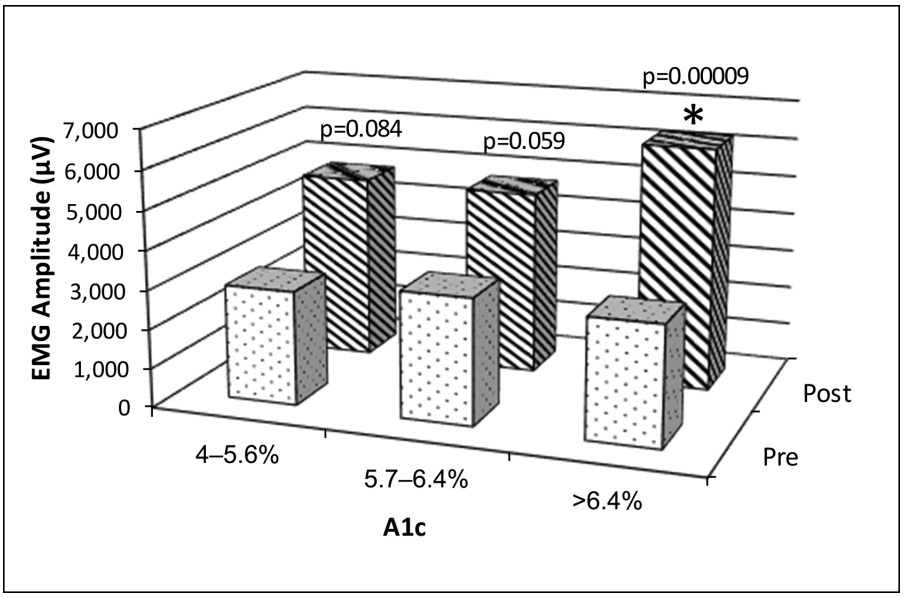

Fig. 5 Electromyographic (EMG) responses across hemoglobin A1c levels (A1c). The three columns indicate normal (4–5.6%), prediabetic (5.7–6.4%), and diabetic (> 6.4%) levels at the time of nerve decompression surgery. EMG responses improved in all A1c levels but were significant only at the diabetic level.

Table 4 Electromyographic responses per hemoglobin A1c levels

A1c level, %	Muscles tested, *n*	Mean Pre EMG, μV	Mean Post EMG, μV	EMG improvement, %
4–5.6	3	2,914 ± 870	4,751 ± 1,086	63.0
5.7–6.4	16	3,210 ± 3,292	4,718 ± 4,435	47.0
> 6.4	29	3,040 ± 2,684	6,228 ± 4,336	104.9

Abbreviations: A1c, hemoglobin A1c; EMG, electromyography.

suggestions on the effect of treating the secondary entrapment and not primary metabolic disease.

Analyzing the EMG results with reference to patient clinical attributes and demographic data provided several insights. As a whole, these results begin to offer guidance for patient selection for this procedure. The most interesting result is that, given the presence of DSPN, adequate circulation, and a positive Tinel's sign,[4] improved

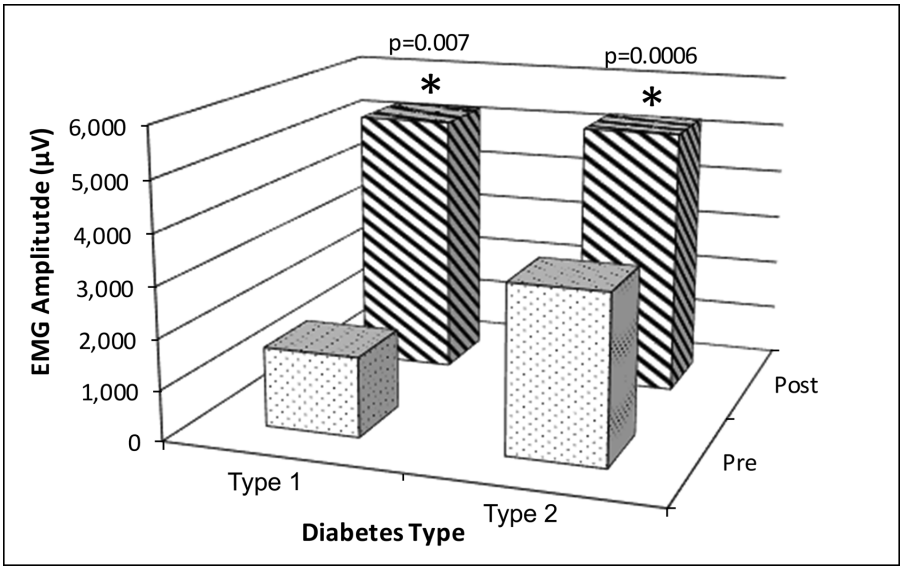

Fig. 6 Significant improvements were observed in electromyographic (EMG) response in patients with type 1 diabetes mellitus (DM1) and DM2. DM 1: n: 9; Pre: 1,573 μV ± 1,520 μV; Post: 5,222 μV ± 3,197 μV; percentage change: 331.9%. DM2: n: 47; Pre: 3,296 μV ± 2,822 μV; Post: 5,268 μV ± 4,407 μV; percentage change: 159.8%.

Table 5 Relationships between diabetes type, disease duration, body mass index, hemoglobin A1c, and electromyographic response

Diabetes type	Muscles measured, *n*[a]	Disease duration, y	BMI	A1c	Mean Pre EMG, μV	Mean Post EMG, μV	EMG improvement, %
1	9	22.3 ± 16.0	27.7 ± 3.57	8.01 ± 0.84	1,573 ± 1,520	5,222 ± 3,197	331.9
2	42	9.9 ± 6.5	33.5 ± 6.39	6.70 ± 1.09	3,422 ± 2,868	5,843 ± 4,306	170.7

Abbreviations: A1c, hemoglobin A1c; BMI, body mass index; EMG, electromyography.
[a]There were five fewer type 2 data points than shown in ►**Fig. 6** due to missing disease duration data.

neuromuscular function is possible regardless of high BMI and A1c levels, long disease duration, or type of diabetes. Further, as reported in our first article,[1] this improvement was seen within minutes of the decompression. The significance of the retrospective data on this small group of patients is unknown, and a better understanding will emerge as more patients are analyzed in future studies by others.

Sex

Analyzing the EMG results across sex showed that the surgery worked for both male and female patients as

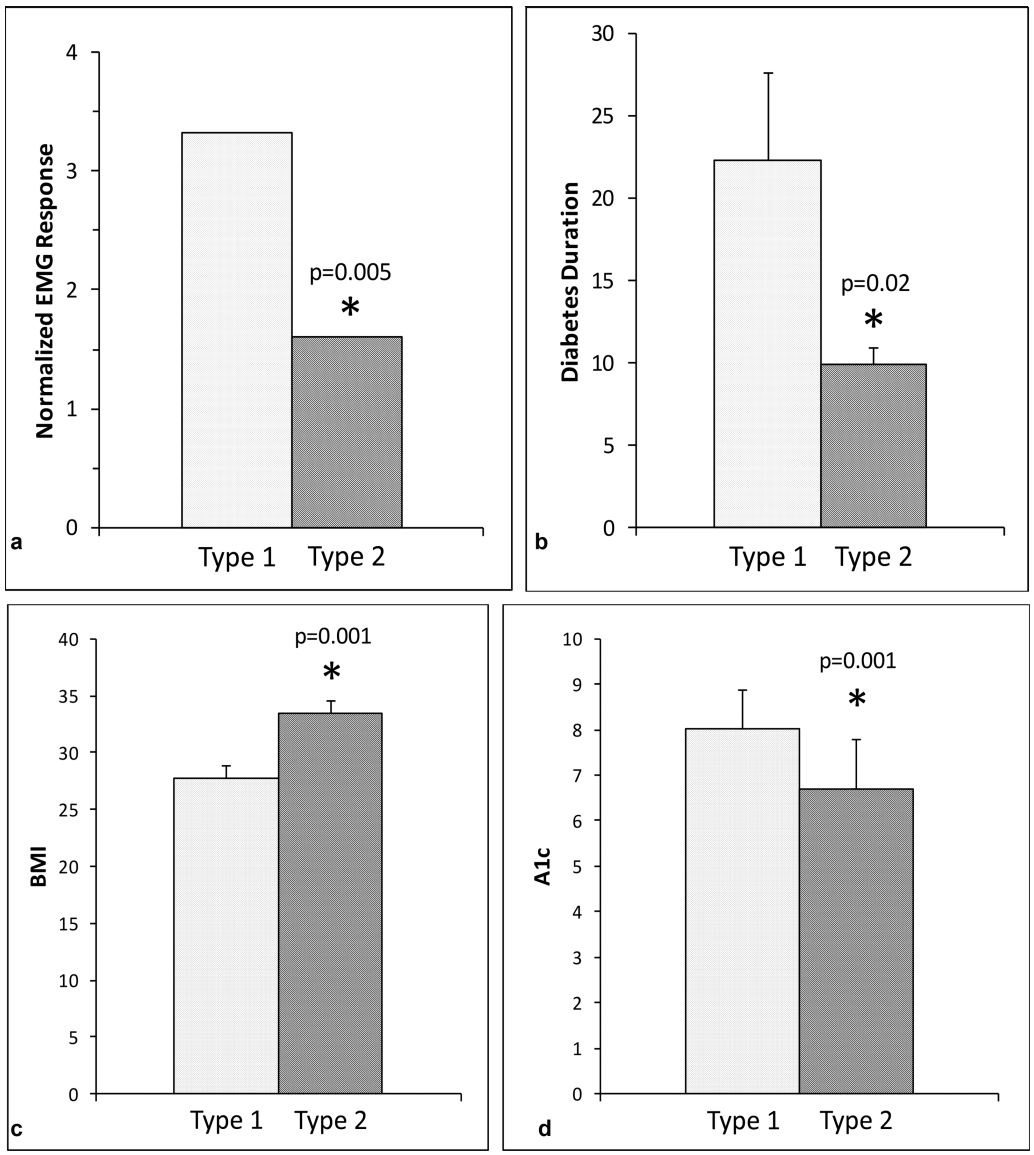

Fig. 7 Patients with type 1 diabetes mellitus (DM1) showed greater percentage improvement in electromyography (EMG) after nerve decompression than DM2 patients. DM type was compared with other attributes that showed trends to look for correlations. (**a**) DM1 patients had significantly better EMG improvements with average amplitude increases of 331.9% versus 170.7% for DM2 patients. (**b**) Patients with DM1 had the disease significantly longer than those with DM2. (**c**) Body mass index (BMI) levels were significantly lower in DM1 patients. (**d**) DM1 patients had significantly higher A1c levels than DM2 patients.

expected, although possibly better for men (►**Fig. 1**). Although the results suggested a greater improvement in men over women, the *t* test showed no significant difference.

Age

It was interesting that patients in every age group showed improved EMG after CFN decompression. Although the five patients (eight muscles) in the oldest group did not show significant improvement, they did have a mean 33.3% increase in EMG amplitude (►**Table 1**). It appeared that improvements were greatest in the younger patients, but both scatterplot and odds ratio analyses failed to show significant differences in the percentage EMG change. These results suggest that an improved outcome can be seen in all age groups. Again, more studies are needed to confirm this.

Duration of Diabetes

One unexpected finding was that in these patients, all durations of diabetes out to 3 decades showed significant EMG improvement. There was one patient who had the disease for 62 years and still showed an improvement of 11.3% in her TA. As with BMI, there was a positive relationship between increasing EMG improvement and increasing disease duration for the first 3 decades (►**Table 3**).

In a recent report on 1,526 patients with DSPN and lower limb ND, Zhong et al also found nerve conduction velocity (NCV) and temperature perception improvements in patients with short or long DM duration using a 5-year segregation point. Significantly better results were seen in their patients with short duration DM.[5] Our analysis does not examine a 5-year duration group, but we saw a similar trend in clinical outcome, with decreasing pre- and post-decompression EMG absolute values with disease duration. However, in our study, the percentage changes in EMG did increase with disease duration (►**Table 3**).

We performed an odds ratio analysis between each of the duration groups, but no significant bias was seen (data not shown). These results suggest that the surgery can be successfully performed in patients with diabetes out to 3 decades, and possibly longer, if there are still viable axons in the nerve (i.e., as demonstrated by a positive Tinel's sign or electrodiagnostic testing). Further, the odds ratio analyses suggest that no age group is likely to have worse results.

The positive connection between duration of disease and percentage of EMG improvement may be related to increasing sorbitol accumulation within the nerve via the polyol pathway pathology. As the sorbitol content of nerve increases, the osmolarity within the nerve increases, resulting in intraneural fluid migration and swollen nerves that can be visually striking when exposed surgically. Further, an increase in advanced glycation end products (AGEs) will shrink, toughen, and reduce compliance of the fibrous tissue elements of the tunnel. These effects of the polyol pathway pathology and AGEs will result in increased pressure as the nerve swelling progresses. This is a dynamic process during joint movement and will affect the entire length of the nerve that glides through the tunnel. Swollen nerves in patients with DSPN were also shown with ultrasound imaging.[6] Increasing exposure to AGEs is accompanied by increased collagen stiffness and tensile strength and a decreased susceptibility of the tunnels to degradative enzymes.[7] AGEs are also linked to increased expression of intercellular adhesion molecule-1.[8] These features act to decrease the compliance of the tunnels even further and contribute to reduced nerve gliding.[9–11]

Axonal demyelination, nodal dysfunction, and axonal atrophy occur and progress in patients with diabetic neuropathy.[12–15] This study demonstrates that in spite of this well-documented pathology, viable motor axons remain in the CFN even out to $\geq$ 30 years duration of disease. The improved intraoperative EMG responses after ND suggest some of the axons are latent due to impingement at the tunnels and can show improved function following decompression within minutes. It was demonstrated that axons can remain functional through chronic demyelination,[16–18] and it is well known that demyelinated fibers can maintain some function in multiple sclerosis.[19–21] Further, this retained function is due, at least in part, to increased density of voltage-gated sodium channels and voltage-gated potassium channels in the demyelinated internode and paranode regions of the axon, respectively.[22–25]

Body Mass Index

There is an interesting relationship between EMG response to CFN decompression and BMI. EMG improvement was seen across all levels of BMI from normal weight to obese class III. However, EMG increases were only significant in the three obese classes (►**Fig. 4a**). Further, the EMG improvements grew with each successive BMI level (►**Table 3**). The positive interaction between EMG improvement and BMI level suggests that the greater the pressure around the CFN, the greater the improvement after decompression. Again, this would be true as long as there is axonal viability within the CFN. This is consistent with Dellon's hypothesis in that mechanical impingement on the nerve is a contributory cause of symptoms found in DSPN. It also underscores why a positive Tinel's sign is so important in selecting patients for this procedure, which indicates both viable axons and a nerve irritant or recovery response.[4]

Hemoglobin A1c

Similar to BMI and diabetes duration, there was a trend of increasing percentage EMG improvement with increasing A1c levels. This was also the case with decreasing *p* values with increasing A1c levels (4–5.6%: $p = 0.08$; 5.7–6.4%: $p = 0.06$; $> 6.4\%$: $p > 0.0001$; ►**Fig. 5**).

Yet as with BMI, the fact that the best responses were seen in patients with high A1c levels is consistent with the concept that nerve impingement plays a significant role in symptom generation in these patients. This is consistent also with the fact that high A1c levels are a risk factor for the development of DSPN.[26] Chronic hyperglycemia leads to a shift in equilibrium of the polyol pathway in insulin-independent tissue (e.g., nerves) toward increased sorbitol production, hyperosmolarity, and swelling.[27–29] The CFNs in

these patients have abnormal diameters, often as high as 12 mm (J.A., unpublished data) and a yellowish color, appearing similar to adipose tissue, as shown in ►**Fig. 3** of our previous article.[1] Swollen nerves are at risk of impingement at the tunnels like the fibular tunnel, and high glucose levels could contribute to swollen nerves and secondary compression in the tunnels. Given this rationale, improved EMG values within minutes after ND would be expected if weakened EMG signals are due at least in part to nerve compression, provided there are still viable axons within the nerve.

Type 1 Versus Type 2 Diabetes

Patients with either DM1 or DM2 benefited from the surgery, with both groups showing significant increases in EMG amplitude. The final absolute EMG values were the same; however, differences were found in percentage of improvement. It is not surprising that DM1 patients had longer disease durations (22.3 years) than DM2 patients (9.9 years), and the difference was significant ($p < 0.05$; ►**Fig. 6b**). It follows that patients with DM1 disease might have had greater progression of neuropathy before surgery, resulting in lower initial EMG amplitudes. What was unexpected was that the post-ND neuromuscular function was similar for both groups, with final absolute EMG values of 5,222 $\mu V \pm 3{,}197$ μV for DM1 and 5,268 $\mu V \pm 4{,}407$ μV for DM2 cases. This suggests that before ND, there are similar numbers of *viable* motor units independent of the type of diabetes; however, in DM1 patients there are more *latent* motor units. It would be interesting to conduct motor unit number estimates (MUNEs) in these patients before and after ND. However, interpreting MUNE results would be difficult in this patient population because of the compromised neuromuscular function from the metabolic neuropathy and the compression neuropathy,[30] although even a rough initial estimate would be of interest.

The difference in EMG improvement between DM1 and DM2 patients, and the trends seen in the disease duration, BMI, and A1c results suggested possible correlations. When analyzed in the context of diabetes types, as shown in ►**Fig. 7**, significant differences were observed in each of the clinical attributes. DM1 cases had higher normalized EMG responses, A1c levels, and longer diabetes duration, but lower BMI values. Although some of these results were expected (i.e., diabetes duration and BMI), the others were less so. To determine if any of these attributes have predictive value, a multivariate regression analysis was conducted.

Potential Predictors of Neuromuscular Improvement

There is a paucity of clinical indicators for patient selection for ND in painful DSPN. The only known article showed that a positive Tinel sign is a good predictor of pain relief with 80% good outcome if positive and only 50% if negative.[4] The results here show two positive predictors of improved EMG (i.e., high BMI and DM1), and an absence of negative predictors of those that were studied (i.e., sex, advanced age, long DM duration, excessively high BMI and A1c levels, or DM type). Although level 1 studies are needed, these results showed that patients in all of our categories had the potential for improved neuromuscular function. These results are consistent with Dellon's hypothesis that secondary nerve entrapments are present in DSPN and amenable to surgical treatment. Further, this study is also consistent with the validity of the predictive value of the positive Tinel's sign. Taken as a whole, although surprising, none of these factors exclude the DSPN patients from the possibility of improved neuromuscular function with ND surgery.

Other Nerve Decompression Studies

It is worth comparing the immediate EMG changes in our cohort with the long-term reports of clinical results of ND in painful DSPN. Rozen et al, in an randomized controlled study of painful DSPN patients, showed significant long-lasting pain relief in ND patients who continued to improve out to 4.5 years.[31] This is consistent with the positive pain results of other studies with 1- to 2-year follow-ups.[5,32–35]

Macaré van Maurik et al studied the effect of ND on pain and sensibility in 42 patients in a single-center randomized controlled study.[36] A significant improvement in VAS scores at 1 year (3.5 vs. 6.1; $p < 0.001$) was noted, but not for Semmes Weinstein monofilament sensibility results (3.6 vs. 4.0; $p = 0.242$). Although there was a significant improvement in VAS scores at 1 year, the improvement was gradually diminishing from 3 months to 1 year. Rinkel et al evaluated 5-year postoperative results in 31 of 42 cases in the Macaré van Maurik cohort.[37] By 5 years, the trend of diminishing improvement just mentioned had continued, but the VAS scores were no longer significantly different from baseline.

Macaré van Maurik et al published a report concluding that, by their methods, "decompression of nerves of the lower extremity in patients with painful diabetic polyneuropathy has no beneficial effect on nerve conduction study variables 12 months after surgery."[38] This result contradicts our intraoperative findings using the NIM (Medtronic, Jacksonville, FL, USA) as well as those of Dellon,[39] and the significant NCV improvement found by both Zhang and colleagues at 3 months[35] and Liao et al at 2 years.[40] Methods and time frame differ because the Dutch study measured Compound Muscle Action Potential (CMAP) preoperatively and at 1 year postoperatively, whereas the NIM EMG pre- and postoperative recordings were intraoperative only. It may be that sensitivity of the methods differs enough to explain the discrepancy or that the intraoperative result we see is not maintained or measurable by their method at 12 months. This is certainly a topic of interest to be further investigated.

We appreciate that our results conflict with the current hypothesis that views DSPN as a progressive and irreversible length-dependent axonopathy of solely metabolic origin. This is one reason that the ND approach has been difficult for neurologists to accept. However, studies in the rat DSPN model now show that the decline in touch/pressure sensation, allodynia, decreased motor nerve conduction velocity, and degeneration of the myelin sheath following induction of diabetes and peripheral nerve entrapment can improve. ND improves all these measures toward normal levels.[41] These same authors report in a related article that in

similar diabetic rats, "function analyses of DEGs [differentially expressed genes] demonstrated that biological processes related to inflammatory response, extracellular matrix component, and synaptic transmission were upregulated after diabetes induction, and chronic nerve compression further enhanced those changes. While processes related to lipid and glucose metabolism, response to insulin, and apoptosis regulation were inhibited after diabetes induction, chronic nerve compression further enhanced these inhibitions."[42] Thus the application of ND to treat DSPN has some scientific basis and support.

Study Limitations

The present study had several limitations. This was a single-center retrospective study, with a small study size. Only acute results and clinical correlations between EMG and patient clinical data were analyzed. No pre- or postoperative EMG, sensory, or motor function data were available. Therefore, this study was not designed to address long-term clinical outcomes.

The use of propofol, morphine, and lidocaine/epinephrine intraoperatively might raise concerns about interfering with EMG recordings. We feel that the impact of anesthetics was minimal for the following reasons. The time from anesthesia administration to first recordings was on average 30 minutes, and the average time from EMG pre-release to post-release recordings was 2 to 10 minutes, and the time from neurolysis to post-recordings was only 1 minute. Given the relatively short time to reach peak plasma levels for both propofol and morphine ($\sim$ 20 minutes), and long half-life of each (propofol half-life: 13.1–44.7 hours; morphine half-life: 4.5 ± 0.3 hours), it seems unlikely that the impact on EMG would be significantly different in the 10 minutes between the Pre- and Post recordings. A similar argument applies to the effects of 1% lidocaine with epinephrine, which has an expected onset of 30 seconds and duration of 6.5 hours after subcutaneous injections.[43]

Conclusion

This is the first article to examine the relationship of objective intraoperative electrophysiologic improvement after ND surgery to patient demographic and clinical data. These results are consistent with Dellon's proposed hypothesis that DSPN is multifactorial with the well-known metabolic neuronal effect combined with a secondary nerve enlargement and impingement that contributes in some part to the symptoms. Importantly, this entrapment is amenable to improvement with surgical ND. In this study, patients with comorbidities that could exacerbate nerve entrapment, such as high BMI and A1c levels, showed greater improvement in EMG amplitudes after nerve release. One of the important findings of our first article was the existence of latent but viable axons in the CFN that are capable of rapid improvement after surgical decompression.[1] Given that there are latent axons in the CFN of these patients, and assuming the deleterious impingement effect is cumulative, longer duration might predict greater progression of neuropathy. However, our data showed that patients with disease duration out to 30 years are still capable of rapid EMG improvement. How axons can remain latent but viable and potentially functional for decades in this DSPN population is an unknown and intriguing topic for future study.

Our results demonstrate that with the current patient selection criteria (DSPN diagnosis, adequate circulation, and positive Tinel's sign at the fibular neck),[1] patients with DSPN can experience acute improvement in CFN nerve function with ND regardless of age, sex, diabetes type or duration, or high BMI or A1c levels. Although the results are encouraging, it is only a first step, and more studies are required before patient selection criteria for this surgery are optimized.

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Conflict of Interest

Dwayne S. Yamasaki reports that he was an employee of Medtronic that manufactured and sold the NIM nerve monitor used in the study. He was not involved in the study enrollment or treatments; however he did analyze the data and participated in the writing of the manuscript.

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