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ORIGINAL RESEARCH

Treatment of Painful Diabetic Neuropathy with 10 kHz Spinal Cord Stimulation: Long-Term Improvements in Hemoglobin A1c, Weight, and Sleep Accompany Pain Relief for People with Type 2 Diabetes

David C Klonoff[1], Brian L Levy[2], Michael J Jaasma[3], Manish Bharara[3], Deborah R Edgar[4], Christian Nasr[5], David L Caraway[3], Erika A Petersen[6], David G Armstrong[7]

[1]Diabetes Research Institute, Mills-Peninsula Medical Center, San Mateo, CA, USA; [2]New York University Grossman School of Medicine, New York, NY, USA; [3]Nevro Corp, Redwood City, CA, USA; [4]Commexus Ltd, Dunblane, Scotland, UK; [5]Division of Endocrinology, Department of Internal Medicine, The University of Arizona College of Medicine - Phoenix, Phoenix, AZ, USA; [6]Department of Neurosurgery, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [7]Department of Surgery, Keck School of Medicine of University of Southern California, Los Angeles, CA, USA

Correspondence: David C Klonoff, Diabetes Research Institute, Mills-Peninsula Medical Center, 100 South San Mateo Drive, Room 1165, San Mateo, CA, 94401, USA, Tel +1650-218-1142, Email dklonoff@diabetestechnology.org

Purpose: The recent SENZA-PDN study showed that high-frequency (10kHz) spinal cord stimulation (SCS) provided significant, durable pain relief for individuals with painful diabetic neuropathy (PDN), along with secondary benefits, including improved sleep quality and HRQoL. Given that metabolic factors and chronic neuropathic pain are related, we evaluated potential secondary effects of 10kHz SCS on hemoglobin A1c (HbA1c) and weight in SENZA-PDN participants with type 2 diabetes (T2D).

Patients and Methods: This analysis included 144 participants with T2D and lower limb pain due to PDN who received 10kHz SCS during the SENZA-PDN study. Changes in HbA1c, weight, pain intensity, and sleep were evaluated over 24 months, with participants stratified according to preimplantation HbA1c (>7% and >8%) and body mass index (BMI; ≥30 and ≥35 kg/m^2).

Results: At 24 months, participants with preimplantation HbA1c >7% and >8% achieved clinically meaningful and statistically significant mean reductions in HbA1c of 0.5% ($P = 0.031$) and 1.1% ($P = 0.004$), respectively. Additionally, we observed a significant mean weight loss of 3.1 kg ($P = 0.003$) across all study participants. In subgroups with BMI ≥30 and ≥35 kg/m^2, weight reductions at 24 months were 4.1 kg ($P = 0.001$) and 5.4 kg ($P = 0.005$), respectively. These reductions were accompanied by a mean pain reduction of 79.8% and a mean decrease in pain interference with sleep of 65.2% at 24 months across all cohorts.

Conclusion: This is the first study of SCS to demonstrate long-term, significant, and clinically meaningful reductions in HbA1c and weight in study participants with PDN and T2D, particularly among those with elevated preimplantation HbA1c and BMI. Although the mechanism for these improvements has yet to be established, the results suggest possible direct and indirect metabolic benefits with 10kHz SCS in addition to durable pain relief.

Trial Registration: ClincalTrials.gov Identifier, NCT03228420.

Keywords: diabetic peripheral neuropathy, painful diabetic neuropathy, spinal cord stimulation, neuromodulation, neuropathic pain

Introduction

Diabetic neuropathy (DN) affects approximately 50% of people with diabetes during their lifetime.[1] Typically, nerve fiber damage begins bilaterally in the feet and gradually progresses proximally to the lower legs.[1] The symptoms of DN vary and may include pain, numbness, and paresthesia.[1] As the condition progresses, decreased sensation and proprioception in the feet heightens the risk of falls, fractures, foot ulceration, and consequent lower extremity amputation.[1–7]

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Among the various symptoms of DN, neuropathic pain is particularly prevalent and debilitating, affecting up to 30% of individuals with DN.[1] This pain is typically persistent, severe, and worse at night, significantly impairing patients' sleep, daily activities, functionality, mood, and overall health-related quality of life (HRQoL).[8] Although the reasons remain unclear as to why only some patients with DN develop neuropathic pain, studies suggest a potential association between metabolic factors, such as high body mass index (BMI) and suboptimal glycemic control.[9–12] Additionally, some evidence suggests that individuals with painful diabetic neuropathy (PDN), compared to those with painless DN, have a higher BMI and worse glycemic control.[13–15]

Symptom management is the mainstay of PDN treatment, with recommended analgesic options that include gabapentinoids, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants.[16] However, the results of randomized controlled trials (RCTs) of these medications have been disappointing, and long-term adherence is generally poor because of limited efficacy and/or poor tolerability.[17,18] Overall, most patients with PDN experience insufficient pain relief with current pharmacological treatments,[19] leaving a substantial unmet treatment need among this patient population.

Spinal cord stimulation (SCS) is an alternative nonpharmacological therapy for treating neuropathic pain, with Level 1 evidence supporting its use in treating axial back/lumber radiculopathy, neuralgia, and complex pain regional pain syndrome.[20–22] Given the success of SCS for intractable neuropathic pain in other indications, there has been increasing interest in using the therapy to treat PDN pain symptoms. High-frequency 10 kHz SCS (10 kHz SCS) emerged a decade ago as an alternative SCS modality. Unlike LF-SCS, 10 kHz SCS provides pain relief without the sensation of paresthesia. The SENZA-PDN RCT recently evaluated the safety and effectiveness of 10 kHz SCS in patients with lower limb pain associated with refractory PDN. After 6 months of therapy, patients treated with 10 kHz SCS reported a 76% reduction in pain,[23,24] which was significantly higher than the corresponding pooled outcome of the LF-SCS RCTs in an indirect comparison.[24] Furthermore, pain relief with 10 kHz SCS was durable at 24 months in the SENZA-PDN study: 90% of patients reported at least 50% pain relief,[25] which compares favorably with the reported 24-month responder rate for LF-SCS of 41%.[26] In addition to pain reduction, 10 kHz SCS also significantly improved sleep quality and HRQoL, and most patients demonstrated evidence of improved sensory function on assessment. A small feasibility study in PDN patients with 10 kHz SCS built upon this initial finding, with lower limb nerve biopsy showing increased intraepidermal nerve fiber density (IENFD) following 6 months of therapy.[27]

Obesity and poor glycemic control can both increase inflammatory processes, resulting in damage to intraepidermal nerve fibers, which occurs in diabetic neuropathy.[28] In turn, chronic neuropathic pain can worsen glycemic control.[29] In addition to treating chronic neuropathic pain, there is evidence that SCS can reduce inflammation[30] and sympathetic tone.[31] This suggests that chronic neuropathic pain, obesity, and poor glycemic control may amplify each other through inflammatory processes. The interrelationship between chronic neuropathic pain and these metabolic factors leads us to hypothesize that 10 kHz SCS may have secondary effects on hemoglobin A1c (HbA1c) and weight in persons with T2D and PDN. To explore our hypothesis, we extended our analysis of data from the SENZA-PDN study to assess changes in HbA1c and weight in study participants with T2D who received 10 kHz SCS for 24 months, with additional stratification by preimplantation glycemic and BMI status. We also examined pain relief and sleep outcomes in the same T2D population and stratified subgroups. We made these observations because chronic pain and sleep problems both lead to increased inflammatory processes and metabolic dysfunction, which could confound these comparisons. These post hoc evaluations are exploratory to inform future controlled studies and are complementary to the original SENZA-PDN study findings.[25]

Materials and Methods

Study Design and Participants

Here, we report a post hoc analysis of the SENZA-PDN study data. A full description of the original SENZA-PDN study methods and primary study results up to 24 months postimplantation have previously been published.[23,25,32–34] The study included adults ≥22 years of age with a diagnosis of diabetes, PDN symptoms for at least 12 months that were refractory to current or previous treatment with a gabapentinoid and ≥1 other class of analgesic drug, lower limb pain intensity of ≥5 cm on a 10-cm visual analog scale (VAS), and an HbA1c ≤10% (86 mmol/mol). Individuals with upper extremity pain due to diabetic neuropathy of ≥3 cm on a 10-cm VAS, BMI >45 kg/m^2, or daily opioid dosage >120 mg morphine

equivalents were excluded. Prior to study initiation, Institutional Review Board (IRB) approval was obtained from the central IRB (Western IRB, #20171535) and local site IRBs when required. The SENZA-PDN study was conducted in accordance with the Declaration of Helsinki as well as good clinical practices and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants who met eligibility requirements and provided their written informed consent were randomly assigned (1:1) to conventional medical management (CMM) alone or 10 kHz SCS combined with CMM alone (10 kHz SCS +CMM), with CMM comprising standard of care treatments[35] for PDN managed by the study investigators. Throughout the study, the treating physicians (independent of the study investigators) managed glycemic control per their standard of care. At the end of the 6-month randomized phase, participants could cross over to the other treatment arm if they met prespecified criteria, which included having less than 50% pain relief from baseline. Participants who underwent permanent implantation of a 10 kHz SCS system (including the original recipients of 10 kHz SCS+CMM and those who received the therapy after crossing over from the CMM alone arm) were followed for 24 months postimplantation.

Assessments were conducted at preimplantation and during follow-up to measure various parameters. HbA1c was determined at preimplantation and 3, 6, 12, 18, and 24 months postimplantation using standard laboratory blood tests at the local institution or through Quest Diagnostics laboratory. Weight and BMI were recorded at preimplantation and 3, 6, 12, and 24 months. Additionally, the intensity of lower limb pain (0–10 cm VAS) and pain interference with sleep (Pain and Sleep Questionnaire Three-Item Index, PSQ-3; 0–10 cm scale) were documented at preimplantation and 3, 6, 9, 12, 18, and 24 months, along with data on diabetes medication usage. The current analysis evaluated results for study participants diagnosed with T2D. We excluded individuals with type 1 diabetes (T1D) from this analysis because of the distinct differences in HbA1c management between T1D and T2D and the relatively small number of randomized participants with T1D (5.1%, 11 of 216).

Intervention

Individuals receiving 10 kHz SCS underwent implantation with temporary trial leads placed in the epidural space. The leads were connected to an external trial stimulator for a period of 5–7 days, as per standard clinical practice. Participants who experienced at least 50% pain relief compared to baseline were eligible to receive a permanent 10 kHz SCS system (Nevro Corp., Redwood City, California). For the SCS temporary trial and permanent implant, the device was programmed to deliver paresthesia-free electrical pulses at 10 kHz frequency, 30 μs pulse width, and an amplitude adjusted for optimal pain relief.

Statistical Analysis

In the present study, we analyzed changes in HbA1c, weight, pain intensity (0–10 cm VAS), and pain interference with sleep (PSQ-3; 0–10 cm scale) among all SENZA-PDN participants diagnosed with T2D who received a permanent 10 kHz SCS system. Our analyses also stratified participants by (1) preimplantation HbA1c, with suboptimal blood glucose control categorized by HbA1c >7% (53 mmol/mol) and >8% (64 mmol/mol), and (2) preimplantation BMI, with obesity status categorized by BMI ≥30 kg/m^2 (at least Class I obesity) and ≥35 kg/m^2 (at least Class II obesity).[36]

Statistical analyses were conducted in SAS (Version 9.4, SAS Institute Inc., Cary, NC). Results are presented for all available data at each study visit. In addition, we utilized last-observation-carried-forward for the preimplant HbA1c values of 7 participants who crossed over from receiving CMM alone to 10 kHz SCS+CMM at the 6-month time point. These individuals had missed the immediate preimplantation HbA1c analysis but had a prior HbA1c analysis while undergoing CMM alone treatment. To statistically evaluate time effects, missing data were first imputed via a multiple imputation procedure using all available data for that outcome. Subsequently, we analyzed each imputed dataset with a repeated measures linear model that included time as a fixed effect and subject as a random effect, with an autoregressive correlation structure of order 1. We summarized these results using a missing data multiple imputation procedure. Missing data was imputed using the non-missing Hba1c values for each subject. This multiple imputation procedure has been shown to better estimate p-values and confidence intervals than single imputation procedures, which do not account for the variability between random imputations.[37] Continuous variables are expressed as mean values ± standard error of the mean (SEM) unless otherwise noted, while categorical variables are reported as counts and percentages.

Results

Study Population and Demographics

In total, 113 participants were randomized to receive 10 kHz SCS combined with CMM (10 kHz SCS+CMM) and 103 to receive CMM alone. After the 6-month randomized phase of the study, no participants from the original 10 kHz SCS +CMM group crossed over to receive CMM alone. In contrast, 93% (77 of 83) of eligible participants from the original CMM alone group opted to cross over to receive 10 kHz SCS+CMM. Our analysis here included 144 randomized participants from the SENZA-PDN study who had T2D and received a permanent 10 kHz SCS system. The full participant disposition for the 24-month study period has previously been published.[25]

At baseline, the 144 permanently implanted participants with T2D had a mean age (± SD) of 61.2 ± 9.8 years, and 61% were male. The cohort had median durations (interquartile range) of diabetes and PDN symptoms of 11.0 (6.8–16.3) and 6.0 years (3.0–10.0), respectively. At the preimplantation assessment, the mean HbA1c (± SD) for this group was 7.5 ± 1.2% (58 ± 13 mmol/mol), and the mean preimplantation BMI (± SD) was 34.3 ± 5.4 kg/m^2.

Changes in Glycemic Control

Preimplantation glycemic control was suboptimal among the study participants, with a mean HbA1c of 7.5 ± 0.1% (58.0 ± 1.1 mmol/mol). After 24 months of 10 kHz SCS, the mean HbA1c across all implanted participants showed a nonsignificant mean reduction of 0.3 ± 0.1% (2.8 ± 1.4 mmol/mol).

At preimplantation, the mean HbA1c in the subgroup with preimplantation HbA1c >7% (53 mmol/mol) was 8.2 ± 0.1% (66.4 ± 1.1 mmol/mol). Over 24 months, this subgroup demonstrated a gradual improvement in glycemic control (Figure 1A and B), with the reduction in mean HbA1c reaching statistical significance at the 18-month follow-up (P = 0.032). At the 24-month assessment, the mean HbA1c decreased to 7.7 ± 0.2%, representing a statistically significant mean reduction of 0.5 ± 0.2% (5.8 ± 2.0 mmol/mol; P = 0.031).

Participants with preimplantation HbA1c >8% (64 mmol/mol) experienced the greatest improvement in glycemic control (Figure 1A and B). Prior to implantation, the mean HbA1c in this cohort was 8.9 ± 0.1% (73.6 ± 1.3 mmol/mol). A significant reduction in the mean HbA1c was observed after 6 months of 10 kHz SCS (P = 0.045), with significant improvements also observed at the 12-, 18-, and 24-month evaluations (P = 0.004, P = 0.009, and P = 0.004, respectively). At the 24-month visit, the mean HbA1c in this subgroup was 7.8 ± 0.3%, with a significant mean reduction of 1.1 ± 0.2% (11.8 ± 2.7 mmol/mol; P = 0.004).

Changes in Weight

Throughout the study, we observed a gradual reduction in the mean weight of the implanted participants (Figure 2A), which reached statistical significance at the 24-month assessment (P = 0.003; Figure 2B). Prior to implantation, the mean weight across all implanted participants was 104.7 ± 1.5 kg. After 24 months of 10 kHz SCS, weight in these participants decreased significantly by a mean of 3.1 ± 1.0 kg (P = 0.003), equivalent to a 2.9% ± 1.0% mean weight loss.

In the subgroup with a preimplantation BMI ≥30 kg/m^2, weight loss reached statistical significance at an earlier stage than the whole cohort (Figure 2B). From a mean preimplantation weight of 110.2 ± 1.5 kg, we observed a statistically significant mean weight reduction of 2.9 ± 0.9 kg at 12 months (P = 0.016). This effect persisted at the 24-month assessment, with a significant mean weight reduction of 4.1 ± 1.2 kg (P = 0.001), equivalent to a 3.9% ± 1.1% mean weight loss.

Similarly, participants with preimplantation BMI ≥35 kg/m^2 also experienced a decrease in mean weight during the study (Figure 2A and B). The mean preimplantation weight of this subgroup was 117.5 ± 1.9 kg. After 24 months of 10 kHz SCS, we observed a mean weight reduction of 5.4 ± 1.7 kg (P = 0.005), corresponding to a 4.6% ± 1.5% mean weight loss.

Changes in Lower Limb Pain Intensity

During the study, 10 kHz SCS provided significant pain relief in the implanted participants (Figure 3). After 24 months, the mean VAS score for lower limb pain decreased from 7.5 ± 0.1 cm at preimplantation to 1.5 ± 0.2 cm (P < 0.001), with a mean reduction of 79.8% ± 2.0%. Furthermore, we observed a similar pattern of pain relief over 24 months when

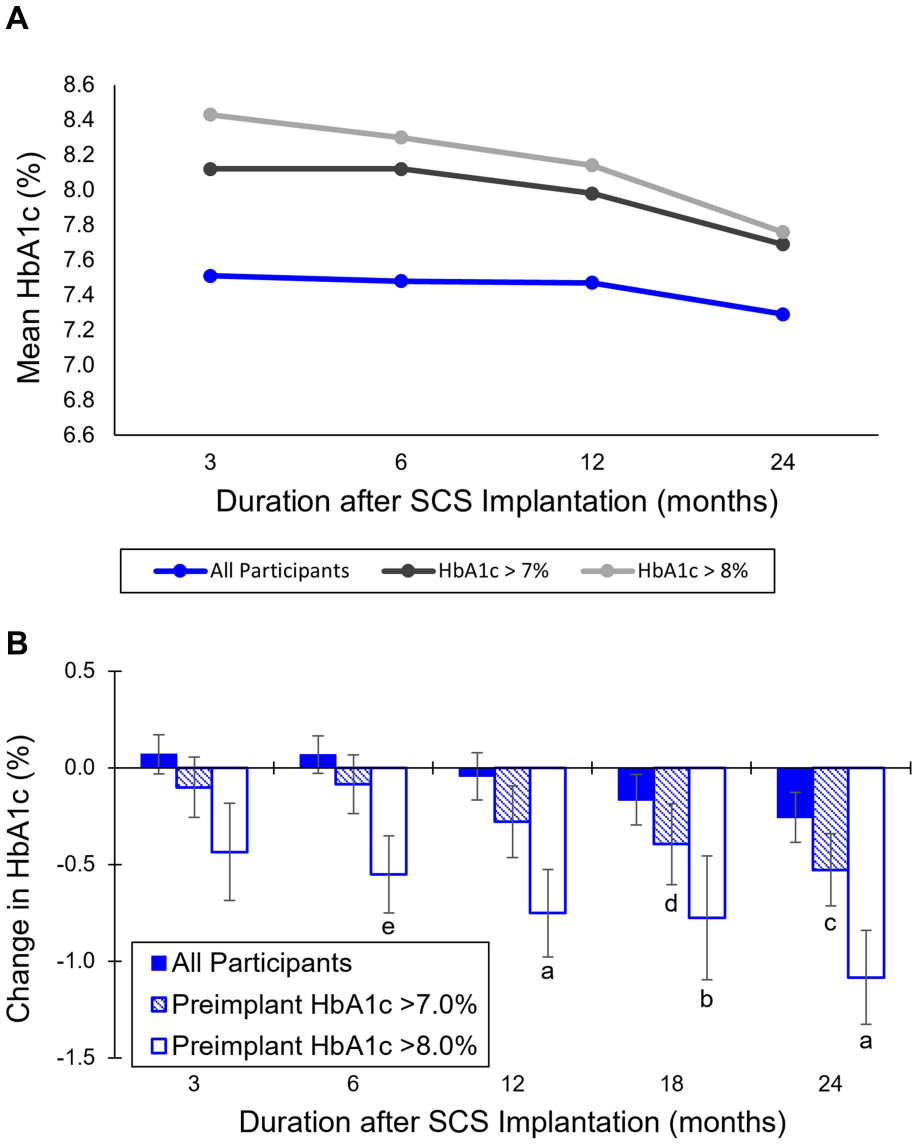

Figure 1 Change in HbA1c. At preimplantation, there were 144 total participants. For the HbA1c subgroups, 84 participants had HbA1c >7% (53 mmol/mol) and 44 participants had HbA1c >8% (64 mmol/mol). Error bars represent SEM. (**A**) Mean HbA1c (%) over time. (**B**) Mean change in HbA1c (%) over time.
Notes: [a] $P = 0.004$ vs preimplantation. [b] $P = 0.009$ vs preimplantation. [c] $P = 0.031$ vs preimplantation. [d] $P = 0.032$ vs preimplantation. [e] $P = 0.045$ vs preimplantation.
Abbreviations: HbA1c, Hemoglobin A1c; SCS, Spinal Cord Stimulation; SEM, Standard Error of the Mean.

stratifying participants by preimplantation HbA1c and BMI. Specifically, in the subgroup with preimplantation HbA1c >7% (53 mmol/mol), the mean VAS score for lower limb pain decreased by a mean of 83.9% ± 2.2% (from a mean of 7.5 ± 0.2 to 1.2 ± 0.2 cm) and by a mean of 80.0% ± 3.5% (from a mean of 7.5 ± 0.2 to 1.5 ± 0.3 cm) in those with preimplantation HbA1c >8% (64 mmol/mol). Likewise, the mean VAS score for lower limb pain decreased by a mean of 79.9% ± 2.3% (from a mean of 7.6 ± 0.2 to 1.5 ± 0.2 cm) in the subgroup with preimplantation BMI ≥30 kg/m^2 and by a mean of 80.5% ± 3.1% (from a mean of 7.8 ± 0.2 to 1.5 ± 0.3 cm) in those with preimplantation BMI ≥35 kg/m^2.

Individuals who experienced at least a 50% reduction in pain from their preimplantation assessment were classified as treatment responders. Among the study participants, the responder rate after 24 months of 10 kHz SCS was 89.4% (118 of 132), and this result was consistent regardless of the preimplantation HbA1c or BMI category.

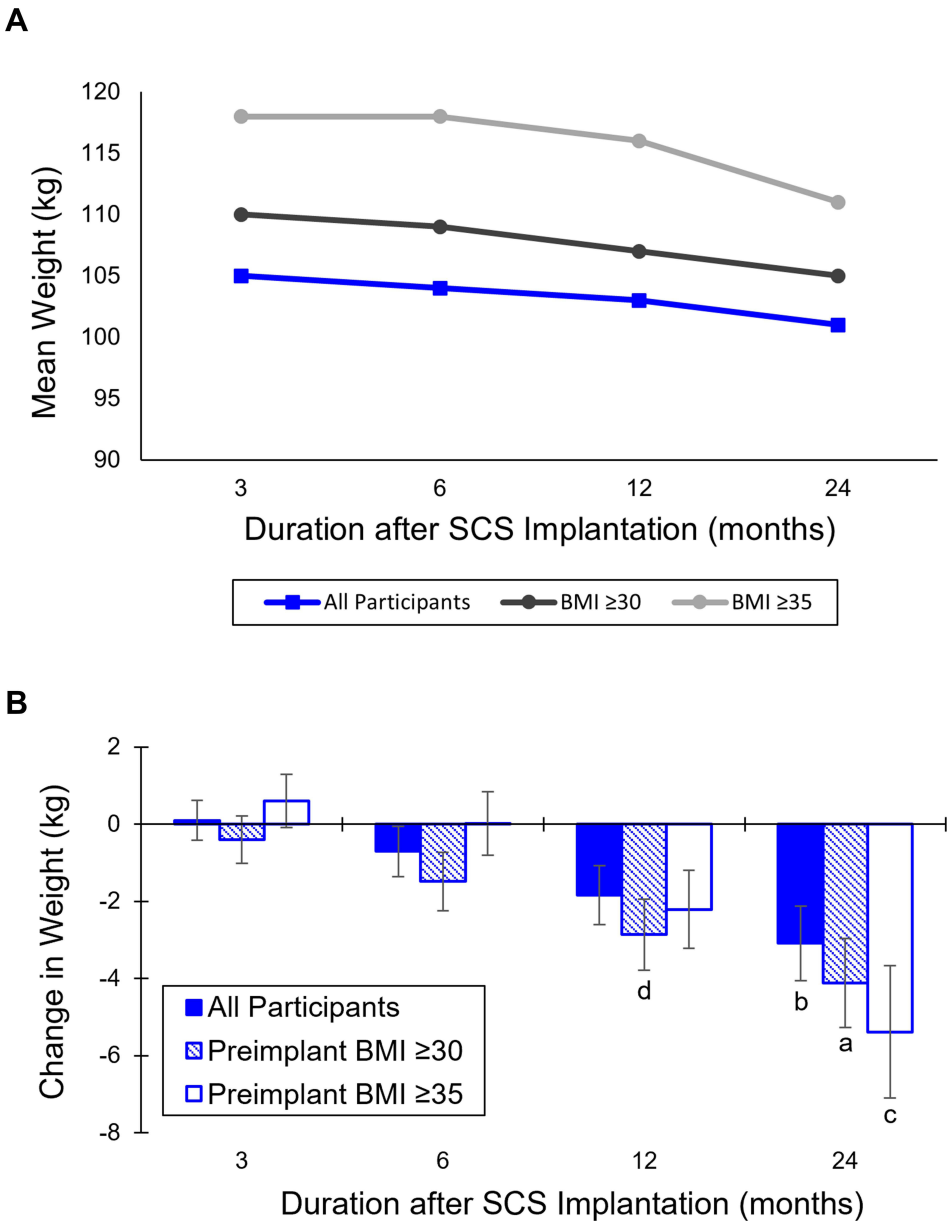

Figure 2 Change in weight. At preimplantation, there were 144 total participants. For the BMI subgroups, 111 participants had BMI ≥30 kg/m^2 and 58 participants had BMI ≥35 kg/m^2. Error bars represent SEM. (**A**) Mean weight (kg) over time. (**B**) Mean change in weight (kg) over time.
Notes: [a] $P = 0.001$ vs preimplantation. [b] $P = 0.003$ vs preimplantation. [c] $P = 0.005$ vs preimplantation. [d] $P = 0.016$ vs preimplantation.
Abbreviations: BMI, Body Mass Index (kg/m^2); SCS, Spinal Cord Stimulation; SEM, Standard Error of the Mean.

Changes in Pain Interference with Sleep

The study participants reported high pain interference with sleep at their preimplantation assessment, as indicated by a mean score of 6.4 ± 0.2 cm on the PSQ-3 (0–10 cm scale). The initiation of 10 kHz SCS led to a significant, durable reduction in pain interference with sleep (Figure 4). After 24 months, study participants experienced a highly significant improvement in sleep quality, with the PSQ-3 score decreasing by a mean of 65.2%, corresponding to a mean value of 1.9 ± 0.2 cm ($P < 0.001$).

We observed similar improvements in sleep quality after 24 months of 10 kHz SCS in the HbA1c and BMI subgroups. In particular, the mean PSQ-3 score reduced by a mean of 68.2% (from a mean of 6.7 ± 0.3 to 1.9 ± 0.3 cm) among the participants with preimplantation HbA1c >7% (53 mmol/mol) and by a mean of 66.3% (from a mean of 6.9 ± 0.4 to 2.0 ± 0.3 cm) among those with preimplantation HbA1c >8% (64 mmol/mol). Similarly, the mean PSQ-3

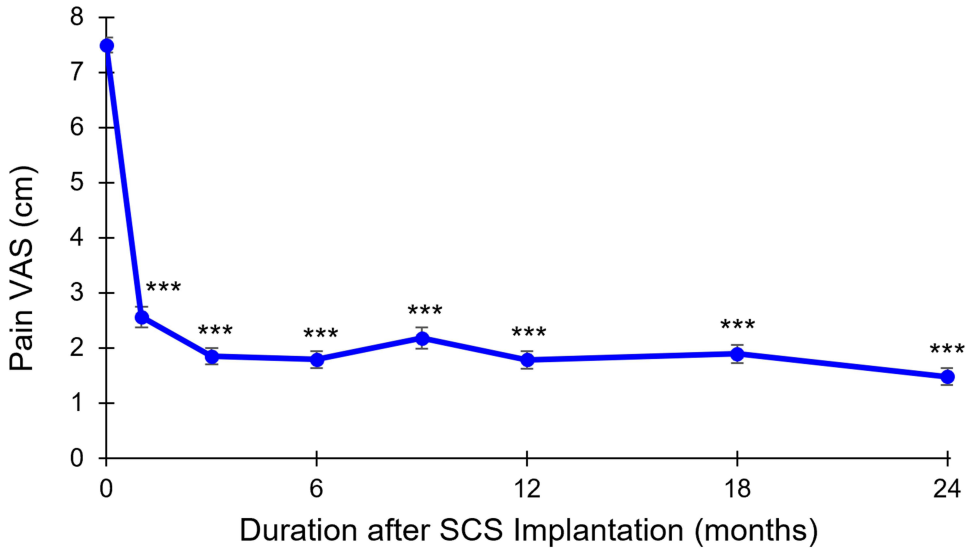

Figure 3 Mean pain score (Visual Analog Scale, VAS; 0–10 cm scale) over time, all participants. At preimplantation, there were 144 total participants. Error bars represent SEM.
Note: ***$P < 0.001$ vs preimplantation.
Abbreviations: SCS, Spinal Cord Stimulation; SEM, Standard Error of the Mean.

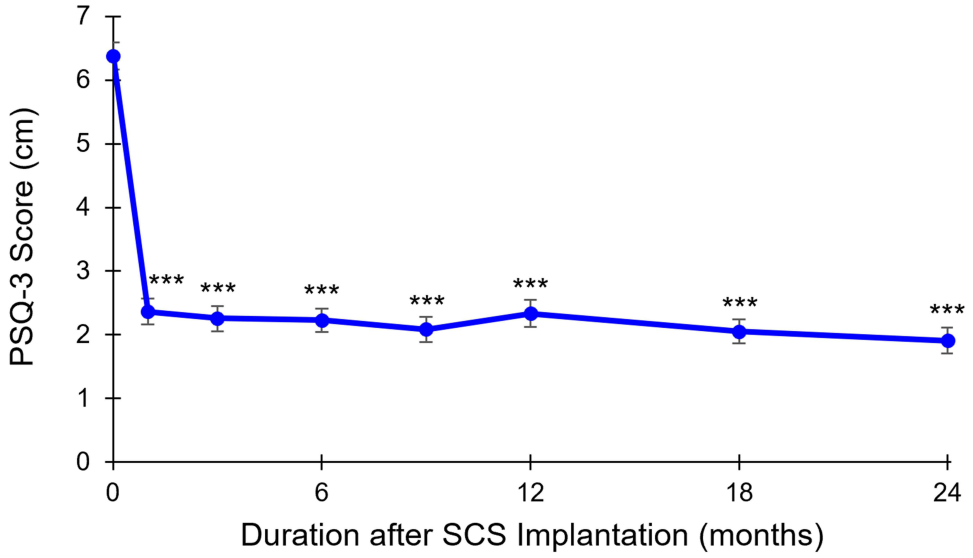

Figure 4 Mean pain interference with sleep (Pain and Sleep Questionnaire Three-Item Index, PSQ-3; 0–10 cm scale) over time, all participants. At preimplantation, there were 144 total participants. Error bars represent SEM.
Note: ***$P < 0.001$ vs preimplantation.
Abbreviations: SCS, Spinal Cord Stimulation; SEM, Standard Error of the Mean.

score in individuals with preimplantation BMI ≥30 kg/m^2 reduced by a mean of 65.0% (from a mean of 6.6 ± 0.2 to 1.9 ± 0.2 cm) and by a mean of 66.1% (from a mean of 7.1 ± 0.3 to 2.1 ± 0.3 cm) in those with preimplantation BMI ≥35 kg/m^2.

Discussion

Secondary Effects of 10 kHz SCS on Glycemic Control

While 10 kHz SCS is indicated to treat lower limb pain symptoms in people with refractory PDN, our analysis revealed additional benefits in glycemic control, particularly among those with elevated preimplantation HbA1c. After 24 months

of treatment with 10 kHz SCS, study participants with preimplantation HbA1c >7% (53 mmol/mol) and >8% (64 mmol/mol) experienced statistically significant mean reductions in HbA1c of 0.5% (5.8 mmol/mol) and 1.1% (11.8 mmol/mol), respectively. These improvements in HbA1c are considered clinically meaningful by healthcare professionals (ie, ≥0.5%).[38,39] Interestingly, the improvements in HbA1c in our subgroups are consistent with those reported for many oral and non-insulin injectable glucose-lowering medications versus placebo (0.6–1.5%).[40]

Secondary Effects of 10 kHz SCS on Weight Loss

According to the American Diabetes Association (ADA) on Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes (2023), clinical benefits in individuals with T2D typically emerge with a weight loss of 3% to 5%.[41] Our study observed statistically significant weight reductions within this range in all analyzed groups, suggesting beneficial longer-term effects for the study participants. Specifically, at 24 months, the mean percent weight loss was 2.9% among all participants, 3.9% in those with preimplantation BMI ≥30 kg/m^2, and 4.6% in those with preimplantation BMI ≥35 kg/m^2. In addition, the mean absolute reductions in weight, ranging from 3.1 to 5.4 kg, are at the higher end of the range reported for many glucose-lowering medications (such as glucagon-like peptide 1 receptor agonists)[42] versus placebo, that is, 0.3 to 3.8 kg.[43]

Mechanism of Action for Observed Reductions in HbA1c and Weight

The observed improvements in HbA1c and weight among our study participants are promising indicators of the potential secondary benefits of 10 kHz SCS treatment in aiding glycemic management and weight loss in individuals with T2D and refractory PDN. However, since the main objective of the SENZA-PDN study was to evaluate the safety and effectiveness of 10 kHz SCS for the treatment of the pain symptoms associated with PDN, our analysis here cannot elucidate the underlying reason for the observed improvements in HbA1c and weight. We can only hypothesize that they could be related to a reduction in the inflammatory processes and metabolic dysfunction associated with chronic pain,[29] as well as increased activity after pain relief. Other studies have suggested that SCS may affect insulin sensitivity or insulin production through a direct mechanism such as stimulation-induced neuropeptide release[44,45] or indirectly through the reduction in chronic pain.[29,46] These hypotheses require a future investigation to identify the main drivers for the observed HbA1c and weight improvements. A published case study also showed weight reduction incident with SCS,[47] but currently, no definitive evidence exists to support SCS playing a direct role in impacting blood glucose and weight reductions.

The substantial pain relief provided by 10 kHz SCS treatment results in better sleep and significantly improved health-related quality of life.[25] We hypothesized that the consequent reduction in stress associated with severe PDN pain enables patients to focus more on glycemic management, adopt healthier eating habits, and engage in a more active lifestyle—all of which can contribute to lowering HbA1c and reducing weight. Furthermore, when pain is no longer the patient's primary concern, treating physicians can also devote more time and attention to glycemic management, potentially leading to improved metabolic control.

A medical device intervention such as SCS may also impact the amount of time a T2D/PDN patient spends with their clinician compared to routine CMM. During device follow-up visits, healthcare professionals may have more opportunities to positively influence patients to improve their glycemic control and weight management.

10 kHz SCS Vs Other Treatment Options for PDN

With 10 kHz SCS, we observed significant, consistent improvements in pain levels and sleep quality over 24 months in patients with T2D and refractory lower limb pain due to PDN. These improvements were independent of preimplantation glycemic control (HbA1c >7% or >8%) or body mass index (BMI ≥30 or ≥35 kg/m^2). Specifically, the entire cohort of study participants experienced a mean reduction in pain of 80% and a mean decrease in pain interference with sleep of 65%. Furthermore, 89% of the participants were treatment responders to 10 kHz SCS (ie, ≥50% pain relief), a remarkable proportion given the challenging and intractable nature of PDN pain, and this improvement was also independent of preimplantation glycemia or weight. These results, similar to those from the original SENZA-PDN study (which included participants with both T1D and T2D), demonstrate that 10 kHz SCS is a highly effective and durable treatment for the

pain symptoms associated with PDN. In contrast, the efficacy of LF-SCS in a similar group of patients with PDN was markedly lower after a treatment period of 24 months, providing only 39% pain relief and a responder rate of 41%.[26]

Dorsal root ganglion (DRG) stimulation may offer additional benefits over LF-SCS for patients who can tolerate paresthesia, considering its high responder rate and reported ability to provide effective paresthesia coverage in the feet.[48] There is also some early evidence suggesting potential improvements to IENFD in DRG stimulation patients with painful polyneuropathy; however, the analysis did not reach statistical significance.[49] A small feasibility study of 10 kHz SCS in PDN has shown more promising results, demonstrating a significant increase in IENFD in both the proximal thigh and distal legs after 6 months of treatment.[27]

Treatment results with 10 kHz SCS also appear more favorable than current pharmacological options for neuropathic pain. A comprehensive meta-analysis reported that less than half of neuropathic pain patients who receive currently recommended analgesics achieve a 50% reduction in pain, with the number needed to treat (NNT; the number of patients that need to be treated before we expect one additional patient to be a treatment responder versus the control treatment) for 50% pain relief ranging from 4 to 10.[17,50] In contrast, 10 kHz SCS provided a far superior NNT of 1.3.[25]

Limitations

This study has several limitations to consider, including the post hoc nature of our current analyses and those inherent to the original SENZA-PDN study. Given the nature of the intervention, the SENZA-PDN study participants, investigators, and site staff were aware of the assigned treatment. This lack of blinding introduces a potential source of bias, particularly when relying on patient-reported outcomes, such as pain intensity. In addition, we could not compare the 24-month outcomes in those who received 10 kHz SCS+CMM to the control group, primarily because of the high crossover rate from CMM only to 10 kHz SCS+CMM. However, the consistent pain relief reported throughout the 24-month study duration and a relatively steady improvement in HbA1c and weight provide compelling evidence of the positive treatment effect of 10 kHz SCS.

The SENZA-PDN study was conducted during the COVID-19 pandemic, which led to unavoidable missed study visits. During the pandemic, numerous clinical research sites prohibited in-person study visits for varying periods, resulting in some missed HbA1c blood draws. Furthermore, some participants chose to skip blood draw visits as a precautionary measure. Nonetheless, our statistical methods incorporated multiple imputations for missing values to ensure a robust analysis and minimize the potential impact of missing data.

It is also important to note that the ongoing diabetes medication management throughout the SENZA-PDN study is a potential confounding factor in our current analyses. To exclude this possible issue, we conducted analyses to assess whether adjustments, additions, or discontinuations of diabetes medications may have impacted HbA1c and weight changes during the study. A board-certified endocrinologist (author BL), blinded to the HbA1c and weight results, reviewed the diabetes medication data for each participant to determine whether overall dosing had changed at the 24-month time point versus preimplantation. The analysis revealed that changes in individuals' diabetes medication management were unlikely to have impacted their HbA1c or weight. For example, among patients with preimplantation HbA1c >8.0% (64 mmol/mol), the mean reduction in HbA1c was 1.1 ± 0.3% (n = 14), 1.0 ± 0.6% (n = 13), and 1.2 ± 0.4% (n = 9) in those whose overall diabetes medication dose was increased, unchanged, or decreased, respectively. Similarly, among patients with preimplantation HbA1c >7.0% (53 mmol/mol), the mean reduction in HbA1c was 0.7 ± 0.2% (n = 27), 0.3 ± 0.4% (n = 26), and 0.7 ± 0.4% (n = 14) for patients whose overall diabetes medication dose was increased, unchanged, or decreased, respectively. Furthermore, when evaluating dosing changes for GLP-1 receptor agonists and SGLT-2 inhibitors among all participants, mean weight loss was 2.8 ± 2.0 kg (n = 17), 3.1 ± 1.1 kg (n = 107), and 4.2 ± 5.9 kg (n = 3) in those whose dosing of these medications was increased, unchanged, or decreased, respectively. These findings suggest that changes in diabetes medication were not the primary driver of the observed reductions in HbA1c or weight.

One participant in our cohort underwent a gastric bypass procedure after receiving a 10 kHz SCS implant, which improved weight loss for this participant. However, we performed a sensitivity analysis and found that excluding this participant from the weight loss analysis cohorts did not affect the statistical significance of weight loss outcomes at any of the study time points.

Finally, our study outcomes were derived from a specific patient population under controlled clinical trial conditions over a limited period of 24 months. Longer-term studies are required to confirm the efficacy and safety of 10 kHz SCS for PDN in a real-world setting. In particular, it would be beneficial to determine the optimal patient selection criteria and timing of SCS in the progression of this disease and to analyze the cost-effectiveness of integrating the therapy into routine clinical practice.

Conclusion

This is the first study in SCS to demonstrate long-term, significant, and clinically meaningful reductions in HbA1c and weight in participants with PDN and T2D. Notably, we observed these improvements among those with elevated preimplantation HbA1c (>7% and >8%) and BMI (≥30 and ≥35 kg/m^2). The long-lasting pain relief (79.8%) and improved sleep quality (65.2%) provided by 10 kHz SCS may have enabled the study participants to focus more on glycemic management and positive lifestyle changes, contributing to the observed clinically meaningful reductions in HbA1c (≥0.5%) and weight (3% to 5%). Further research is required to confirm these results over a longer term in a real-world setting. In addition, future studies may be designed that directly measure inflammatory biomarkers and activity, which could help elucidate other potential mechanisms for these improvements in weight and glycemic control in patients treated with 10 kHz SCS. In summary, the multifaceted benefits of 10 kHz SCS demonstrated in this analysis highlight this treatment as an effective and holistic approach to PDN management.

Abbreviations

ADA, American Diabetes Association; BMI, Body mass index; DN, diabetic neuropathy; HbA1c, hemoglobin A1c; HRQoL, health-related quality of life; IRB, institutional review board; LF-SCS, low-frequency spinal cord stimulation; NNT, number needed to treat; PDN, painful diabetic neuropathy; PSQ-3, Pain and Sleep Questionnaire Three-Item Index; RCT, randomized controlled trial; SCS, spinal cord stimulation; SD, standard deviation; SEM, standard error of the mean; T1D, type 1 diabetes; T2D, type 2 diabetes; VAS, visual analog scale.

Data and Resource Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

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References

1. Pop-Busui R, Ang L, Boulton AJM, et al. *Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy*. Arlington (VA): American Diabetes Association; 2022.
2. Kim JH, Jung MH, Lee JM, et al. Diabetic peripheral neuropathy is highly associated with nontraumatic fractures in Korean patients with type 2 diabetes mellitus. *Clin Endocrinol*. 2012;77(1):51–55. doi:10.1111/j.1365-2265.2011.04222.x
3. Timar B, Timar R, Gaita L, et al. The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: a cross-sectional study. *PLoS One*. 2016;11(4):e0154654. doi:10.1371/journal.pone.0154654
4. Huang ZH, Li SQ, Kou Y, et al. Risk factors for the recurrence of diabetic foot ulcers among diabetic patients: a meta-analysis. *Int Wound J*. 2019;16(6):1373–1382. doi:10.1111/iwj.13200
5. Kiyani M, Yang Z, Charalambous LT, et al. Painful diabetic peripheral neuropathy: health care costs and complications from 2010 to 2015. *Neurol Clin Pract*. 2020;10(1):47–57. doi:10.1212/CPJ.0000000000000671
6. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367–2375. doi:10.1056/NEJMra1615439
7. Armstrong DG, Tan TW, Boulton AJM, et al. Diabetic foot ulcers a review. *JAMA*. 2023 doi:10.1001/jama.2023.10578
8. Alleman CJ, Westerhout KY, Hensen M, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. *Diabetes Res Clin Pract*. 2015;109(2):215–225. doi:10.1016/j.diabres.2015.04.031
9. Themistocleous AC, Ramirez JD, Shillo PR, et al. The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. *Pain*. 2016;157(5):1132–1145. doi:10.1097/j.pain.0000000000000491
10. Ziegler D, Landgraf R, Lobmann R, et al. Painful and painless neuropathies are distinct and largely undiagnosed entities in subjects participating in an educational initiative (PROTECT study). *Diabetes Res Clin Pract*. 2018;139:147–154. doi:10.1016/j.diabres.2018.02.043
11. Pai YW, Tang CL, Lin CH, et al. Glycaemic control for painful diabetic peripheral neuropathy is more than fasting plasma glucose and glycated haemoglobin. *Diabetes Metab*. 2021;47(1):101158. doi:10.1016/j.diabet.2020.04.004
12. Calcutt NA. Diabetic neuropathy and neuropathic pain: a (con)fusion of pathogenic mechanisms? *Pain*. 2020;161(Suppl 1):S65–S86. doi:10.1097/j.pain.0000000000001922
13. Spallone V, Morganti R, D'Amato C, et al. Clinical correlates of painful diabetic neuropathy and relationship of neuropathic pain with sensorimotor and autonomic nerve function. *Eur J Pain*. 2011;15(2):153–160. doi:10.1016/j.ejpain.2010.06.011
14. Yang J, Yang X, Zhao D, et al. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetic polyneuropathy. *J Diabetes Invest*. 2021;12(5):828–836. doi:10.1111/jdi.13394
15. Oyibo SO, Prasad YD, Jackson NJ, et al. The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study. *Diab Med: J British Diab Assoc*. 2002;19(10):870–873. doi:10.1046/j.1464-5491.2002.00801.x
16. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(1):136–154. doi:10.2337/dc16-2042
17. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–173. doi:10.1016/S1474-4422(14)70251-0
18. Yang M, Qian C, Liu Y. Suboptimal treatment of diabetic peripheral neuropathic pain in the United States. *Pain Med*. 2015;16(11):2075–2083. doi:10.1111/pme.12845
19. Finnerup NB, Haroutounian S, Baron R, et al. Neuropathic pain clinical trials: factors associated with decreases in estimated drug efficacy. *Pain*. 2018;159(11):2339–2346. doi:10.1097/j.pain.0000000000001340
20. Deer TR, Grider JS, Lamer TJ, et al. A systematic literature review of spine neurostimulation therapies for the treatment of pain. *Pain Med*. 2020;21(7):1421–1432. doi:10.1093/pm/pnz353
21. Grider JS, Manchikanti L, Carayannopoulos A, et al. Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review. *Pain Physician*. 2016;19(1;1):E33–54. doi:10.36076/ppj/2016.19.E33
22. Lamer TJ, Moeschler SM, Gazelka HM, et al. Spinal stimulation for the treatment of intractable spine and limb pain: a systematic review of RCTs and meta-analysis. *Mayo Clin Proc*. 2019;94(8):1475–1487. doi:10.1016/j.mayocp.2018.12.037
23. Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of high-frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: a randomized clinical trial. *JAMA Neurol*. 2021;78(6):687–698. doi:10.1001/jamaneurol.2021.0538
24. Hoelzer BC, Edgar D, Lu SP, et al. Indirect comparison of 10 kHz Spinal Cord Stimulation (SCS) versus traditional low-frequency SCS for the treatment of painful diabetic neuropathy: a systematic review of randomized controlled trials. *Biomedicines*. 2022;10(10). doi:10.3390/biomedicines10102630
25. Petersen EA, Stauss TG, Scowcroft JA, et al. Long-term efficacy of high-frequency (10 kHz) spinal cord stimulation for the treatment of painful diabetic neuropathy: 24-Month results of a randomized controlled trial. *Diabetes Res Clin Pract*. 2023;203:110865. doi:10.1016/j.diabres.2023.110865
26. van Beek M, Geurts JW, Slangen R, et al. Severity of neuropathy is associated with long-term spinal cord stimulation outcome in painful diabetic peripheral neuropathy: five-year follow-up of a prospective two-center clinical trial. *Diabetes Care*. 2018;41(1):32–38. doi:10.2337/dc17-0983
27. Chen J, Frizzi K, Zardouz S, et al. High-frequency spinal cord stimulation (10 kHz) alters sensory function and nerve fiber density in painful diabetic neuropathy: a pilot prospective open-label study. *Pain Med*. 2023;24(Supplement_2):S33–S40. doi:10.1093/pm/pnad096
28. Baum P, Toyka KV, Bluher M, et al. Inflammatory mechanisms in the pathophysiology of diabetic peripheral neuropathy (DN)-new aspects. *Int J Mol Sci*. 2021;22 (19):10835. doi:10.3390/ijms221910835

29. Nilsson PM, Kandell-Collen A, Andersson HI. Blood pressure and metabolic factors in relation to chronic pain. *Blood Press*. 1997;6(5):294–298. doi:10.3109/08037059709062085
30. Kinfe TM, Muhammad S, Link C, et al. Burst spinal cord stimulation increases peripheral antineuroinflammatory interleukin 10 levels in failed back surgery syndrome patients with predominant back pain. *Neuromodulation*. 2017;20(4):322–330. doi:10.1111/ner.12586
31. Goudman L, Brouns R, Linderoth B, et al. Effects of spinal cord stimulation on heart rate variability in patients with failed back surgery syndrome. *PLoS One*. 2019;14(7):e0219076. doi:10.1371/journal.pone.0219076
32. Mekhail NA, Argoff CE, Taylor RS, et al. High-frequency spinal cord stimulation at 10 kHz for the treatment of painful diabetic neuropathy: design of a multicenter, randomized controlled trial (SENZA-PDN). *Trials*. 2020;21(1):87. doi:10.1186/s13063-019-4007-y
33. Petersen EA, Stauss TG, Scowcroft JA, et al. Durability of high-frequency 10-khz spinal cord stimulation for patients with painful diabetic neuropathy refractory to conventional treatments: 12-month results from a randomized controlled trial. *Diabetes Care*. 2022;45(1):e3–e6. doi:10.2337/dc21-1813
34. Petersen EA, Stauss TG, Scowcroft JA, et al. High-frequency 10-kHz spinal cord stimulation improves health-related quality of life in patients with refractory painful diabetic neuropathy: 12-month results from a randomized controlled trial. *Mayo Clin Proc Innov Qual Outcomes*. 2022;6(4):347–360. doi:10.1016/j.mayocpiqo.2022.05.003
35. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85(3):S3–14. doi:10.4065/mcp.2009.0649
36. Defining adult overweight & obesity, Available from: https://www.cdc.gov/obesity/basics/adult-defining.html. (2023, accessed 23, May 2023.).
37. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91(434):473–489. doi:10.1080/01621459.1996.10476908
38. Lenters-Westra E, Schindhelm RK, Bilo HJ, et al. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. *Neth J Med*. 2014;72(9):462–466.
39. Little RR, Rohlfing CL. The long and winding road to optimal HbA1c measurement. *Clin Chim Acta*. 2013;418:63–71. doi:10.1016/j.cca.2012.12.026
40. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. *Ann Intern Med*. 2020;173(4):278–286. doi:10.7326/M20-0864
41. ElSayed NA, Aleppo G, Aroda VR, et al. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of care in Diabetes—2023. *Diabetes Care*. 2023;46(Supplement_1):S128–S139. doi:10.2337/dc23-S008
42. Powell J, Taylor J. Use of dulaglutide, semaglutide, and tirzepatide in diabetes and weight management. *Clin Ther*. 2024;46(3):289–292. doi:10.1016/j.clinthera.2023.12.014
43. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Obes Metab*. 2021;23(9):2116–2124. doi:10.1111/dom.14451
44. Morgalla MH, Fritschle H, Vosseler A, et al. Influence of spinal cord stimulation on insulin sensitivity in chronic pain patients. *Exp Clin Endocrinol Diabetes*. 2022;130(01):17–21. doi:10.1055/a-1525-3339
45. Kapural L, Hayek SM, Stanton-Hicks M, et al. Decreased insulin requirements with spinal cord stimulation in a patient with diabetes. *Anesthesia Analg*. 2004;98:745–746. doi:10.1213/01.ane.0000102674.41527.1e
46. Aldossari KK, Shubair MM, Al-Zahrani J, et al. Association between chronic pain and diabetes/prediabetes: a population-based cross-sectional survey in Saudi Arabia. *Pain Res Manag*. 2020;2020:8239474. doi:10.1155/2020/8239474
47. Pereira E, Foster A. Appetite suppression and weight loss incidental to spinal cord stimulation for pain relief. *Obes Surg*. 2007;17(9):1272–1274. doi:10.1007/s11695-007-9217-9
48. Liem L, Russo M, Huygen FJ, et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation*. 2013;16(5):471–482. doi:10.1111/ner.12072
49. Koetsier E, Vacchi E, Maino P, et al. Dorsal root ganglion stimulation in chronic painful polyneuropathy: a potential modulator for small nerve fiber regeneration. *Neuromodulation*. 2023;26(8):1772–1780. doi:10.1016/j.neurom.2022.08.455
50. Bailey-Classen A, Parikh A, Adimi N, et al. Concept of the number needed to treat for the analysis of pain relief outcomes in patients treated with spinal cord stimulation. *Biomedicines*. 2022;10(2):497. doi:10.3390/biomedicines10020497