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SYMPOSIUM

Electrical Stimulation as an Adjunctive Treatment of Painful and Sensory Diabetic Neuropathy

Gaurav Thakral, M.D.,[1] Paul J. Kim, D.P.M., M.S.,[2] Javier LaFontaine, D.P.M., M.S.,[1] Robert Menzies, D.P.M.,[3] Bijan Najafi, Ph.D.,[4] and Lawrence A. Lavery, D.P.M., M.P.H.[1]

Abstract

Background:

The objective of this review is to evaluate the use of electrical stimulation to treat diabetic neuropathy. Application of electrical stimulation may provide a novel treatment option for large and small fiber neuropathy in persons with diabetes. Large and small nerve neuropathy alters pain, proprioception, touch perception, and motor function, which cause burning foot pain and serve as protective mechanisms from ulcerations.

Methods:

A content search for clinical trials involving electrical stimulation, neuropathy, and diabetes was conducted through PubMed. Randomized clinical trials and prospective studies with outcome measures affecting the lower extremity function were selected for review.

Results:

We identified eight studies in which electrical stimulation was used to treat diabetic neuropathy. Six studies evaluated small fiber neuropathy. Two studies evaluated patients with both small and large fiber neuropathy and reported significant improvement in vibration and monofilament testing and reduction in symptoms in the electrical stimulation treatment group. Six of the eight painful neuropathy studies identified significant improvement in symptoms. There were no studies that evaluated electrical stimulation to treated diabetic motor neuropathy, fall prevention or postural instability.

Conclusions:

Electrical stimulation may be an effective alternative and adjunctive therapy to current interventions for diabetic peripheral neuropathy.

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Author Affiliations: [1]Department of Plastic Surgery, The University of Texas Southwestern Medical Center, Dallas, Texas; [2]Department of Plastic Surgery, Georgetown University, Washington DC; [3]Diabetic Foot and Wound Center, Department of Medicine, Hamad Medical Corporation, Doha, Qatar; and [4]Department of Surgery, University of Arizona, Tucson, Arizona

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Corresponding Author: Lawrence A. Lavery, D.P.M., Department of Plastic Surgery, The University of Texas Southwestern Medical Center, 1801 Inwood Rd., Dallas, TX 75390-9132; email address larry.lavery@utsouthwestern.edu

Introduction

There is a worldwide epidemic of diabetes. By 2030, there is a projected increase of 7.7% in the worldwide prevalence of diabetes, with a 20% increase in developed countries.[1] One of the most common complications in people with diabetes is neuropathy. Diabetic peripheral neuropathy affects 60% to 70% of people with diabetes.[2–5] Currently, there is no treatment for large fiber neuropathy that is associated with sensory neuropathy or loss of protective sensation. The traditional treatment for small fiber neuropathy or painful diabetic neuropathy has focused on drug therapies. Drug therapies are associated with multiple side effects, such as somnolence (10–60%), lethargy (16–20%),[6–8] and a two-fold increased risk of falls.[6,8,9] A potentially safer treatment option is electrical stimulation. Electrical stimulation has few contraindications and side effects and no known drug interactions.[10] Pain studies with electrical stimulation have been conducted for postoperative pain,[11] labor pain,[12,13] angina,[14–16] pain after trauma,[17] and low back pain.[10,12,13] Electrical stimulation offers a safe and cost-effective option for pain management.[18] The objective of this review is to evaluate the use of electrical stimulation to treat diabetic neuropathy.

The mechanism of action of electrical stimulation is not known; however, several complementary mechanisms have been proposed to explain the effect of electrical stimulation on nerve injury or neuropathy. In diabetes, nerve damage has been associated with microvascular disease to the nerve. Five clinical studies have reported a significant increase in cutaneous circulation in humans after application of electrical stimulation.[19–23] In addition, Zhao and coauthors[24] and Kanno and coauthors[25] reported an increase in vascular endothelial growth factor with the application of electrical stimulation. Vascular endothelial growth factor is a growth factor thought to be a primary angiogenic factor. Thus, an increase in angiogenesis may improve microcirculation associated with neuropathy and reduce symptoms and improve nerve function.[24,25] Other studies have shown marked increases in beta endorphin and met-enkephalin,[26] increased expression of calcitonin gene regulating protein in the dorsal root,[27] reduced inflammatory markers,[28] and increased expression of nerve growth factor.[29]

The analgesia effect of electrical stimulation to treat painful peripheral neuropathy has been suggested to occur by stimulation of cutaneous afferent fibers at the site of application. Laboratory studies suggest that electrical stimulation reduces pain through nociceptive inhibition at the presynaptic level in the dorsal horn. This limits central transmission of pain signals. Large-diameter fibers are thought to be activated by high-frequency electrical stimulation.[30]

Methods

We identified eight randomized clinical trials and prospective studies that used electrical stimulation to treat diabetic neuropathy (**Table 1**). We searched for English-language studies in MEDLINE for electrical stimulation with diabetic neuropathy and peripheral neuropathy. Case studies and clinical trials focused on children and congenital disability were excluded. Out of the total identified studies, we excluded studies that delivered electrical stimulation to the spinal cord,[31,32] used static magnetic devices,[33] included less than 14 subjects,[34] or were retrospective studies.[35]

Electrical Stimulation and Painful Neuropathy

We identified eight studies that used electrical stimulation to treat painful neuropathy.[36–43] Six of the eight studies reported a significant improvement in symptoms of painful neuropathy. Even though there are several studies that support the use of electrical stimulation to treat painful neuropathy, in general, the studies have a very short duration and small study populations (**Table 1**). In several studies, the analysis is misleading because the main analysis is performed on the change from baseline to the end of study outcomes within treatment or sham groups rather than comparing the changes between treatment groups. Placebo effects are common in pain studies, and often sham treatment groups have a significant improvement from baseline.[39,44,45] Therefore, cohort studies or randomized clinical trials that report "significant" changes from baseline to "end of therapy" are often misleading because of the dramatic effect of placebo. The main analysis should compare the active and sham groups. The large placebo effect that is common in pain studies often translates into "no significant difference" between active and sham treatment even if there is a change within a treatment group compared with baseline.

Table 1.
Painful and Sensory Neuropathy[a]

First author	Device of interest	Treatment specification: voltage, current, phase duration, frequency	Study design	Population	Outcome
Hamza[36]	Percutaneous electrical nerve stimulation	15 and 30 Hz every 3 s, maximum 25 mA, pulse width 0.5 ms 30 min, 3 times a week, for 3 weeks	Investigator blinded, randomized clinical trial, crossover study with 1-week washout period	Diabetic painful neuropathy initially in treatment (n = 25) or sham (n = 25)	Pain VAS: decreased in treatment (6.2 to 2.5; $p < .05$) and sham (6.4 to 6.3; $p > .05$; $p < .05$) Daily oral nonopioid analgesic: use reduced for treatment (49%; $p < .05$) and sham (14%; $p > .05$; $p < .05$) AE: none
Humpert[37]	Transcutaneous electrical nerve stimulation	Pulse width 4 ms, <35 mA, <35 V, 20 Hz, 60 min, twice per week, 4 weeks	Prospective cohort study	Diabetic sensory and painful neuropathy (n = 92)	Paresthesia: decreased from baseline (5.2) to week 4 (3.8; $p < .01$) Burning sensation: decreased from baseline (5.2) to week 4 (3.7; $p < .01$) Sleep disturbance: decreased from baseline (4.8) to week 4 (3.4; $p < .01$) Numbness: decreased from baseline (5.4) to week 4 (4.6; $p < .001$) Pain: decreased from baseline (5.1) to week 4 (3.7; $p < .01$) AE: none
Bosi[38]	Frequency-modulated electromagnetic neural stimulation	Variable asymmetric sequence from 0–255 V, 1–50 Hz, 10–40 ms 30 min, 10 treatments over 3 weeks Span: 7 weeks	Double blind, randomized clinical trial crossover with 1-week washout period	Diabetic sensory and painful neuropathy initially in treatment (n = 15) or sham (n = 16)	Vibration perception threshold: decreased in treatment (35.5 to 33.4; $p = .0001$) and placebo (34.7 to 34.2; $p > .05$) Monofilament: increased detection in treatment (3.2 to 4.4; $p = .0077$) and decreased in placebo (3.9 to 3.8; $p > .05$) Daytime pain VAS: decreased in treatment (37.1 to 26.2; $p = .0025$) and increased in placebo (31.2 to 31.9; $p > .05$) Nighttime pain VAS: decreased in treatment (38.1 to 28.5; $p = .0107$) and placebo (33.3 to 30.4; $p > .05$) AE: not significant
Kumar[39]	Transcutaneous electrical nerve stimulation	H-wave machine, 25–35 V, pulse width 4 ms, >2 Hz, 12 weeks	Single blinded, randomized clinical trial	Diabetic painful neuropathy treatment: n = 14 Sham: n = 9	Pain VAS: decreased in treatment (3.2 to 1.4; $p < .01$) and sham (2.8 to 1.9; $p < .03$) Neuropathic symptom VAS: decreased in treatment (66 ± 10%) and sham (55 ± 12%) AE: none
Kumar[40]	Transcutaneous electrical nerve stimulation	H-wave machine, 25–35 V, pulse width 4 ms, >2 Hz, 30 min, daily, 4 weeks	Single blinded, randomized clinical trial	Diabetic painful neuropathy treatment: n = 18 Sham: n = 13	Pain VAS: decreased in treatment (3.17 to 1.44; $p < .01$) and sham (2.92 to 2.38; $p = .04$) Neuropathic symptom VAS: decreased in treatment (52 ± 7%) and sham (27 ± 10%; $p < .05$) AE: none
Reichstein[41]	High-frequency stimulation and transcutaneous electrical nerve stimulation	Transcutaneous electrical nerve stimulation: pulse width 4 ms, ≤35 mA, ≤35 V, 180 Hz High-frequency: ≤350 mA, ≤70 V, 4,096–32,768 Hz, 30 min, 3 days	Randomized clinical trial	Diabetic painful neuropathy transcutaneous electrical nerve stimulation: n = 21 High-frequency: n = 20	Neuropathic symptoms: improvement in transcutaneous electrical nerve stimulation (33%) and high-frequency (80%; $p < .05$) Nonpainful neuropathy subgroup: improvement in high-frequency (100%; n = 7) was greater than transcutaneous electrical nerve stimulation (44%; n = 9; $p < .05$) Painful neuropathy subgroup: improvement in high-frequency (69%; n = 13) was greater than transcutaneous electrical nerve stimulation (25%; n = 12; $p < .05$) Total symptom score: reduction more pronounced in high-frequency (7.0 to 4.6; $p < .005$) than transcutaneous electrical nerve stimulation (6.6 to 5.4; $p < .05$) AE: none

Table 1. Continued

First author	Device of interest	Treatment specification: voltage, current, phase duration, frequency	Study design	Population	Outcome
Oyibo[42]	High voltage, low amperage pulsed galvanic stimulation	Treatment: 50 V, 80 pps for first 10 min then 8 pps for 10 min, 50 μA Sham: 5 V, 5 μA Subthreshold daily, every hour for 8 cycles, 6 weeks	Double blind, randomized clinical trial, crossover study with 1-week washout period	Diabetic painful neuropathy (n = 14)	Pain VAS: reduction in pain score in treatment (40.1) and control (49.2; p = .70) Sleep disturbance VAS: reduction in treatment (31.1) and control (42.6; p = .70) AE: worsening symptom in treatment (n = 2), dermatitis in sham (n = 2)
Weintraub[43]	Pulsed electromagnetic field	Treatment: varying intensity and polarity 10–30 min session for 2 h maximum, daily, 12 weeks	Double blind, randomized clinical trial	Diabetic painful neuropathy Treatment: n = 90 Sham: n = 104	Pain VAS: reduced in treatment (5.59 to 4.05) and sham (5.45 to 4.13; $p > .05$) Sleep disturbance VAS: reduced in treatment (4.63 to 4.23) and sham (4.23 to 2.96; $p > .05$) Patient assessment of global change (% much or very much): treatment (43.7%) and sham (38.5%; $p < .05$)

[a] VAS, visual analog scale; AE, adverse event.

Kumar and coauthors[39,40] conducted two randomized clinical studies using electrical stimulation for painful neuropathy. In both studies, Kumar and coauthors[39,40] used the same "H-wave" device for active treatment delivering biphasic decaying waveform pulse width of 4 ms and 25–35 V through surface electrodes. An important limitation in both studies was the small sample size (31 and 23 subjects). In the first study, Kumar and coauthors[40] evaluated 31 subjects that were assigned to receive H-wave or sham electrical stimulating for 30 min daily for 4 weeks in-clinic. There was a significant reduction in pain score for both H-wave treatment (3.17 to 1.44; $p < .01$) and sham treatment (2.92 to 2.38; $p < .04$) from baseline to end of study. The authors compared the visual analog scale scores at the end of the study for H-wave and sham treatments ($p < .03$); however, no group-to-group analysis of the change in pain from baseline to end of study was reported. In addition, overall neuropathic symptoms were compared at end of study. H-wave patients reported significantly higher scores subjective (52 ± 7%) and compared with sham treatment (27 ± 10%; $p < .05$).[40] Despite the high placebo effect, as noted by the authors, there was significant improvement in neuropathic symptom score.

In the second study, 23 people with diabetes who failed or partially responded to amitriptyline for pain control were randomized to receive H-wave electrical stimulation or sham with amitriptyline.[39] At the end of 12 weeks, there was a reduction in pain in H-wave treatment (3.2 to 1.4; $p < .01$) and sham treatment (2.9 to 1.9; $p < .03$) groups. The pain score reduction was greater in the treatment group (1.8 ± 0.3) than shams (0.9 ± 0.3; $p < .03$). Eleven percent (n = 1) of sham subjects converted from "daily active impairment with mild burning and uncomfortable feelings" to "asymptomatic" in 4 weeks.[39] Thirty-six percent (n = 5) of H-wave patients who failed to respond to amitriptyline alone were asymptomatic at end of study.[39] No adverse events were reported in this study.

Reichstein and coauthors[41] performed the only randomized clinical trial that compared two types of electrical stimulation to treat neuropathy. Forty-one patients with painful diabetic neuropathy were randomized to receive either high-frequency electrical stimulation on the femoral muscles or transcutaneous electrical nerve stimulation over the lower extremities.[41] Both devices were portable and used at home by study subjects. Patients were excluded if their glycated hemoglobin was greater than 11%, if they had a previous foot ulcer, or if they used medications to treat painful neuropathy. Both groups received therapy 30 min daily for three consecutive days. Patients were divided into groups with painful and non-painful neuropathy symptoms. The group treated with high-frequency electrical stimulation had a higher proportion of "responders" (80%) compared with the transcutaneous electrical nerve stimulation group (33%; $p < .05$). The authors defined responders as alleviation of at least one symptom by three or more points. Subgroup analysis revealed high-frequency electrical stimulation treatment was more effective

than transcutaneous electrical nerve stimulation for nonpainful (100 versus 44%; $p < .05$) and painful (69 versus 25%; $p < .05$) neuropathy. Symptom reduction was noted after completion of the first treatment and lasted up to 2 days after the last treatment.[41]

Oyibo and coauthors[42] assessed 14 diabetes patients with peripheral neuropathy for pain and sleep disturbance through the application of pulsed galvanic monophasic stimulation with nylon stocking electrodes. Fifty volts of pulsed direct current were delivered at 80 pulses per second for the first 10 min then 8 pulses per second for 10 min each hour for 8 h every night.[42] Patients with painful neuropathy symptoms for at least 6 months without relief form pharmacological therapies were randomized to receive 6 weeks of active or sham treatment followed by a 4-week washout period prior to crossover. The shams group received a small current of 5 V in order to activate the light on the device. When changes for each treatment were compared from baseline to "end of therapy," there was a significant reduction in pain for active treatment (6.2 to 3.1; $p = .003$) and sham (7.1 to 3.6; $p = .02$) and sleep disturbance for active treatment (5.9 to 3.5; $p = .003$) and sham (6.5 to 3.8; $p = .02$). A comparison of groups showed no difference in pain ($p = .70$) or sleep disturbance scores ($p = .70$). One of the novel aspects of this study was that the time the patient used the device during the study could be downloaded at each study evaluation. Compliance data downloaded from the device showed inconsistent use by patients. In addition, the authors noted a high drop rate in the first phase of the study for both active treatment (47%) and sham groups (60%) because of worsening symptoms (active treatment, 13%) or dermatitis (sham, 13%), or because therapy was not helpful (active treatment, 23%; sham, 27%) or was intolerable/inconvenient (active group, 13%; sham, 23%).[42]

Hamza and coauthors[36] randomly assigned 50 patients with type 2 diabetes with painful neuropathy for greater than 6 months to receive percutaneous electrical nerve stimulation or sham for 30 min three times a week for 3 weeks. After completing a 1-week washout period, all subjects crossed over to the active treatment arm. The authors used the highest tolerable levels of subcutaneous electrical stimulation delivered through needles for painful diabetic peripheral neuropathy symptom control. In the percutaneous electrical nerve stimulation treatment group, there was a significant difference from baseline to end of study in the use of oral analgesics (3.3 to 1.3 pills/day; $p < .05$) and activity (5.2 to 7.9; $p < .05$) and sleep (5.8 to 8.3; $p < .05$) scores. In the sham group, there was no improvement in oral analgesic use (3.1 to 2.9 pills/day; $p > .05$), but there was an improvement in activity (5.9 to 6.3; $p < .05$) and sleep (6.8 to 7.1; $p > .05$) scores. Analysis of difference between the two study groups was not provided, but the strong placebo effect and small sample size would suggest there would be no difference in active percutaneous electrical nerve stimulation and sham therapies. After discontinuation of treatment, pain scores returned to pretreatment levels (**Table 1**).[36] The reoccurrence of pain suggests that no permanent nerve changes occurred during the 3-week study. So either a longer treatment period is needed for sustained clinical improvement or treatment with electrical stimulation needs to be continuous to continue to have improved symptoms. There was a progressive improvement of outcome measurements week to week. A longer study may show a plateau in pain reduction, thereby identifying the duration of treatment needed for proper evaluation of symptom management via PENS.

Bosi and coauthors[38] conducted a randomized double blind controlled trial with 31 people with type 1 or type 2 diabetes, peripheral neuropathy, decreased nerve conduction velocity (<40 m/s), and increased vibration perception threshold (>25 V). The study consisted of 10 treatments with frequency-modulated electromagnetic neural stimulation or sham followed by a 1-week washout prior to crossing over to the other study phase. Each study visit was administered at least 24 h apart, and all 10 sessions took place within 3 weeks. In the active phase, there was a significant change from baseline to end of study in daytime pain (37.1 to 26.2; $p = .003$) and night time pain (38.1 to 28.5; $p = .01$). In the sham phase, there was no significant changes identified in daytime pain (31.2 to 31.9; $p > .05$) and nighttime pain (33.3 to 30.4; $p > .05$). No analysis comparing treatment phase with sham was reported.[38]

Weintraub and coauthors[43] conducted a multicenter randomized double-blind study with 225 persons with diabetes and moderate–severe constant pain of at least 6 months. Patients with painful neuropathy were randomized to use pulsed electromagnetic field or sham therapy at home for 2 h maximum each day in sessions of 10 to 30 min for 3 months. Subjects were allowed to continue using pain medication, but no new analgesics could be added. There was a significant increase in patients' global impression of change in patients who received active treatment (43.7%) and

sham therapy (30.6%; $p = .04$), reporting "very much or much improvement." Difference in groups from baseline to 3 months were not significant for changes in visual analog scale ($p = .96$), neuropathic pain score ($p = .58$), and sleep scores ($p = .49$). Approximately the same proportion of subjects withdrew from the study in both active treatment (16%) and sham treatment (12%) for protocol violation (3 versus 2%), allodynia (2 versus 2%), other medical condition (3 versus 3%), and lost to follow-up (8 versus 6%).[43]

Weintraub and coauthors[43] conducted a biopsy substudy examining epidermal nerve fiber density from 3 mm punch skin biopsy from the proximal and distal lateral thigh and the distal leg. There was an increase in epidermal nerve fiber density crossing into the epidermis from baseline in the active group (1.33 to 2.04 nerve fibers/mm; $n = 17$) compared with a decrease in sham group (1.05 to 0.83 nerve fibers/mm; $n = 18$) at the distal leg, but the change was not statistically significant ($p = .10$).[43] Intraepidermal nerve fibers are an indication of sensory neuropathy. In the healthy subject, the distal part of the leg contains 13.8 ± 6.7 fibers/mm, with the fifth percentile having 3.8 fibers/mm.[46] In the small biopsy substudy, electrical stimulation was able to increase the density of intraepidermal fibers toward the fifth percentile of healthy controls. A larger study is needed to assess the potential for increasing epidermal nerve density through long-term electrical stimulation.

Humpert and coauthors[37] reported the results of a prospective cohort studies of 92 persons with diabetes treated twice a week for 4 weeks with transcutaneous electrical nerve stimulation for painful neuropathy. Results of the study indicated that 73% of study subjects reported subjective improvement of neuropathic symptoms. There was a significant difference in the change in total symptom scores at end of week 1 ($p > .05$) and week 4 ($p < .001$). After 1 week of therapy, subjects in the upper tertile of baseline neuropathy scores showed improvement in mean symptom score ($p < .05$), paresthesia ($p < .05$), pain ($p < .01$), burning sensation ($p < .001$), sleep disturbance ($p < .001$), and numbness ($p < .01$). No individual symptom improvement was reported for patients in the second or lower tertile for the remainder of the study population after 2 weeks. After 4 weeks of therapy, all tertiles had a significant improvement in total symptom score ($p < .01$). The most prominent reduction in symptoms scores at 4 weeks occurred for burning sensation (8.5 to 4.9; $p < .001$) and sleep disturbance (7.9 to 4.6; $p < .001$) as well as a 24% reduction in numbness (5.4 to 4.6; $p < .01$). A subanalysis between responders and nonresponders showed higher baseline neuropathic symptom scores in nonresponders (7.8 versus 7.2; $p = .04$). Nonresponders trended to be older (69 versus 65 years; $p = .07$).[37]

Electrical Stimulation and Sensory Neuropathy

We identified two studies that evaluated changes in large-fiber sensory neuropathy or large-fiber neuropathy symptoms with electrical stimulation. Bosi and coauthors[38] showed a decrease in vibration perception threshold ($p = .0001$) and an increase in monofilament detection ($p = .008$) after electrical stimulation treatment in diabetic peripheral neuropathy[38] (**Table 1**). Patients were excluded if vibration perception at the big toe was greater than 25 V or if there was a history of foot ulcers, decreased lower extremity perfusion (ankle–brachial index <0.9 or transcutaneous partial pressure of oxygen <50), or presence of any other severe disease. After 3 weeks of active treatment and sham, vibration perception threshold improved for both groups (34.7 to 34.2, $p > .05$; 35.5 to 33.4, $p = .0001$). Monofilament insensitivity for nine areas decreased for the treatment group (5.8 to 4.6; $p = .008$) but not for the shams group (5.1 to 5.2; $p > .05$). A reduction in vibration perception threshold ($p < .05$) and monofilament insensitivity ($p < .001$) was reported up to 4 months.[38] Humpert and coauthors[37] reported a significant improved in symptoms of paresthesias and numbness with electrical stimulation, but no measures of large-fiber neuropathy were evaluated.

Conclusion

Electrical stimulation may be an effective alternative and adjunctive therapy to current interventions for diabetic peripheral neuropathy. Electrical stimulation provided improvement in symptoms of painful neuropathy (six studies) and sensory neuropathy (one study) in persons with diabetes. Several studies reported significant placebo effects in the sham therapy group.[37–40] Placebo effects are common in pain studies and one of the reasons between-group statistical comparisons are needed. Changes in medications for pain and objective measures of activity and sleep can now be objectively measured with computerized activity devices and may provide additional insights into treatment

outcomes. Unfortunately, all of the current studies are small. None of the studies provide head-to-head comparisons with drug therapy, and all of the studies are of a relatively short duration. Comparison of costs, side effects, and clinical outcomes for treatments with electrical stimulation for painful neuropathy with large study populations need to be performed.

There is only one study that evaluated objective measures of sensory neuropathy and electrical stimulation. This is one of the most important factors in the causal pathway to ulceration, infection, and amputation, and there are currently no effective treatments for large-fiber neuropathy. Bosi and coauthors[38] reported an improvement in monofilament testing and vibration sensation in the electrical stimulation treatment group, so at least one study supports "proof of concept" to improve sensation. If electrical stimulation can improve peripheral sensation, it could dramatically change one of the pivotal disease factors in the diabetic foot.

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