Lower Extremity Nerve Decompression for Diabetic Peripheral Neuropathy: A Systematic Review and Meta-analysis

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Background: Diabetic peripheral neuropathy (DPN) is a leading cause of morbidity. This systematic review and meta-analysis evaluate the efficacy of lower extremity nerve decompression in reducing DPN symptoms and complications.

Methods: A database search was performed using Medline, Embase, Google Scholar, and Cochrane Central Register of Controlled Trials. Articles addressing surgical decompression of lower limb peripheral nerves in patients with diabetes were screened for inclusion. Two independent reviewers undertook the assessment. Methodological quality measures were the Cochrane risk of bias and Newcastle-Ottawa scale.

Results: The pooled sample size from 21 studies was 2169 patients. Meta-analysis of 16 observational studies showed significant improvement in the visual analog scale (VAS) ($P < 0.00001$) and two-point discrimination ($P = 0.003$), with strong reliability. Decompression of the tarsal tunnel region had the highest improvement in VAS (MD, 6.50 [95% CI, 3.56–9.44]). A significant low-risk ratio (RR) of ulcer development and lower limb amputation was detected ($P < 0.00001$). Lowest RR of ulcer development was detected with tarsal tunnel release [RR, 0.04 (95% CI, 0.00–0.48)]. Improvements in VAS, two-point discrimination, and nerve conduction velocity were nonsignificant in the meta-analysis of five randomized controlled trials (RCTs). The RCT analysis was limited to only two studies for each outcome.

Conclusions: Meta-analysis of observational studies highlights the efficacy of lower extremity nerve decompression in reducing DPN symptoms, ulcerations, and amputations. Releasing the tibial nerve in the tarsal tunnel region was the most effective observed procedure. Nevertheless, high-quality RCTs are required to support the utility of this intervention in DPN. (Plast Reconstr Surg Glob Open 2022;10:e4478; doi: 10.1097/GOX.0000000000004478; Published online 18 August 2022.)

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METHODOLOGY

Protocol and Eligibility Criteria
This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The intervention group consisted of adults with DPN who underwent surgical decompression of peripheral nerves in the lower extremity, whereas the control group included patients with a contralateral nonoperated leg or patients with DPN who did not have surgery. The primary outcome of interest of this study was postoperative clinical improvement. This was evaluated by reviewing the pain visual analog scale (VAS) or the two-point discrimination (2PD) sensory test. The secondary outcomes were changes in nerve conduction velocity (NCV), ulcer development, and the need for lower limb amputation. Studies among patients with an established diagnosis of compression neuropathies, in vitro or animal studies, review papers, expert opinions, case reports, and non-English articles were excluded from this systematic review.

Search Strategy and Study Selection
The present systematic review was carried out using Medline, Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials. The period covered was from inception to November 1, 2021. The key terms used were “nerve decompression” or “nerve release” or “tunnel release” or “surgical release” or “compression neuropathy” and “diabetes” or “diabetic neuropathy” or “peripheral neuropathy” or “painful neuropathy.” The abstracts of all related articles addressing surgical decompression of lower limb peripheral nerves in patients with diabetes were reviewed. The reference lists of articles included in this review and recent related reviews were examined. Relevant articles published in English peer-reviewed journals were selected. Titles and abstracts were screened to assess the eligibility of the identified articles. A full-text review for inclusion and data extraction was done by two independent reviewers (W.A. and T.A.). Interrater reliability was analyzed to confirm agreement. When data or eligibility was in question, this was discussed with the senior author to reach consensus.

Data Extraction
The following data were extracted from each article: author, year of publication, journal, country, study design, mean age, sample size, funding, indication for surgery, type of intervention, control treatment, other comparison treatment, follow-up time, outcome measurement, and results. The extracted data were collected in a structured Excel spreadsheet (Microsoft Corp., Redmond, Wash.).

Statistical Analysis
Statistical analyses were performed with Review Manager Version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark). The Cochrane risk of bias assessment tool was used to assess the methodologic quality of identified randomized-controlled trials (RCTs). The Newcastle-Ottawa scale (NOS) was used to evaluate observational studies, assessing three sections: (1) representativeness of the study population, (2) comparability of cohorts, and (3) evaluation of outcomes (follow-up).

Takeaways
**Question:** Can lower extremity nerve decompression reduce symptoms and complications of diabetic peripheral neuropathy (DPN)?

**Findings:** Meta-analysis of observational studies highlights the efficacy of nerve decompression in reducing DPN symptoms, ulcerations, and amputations. Tibial nerve release in the tarsal tunnel region was the most effective procedure. Randomized controlled trial (RCT) analysis showed nonsignificant improvement following surgery. This analysis of RCTs was limited by high heterogeneity and low number of studies.

**Meaning:** Success of lower extremity nerve decompression in reducing DPN symptoms and complications is strongly supported by observational studies. Nevertheless, high-quality RCTs are required to support the utility of this intervention in this patient population.

RESULTS

Study Selection
The database search identified 250 articles, whereas 16 others were identified through manual review of the selected articles’ references (Fig. 1). Following the screening of titles and abstracts from the initial search, 50 articles were selected for full-text review. After the full-text review, nine articles were excluded because they did not satisfy the inclusion criteria or had inappropriate outcome reporting, leaving 21 articles eligible for final inclusion. The included
studies are five RCTs and 16 observational studies. The pooled sample size of patients from all studies was 2169, of which 612 were from RCTs and 1557 from observational studies. The level of evidence of all studies included in this review ranged from levels I to III on the Oxford Center for Evidence-Based Medicine scale. Tables 1–4 summarize the characteristics of these studies.

Quality Assessment and Risk of Bias

The Cochrane risk of bias assessment tool was utilized. All the RCTs included in this review were judged to be at low risk of bias for outcome assessment blinding. A high proportion of the RCTs (75%) mentioned a low risk of bias for randomization, and selective outcome reporting had incomplete outcome data. However, a high risk of bias for allocation concealment was detected in all RCTs. Similarly, more than half of the RCTs were at a high risk of bias for blinding of patients and personnel (Fig. 2). Observational studies were assessed using NOS. All included studies were judged to be at a low risk of bias for the follow-up criteria, and most mentioned a low risk of bias for the representativeness of the study population. However, a high risk of bias for comparability criteria was detected in 75% of studies because they did not describe a control group (Fig. 3).

To account for bias related to duplicate study effects, publications that appeared to be from one data set were not included in the same analysis. Based on Egger’s regression test for RCT studies and the visual examination of the funnel plot, no proof of publication bias was detected for any of the three outcomes analyzed [P (VAS), 0.56; P (2PD), 0.62; P (NCV), 0.87; Fig. 4]. Similarly, no proof of publication bias was detected in observational studies for any of the four outcomes analyzed [P (VAS), 0.08; P (2PD), 0.12; P (ulcer development), 0.06; P (amputation), 0.34; Fig. 5].

ASSESSMENT OF HETEROGENEITY

RCT Studies

**VAS Outcome**

Two of the five included RCTs reported VAS outcomes. As heterogeneity was high ($\chi^2$, 16.87; $P < 0.0001$; $I^2$, 94%), a random effects model was adopted. Pooled analysis
Table 1. Summary of the Randomized Controlled Trials Included in This Review

| Authors          | Year | Title                                                                 | Country     | Journal                  | Primary Outcome | Secondary Outcome | Complications |
|------------------|------|----------------------------------------------------------------------|-------------|--------------------------|-----------------|------------------|---------------|
| Zhang et al      | 2013 | Evaluation of the clinical efficacy of peripheral nerve decompression in diabetic peripheral neuropathy | China       | JNLS                     | Yes             | NCS              | Wound dehiscence |
| van Maurik et al | 2014 | Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic polyneuropathy | The Netherlands | JPRS                     | Yes             | VAS              | Hematoma (n=1) and wound infection |
| van Maurik et al | 2015 | Effect of lower extremity nerve decompression on health-related quality of life and perception of pain in patients with painful diabetic polyneuropathy | The Netherlands | J Clin Neurophysiol    | Yes             | NCS              | Hematoma (n=1) and wound infection |
| van Maurik et al | 2015 | Surgical peripheral nerve decompression for the treatment of painful diabetic foot | The Netherlands | PRS                      | No              | NCS              | Wound infection (n=1) |

Hoffmann-Tinel Sign

| Authors          | Year | Title                                                                 | Country     | Journal                  | Primary Outcome | Secondary Outcome | Complications |
|------------------|------|----------------------------------------------------------------------|-------------|--------------------------|-----------------|------------------|---------------|
| Zhang et al      | 2013 | Evaluation of the clinical efficacy of peripheral nerve decompression in diabetic peripheral neuropathy | China       | JNLS                     | Yes             | NCS              | Wound dehiscence |
| van Maurik et al | 2014 | Value of surgical decompression of compressed nerves in the lower extremity in patients with painful diabetic polyneuropathy | The Netherlands | JPRS                     | Yes             | VAS              | Hematoma (n=1) and wound infection |
| van Maurik et al | 2015 | Effect of lower extremity nerve decompression on health-related quality of life and perception of pain in patients with painful diabetic polyneuropathy | The Netherlands | J Clin Neurophysiol    | Yes             | NCS              | Hematoma (n=1) and wound infection |
| van Maurik et al | 2015 | Surgical peripheral nerve decompression for the treatment of painful diabetic foot | The Netherlands | PRS                      | No              | NCS              | Wound infection (n=1) |

2PD Outcome

Two of the five included RCTs reported 2PD outcomes. As heterogeneity was high ($\chi^2$, 52.32; $P < 0.0001$; $F$, 94%), a random effects model was adopted. Based on our pooled analysis, the preoperative versus postoperative 2PD changes were not statistically significant (mean difference, 7.28; 95% CI, –3.02 to 17.59; $P = 0.17$; Fig. 6B).

NCV Outcome

Two of the five included RCTs reported NCV outcomes. As heterogeneity was high ($\chi^2$, 48.19; $P < 0.00001$; $F$, 98%), a random effects model was adopted. Pooled analysis showed a nonsignificant difference ($P = 0.43$) in NCV (mean difference, –3.90; 95% CI, –13.61 to 5.81) after surgery (Fig. 6C).

Observational Studies

**VAS Outcome**

Nine of the 25 included observational studies reported VAS outcomes. As heterogeneity was low ($\chi^2$, 8.60; $P = 0.38$; $F$, 7%), a fixed-effects model was adopted. Pooled analysis showed a significant improvement ($P < 0.00001$) on VAS (mean difference, 5.10; 95% CI, 4.04–6.16) after surgery (Fig. 7A).

**2PD Outcome**

Three of the 25 included observational studies reported 2PD outcomes. As heterogeneity was low ($\chi^2$, 0.89; $P = 0.64$; $F$, 0%), a fixed-effects model was adopted. Pooled analysis showed a significant improvement ($P = 0.003$) in 2PD (mean difference, 6.46; 95% CI, 2.22–10.69) after surgery (Fig. 7B).

**Ulcer Development**

Six of the 25 included observational studies reported the prevalence of ulcer development. As heterogeneity was high ($\chi^2$, 59.98; $P < 0.00001$; $F$, 92%), a random-effects model was adopted. The forest plot analysis showed that the risk of ulcer development was significantly low (RR, 0.11; 95% CI, 0.05–0.23; $P < 0.00001$; Fig. 7C).

**Amputations**

Five of the 25 included observational studies reported amputation prevalence. As heterogeneity was high ($\chi^2$, 16.47; $P = 0.002$; $F$, 76%), a random-effects model was adopted. The forest plot analysis showed that amputation was significantly low (RR, 0.01; 95% CI, 0.00–0.09; $P < 0.00001$; Fig. 7D).

**Sensitivity Analysis**

The outcomes in observational studies did not differ substantially, indicating strong reliability of the meta-analysis. In the leave-one-out sensitivity analysis, the mean difference between VAS and 2PD ranged from 4.89 (95% CI, 3.76–6.03) to 5.93 (95% CI, 4.71–7.15) and from 5.46 (95% CI, 0.74–10.18) to 7.32 (95% CI, 1.48–13.16), respectively.
Table 2. Summary of the Observational Studies Included in This Review

| Authors                  | Year | Title                                                                 | Country | Journal     | Study Type | Intervention          | Hoffmann-Tinel Sign | Primary Outcome | Complications                              |
|--------------------------|------|----------------------------------------------------------------------|---------|-------------|------------|------------------------|---------------------|-----------------|---------------------------------------------|
| Wei et al.               | 1995 | Treatment of hyperesthetic neuropathic pain in diabetic neuropathy    | USA     | Ann Surg    | Prospective | Tarsal tunnel          | Yes                 | VAS             | Ulceration (n = 1)                          |
|                          |      | Decompression of the tarsal tunnel                                   |         |             |            |                        |                     |                 | Superficial wound infection (n = 4)        |
|                          |      |                                                                      |         |             |            |                        |                     |                 | Toe numbness (n = 1)                         |
|                          |      |                                                                      |         |             |            |                        |                     |                 | Wound dehiscence (n = 4)                    |
| Wood et al.             | 2003 | Decompression of peripheral nerves for diabetic neuropathy in the      | USA     | JFAS        | Cohort     | Common peroneal, deep  | Yes                 | VAS             | Wound dehiscence (n = 1)                    |
|                          |      | lower extremity                                                      |         |             |            | peroneal, and tarsal tunnel |                     |                 | Amputation (n = 1)                           |
|                          |      |                                                                      |         |             |            |                        |                     |                 | Feet infections (n = 1)                     |
|                          |      |                                                                      |         |             |            |                        |                     |                 | Wound dehiscence (n = 1)                    |
| Aszmann et al.          | 2004 | Changing the natural history of diabetic neuropathy: incidence of      | USA     | Ann Plast    | Retrospective| Common peroneal, deep  | Yes                 | Ulcer or       | Ulceration (n = 2)                          |
|                          |      | ulcer/amputation in the contralateral limb of patients with a         | Surg    | Surg         |            | peroneal, and tarsal tunnel |                     | amputation     | Delayed wound healing (n = 5)               |
|                          |      | unilateral nerve decompression procedure                              |         |             |            |                        |                     |                 | Subcutaneous hematomma (n = 1)               |
| Rader et al.            | 2005 | Surgical decompression in lower extremity diabetic peripheral          | USA     | JAPMA       | Prospective | Common peroneal, deep  | Yes                 | VAS             | Ulceration (n = 4)                          |
|                          |      | neuropathy                                                           |         |             |            | peroneal, and tarsal tunnel |                     |                 | Wound dehiscence (n = 1)                    |
|                          |      |                                                                      |         |             |            |                        |                     |                 | Feet infections (n = 1)                     |
| Valdivia et al.         | 2005 | Surgical treatment of peripheral neuropathy: outcomes from            | USA     | JAPMA       | Prospective | Common peroneal, deep  | Yes                 | VAS             | Ulceration (n = 4)                          |
|                          |      | 100 consecutive decompressions                                        |         |             |            | peroneal, and tarsal tunnel |                     |                 | Wound dehiscence (n = 1)                    |
| Siemionow et al.        | 2006 | Clinical outcome of peripheral nerve decompression in diabetic        | Poland  | Ann Plast    | Prospective | Common peroneal, deep  | Yes                 | 2PD            | Ulceration (n = 2)                          |
|                          |      | and non-diabetic peripheral neuropathy                               |         | Surg         |            | peroneal, and tarsal tunnel |                     |                 | Delayed wound healing (n = 5)               |
| Karagöz et al.          | 2008 | Early and late results of nerve decompression procedures in           | Turkey  | J Reconst    | Cohort     | Common peroneal, deep  | Yes                 | VAS             | Ulceration (n = 4)                          |
|                          |      | diabetic neuropathy; a series from Turkey                            |         | Microsurg    |            | peroneal, and tarsal tunnel |                     |                 | Wound dehiscence (n = 1)                    |
| Dellon et al.           | 2012 | Prevention of ulceration, amputation, and reduction of hospitalization| USA     | J Reconst    | Prospective | Tarsal tunnel          | Yes                 | Ulcer or       | Ulceration (n = 4)                          |
|                          |      | outcomes of a prospective multicenter trial of tibial neurolysis in   |         | Microsurg    |            |                        |                     | amputation     | Delayed wound healing (n = 5)               |
|                          |      | patients with diabetic neuropathy                                    |         |             |            |                        |                     |                 | Subcutaneous hematomma (n = 1)               |
|                          |      | (a) A positive Tinel sign as predictor of pain relief or sensory      |         |             |            |                        |                     |                 | Delayed wound healing (n = 5)               |
|                          |      | recovery after decompression of chronic tibial nerve compression      |         |             |            |                        |                     |                 | Not reported                                |
|                          |      | in patients with diabetic neuropathy                                 |         |             |            |                        |                     |                 |                                            |
|                          |      | (b) Low long-term risk of foot ulcer recurrence after nerve           |         |             |            |                        |                     |                 |                                            |
|                          |      | decompression in diabetic neuropathy cohort                          |         |             |            |                        |                     |                 |                                            |
| Nickerson and Rader et  | 2013 | Low long-term risk of foot ulcer recurrence after nerve decompression | USA     | JAPMA       | Retrospective | Common peroneal, deep  | Yes                 | Ulcer or       | Ulceration (n = 4)                          |
|                          |      | in diabetic neuropathy cohort                                       |         |             |            | peroneal, and tarsal tunnel |                     | amputation     | Delayed wound healing (n = 5)               |
|                          |      |                                                                      |         |             |            |                        |                     |                 | Subcutaneous hemotoma (n = 1)               |
| Liao et al.             | 2014 | Surgical decompression of painful diabetic peripheral neuropathy:    | China   | PLOS        | Retrospective | Common peroneal, deep  | Yes                 | VAS             | Ulceration (n = 4)                          |
|                          |      | the role of pain distribution                                        |         | ONE         |            | peroneal, and tarsal tunnel |                     |                 | Wound dehiscence (n = 1)                    |
|                          |      |                                                                      |         |             |            |                        |                     |                 |                                            |
| Anderson et al.         | 2017 | Acute improvement in intraoperative EMG following common fibular      | USA     | JNLS        | Retrospective | Common peroneal nerve  | Yes                 | EMG             |                                            |
|                          |      | nerve decompression in patients with symptomatic diabetic            |         |             |            | decompression           |                     |                 |                                            |
|                          |      | sensorimotor peripheral neuropathy                                   |         |             |            |                        |                     |                 |                                            |
|                          |      | 1. EMG results                                                       |         |             |            |                        |                     |                 |                                            |
| Wang et al.             | 2018 | Two-point discrimination predicts pain relief after lower limb nerve | China   | JPRS        | Retrospective | Common peroneal, deep  | Yes                 | VAS             |                                            |
|                          |      | decompression for painful diabetic peripheral neuropathy             |         |             |            | peroneal, and tarsal tunnel |                     |                 |                                            |
|                          |      |                                                                      |         |             |            |                        |                     |                 |                                            |
| Liao et al.             | 2018 | Mechanical allodynia predicts better outcome of surgical              | China   | J Reconst    | Prospective | Common peroneal, deep  | Yes                 | VAS             |                                            |
|                          |      | decompression for painful diabetic peripheral neuropathy             |         | Microsurg    |            | peroneal, and tarsal tunnel |                     |                 |                                            |
|                          |      |                                                                      |         |             |            |                        |                     |                 |                                            |
| Sarmiento et al.        | 2019 | Tibial nerve decompression for the prevention of the                  | USA     | BMJ Open     | Comprehensive | Tarsal tunnel          | N/A                 | Ulcer or       | Ulceration (n = 4)                          |
|                          |      | diabetic foot: a cost–utility analysis using Markov Model            |         |             |            |                        |                     | amputation     | Delayed wound healing (n = 5)               |
|                          |      | simulations                                                          |         |             |            |                        |                     |                 | Not reported                                |
| Agarwal and Sharma      | 2021 | Our experience of reinnervation of sole in diabetic                  | India   | J Clin Orthop| Prospective | Tarsal tunnel, SN nerve | Yes                 | VAS             | Ulceration (n = 4)                          |
|                          |      | sensorimotor polyneuropathy: a chance to change the natural history  |         | Trauma       |            | transfer               |                     |                 | Wound dehiscence (n = 1)                    |
|                          |      | of disease                                                           |         |             |            |                        |                     |                 | Delayed wound healing (n = 1)               |

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Ann Plast Surg, Annals of Plastic Surgery; An Surg, Annals of Surgery; EMG, electromyography; JAPMA, Journal of American Podiatric Medical Association; J Clin Orthop Trauma, Journal of Clinical Orthopedics and Trauma; JFAS, Journal of Foot and Ankle Surgery; JNLS, Journal of Neurological Surgery; JPRS, Journal of Plastic and Reconstructive Surgery; J Reconst Microsurg, Journal of Reconstructive Microsurgery; SN, saphenous nerve.
respectively. Similarly, the RRs of ulcer development and amputation varied from 0.08 (95% CI, 0.01–0.51) to 0.19 (95% CI, 0.13–0.28) and 0.01 (95% CI, 0.00–0.06) to 0.04 (95% CI, 0.02–0.08), respectively (Table 5).

Subgroup Analysis
A subgroup analysis was performed for the VAS, ulcer development, and amputation outcomes in the observational studies. The 2PD outcome was excluded due to the limited number of articles. The mean difference or RR differed following the study period and number of participants. The mean difference did not differ significantly for VAS outcomes, depending on the study period or number of patients ($P > 0.05$). However, both the study period and number of patients constituted a source of heterogeneity in ulcer development outcomes ($P < 0.05$). Similarly, when the study period was adopted as a moderator in amputation outcomes, the RR differed significantly between the studies ($P < 0.05$). The RR of amputation exhibited a higher trend in studies performed before 2010 than in those performed after 2010 (RR, 0.03 and 0.01, respectively; Table 6). Releasing the tarsal tunnel region tended to be the most effective procedure among the different combinations of lower limb nerve decompressions in terms of type of intervention (Tables 7, 8).

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### Table 3. Demographics of the Randomized Controlled Trials Included in This Review

| Authors            | No. Patients | Follow-up | Mean Age ± SD (Y) | Gender (M:F) |
|--------------------|--------------|-----------|-------------------|--------------|
| Zhang et al⁹       | Cases: 560 controls: 40 | 18 mo     | 58 ± 11.32       | 260 M:F 300  |
| van Maurik et al¹⁰ | Cases: 38 controls: 38 (contralateral limb) | 12 mo     | 62.7 ± 10.2      | 22 M:F 16    |
| van Maurik et al¹¹ | Cases: 40 controls: 40 (contralateral limb) | 12 mo     | 61.2 ± 11        | 26 M:F 26    |
| van Maurik et al¹² | Cases: 38 controls: 38 (contralateral limb) | 12 mo     | 61.7 ± 10.2      | 26 M:F 26    |
| Best et al¹³       | Cases: 12 controls: 10 | 12 mo     | 64 ± 6.4         | 6 M:F 6      |

### Table 4. Demographics of the Observational Studies Included in this Review

| Authors             | No. Patients | Mean Follow-up | Mean Age (Y) | Gender (M:F) |
|---------------------|--------------|----------------|--------------|--------------|
| Wieman and Patel¹⁴ | 26           | 13 mo          | 59.6         | 11 M:F 15    |
| Wood and Wood¹      | 33           | 3 mo           | Not reported | Not reported |
| Aszmann et al¹⁶     | 50           | 4 y            | Not reported | Not reported |
| Rader¹⁶             | 39           | 15 mo          | Range (38-83)| Not reported |
| Valdivia et al¹⁷    | 100          | 12 mo          | 63.1         | 56 M:F 44    |
| Siemionow et al¹⁷   | 32           | 6 mo           | 49.5         | 10 M:F 22    |
| Karagöz et al¹⁸     | 24           | 8 mo           | 48           | 8 M:F 16     |
| Dellon et al²⁴      | 628          | 12 mo          | Not reported | Not reported |
| Dellon et al²⁵      | 628          | 4 y            | Not reported | Not reported |
| Nickerson and Rader¹⁷ | 65         | 3 y            | 74.5         | Not reported |
| Liao et al²⁶        | 506          | 4 y            | 50           | 108 M:F 198  |
| Anderson et al²⁰    | 40           | 12 mo          | 64.8         | 22 M:F 18    |
| Wang et al²⁷        | 34           | 12 mo          | 56.4         | 19 M:F 15    |
| Liao et al²⁸        | 148          | 2 y            | 58.5         | 57 M:F 91    |
| Sarmiento et al²⁶   | 1677 (simulation model) |           | Not reported | Not reported |
| Agarwal and Sharma¹ | 32           | 6 mo           | 35.6         | 18 M:F 14    |

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Fig. 2. Risk of bias graph: authors’ judgments of included randomized controlled trials using the Cochrane risk-of-bias tool.

- **Random sequence generation (selection bias)**: Low risk of bias
- **Allocation concealment (selection bias)**: Low risk of bias
- **Blinding of participants and personnel (performance bias)**: Low risk of bias
- **Blinding of outcome assessment (detection bias)**: Low risk of bias
- **Incomplete outcome data (attrition bias)**: Low risk of bias
- **Selective reporting (reporting bias)**: Low risk of bias
- **Other bias**: Low risk of bias
DISCUSSION

This study is a detailed systematic review and meta-analysis that specifically examines lower extremity peripheral nerve decompression in DPN. Although Tu et al.30 previously published a systematic review of DPN, most of the articles included in their study focused on carpal tunnel release. With regard to the lower extremity, their analysis was limited to four observational studies, with no reporting of the late sequelae of DPN. Dellon31 reported a meta-analysis focused on decompressing the tibial nerve branches at the ankle with 80% improvement in VAS.31 A meta-analysis by Baltodano et al.32 including 875 diabetic patients was published in 2013. Their study showed a significant improvement in VAS (91%) and sensibility (69%). Additionally, the incidence of postoperative ulceration and amputation was significantly reduced. Our pooled analysis included a total of 21 articles, five RCTs, and 16 observational studies, with 2169 patients. The meta-analysis of observational studies showed that VAS and 2PD outcomes significantly improved after peripheral nerve
decompression ($P < 0.00001$ and $P = 0.003$, respectively). Moreover, we detected a significantly low RR of both ulcer development and the need for lower limb amputation ($P < 0.05$). A low number of complications associated with peripheral nerve decompression in DPN were observed (Tables 1, 2).

Peripheral neuropathies have been described in patients with primary (types 1 and 2) and secondary diabetes. This suggests a common etiology based on chronic hyperglycemia, leading to progressive nerve fiber loss. This is the most common of all the late complications of diabetes and creates much suffering among diabetic patients. The late sequelae of peripheral neuropathy include foot ulceration, Charcot neuroarthropathy, and amputation. Peripheral nerve decompression in patients with DPN was explored as a treatment option in multiple studies. Tu et al. reported significant improvement in symptom severity and the functional status of the upper extremities following carpal tunnel release in patients with DPN. In addition, electrodiagnostic studies of the median nerve showed significant improvements in distal motor latency and sensory conduction velocity. The meta-analysis by Tu et al. included only four observational studies exploring lower extremity peripheral nerve decompression. Their study reported clinically and statistically significant improvements in VAS scores and 2PD, which supports our findings. However, the clinical application of this surgical intervention is still low. This could be due to the lack of convincing evidence for performing surgery in a metabolic disease setting.

Improvements in DPN symptoms following peripheral nerve decompression were investigated in multiple studies. Theories related to nerve swelling and edema are often offered as explanations for improvement. The hydrophilic property of sorbitol can lead to increased water content within the nerves of diabetic patients. Additionally, the inflammatory reaction to oxygen-derived free radicals secondary to hyperglycemia and dyslipidemia results in further edema formation. Increased nerve volume leads to a high possibility of compression while passing through an anatomical fibro-osseous tunnel. This can produce nerve ischemia, axonal loss, and demyelination injury.
Despite the observed clinical improvement in DPN symptoms following peripheral nerve decompression, clearly, no changes are anticipated to the underlying metabolic neuropathy. 37 Similarly, small favorable changes that might be observed on electrodiagnostic testing are unlikely to be due to effects on the metabolic neuropathy, but rather related to the decompression itself.

In 1992, Dellon 5 reported 85% improvement of DPN symptoms following tibial nerve decompression in the ankle. Aszmann et al 3 observed that peripheral nerve decompression in patients with diabetes improves sensibility and sensory impairment, and restores protective sensation. 38 Peripheral nerve decompression also enhances microcirculation in the feet, 39 improves the plantar sensation, and prevents ulcers and their associated complications. 40 Nerve decompression had a positive effect on the hemodynamic and morphological parameters of arteries as they pass through anatomical tunnels. Furthermore, nerve decompression improved the neurological function of entrapped nerves in addition to pedal sensibility and balance. 41,42 Nerve decompression was found to be an effective and safe treatment for intractable painful DPN with superimposed nerve compression. 43 Anderson et al 29 observed significant improvement in intraoperative electromyography (EMG) immediately following nerve decompression. In addition, two studies from the same group, Zhong et al 44 and the RCT by Zhang et al, 9 reported that DPN patients’ NCV improved significantly 18 months after nerve decompression compared with the baseline. Their study suggested that early diagnosis and subsequent peripheral nerve decompression were associated with a favorable clinical outcome.

Fig. 6. Forest plots of pooled analysis of outcomes in RCTs. A, VAS, B, 2PD, C, NCV.

Fig. 7. Forest plots of observational studies. A, VAS, B, 2PD, C, Ulcer development, D, Amputation.
### Table 5. Leave-one-out Sensitivity Analysis of Mean Difference of Analyzed Outcomes among Observational Studies

| Outcome       | Study Excluded          | Mean Difference or RR (95% CI) | P       |
|---------------|-------------------------|-------------------------------|---------|
| VAS           | Anderson et al<sup>29</sup> | MD, 5.93 (4.71–7.15)          | <0.00001|
|               | Dellon et al<sup>25</sup>  | MD, 4.89 (3.76–6.03)          | <0.00001|
|               | Karagoz et al<sup>33</sup> | MD, 5.09 (4.01–6.17)          | <0.00001|
|               | Liao et al<sup>21</sup>   | MD, 5.06 (3.94–6.19)          | <0.00001|
|               | Liao et al<sup>22</sup>   | MD, 4.98 (3.79–6.16)          | <0.00001|
|               | Wang et al<sup>27</sup>    | MD, 5.09 (3.98–6.20)          | <0.00001|
|               | Rader<sup>16</sup>       | MD, 4.98 (3.89–6.07)          | <0.00001|
|               | Valdivia et al<sup>17</sup> | MD, 4.97 (3.89–6.06)        | <0.00001|
| 2PD           | Liao et al<sup>20</sup>   | MD, 5.46 (0.74–10.18)         | 0.02    |
|               | Siemionow et al<sup>17</sup> | MD, 7.32 (1.48–13.16)   | 0.01    |
|               | Wood and Wood<sup>4</sup> | MD, 6.98 (1.80–12.17)         | 0.008   |
| Ulcer         | Agarwal and Sharma<sup>1</sup> | RR, 0.08 (0.03–0.21)    | <0.00001|
|               | Aszmann et al<sup>17</sup> | RR, 0.08 (0.03–0.21)         | <0.00001|
|               | Nickerson and Rader<sup>19</sup> | RR, 0.10 (0.04–0.25)  | <0.00001|
|               | Sarmiento et al<sup>26</sup> | RR, 0.08 (0.01–0.51)    | <0.00001|
|               | Wieman and Patell<sup>14</sup> | RR, 0.12 (0.05–0.26)  | <0.00001|
| Amputation    | Agarwal and Sharma<sup>1</sup> | RR, 0.01 (0.00–0.12)    | 0.0001  |
|               | Aszmann et al<sup>17</sup> | RR, 0.02 (0.00–0.13)         | 0.0002  |
|               | Nickerson and Rader<sup>19</sup> | RR, 0.04 (0.02–0.08)  | <0.00001|
|               | Wieman and Patell<sup>14</sup> | RR, 0.01 (0.00–0.11)  | <0.00001|

ND, non-detectable.

### Table 6. Subgroup Analysis for the Mean Difference and RR of Analyzed Outcomes among Observational Studies

| Outcomes       | Subgroups | No. Studies | Mean Difference or RR (95% CI) | P       | Heterogeneity |
|----------------|-----------|-------------|-------------------------------|---------|---------------|
| VAS            | Study period |            |                               |         |               |
|                | Before 2010 | 4           | MD, 6.47 (4.22–8.72)          | <0.00001| 0.51          | 0.92          |
|                | After 2010  | 5           | MD, 4.71 (3.51–5.91)          | <0.00001| 6.27          | 0.18          |
|                | <100        | 5           | MD, 4.23 (2.74–5.72)          | <0.00001| 5.22          | 0.27          |
|                | >100        | 4           | MD, 5.98 (4.48–7.48)          | <0.00001| 0.75          | 0.86          |
| VAS            | No. patients |           |                               |         |               |
|                | Before 2010 | 2           | RR, 0.13 (0.01–1.50)          | 0.08    | 5.39          | 0.02          |
|                | After 2010  | 4           | RR, 0.09 (0.03–0.26)          | <0.00001| 51.60         | 0.00001       |
|                | <100        | 4           | RR, 0.20 (0.10–0.37)          | <0.00001| 8.68          | 0.03          |
|                | >100        | 2           | RR, 0.03 (0.00–1.04)          | 0.05    | 48.89         | 0.00001       |
| Ulcer          | Study period |            |                               |         |               |
|                | Before 2010 | 2           | RR, 0.03 (0.01–0.12)          | <0.00001| 0.75          | 0.39          |
|                | After 2010  | 3           | RR, 0.01 (0.00–0.22)          | 0.005   | 15.45         | 0.00004       |
| Ulcer          | No. patients |           |                               |         |               |
|                | Before 2010 | 4           | RR, 0.04 (0.02–0.08)          | 0.64    | 1.69          | 0.64          |
|                | >100        | 1           | ND                            | ND      | ND            | ND            |

ND, non-detectable.

### Table 7. Subgroup Analysis of the Type of Intervention in Observational Studies

| Outcomes       | Subgroups | No. Studies | Mean Difference or RR (95% CI) | P       | Heterogeneity |
|----------------|-----------|-------------|-------------------------------|---------|---------------|
| VAS            | Intervention |           |                               |         |               |
|                | Common peroneal, deep peroneal, and tarsal tunnel | 7         | MD, 5.81 (4.48–7.15)          | <0.00001| 1.05          | 0.98          |
|                | Common peroneal nerve decompression | 1         | MD, 2.50 (3.94–4.66)          | 0.02    | ND            | ND            |
|                | Tarsal tunnel |           | MD, 6.50 (3.56–9.44)          | <0.00001| ND            | ND            |
| Ulcer          | Intervention |           |                               |         |               |
|                | Tarsal tunnel |           | RR, 0.04 (0.00–0.48)          | 0.01    | 51.25         | 96            |
|                | Common peroneal, deep peroneal, and tarsal tunnel | 1         | RR, 0.32 (0.19–0.55)          | <0.00001| ND            | ND            |
|                | Tarsal tunnel, SN nerve transfer | 1         | RR, 0.28 (0.14–0.55)          | 0.0002  | ND            | ND            |
|                | Common peroneal and tarsal tunnel | 1         | RR, 0.14 (0.07–0.25)          | <0.00001| ND            | ND            |
| Amputation     | Intervention |           |                               |         |               |
|                | Tarsal tunnel |           | RR, 0.01 (0.00–0.35)          | 0.01    | 7.28          | 0.007         |
|                | Common peroneal, deep peroneal, and tarsal tunnel | 1         | RR, 0.01 (0.00–0.16)          | 0.001   | ND            | ND            |
|                | Tarsal tunnel and SN nerve transfer | 1         | RR, 0.05 (0.02–0.15)          | <0.00001| ND            | ND            |
|                | Common peroneal and tarsal tunnel | 1         | RR, 0.02 (0.00–0.24)          | 0.003   | ND            | ND            |

ND, non-detectable; SN, saphenous nerve.
The findings from this meta-analysis highlight the efficacy of peripheral nerve decompression among DPN patients. This was demonstrated by the significant improvement in VAS and 2PD after operation in observational studies. Further analysis of observational studies showed a significant low RR of ulcer development and amputation following intervention. On the other hand, pooled data meta-analysis of VAS, 2PD, and NCV outcomes were not significantly improved after operation in the RCT studies. This could be attributed to high heterogeneity and a limited number of RCTs included in the analysis of each outcome measure. Thus, large-scale clinical studies are needed to provide stronger evidence that would support offering this intervention to patients with DPN.

The subgroup analyses detected a tendency towards decompression of the tarsal tunnel region as the most effective procedure in reducing symptoms and complications of DPN. This is likely related to the importance of plantar sensation in preventing repeated trauma to the foot. The Dellon's approach was followed in multiple studies for decompressing the tibial nerve and its branches in the tarsal tunnel region. This included the surgical release of four tunnels: (1) tarsal tunnel, (2) medial plantar tunnel, (3) lateral plantar tunnel, and (4) calcaneal tunnel. The Hoffmann-Tinel sign was utilized as an indication for surgery in most of the studies included in this review (Tables 1, 2). A positive test was previously shown to have a 92% positive predictive value for a favorable outcome following the decompression of tarsal tunnels in DPN.55

**Limitations**

Despite the low heterogeneity shown in the outcomes of the observational studies included in our meta-analysis, RCT studies had high heterogeneity for VAS, 2PD, and NCV. This could be attributed to the limited number of articles included in the analysis of each outcome. Other RCTs were excluded from the analysis due to variability in surgical intervention or reported outcome measures. However, to control for the previously stated limitations, sensitivity analyses were conducted. The results indicated the strong reliability of the meta-analysis and the absence of publication bias for the outcomes analyzed.

**CONCLUSIONS**

The meta-analysis of observational studies in this report highlights the efficacy of lower extremity peripheral nerve decompression in reducing symptoms, ulcerations, and amputations related to DPN. Releasing the tibial nerve in the tarsal tunnel region was the most effective observed procedure. Nevertheless, high-quality RCTs are required to support the utility of this intervention in this patient population.

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