

## EFFECTIVENESS OF NEGATIVE PRESSURE WOUND THERAPY IN NEUROPATHIC DIABETIC FOOT ULCERS: AN UMBRELLA REVIEW PROTOCOL ÚČINNOST PODTLAKOVÉ LÉČBY U NEUROPATICKÝCH DIABETICKÝCH ULCERACÍ NOHY: PROTOKOL SYSTEMATICKÉHO REVIEW TYPU „UMBRELLA“

KLUGAR Miloslav<sup>1,2,3</sup>, KANTOROVÁ Lucia<sup>1,3</sup>, POKORNÁ Andrea<sup>1,2,3,4</sup>, HÁJEK Michal<sup>5,6</sup>,  
VRBOVÁ Tereza<sup>1,3</sup>, JIRKOVSKÁ Alexandra<sup>7</sup>, DUBSKÝ Michal<sup>7</sup>, FEJFAROVÁ Vladimíra<sup>7</sup>,  
JIRKOVSKÁ Jarmila<sup>8</sup>, KOLIBA Miroslav<sup>9</sup>, KUČERA Dušan<sup>10</sup>, KRAWCZYK Petr<sup>11</sup>, SIXTA Bedřich<sup>7</sup>,  
WOSKOVÁ Veronika<sup>7</sup>, FIALOVÁ Zuzana<sup>7</sup>, KLUGAROVÁ Jitka<sup>1,2,3</sup>

<sup>1</sup> České národní centrum Evidence-Based Healthcare a Knowledge Translation (Cochrane Česká republika, České CEHBC: JBI centrum excellence, GRADE centrum Masarykovy univerzity), Institut biostatistiky a analýz, Lékařská fakulta, Masarykova Univerzita, Brno, Česká republika

<sup>2</sup> Ústav zdravotnických informací a statistiky České republiky, Praha, Česká republika

<sup>3</sup> Agentura pro zdravotnický výzkum České Republiky, Praha, Česká republika

<sup>4</sup> Katedra ošetřovatelství, Lékařská fakulta, Masarykova Univerzita, Brno, Česká republika

<sup>5</sup> Centrum hyperbarické medicíny, Městská nemocnice Ostrava, Ostrava, Česká republika

<sup>6</sup> Katedra biomedicínských oborů, LF Ostravské univerzity v Ostravě, Ostrava – Vítkovice, Česká republika

<sup>7</sup> Centrum diabetologie, Institut klinické a experimentální medicíny, Praha, Česká republika

<sup>8</sup> Univerzita Karlova v Praze, 1. lékařská fakulta, Interní klinika 1. LF UK a ÚVN Praha, Praha, Česká republika

<sup>9</sup> Diabetologická a podiatrická ambulance, Vratimov, Česká republika

<sup>10</sup> Vaskulární centrum, Vítkovická nemocnice a. s., Ostrava, Česká republika

<sup>11</sup> Ústav rehabilitace, LF Ostravské univerzity v Ostravě, Ostrava – Vítkovice, Česká republika

### ABSTRACT

**Background:** Neuropathic Diabetic Foot Ulcers (DFU) is a serious complication of diabetes and can often lead to amputation. Several therapeutic methods exist, among the more novel ones being the Negative Pressure Wound Therapy (NPWT), which might be effective and relatively safe, and is being widely used.

**Objective:** The objective of this umbrella review will be to investigate the effectiveness of NPWT in neuropathic DFU.

**Inclusion criteria:** Population – the patients of all ages with diabetes suffering from chronic neuropathic non-healing wounds in the foot will be included. Intervention – negative Pressure Wound Therapy. Comparison – standard therapy (any standard care). Outcomes – standardized measures of the effectiveness of the intervention for wound healing. Only systematic reviews will be included.

**Methods:** We will follow the methodology of the Joanna Briggs Institute for umbrella reviews. We will search ten databases by Epistemonikos platform to identify any relevant systematic reviews. No language or geographical limit will be applied. Two independent reviewers will carry out screening, critical appraisal, and data extraction. Results will be presented in a tabular and narrative form, and meta-analysis will be performed. The certainty of evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

**Key words:** Negative pressure wound therapy. Non-healing ulcers. Neuropathic diabetic Foot ulcer. Meta-analysis. Umbrella review.

### ABSTRAKT

**Úvod:** Neuropatická ulcerace na nohou (DFU) je závažnou komplikací diabetu a může často vést k amputaci. Existuje

několik terapeutických metod, kdy mezi novější patří podtlaková terapie (NPWT), která se zdá být účinnou, relativně bezpečnou a poměrně široce používanou léčebnou metodou.

**Cíl:** Cílem tohoto „umbrella“ review bude zkoumat účinnost NPWT při neuropatické DFU.

**Kritéria pro zařazení:** Populace – budou zahrnuti pacienti všech věkových skupin s diabetem trpící chronickými neuropatickými nehojícími se ranami na noze. Intervence – podtlaková terapie. Srovnání – standardní terapie (jakákoli standardní péče). Výsledky – standardizovaná měření účinnosti při hojení ran. Zahrnuti budou pouze systematická review.

**Metody:** Budeme postupovat podle metodiky Joanna Briggs Institute pro „umbrella“ review. Prohlédáme deset databází platformou Epistemonikos, abychom identifikovali relevantní systematická review. Nebude použito žádné jazykové ani zeměpisné omezení. Dva nezávislí recenzenti provedou analýzu relevance, kritické hodnocení a extrakci dat. Jistota důkazů bude hodnocena pomocí přístupu GRADE (Grading of Assessment Assessment, Development, and Evaluation).

**Klíčová slova:** Podtlaková terapie. Nehojící se ulcerace. Neuropatické ulcerace s diabetickou nohou. Meta-analýza. Umbrella review.

### INTRODUCTION

Diabetic foot has a potential risk of developing pathologic conditions in the lower limb, including ulceration, infection and destruction of the deeper tissues, with its underlying neurological abnormalities, peripheral arterial disease and metabolic com-

plications [1, 2]. An ulcer is usually formed as a result of damage to the epidermis based on neuro-pathic or ischaemic changes or their combination in the area. Most of such ulcers are very hard to heal and diabetic patients have 10- to 20- fold higher risk of losing a lower limb as a result of the condition than people without diabetes [3, 4]. Moreover, recurrency of DFU is frequent (57.5 % according to one primary study) but may be amenable to targeted interventions [5].

Healing is always difficult in the diabetic foot after ulceration develops, which is a major debilitating condition affecting diabetic patients. The main treatment methods applied for the management of diabetic ulcers are ulcer debridement, infection control, and off-loading and wound contact dressings (Advanced Moist Wound Therapy). However, the overall quality of evidence to support the use of any single dressing product or the type of treatment over another is relatively low and inconclusive.

Among the relatively novel treatment options for diabetic ulcers, being developed in the 1990s, is the Negative Pressure Wound Therapy (NPWT), which is a non-invasive technique that uses a negative pressure controlled by a device. It involves the application of a wound foam dressing through which a negative pressure is applied, with wound and tissue fluid being collected into a canister [6-8]. It has been proposed as another effective alternative in treating chronic ulcers, among other types of wounds [8]. The technique's specific healing mechanisms have not been conclusively explored [9], however, generally it promotes healing by collecting exudate, reducing the frequency of dressing changes, keeping even the anatomically challenging wounds clean, and reducing odour [10].

There is evidence in primary studies and systematic reviews that suggests NPWT is effective and relatively safe to use for the healing of diabetic ulcers [10-13]. A preliminary search of Epistemonikos and PROSPERO carried out on 1 December 2020 has shown that there is a number of systematic reviews published on the topic. However, no umbrella review has been published so far. Therefore, an umbrella review is warranted and beneficial under such circumstances. The purpose of this umbrella review will be to assess the effectiveness of NPWT on the healing of neuropathic DFU compared to other types of therapy.

## REVIEW QUESTION

What is the effectiveness of Negative Pressure Wound Therapy (Intervention) compared to standard therapy (Comparison) on healing parameters (Outcomes) in patients with neuropathic diabetic foot ulcers (Population)?

## METHODS

### Inclusion criteria

*Population:* The review will include patients with neuropathic diabetic foot ulcers.

*Intervention:* The main intervention of interest in this review is the Negative Pressure Wound Therapy.

*Comparison:* All types of other standard therapies will be considered for inclusion (the best standard local care of ulcerations).

*Outcomes:* This review will consider studies that assessed parameters of wound healing in standardized ways, such as wound closure, wound size reduction, wound bed condition (the type of wound bed according to the Wound healing continuum), exudate, odour, pain, HRQoL, hyperoxia, ischemic parameters, duration of healing, complications; and amputation rate.

*Types of studies:* This umbrella review will consider systematic reviews and meta-analyses of any study designs published in any language and location.

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for Umbrella reviews [14-16].

### Search Strategy

The search strategy will aim to locate both published research syntheses. An initial limited search of Epistemonikos was undertaken to identify systematic reviews on the topic. The text words contained in the titles and abstracts of relevant systematic reviews and the index terms used to describe the articles have been used to develop a full search strategy for Epistemonikos (full search strategy: ("negative pressure therapy" OR "negative pressure wound therapy" OR NPWT) AND (ulcer\* OR wound\*) AND diabet\*). Epistemonikos is the platform by which we will search the following databases and journals: Cochrane Database of Systematic Reviews (CDSR); Pubmed Last searched; EMBASE; CINAHL (The Cumulative Index to Nursing and Allied Health Literature); PsycINFO; LILACS (Literatura Latinoamericana y del Caribe

en Ciencias de la Salud); Database of Abstracts of Reviews of Effects (DARE); The Campbell Collaboration online library; JBI Evidence Synthesis; EPPI-Centre Evidence Library. The reference list of all syntheses selected for critical appraisal will be screened for additional systematic reviews. This search strategy is optimal to identify the systematic reviews of interest [17].

### Study Selection

Following the search, all identified citations will be loaded into EndNote X9 (Clarivate Analytics, PA, USA) and duplicates will be removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant papers will be retrieved in full and their citation details imported into the Joanna Briggs Institute's System for the Unified Management, Assessment and Review of Information (JBI SUMARI; The Joanna Briggs Institute, Adelaide, Australia) [18]. The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for excluding full-text articles that do not meet the inclusion criteria will be recorded and reported in the umbrella review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer. The search results will be reported in full in the final report and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram [19].

### Assessment of Methodological Quality

Eligible syntheses will be critically appraised by two independent reviewers for methodological quality using the standardized critical appraisal instrument from the Joanna Briggs Institute [18]. In case of missing or additional data for clarification, the authors of screened papers will be contacted. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in a narrative form and a table.

Following the critical appraisal, syntheses that do not meet a quality threshold will be excluded. The decision to include a review will be based on a cut-off value of 4. Reviews with scores 0 – 3 will be considered to be of a very low-quality; moreover, 4 – 6 will be considered a low-quality score; 7 – 9

will be considered a moderate-quality score; and 10 – 11 will be considered a high-quality score.

### Data Extraction

Data will be extracted from syntheses included in the review by two independent reviewers using the standardized Joanna Briggs Institute data extraction tool in JBI SUMARI [18]. Authors of screened papers will be contacted to request missing or additional data where required.

### Data Summary

The data extracted from the selected reviews will be tabulated and accompanied by narrative synthesis to address the review objective. The number of studies that inform the outcome, the number of participants (from included studies), and the heterogeneity of the results of included reviews will be reported. Additionally, overlaps of original research studies in each of the included research syntheses will also be clearly indicated. In other words, the studies that are included in multiple syntheses will be clearly noted.

JBI SUMARI and RevMan v5.3 (Copenhagen, The Nordic Cochrane Centre, Cochrane) will be used if meta-analyses are possible. Results of the meta-analysis will be provided in risk ratio for studies with dichotomous data and mean difference for studies with continuous data. Confidence intervals (95%) will also be provided. Statistical heterogeneity of the meta-analysis will also be evaluated by means of the  $I^2$  statistic. If the meta-analysis presents high statistical heterogeneity, the random-effects model will be used; if the meta-analysis presents low statistical heterogeneity, the fixed effects model will be used. For meta-analysis with high statistical heterogeneity, sensitivity analysis will be performed, removing studies one by one, repeating the calculations to check for similar results, and determining the possible influence of each study.

Where statistical pooling is not possible, the findings will be presented in a narrative form that includes tables and figures to aid in data presentation, where appropriate. The influence of the quality of included reviews on the results will be explored by sensitivity analyses where studies of lower quality will be analysed separately from those of moderate and high quality as is explained above.

The findings of the umbrella review will be provided in a tabular form in a "Summary of Evidence" table. This table will include the intervention name,

the included systematic review(s), and a simple, visual indication of the results. Green will indicate the intervention is beneficial (effective), amber that there is no difference in the investigated comparison, and red that the results suggest the intervention is detrimental or less effective than the comparator.

### Assessing certainty in the findings

The certainty of the evidence will be determined using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, and a Summary of Findings (SoF) will be created using GRADEpro (McMaster University, ON, Canada). [20] For the outcomes assessed, GRADE evaluates the number of studies incorporated into the analysis, studies' design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. For the risk of bias, inconsistency, indirectness, imprecision, and publication bias, the certainty of the evidence may be downgraded one or two levels. Based on this evaluation, the certainty of the evidence for each outcome may be very low, low, moderate, or high.

### Conflict of interest

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study. Here is an only intellectual conflict of interest regarding affiliation of Dr Klugar, Prof. Pokorná, Dr Kantorová and Dr Klugarová to the Cochrane Czech Republic, Czech Republic Centre for Evidence-Based Healthcare: The Joanna Briggs Institute Centre of Excellence and Masaryk University GRADE Centre.

### Funding

Work on this paper was supported by the project entitled "Clinical Practice Guidelines" with registration number CZ.03.2.63/0.0/0.0/15\_039/0008221 led by the Czech Health Research Council and in partnership with the Ministry of Health of the Czech Republic and the Institute of Health Information and Statistics of the Czech Republic and a grant number LTC20031 – "Towards an International Network for Evidence-based Research in Clinical Health Research in the Czech Republic". The funder had no involvement and did not influence the research.

### REFERENCES:

- [1] NEWRICK P. *International consensus on the diabetic foot*. 2000, British Medical Journal Publishing Group. p. 642.
- [2] APELQVIST J., WILLY C., FAGERDAHL A. et al. Negative Pressure Wound Therapy—overview, challenges and perspectives. *J Wound Care*. 2017; 26 (Suppl 3): S1-S113.
- [3] MORRIS A.D., MCALPINE R., STEINKE D. et al. Diabetes and lower-limb amputations in the community: a retrospective cohort study. *Diabetes Care*. 1998; 21 (5): 738-743.
- [4] WROBEL J.S., MAYFIELD J.A., REIBER G.E. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. *Diabetes care*. 2001; 24 (5): 860-864.
- [5] DUBSKÝ M., JIRKOVSKÁ A., BEM R. et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. *International wound journal*. 2013; 10 (5): 555-561.
- [6] BORYS S., LUDWIG-SLOMCZYNSKA A.H., SEWERYN M. et al. Negative pressure wound therapy in the treatment of diabetic foot ulcers may be mediated through differential gene expression. *Acta Diabetologica*. 2019; 56 (1): 115-120.
- [7] LIU S., HE C.Z., CAI Y.T. et al. Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis. *Therapeutics and clinical risk management*. 2017; 13: 533-544.
- [8] BLUME P.A., WALTERS J., PAYNE W. et al. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multi-center randomized controlled trial. *Diabetes care*. 2008; 31 (4): 631-636.
- [9] GLASS G., MURPHY G., ESMAEILI A. et al. Systematic review of molecular mechanism of action of negative-pressure wound therapy. *British Journal of Surgery*. 2014; 101 (13): 1627-1636.
- [10] DUMVILLE J.C., WEBSTER J., EVANS D. et al. Negative pressure wound therapy for treating pressure ulcers. *Cochrane Database of Systematic Reviews*. 2015 (5).
- [11] GAME F., HINCHLIFFE R., APELQVIS J. et al. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes/ metabolism research and reviews*. 2012; 28: 119-141.
- [12] XIE X., MCGREGOR M., DENDUKURI N. The clinical effectiveness of negative pressure wound therapy: a systematic review. *Journal of wound care*. 2010; 19 (11): 490-495.
- [13] VIKATMAA P., JUUTILAINEN V., KUUKASJÄRVI P. et al. Negative pressure wound

- therapy: a systematic review on effectiveness and safety. *European Journal of Vascular and Endovascular Surgery*. 2008; 36 (4): 438-448.
- [14] JBI. *Joanna Briggs Institute Reviewers' Manual: 2017 edition*. 2017, The University of Adelaide, South Australia: The Joanna Briggs Institute.
- [15] KLUGAROVA J., KLUGAR M., MARECKOVA J. et al. Methodology of systematic review development I: The effectiveness of hyperbaric oxygen therapy on mortality in adults with craniotrauma. *Ceska a Slovenska Neurologie a Neurochirurgie*. 2015; 78( 5): 555-561.
- [16] KLUGAR M., KLUGAROVÁ J. Using evidence synthesis and clinical practice guidelines in everyday decision-making process: is it real or a dream? *International journal of evidence-based healthcare*. 2019; 17: S1-S2.
- [17] GOOSSEN K., HESS S., LUNNY C. et al. Database combinations to retrieve systematic reviews in overviews of reviews: a methodological study. *BMC Med Res Methodol*. 2020; 20 (1): 138.
- [18] MUNN Z., AROMATARIS E., TUFANARU C. et al. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). *International journal of evidence-based healthcare*. 2019; 17 (1): 36-43.
- [19] MOHER D., LIBERATI A., TETZLAFF J. et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med*. 2009; 6 (7): e1000097.
- [20] GUYATT G.H., OXMAN A.D., SCHÜNEMAN H.J et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of clinical epidemiology*. 2011; 64 (4): 380-382.