Acta Diabetologica
https://doi.org/10.1007/s00592-024-02353-7

REVIEW ARTICLE

Prevention of foot ulcers recurrence in patients with diabetes: a systematic review and meta-analysis of randomized controlled trials for the development of the italian guidelines for the treatment of diabetic foot syndrome

Roberto Da Ros[1,12] · Antonio Volpe[2] · Corrado Bordieri[3] · Rodolfo Tramonta[4] · Andrea Bernetti[5] · Alessia Scatena[6] · Luca Monge[7] · Benedetta Ragghianti[8] · Antonio Silverii[8] · Luigi Uccioli[9] · Cristiana Vermigli[10] · Matteo Monami[8] · Cesare Miranda[11] · for the Panel of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome and on behalf of SID and AMD

Received: 7 April 2024 / Accepted: 5 August 2024

Abstract

Aim To compare the effectiveness of preventive interventions in reducing reccurrent diabetic foot ulcers. Meta-analysis (MA) was conducted to address clinical questions on this topic of the Italian guidelines on diabetic foot.

Methods This MA includes randomized controlled trials evaluating the effectiveness of various preventive interventions, namely: treatment of pre-ulcerative foot lesions, structured educational programs, psychological interventions and the use of therapeutic footwear to relieve plantar pressure in people with diabetes mellitus and a history of previous ulcers.

Results A total of 731 studies were identified and 14 were considered eligible for the analysis. We found that treatments of pre-ulcerative foot lesions did not provide any statistically significant effects (MH-OR: 0.84 [0.31, 2.33], $p = 0.74$, $I^2 = 38\%$). Conversely, structured educational programs were associated with a trend toward reduction of ulcer recurrence risk (MH-OR: 0.13 [0.01, 1.64], $p = 0.10$, $I^2 = 88\%$). No randomized controlled studies assessing the efficacy of psychological interventions have been retrieved. The use of therapeutic footwears can effectively reduce the risk of reulceration in diabetic patients with an history of previous DFU, in particular prefabricated rigid-soled therapeutic footwears showed a significant reduction of the risk of ulcer recurrence in comparison with semirigid soles (MH-OR: 0.17 [0.05, 0.57], $p = 0.004$).

Conclusions The study provides low-certainty evidence that, among preventive strategies in patients with previous DFU, rigid-sole therapeutic footwear and structured education programs are capable of reducing the risk of foot re-ulceration.

Keywords Diabetes mellitus · Ulcer recurrence · Prevention · Diabetic foot syndrome

Managed by Annunziata Lapolla.

✉ Roberto Da Ros
roberto.daros@asugi.sanita.fvg.it

1 Azienda Sanitaria Universitaria Giuliana Isontina, Monfalcone, Italy

2 Policlinico Abano Terme, Padua, Italy

3 Universita Cattolica del Sacro Cuore Di Roma, Rome, Italy

4 Civitavecchia, Italy

5 Università del Salento, Lecce, Italy

6 Ospedale San Donato, Arezzo, Italy

7 AMD Italian Association of Clinical Diabetologists, Rome, Italy

8 Azienda Ospedaliero Universitaria Careggi and University of Florence, Florence, Italy

9 SE/CTO Hospitals ASL Roma2, University of Rome Tor Vergata, Rome, Italy

10 Azienda Ospedaliera Santa Maria Della Misericordia, Ospedale Di Perugia, Perugia, Italy

11 Pordenone Hospital, Pordenone, Italy

12 ASUGI Monfalcone-Gorizia, Trieste, Italy

Published online: 05 September 2024

Introduction

Diabetic foot ulcers (DFUs) are a serious complication of diabetes mellitus affecting more than 18 million of patients worldwide [1] with an expected rate of about 30% of patients experiencing at least one foot ulcer in their lifetime [2]. Unfortunately, even after the resolution of an ulcer, patients with diabetes continue to be at very high risk for ulcer recurrence, which is very common, with a proportion ranging from 40 to 65% within subsequent five years [3]. Recurrence rates varied across different Countries (per patient-years rate: 16.9%in Africa, 17.0% in Asia, 17.8% in North America, and 24.9% in Europe [4].

Despite these regional differences, ulcer recurrence is very common and led the scientic community to reconsider the term "healing" that should be probably replaced with "remission" [5].

This change of terminology is not only a semantic issue, but a way for rethinking DFU organizing models with an adequate allocation of resources and actions aimed at providing educational programs for reducing that risk.

Reasons for ulcer recurrence are multifactorial and often both biologic and behavioral. Several factors are well-known, not adequately managed by physicians, such as peripheral neuropathy, foot deformities, plantar stress, and peripheral arterial disease [6].

Other factors increasing the risk of ulcer recurrence can depend from erroneous patients' attitudes, such as the underestimation of warning symptoms (e.g. pain, bleedings, etc.), the lack of appropriate preventive measures (e.g. prescribed footwear, walk barefoot, follow-up podiatric care, etc.) [7], the presence of depressive symptoms not adequately treated [8], or other more common risk factors for incident DFU, such as hypertension, renal impairment, elevated glycated hemoglobin, decreased total protein levels, duration of diabetes, etc. [9–11].

The prevention of recurrent diabetic foot ulcers is crucial to reduce the risk of lower limb amputations and improve the quality of life for diabetic patients, but ulcer prevention remains a neglected opportunity [12]. Several preventive interventions can be adopted to reduce that risk, such as intregrated foot care with structured education programs, pre-ulcerative foot lesions treatment, psychological interventions, and use of therapeutic footwear for plantar pressure relief [13].

The present meta-analysis, aims to provide a comprehensive review of preventive care, including the different types of interventions for the prevention of recurrence foot ulcers, was performed in the process of developing the Italian guidelines for the treatment of Diabetic Foot Syndrome (DFS). These guidelines, which have been promoted by the Italian Society of Diabetology (Società Italiana di Diabetologia, SID) and the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD), are being developed for the inclusion in the Italian National Guideline System (INGS), designed as a standard reference for clinical practice in Italy, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method [14].

The paper will therefore evaluate and compare, whenever possible, the effectiveness and safety of different types of interventions to prevent recurrence foot ulceration, which we grouped as follows: (1) treating pre-ulcerative lesions, (2) structured education programs, (3) psychological interventions (4) footwear with semi-rigid soles or rigid soles. This meta-analysis has been performed to try to give an answer to several clinical questions PICOs (Population Intervention Comparator Outcomes) already specified elsewhere [15].

Methods

We conducted this systematic review in conformity with PRISMA checklist [16] (Table S1) and following a protocol previously published [15].

Search strategy and selection criteria

This meta-analysis is a part of a wider meta-analysis of studies on DFS conducted for the development of the Italian Guidelines on the Treatment of Diabetic Foot Syndrome [15]. The present analysis includes all RCTs, with a duration of at least 26 weeks, who enrolled diabetic patients or reporting subgroup analyses on diabetic with an history of diabetic foot ulcer, but without an active ulcer at the enrollment, comparing different prevention strategies (i.e., pre-ulcerative foot lesions treatment, structured education, psychological interventions, therapeutic footwear with a semirigid or rigid sole). Prevention strategies were defined as interventions performed with the aim of preventing foot ulcers recurrence. The search strategy had been already published elsewhere; [15] briefly, the search string used was: ulcer AND foot AND diabetes. Detailed information on search strategy is reported in Table S2.

No language or date restriction was imposed. A Medline and Embase search were performed up to December 1st, 2023. Further studies were manually searched for in references from retrieved papers.

Two independent reviewers (R.D.R. and C.M.) screened all titles and abstracts of the identified studies for inclusion. Discrepancies were resolved by a third, independent reviewer (M.M.).

Data extraction and collection

Variables of interest were minor and major amputation rate, ulcer recurrence, new ulcers, ulcer-free days, patients' adherence, quality of life, any serious adverse events, previously decided (after voting) by the panel of the Italian Guidelines for the treatment of DFS [15].

Data extraction was performed independently by two of the authors (R.D.R. and C.M.), and conflicts resolved by a third investigator (M.M.).

Titles and abstracts were screened independently by the authors, and potentially relevant articles retrieved in full text. For all published trials, results reported in published papers and supplements were used as the primary source of information. When the required information on protocol or outcomes was not available in the main or secondary publications, an attempt at retrieval was performed consulting the clinicaltrials.gov website.

The risk of bias in RCTs was assessed using the Cochrane recommended tool [17], which includes seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The results of these domains were graded as 'low' risk of bias, 'high' risk of bias, or 'uncertain' risk of bias.

Interventions

Question 1: removing callus, treating haemorrhagic callus, protecting blisters, and draining when necessary, or treating dry skin fissures and cracks not extending into the dermis were considered treatments of pre-ulcerative foot lesions.

Question 2: one-to-one verbal education, group education sessions, video education, e-learning platforms were considered "structured education".

Question 3: we included all RCT exploring any psychological interventions: individual or group psychological, behavioral or social intervention alone or in combination (eg CBT; cognitive therapy; psychodynamic therapy; counselling; family systems or systemic therapy).

Question 4: we included all RCT assessing footwear with semi-rigid soles or rigid soles in comparison with traditional footwear. We considered as therapeutic footwear any type of footwear with a therapeutic effect that cannot be provided by a conventional shoe (eg: custom-made shoes or sandals, custom-made insoles, extra-depth shoes, and custom-made or prefabricated medical-grade footwear etc.) [18].

Endpoints

The primary endpoint was ulcer recurrence (defined as an ulcer occuring on the same foot and at the same site of a previously healed ulcer) [19].

Secondary endpoints were new ulcers (defined as a new ulcer appearing on any other site on the same foot or at any site on the contralateral foot) [19], ulcer-free days (defined as days a person lives without a foot ulcer) [20], patient's adherence (any tool), minor (below the ankle amputation) and major (above the ankle) amputation, quality of life (any tool), and any serious adverse events (SAE during follow-up).

Statistical analyses

Heterogeneity was assessed by I^2 test, whereas Funnel plots were used to detect publication bias for principal endpoints with at least 10 trials.

If data from more than one study on a given outcome were available, a meta-analysis using a random-effects model as the primary analysis was performed. Mantel-Haenzel Odds ratios and 95% confidence intervals (MH-OR, 95% CIs) were either calculated or extracted directly from the publications. Weighted mean differences (WMD) and 95% CIs were calculated for continuous variables.

Sensitivity analysis removing one study at a time for the primary endpoint and secondary endpoints will be performed only if a heterogeneity-related bias can be completely ruled out.

Separate analyses were performed for the primary endpoint for the study duration ($\geq$ or $<$ the median value).

All analyses were performed using Review Manager (RevMan), Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology [14],was used to assess the quality of the body of retrieved evidence, using the GRADEpro GDT software (GRADEpro Guideline Development Tool. McMaster University, 201,526. Available from gradepro.org).

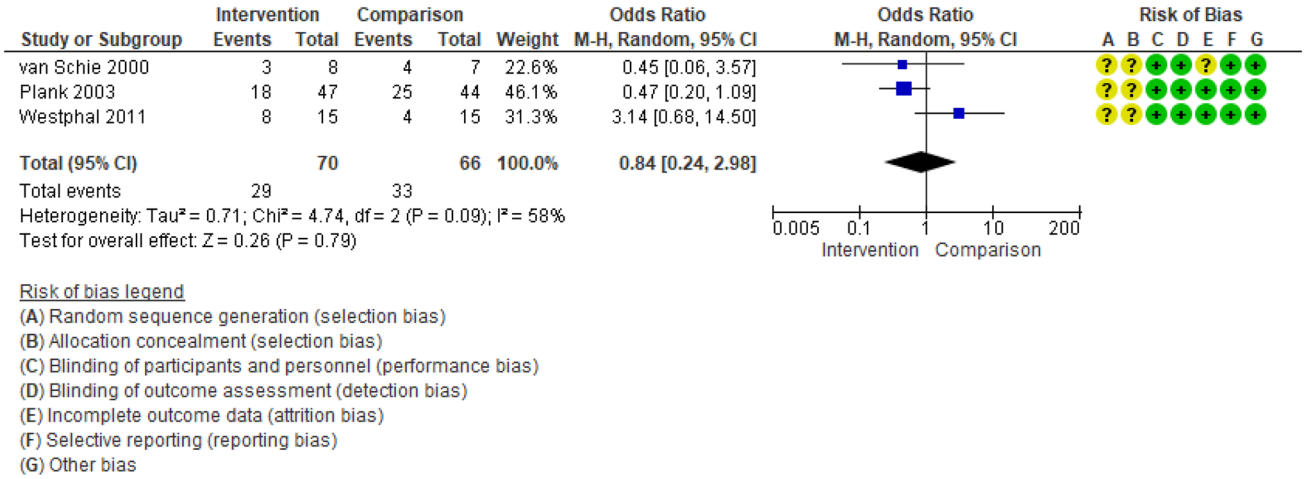
RESULTS

Retrieved trials

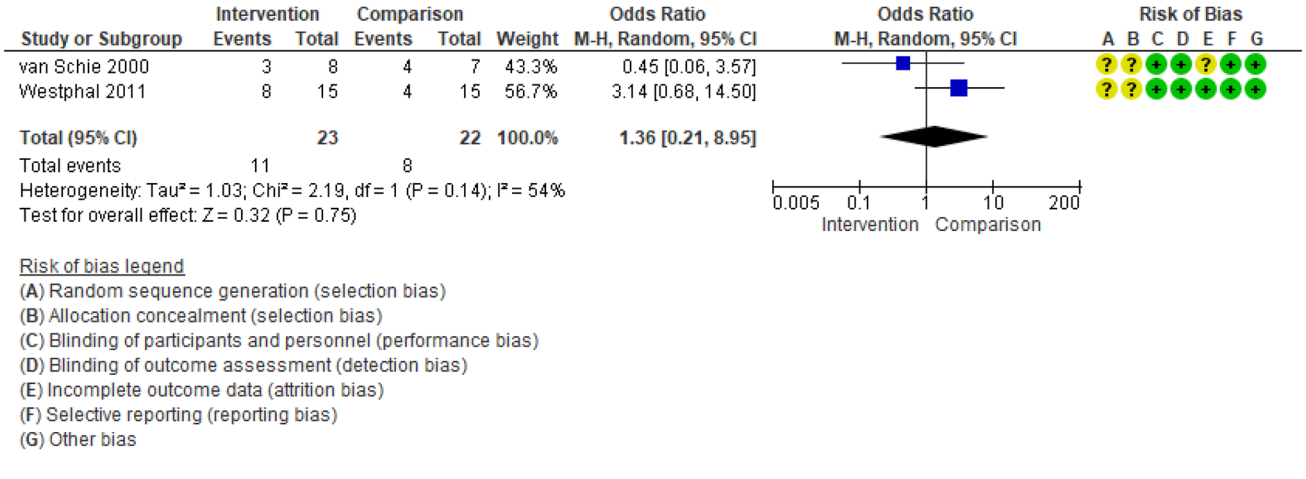
The study flow summary is reported in Fig. 1S of Supporting Information.

Out of 782 items retrieved, 731 were excluded after reading titles and/or abstracts and further 37 were excluded after

Panel A



Panel B



Panel C

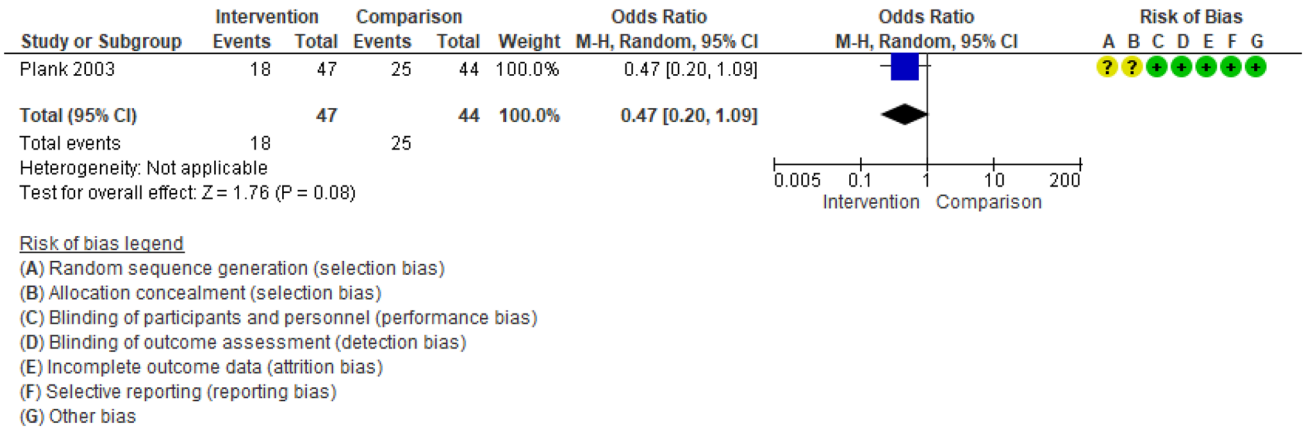


Fig. 1 Effects of preulcerative foot lesions treatment on ulcer recurrence at the endpoint in comparison with standard of care (Panel **A**: any strategies; Panel **B**: injected liquid silicone/gel silicone sheet; Panel C: chiropodist)

reading the full-text (Table 3S). We therefore included 3 [21–23], 5 [24–28], 0, and 6 [29–34], RCTs in the present meta-analysis for question 1, 2, 3, and 4, respectively.

The principal characteristics of the fourteen included studies are reported in Table S4 of Supporting Information.

The quality of studies was heterogeneous and relatively low; all studies were open-label (Fig. 2S and 3S of Supporting Information).

Question 1 – In diabetic patients with previous foot ulcers, is preulcerative foot lesions treatment preferable to no therapy, to prevent ulcers recurrence?

The mean age, proportion of women, and study duration of the 3 trials [21–23], fulfilling all the inclusion criteria was 60 years, 25%, and 52 weeks, respectively. The studies included in the analyses enrolled 176 patients with previous DFU (89 and 87 in the intervention and control group, respectively). The yearly ulcer recurrence rate was 36.0%.

All trials reported data on ulcer recurrence rate showing a non-significant between group difference (any strategies vs. SoC: MH-OR: 0.84 [0.24, 2.98], p = 0.26, $I^2 = 58\%$). When analyzing separately each individual preventing strategies, a non significant trent toward reduction of ulcer recurrence risk was observed for the only one trial [21], comparing chiropodist care vs. standard of care (Fig. 1, Panel C). Insignificant differences were observed for trials [21, 22] using either silicone gel sheets or injected liquid silicone (Fig. 1, Panel A and B).

Major amputation rate was reported for all trials. Only three cases were observed during follow-up (two and one in the interventional and control groups, respectively) [21] with a MH-OR of 1.91 [0.17, 21.85], p = 0.60. Only two studies, all with silicone [22, 23], reported two serious adverse events, all occurred in the control group [22] (MH-OR: 0.13 [0.01, 3.24], p = 0.21). Two studies [21, 23] reported information on all-cause mortality, with 6 deaths [21] (two and four in the intervention and control groups, respectively; MH-OR: 0.44 [0.08, 2.56], p = 0.26). No study reported information either on new ulcerations (in different foot sites) or quality of life/patients' adherence (all pre-planned secondary endpoints [15].

For the primary endpoint, (GRADE) methodology was used to assess the quality of the body of retrieved evidence, which was rated as "very low".

Question 2– In diabetic patients with previous foot ulcers, is structured education provided by diabetic foot units preferable to standard of care to prevent ulcers recurrence?

The mean age, proportion of women, and study duration of the 5 RCTs [24–28] included was 62 years, 38%, and 56 weeks, respectively. The studies included in the analyses enrolled 488 patients with previous DFU (229 and 259 in the intervention and control groups, respectively). Three studies reported information about the primary outcome (ulcer recurrence; n = 235 patients; 446 patient*years). The number of patients with an ulcer recurrence was 99. The yearly ulcer recurrence rate was 22.2%.

Structured education program was associated with a trend toward reduction of the risk of ulcer recurrence (MH-OR: 0.13 [0.01, 1.64], p = 0.10, $I^2 = 88\%$; Fig. 2, panel A). Information on new ulcerations was reported in two studies [24, 25] with insignificant between-group differences (MH-OR: 1.06 [0.60, 1.85], p = 0.85; Fig. 4S).

Two (one case for each group [26]) and sixteen cases (8 cases for each group) [26, 27, 35] of major and minor amputation were reported, respectively. Minor amputation risk was not different between the intervention and control group (MH-OR 0.97 [035,2.73], p = 0.96; Fig. 5S). Three studies [26–28] reported information on all-cause mortality, with 7 deaths (MH-OR: 1.44 [0.30, 6.85], p = 0.65 for intervention vs. control group; Fig. 6S).

No studies reported information on SAE. Quality of life was reported in only two studies [26, 27] adopting different tools preventing a formal meta-analysis. Both the two studies did not observ any significantly between-group differences at the end of follow-up [26, 27].

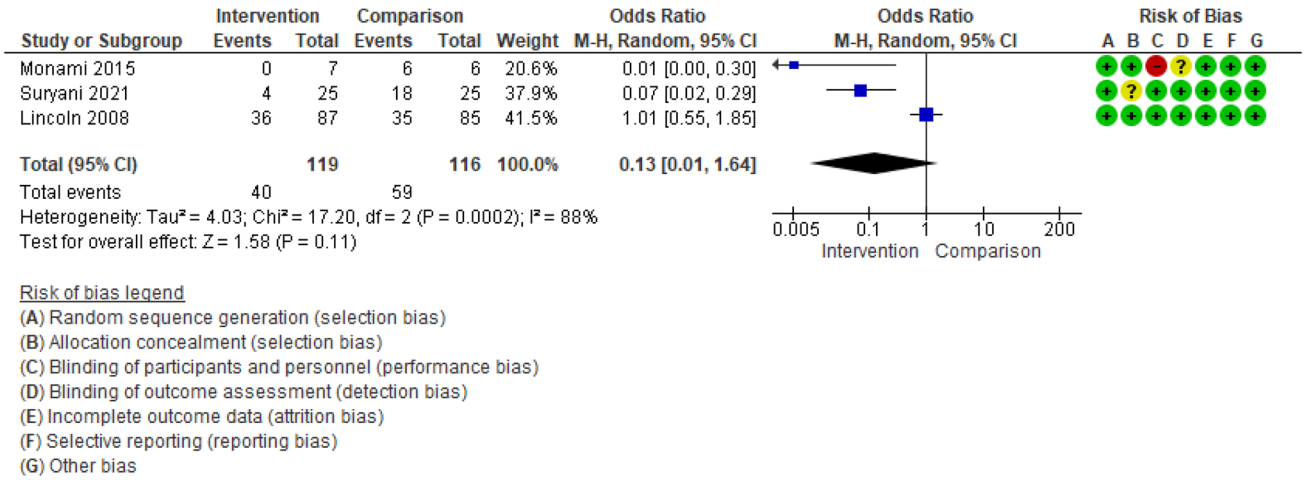
For the primary endpoint, (GRADE) methodology was used to assess the quality of the body of retrieved evidence, which was rated as "very low".

Question 3– In diabetic patients with a previous foot ulcer, is psychological intervention preferable to standard of care to prevent ulcers recurrence?

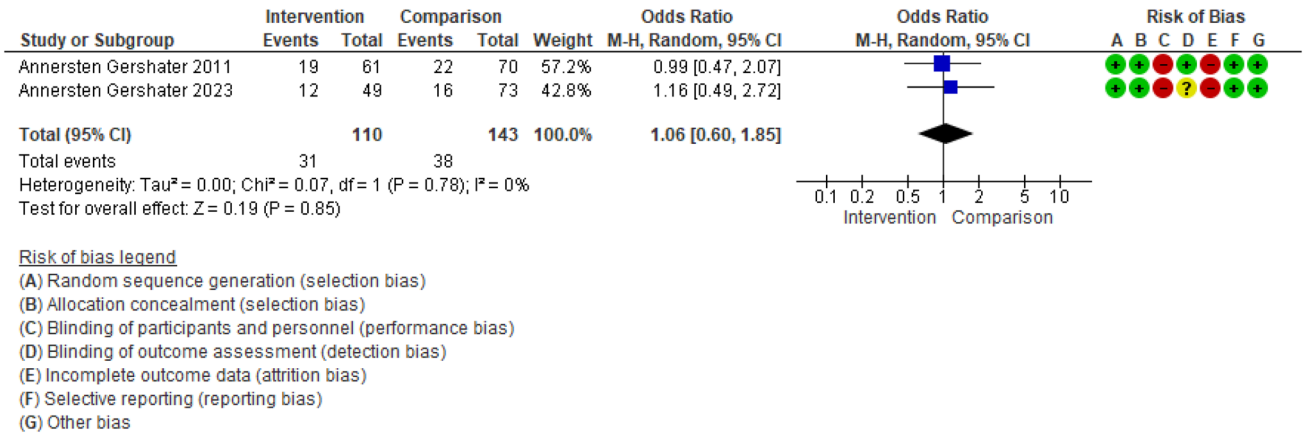
No studies fulfilling the inclusion criteria have been retrieved and therefore no recommendations can be provided for this clinical question.

Question 4 – In diabetic patients with previous plantar foot ulcers, is the use of a therapeutic footwear with a semi-rigid rocker sole or rigid rocker sole preferable to standard of care footwear to prevent ulcers recurrence?

Panel A



Panel B



Panel C

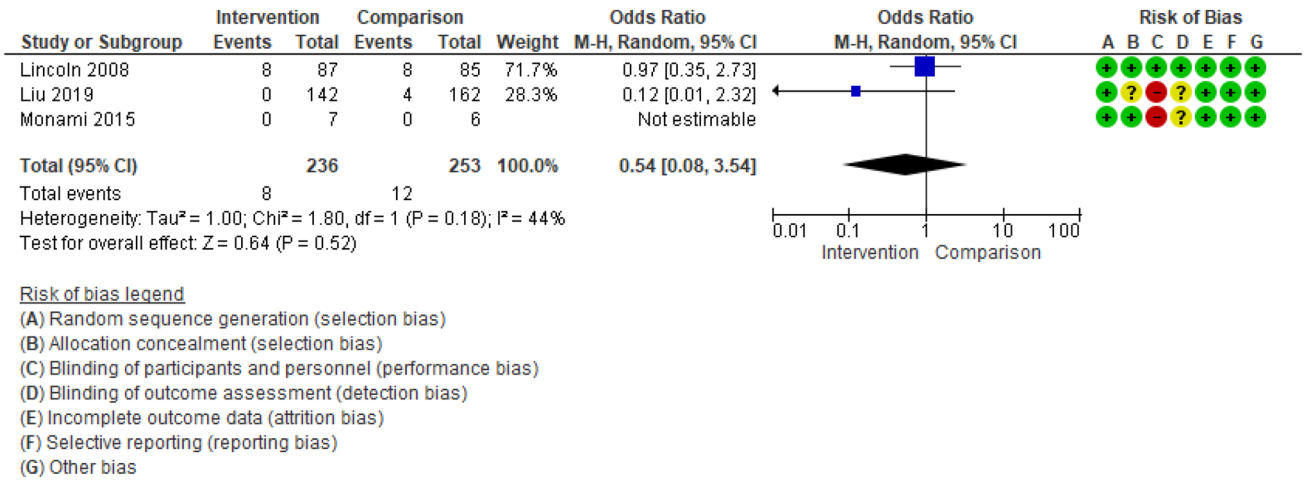


Fig. 2 Effects of structured educational programs on ulcer recurrence (Panel **A**), new ulcers (Panel **B**), and major amputation (Panel **C**) at the endpoint in comparison with standard of care

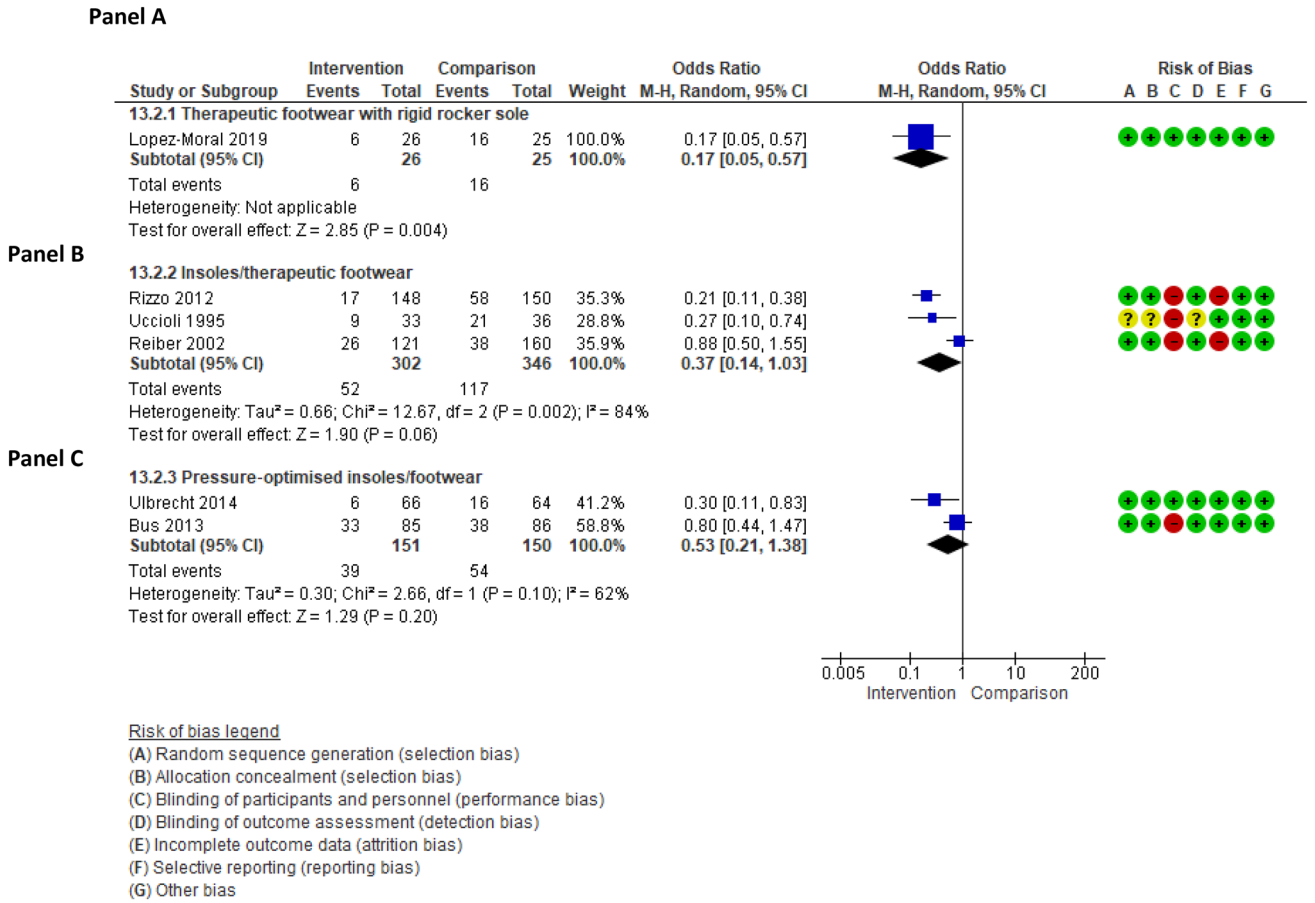


Fig. 3 Effects of pressure relief on ulcer recurrence (Panel A: Therapeutic footwear with rigid rocker sole versus therapeutic footwear with semirigid sole; Panel **B**: Insoles/therapeutic footwear versus own footwear; Panel **C**: Pressure-optimised insoles/footwear versus standard therapeutic insoles/footwear)

The six studies [29, 34] included in the analyses adopted different insoles/therapeutic footwear and compared with different active comparator/standard of care and we therefore decided to divide them in three different subgroups:

1) Insoles/therapeutic footwear pre-fabricated versus own footwear (no therapeutic footwear) [31–33];

2) Pressure-optimised insoles/footwear (custom-made footwear or standardized double extra depth footwear) versus standard therapeutic insoles/footwear [29, 34];

3) Therapeutic footwear with rigid sole versus therapeutic footwear with semirigid sole [30];

All studies reported information on ulcer recurrence (Fig. 3). In the first subgroup [31–33], the intervention was associated with a statistical trend toward reduction of ulcer recurrence (MH-OR: 0.37 [0.14, 1.03], p = 0.06). No statistical between-group differences were observed in the second group (MH-OR: 0.53 [0.21, 1.38], p = 0.20 [29, 34], whereas the use of therapeutic footwear with rigid sole (only one trial) showed a significant reduction of the risk of ulcer recurrence in comparison with semirigid sole (MH-OR: 0.17 [0.05, 0.57], p = 0.004) [30].

All-cause mortality was reported in few studies [29, 31, 34] with no statistical differences between intervention and control group (Fig. 7S).

No studies reported information on either amputation rate or ulcer-free survival (some studies reported only median values without interquartiles ranges preventing any formal meta-analyses[29, 30, 33, 34]). No information on SAE and QoL was available for any of the included studies, with the exception of two trials on the second subgroup [29, 34] using different questionnaires and observing no endpoint between-group differences.

For the primary endpoint, (GRADE) methodology was used to assess the quality of the body of retrieved evidence, which was rated as "very low".

Discussion

Ulcer recurrence represents one of the most common event in the management of diabetic foot syndrome. Prevention of recurrent DFUs is essential to reduce the risk of lower

limb amputations, to improve the quality of life of people with diabetes and to reduce the economic burden on national healthcare systems.

In recent years, several preventive interventions have been proposed, such as foot care integrated with structured education programs, treatment of pre-ulcerative foot lesions, psychological interventions and the use of therapeutic footwears to relieve plantar pressure[13].

There are many systematic reviews and meta-analyses[13, 36–39] on the effectiveness of these interventions. Unfortunately, most of these papers are affected by numerous biases, thus providing not fully reliable results for decision making processes [40].

We conducted a systematic review and meta-analysis of randomized control trials to evaluate the effectiveness of several interventions, commonly adopted to prevent diabetic foot recurrent ulcers. The panelists of the Italian Guidelines for the Treatment of DFS identified a series of clinical questions and possible interventions [15] using the PICO conceptual framework. Other PICOs, possibly of interest for preventing DFU reccurence, such as self-monitoring foot skin temperature, have been rejected by the panel of experts according to the Delphy methodology [41], already adopted by other published clinical guidelines and consensus [42, 43].

Our meta-analysis seems to suggest that treatment of pre-ulcerative foot lesions is unable to reduce DFU recurrence. In particular, the use of silicone gel sheets or injected liquid silicone are not effective in preventing recurrence, while pedicure care shows a non significant trend toward reduction of the risk of recurrent ulcers. However, the paucity and the scarce quality of retrieved studies strongly reduce the relaiability of these analyses and the strength of clinical recommendations. There are, in fact, only one trial [21] and few observational studies suggesting the effectiveness of regular callus removal in order to relieve plantar foot pressure and the subsequent risk of incident foot ulcers [44, 45]. Similarly, few evidence has been retrieved on other strategies, such as the use of silicone devices or topical antifungal nail lacquer [22, 23, 46, 47], showing trivial effects on the incidence of DFU recurrence.

Previous systematic reviews and meta-analyses assessing the effectiveness of structured education programs provided inconclusive results due to the inclusion of few heterogenous studies (i.e. inclusion of patients either with previous ulcers/high risk or low/moderate risk with no subgroup analyses) [13, 37–39]. We limited our meta-analysis only to trials performed on patients with previous DFU, also retrieving two further recently published RCTs [24, 28] in comparison with previous articles [13, 37]. For trials enrolling both primary and secondary prevention cohorts, we tried to retrieve information from the authors of included RCTs on subgroup analyses (i.e., data for patients with previous DFU only). Moreover, differently from other meta-analyses [13, 37], we considered only recurrent ulcers defined as ulcers occured on the same foot and at the same site of a previously healed ulcer. In fact, van Netten and colleagues [37], considered new and recurrent ulcers together (e.g. as done for Gershater et al.'s study [25]) possibly generating distortions in the obtained results.

We were therefore able to perform a formal meta-analysis on some outcomes, such as ulcer recurrence rate (primary outcome), only among patients with previous DFU, finding a trend toward reduction of DFU recurrence rate in patients allocated to structured education programs arm. Despite a limited number of low-quality studies included, we could provide a clinical judgment on the efficacy of education programs as preventive strategy.

Unfortunately, no trials have been retrieved on the possible effectiveness of psychological interventions as preventing strategy in patients with previous DFU. Psycological features are well-know risk factors for incident DFU both in patients with [8] and without [48–50] previous ulcers In fact, depressive symptoms may reduce adherence to prescribed diabetes care, impairing metabolic control [51] and lowering compliance to prescribed foot care (wound dressing, hygiene, etc.). Depression can also have several direct effects on blood pressure, catecholamine secretion [52], platelet function [52], and immune status [53]. The lack of RCTs on the effects of antidepressive pharmacological or nonpharmacological interventions did not allow any formal clinical recommendation on this point.

The present metanalysis also considered therapeutic footwears either with or without semi-rigid/rigid soles as preventing strategy in patients with previous DFU. We included three distinct categories: prefabricated therapeutic insole/footwear versus own footwear, pressure-optimized insoles/footwear (custom-made footwear or standardized double extra depth footwear) versus therapeutic insoles/footwear standard, rigid soled therapeutic prefabricated footwear versus semi-rigid soled therapeutic footwear from each other. Previous meta-analyses [13, 36, 37] on this topic reported heterogeneous results depending from the different inclusion criteria and different footwear and orthotic interventions subgroups considered. In the present paper, as stated above, we decided to restrict analyses only to patients with previous DFU and to limit footwear and insole subgroups only to three distinct categories. Our meta-analysis showed that the use of prefabricated insoles/therapeutic footwears compared to standard footwears reduces the risk of recurrent ulcers. In particular, the use of prefabricated footwear wtih rigid soles seem to confere a higher protection in reducing the risk of ulcer recurrence in comparison with semi-rigid soles. On the other hand, pressure-optimized insoles/footwear (custom-made footwear or standardized double extra depth footwear)

compared to standard therapeutic insoles/footwears did not significantly reduce the risk of recurrent ulcers.

Furthermore, according to Rizzo, the use of prefabricated therapeutic insole/footwear made it possible to avoid approximately 55 ulcers in 12 months with a net saving of €107,505 per year [32]. These results, despite of interest, deserve to be confirmed in further RCTs adequately sized and with longer follow-up.

Several limitations, possibly affecting the reliability of the results obtained, should be recognized. For all items the GRADE of evidence was low or very low due to the inclusion of low-quality studies. The overall quality of a meta-analysis strongly depends on the quality of included studies. Moreover, the majority of the outcomes considered in this paper are affected by considerably high heterogeneity, which has not been adequately explored due to an insufficient number of retrieved RCTs. These concerns could theoretically affect and alter some of the obtained results, suggesting therefore caution in interpreting the overall clinical messages. However, this is the first attempt, for many of the PICO considered, to summarize the existing literature on the principal preventing strategies in patients with an history of DFU in comparison with other meta-analithic publications [13, 36, 54, 55].

Conclusions

In conclusion, to prevenent the burden of recurrent DFUs, we have few possible strategies, mainly represented by patient education and therapeutic footwears/insoles.

In this systematic review and meta-analysis, we found evidence with low- certainty that the use of therapeutic footwear, particularly rigid-soled therapeutic footwears (moderate certainty), can effectively reduce the risk of reulceration in diabetic patients with an history of previous DFU. Furthermore, we found very low-certainty evidence that structured education programs could be of help in preventing reulceration (despite not achieving fully statistical significance).

The overall take-home message of the present systematic review and meta-analysis, performed to develop the first Italian guidelines for the treatment of DFS, is the urgent need of adequately sized high-quality RCTs to strengthen the clinical recommendations for preventing DFU recurrence.

Last but not least, the high relapse rate [56] confirms the need for continuous surveillance of healed patients by multidisciplinary teams (possibly led by diabetologists [57]) to further reduce the risk of recurrent ulcers.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00592-024-02353-7.

Author contributions CM, RDR and MM were involved in each of the following points: (1) Design, (2) Data collection, (3) Analysis, and (4) Writing manuscript. FR, AS, and CV were involved in (1) Manuscript revision. CM, RDR,, AS, LM, LU, CV, AV, CB, RT, BR, GB, and MM were involved in each of the following points: (1) Manuscript revision and (2) Data collection.

Funding This research was performed as a part of the institutional activity of the unit, with no specific funding. All expenses, including salaries of the investigators, were covered by public research funds assigned to the unit.

Declarations

Conflict of interest MM received speaking fees by Athena srl, Zuccato srl, Biocomposites srl, Molteni Therapeutics, and Biomedica. All the other authors did not report any potential COI. All the authors approved the final version of this manuscript.

Human rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent This article does not contain any studies with human participants performed by any of the authors.

References

1. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE (2020) Global Disability Burdens of Diabetes-Related Lower-Extremity Complications in 1990 and 2016. Diabetes Care 43(5):964–974. https://doi.org/10.2337/dc19-1614
2. Hicks CW, Selvin E (2019) Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. Curr Diab Rep 19(10):86. https://doi.org/10.1007/s11892-019-1212-8
3. Armstrong DG, Boulton AJM, Bus SA (2017) Diabetic Foot Ulcers and Their Recurrence. N Engl J Med 376(24):2367–2375. https://doi.org/10.1056/NEJMra1615439
4. Fu XL, Ding H, Miao WW, Mao CX, Zhan MQ, Chen HL (2019) Global recurrence rates in diabetic foot ulcers: A systematic review and meta-analysis. Diabetes Metab Res Rev 35(6):e3160. https://doi.org/10.1002/dmrr.3160
5. Armstrong DG, Mills JL (2013) Toward a change in syntax in diabetic foot care: prevention equals remission. J Am Podiatr Med Assoc 103(2):161–162. https://doi.org/10.7547/1030161
6. Bus SA (2012) Priorities in offloading the diabetic foot. Diabetes Metab Res Rev 28(Suppl 1):54–59. https://doi.org/10.1002/dmrr.2240
7. Waaijman R, de Haart M, Arts ML et al (2014) Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. Diabetes Care 37(6):1697–1705. https://doi.org/10.2337/dc13-2470
8. Monami M, Longo R, Desideri CM, Masotti G, Marchionni N, Mannucci E (2008) The diabetic person beyond a foot ulcer: healing, recurrence, and depressive symptoms. J Am Podiatr Med Assoc 98(2):130–136. https://doi.org/10.7547/0980130
9. Huang ZH, Li SQ, Kou Y, Huang L, Yu T, Hu A (2019) Risk factors for the recurrence of diabetic foot ulcers among diabetic patients: a meta-analysis. Int Wound J 16(6):1373–1382. https://doi.org/10.1111/iwj.13200
10. Monami M, Vivarelli M, Desideri CM, Colombi C, Marchionni N (2009) Mannucci E (2009) Pulse pressure and prediction of incident foot ulcers in type 2 diabetes. Diabetes Care 32(5):897–899. https://doi.org/10.2337/dc08-1679

11. Tang WH, Zhao YN, Cheng ZX, Xu JX, Zhang Y, Liu XM (2023) Risk factors for diabetic foot ulcers: A systematic review and meta-analysis. Vascular. https://doi.org/10.1177/17085381231154805
12. Miranda C, Da Ros R (2020) Prevention of Diabetic Foot Ulcer: A Neglected Opportunity. Transl Med UniSa 22:50–51
13. van Netten JJ, Raspovic A, Lavery LA et al (2020) Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. Diabetes Metab Res Rev 36(Suppl 1):e3270. https://doi.org/10.1002/dmrr.3270
14. Guyatt GH, Oxman AD, Santesso N et al (2013) GRADE guidelines: 12 Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 66(2):158–172. https://doi.org/10.1016/j.jclinepi.2012.01.012
15. Monami M, Scatena A, Miranda C et al (2023) Development of the Italian clinical practice guidelines for the treatment of diabetic foot syndrome: design and methodological aspects. Acta Diabetol 60(11):1449–1469. https://doi.org/10.1007/s00592-023-02150-8
16. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135
17. Higgins JP, Altman DG, Gøtzsche PC et al (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928. https://doi.org/10.1136/bmj.d5928
18. Bus SA, Sacco ICN, Monteiro-Soares M et al (2024) Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev 40(3):e3651. https://doi.org/10.1002/dmrr.3651
19. Örneholm H, Apelqvist J, Larsson J, Eneroth M (2017) Recurrent and other new foot ulcers after healed plantar forefoot diabetic ulcer. Wound Repair Regen 25(2):309–315. https://doi.org/10.1111/wrr.12522
20. van Netten JJ, Bus SA, Apelqvist J et al (2023) Definitions and criteria for diabetes-related foot disease (IWGDF 2023 update). Diabetes Metab Res Rev. https://doi.org/10.1002/dmrr.3654
21. Plank J, Haas W, Rakovac I et al (2003) Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects. Diabetes Care 26(6):1691–1695. https://doi.org/10.2337/diacare.26.6.1691
22. van Schie CH, Whalley A, Armstrong DG, Vileikyte L, Boulton AJ (2002) The effect of silicone injections in the diabetic foot on peak plantar pressure and plantar tissue thickness: a 2-year follow-up. Arch Phys Med Rehabil 83(7):919–923. https://doi.org/10.1053/apmr.2002.33058
23. Westphal C, Neame IM, Harrison JC, Bower VM, Gurr JM (2011) A diabetic foot ulcer pilot study: does silicone gel sheeting reduce the incidence of reulceration? J Am Podiatr Med Assoc 101(2):116–123. https://doi.org/10.7547/1010116
24. Annersten Gershater M, Apelqvist J, Alm Roijer C (2023) Re-Ulceration Is Common in Persons with Diabetes and Healed Foot Ulcer After Participant-Driven Education in Group: A Randomized Controlled Trial. Adv Wound Care (New Rochelle) 12(3):117–126. https://doi.org/10.1089/wound.2021.0007
25. Annersten Gershater M, Pilhammar J, Apelqvist C, Alm-Roijer C (2011) Patient education for the prevention of diabetic foot ulcers Interim analysis of a randomised controlled trial due to morbidity and mortality of participants. Eur Diabetes Nursing 8(3):102–107
26. Lincoln NB, Radford KA, Game FL, Jeffcoate WJ (2008) Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial. Diabetologia 51(11):1954–1961. https://doi.org/10.1007/s00125-008-1110-0
27. Monami M, Zannoni S, Gaias M, Nreu B, Marchionni N, Mannucci E (2015) Effects of a Short Educational Program for the Prevention of Foot Ulcers in High-Risk Patients: A Randomized Controlled Trial. Int J Endocrinol 2015:615680. https://doi.org/10.1155/2015/615680
28. Suryani M, Samekto W, Heri N, Susanto H, Dwiantoro L (2021) Effect of foot-ankle flexibility and resistance exercise in the secondary prevention of plantar foot diabetic ulcer. J Diabetes Complications 35(9):107968. https://doi.org/10.1016/j.jdiacomp.2021.107968
29. Bus SA, Waaijman R, Arts M et al (2013) Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care 36(12):4109–4116. https://doi.org/10.2337/dc13-0996
30. López-Moral M, Lázaro-Martínez JL, García-Morales E, García-Álvarez Y, Álvaro-Afonso FJ, Molines-Barroso RJ (2019) Clinical efficacy of therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polineuropathy: A randomized clinical trial. PLoS ONE 14(7):e0219537. https://doi.org/10.1371/journal.pone.0219537
31. Reiber GE, Smith DG, Wallace C et al (2002) Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. JAMA 287(19):2552–2558. https://doi.org/10.1001/jama.287.19.2552
32. Rizzo L, Tedeschi A, Fallani E et al (2012) Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. Int J Low Extrem Wounds 11(1):59–64. https://doi.org/10.1177/1534734612438729
33. Uccioli L, Faglia E, Monticone G et al (1995) Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes Care 18(10):1376–1378. https://doi.org/10.2337/diacare.18.10.1376
34. Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR (2014) Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. Diabetes Care 37(7):1982–1989. https://doi.org/10.2337/dc13-2956
35. Liu J, Chen T, Wang S, Liu H (2019) The effect of transitional care on the prevention of diabetic foot ulcers in patients at high risk for diabetic foot. International Journal of Diabetes in Developing Countries 39(4):659–666. https://doi.org/10.1007/s13410-019-00736-z
36. Luo B, Cai Y, Chen D et al (2022) Effects of Special Therapeutic Footwear on the Prevention of Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Diabetes Res 2022:9742665. https://doi.org/10.1155/2022/9742665
37. van Netten JJ, Raspovic A, Lavery LA et al (2023) Prevention of foot ulcers in persons with diabetes at risk of ulceration: A systematic review and meta-analysis. Diabetes Metab Res Rev. https://doi.org/10.1002/dmrr.3652
38. Dorresteijn JA, Kriegsman DM, Assendelft WJ, Valk GD (2014) Patient education for preventing diabetic foot ulceration. Cochrane Database Syst Rev 2014(12):Cd001488. https://doi.org/10.1002/14651858.CD001488.pub5
39. Adiewere P, Gillis RB, Imran Jiwani S, Meal A, Shaw I, Adams GG (2018) A systematic review and meta-analysis of patient education in preventing and reducing the incidence or recurrence of adult diabetes foot ulcers (DFU). Heliyon 4(5):e00614. https://doi.org/10.1016/j.heliyon.2018.e00614
40. Crawford F, Nicolson DJ, Amanna AE, Smith M (2022) Reliability of the evidence to guide decision-making in foot ulcer prevention in diabetes: an overview of systematic reviews. BMC Med Res Methodol 22(1):274. https://doi.org/10.1186/s12874-022-01738-y
41. Giannarou L, Zervas E (2014) Using Delphi technique to build consensus in practice. Int J Bus Sci Appl Manage (IJBSAM) 9(2):65–82
42. Russo G, Monami M, Perseghin G et al (2021) The "Early Treatment" Approach Reducing Cardiovascular Risk in Patients with

Type 2 Diabetes: A Consensus From an Expert Panel Using the Delphi Technique. Diabetes Ther 12(5):1445–1461. https://doi.org/10.1007/s13300-021-01045-7
43. De Luca M, Zappa MA, Zese M, et al (2022) Development of the Italian Clinical Practice Guidelines on Bariatric and Metabolic Surgery: Design and Methodological Aspects. Nutrients 15(1). https://doi.org/10.3390/nu15010189
44. Pitei DL, Foster A, Edmonds M (1999) The effect of regular callus removal on foot pressures. J Foot Ankle Surg 38(4):251–5; discussion 306. https://doi.org/10.1016/s1067-2516(99)80066-0
45. Young MJ, Cavanagh PR, Thomas G, Johnson MM, Murray H, Boulton AJ (1992) The effect of callus removal on dynamic plantar foot pressures in diabetic patients. Diabet Med 9(1):55–57. https://doi.org/10.1111/j.1464-5491.1992.tb01714.x
46. Armstrong DG, Holtz K, Wu S (2005) Can the use of a topical antifungal nail lacquer reduce risk for diabetic foot ulceration? Results from a randomised controlled pilot study. Int Wound J 2(2):166–170. https://doi.org/10.1111/j.1742-4801.2005.00097.x
47. Crawford F, Hart R, Bell-Syer S, Torgerson D, Young P, Russell I (2000) Topical treatments for fungal infections of the skin and nails of the foot. Cochrane Database Syst Rev 2:cd001434. https://doi.org/10.1002/14651858.Cd001434
48. Da Silva J, Santos D, Vilaça M et al (2023) Impact of Psychological Distress on Physiological Indicators of Healing Prognosis in Patients with Chronic Diabetic Foot Ulcers: A Longitudinal Study. Adv Wound Care (New Rochelle). https://doi.org/10.1089/wound.2023.0043
49. Iversen MM, Tell GS, Espehaug B et al (2015) Is depression a risk factor for diabetic foot ulcers? 11-years follow-up of the Nord-Trøndelag Health Study (HUNT). J Diabetes Complications 29(1):20–25. https://doi.org/10.1016/j.jdiacomp.2014.09.006
50. Westby M, Norman G, Vedhara K, Game F, Cullum N (2020) Psychosocial and behavioural prognostic factors for diabetic foot ulcer development and healing: a systematic review. Diabet Med 37(8):1244–1255. https://doi.org/10.1111/dme.14310
51. Mazze RS, Lucido D, Shamoon H (1984) Psychological and social correlates of glycemic control. Diabetes Care 7(4):360–366. https://doi.org/10.2337/diacare.7.4.360
52. Nemeroff CB, Musselman DL, Evans DL (1998) Depression and cardiac disease. Depress Anxiety 8(1):71–79
53. Ader R, Cohen N, Felten D (1995) Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 345(8942):99–103. https://doi.org/10.1016/s0140-6736(95)90066-7
54. Crawford F, Nicolson DJ, Amanna AE et al (2020) Preventing foot ulceration in diabetes: systematic review and meta-analyses of RCT data. Diabetologia 63(1):49–64. https://doi.org/10.1007/s00125-019-05020-7
55. Drovandi A, Seng L, Golledge J (2023) Effectiveness of educational interventions for diabetes-related foot disease: A systematic review and meta-analysis. Diabetes Metab Res Rev. https://doi.org/10.1002/dmrr.3746
56. Armstrong DG, Tan TW, Boulton AJM, Bus SA (2023) Diabetic Foot Ulcers: A Review Jama 330(1):62–75. https://doi.org/10.1001/jama.2023.10578
57. Meloni M, Giurato L, Monge L et al (2024) Effect of a multidisciplinary team approach in patients with diabetic foot ulcers on major adverse limb events (MALEs): systematic review and meta-analysis for the development of the Italian guidelines for the treatment of diabetic foot syndrome. Acta Diabetol. https://doi.org/10.1007/s00592-024-02246-9