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REVIEW ARTICLE

Offloading systems for the treatment of neuropathic foot ulcers in patients with diabetes mellitus: a meta-analysis of randomized controlled trials for the development of the Italian guidelines for the treatment of diabetic foot syndrome

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Abstract

Aim To compare the effectiveness of commonly used offloading devices for the treatment of neuropathic foot ulcers in patients with diabetes mellitus. This meta-analysis (MA) has been performed for giving an answer to clinical questions on this topic of the Italian guideline on diabetic foot syndrome.

Methods The present MA includes randomized controlled studies (duration > 12 weeks) comparing, in patients with diabetes mellitus and non-infected neuropathic foot ulcer: any offloading device *vs* either no offloading device or conventional footwear; removable versus non-removable offloading devices; surgical procedure *vs* other offloading approaches. The primary endpoint was ulcer healing.

Results A total of 184 studies were identified, and 18 were considered eligible for the analysis. We found that: any plantar off-loading, when compared to the absence of plantar offloading device, is associated with a higher ulcer healing (MH-OR: 3.13 [1.08, 9.11], $p=0.04$, $I^2=0\%$); total contact cast or nonremovable knee-high walker, compared to other offloading devices, had a higher ulcer healing rate (MH-OR: 2.64 [1.43, 4.89], $p=0.002$, $I^2=51\%$); surgical offloading for active ulcers in combination with post-surgery offloading achieves higher ulcer healing rate when compared to offloading devices alone (MH-OR: 6.77 [1.64, 27.93], $p=0.008$, $I^2=0\%$).

Conclusions Any plantar offloading, compared to the absence of plantar offloading device, is associated with a higher ulcer healing rate. Total contact cast or nonremovable knee-high walker, compared to other offloading devices, is preferable. Surgical offloading for active ulcers, in combination with post-surgery offloading devices, achieves a higher ulcer healing rate when compared to other offloading devices alone. Further studies with a larger cohort of patients with diabetic neuropathic foot ulcers and extended follow-up periods are necessary.

Keywords Diabetes mellitus · Neuropathic foot ulcer · Offloading

Introduction

Diabetes-related foot disease (DFD) is "a disease of the foot of a person with diabetes that includes peripheral neuropathy, peripheral artery disease, infection, ulcers, neuro-osteoarthropathy, gangrene, or amputation," definition recently revised by the International working group on the diabetic foot (IWGDF) [1]. It is the leading cause of amputation, global hospitalizations and disability and represents the 13th largest cause of the total global disease burden [2].

Diabetic foot ulcers develop as a result of diabetic neuropathies (sensory, motor and autonomic). Peripheral artery disease, when present, contributes to the development of the ulcer, and it is a risk factor for poor ulcer healing, infection and amputation [3, 4].

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Prevalence of DFD is increasing, being estimated around (2.6%) of the total global population in 2017 [2]. In Europe, belonging to high-income regions, the prevalence of diabetic foot ulcers varied from 1.0% to 17.0%; the recurrence from 7.0% to 42% [5]; the incidence is expected to dramatically increase in the next decades [2, 6, 7].

The prevention and effective management of DFD are crucial to reduce the risk of lower limb amputations and improve the quality of life for diabetic patients. Offloading is a key component of the treatment protocol for all the spectrum of DFD, aiming to relieve plantar pressure and facilitating healing processes [1, 4]. Various offloading devices (e.g., removable and non-removable, special therapeutic footwear, surgery, and other offloading interventions) have been proposed over the years to reduce mechanical stress, promote wound healing, and prevent further complications [8]. The presence of infection and/or peripheral artery disease may represent a contraindication to some offloading strategies; for this reason, in the present study, we considered offloading of neuropathic foot ulcers, that is, without infection and/or ischemia. Concerning the neuropathic foot ulcer (as defined by IWGDF) [9], several studies [10–12], meta-analyses [3–13], and international guidelines [1] have clearly shown that any therapeutic footwear with offloading properties significantly reduces the risk of incident of neuropathic foot ulcers. Furthermore, in patients with active neuropathic foot ulcers, a higher ulcer healing rate and a shorter time-to-healing have been associated with the use of removable and non-removable offloading devices [14–21]. As a part of a holistic approach, when traditional off-loading treatments fail to heal a plantar ulcer, a surgical approach could be considered [22, 23].

Despite the importance of plantar offloading in the management of neuropathic foot ulcers, the evidence regarding offloading devices/techniques is supported by many studies with high heterogeneity, but a few randomized controlled trials (RCTs) focusing on their comparative effectiveness.

The present meta-analysis, aiming to provide a comprehensive review of individual available offloading devices for the treatment of neuropathic foot ulcers, was performed in the development process of the Italian guidelines for the treatment of Diabetic Foot Syndrome, promoted by the Italian Society of Diabetology (Società Italiana di Diabetologia, SID) and the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD), for the inclusion in the Italian National Guideline System (INGS). The inclusion in INGS requires rigorous methodological steps and formal revision by the National Center for Clinical Excellence of the Ministry of Health. In this respect, the Grading of Recommendations Assessment Development and Evaluations (GRADE) methodology is adopted; it requires identification of specific clinical questions and definition of relevant outcomes for each question, formulated using the PICO (Patient, Intervention, Comparison, Outcome) conceptual framework [24].

Transparency in the development process is one of the main determinants of quality of guidelines. The GRADE manual recommends the explicit publication of clinical questions, relevant outcomes, and summaries of evidence for each outcome [25]. We decided to go beyond the requirements of the GRADE manual, pre-emptively publishing in extenso the whole process leading to clinical questions and definition of critical outcomes. In addition, the search strategy and inclusion criteria for the systematic review and meta-analysis for each outcome have been reported in the present study, allowing the reproducibility of the whole process. It is the policy of this panel to publish extensively, and possibly on peer-reviewed journals, all systematic reviews and meta-analyses that will concur to the formulation of these guidelines. For all questions, RCTs are selected, and the use of non-randomized studies are allowed only for questions related to nonpharmacological (or medical device) treatments [24, 25]. To comply this latter requisite, the present work differentiates from other authoritative publications, such as the IWGDF guidelines [1], currently adopted, and a recent systematic review and meta-analysis by Lazzarini et al. [20].

The paper evaluates and compares, whenever possible, the effectiveness of commonly used offloading devices, answering the following clinical questions:

Question 1—In patients with non-infected neuropathic foot ulcers, is plantar offloading preferable to no plantar offloading device to reduce the risk of lower limbs adverse outcomes?

Question 2—In patients with non-infected neuropathic foot ulcers, is the use of a removable offloading device or therapeutic footwear preferable to conventional footwear, to reduce the risk of lower limbs adverse outcomes?

Question 3—In patients with non-infected neuropathic foot ulcers, is a total contact cast or nonremovable knee-high walker preferable to other offloading devices, to reduce the risk of lower limbs adverse outcomes?

Question 4—In patients with non-infected neuropathic foot ulcers, is the offloading obtained with surgical procedures preferable to that obtained with non-surgical interventions, to reduce the risk of adverse outcomes?

Methods

We conducted this systematic review in conformity with PRISMA checklist [26] (Table 1S) and following a protocol previously published [24].

Eligibility criteria

To be eligible, a study should enroll patients, age 18 or older, with diabetes mellitus and neuropathic foot ulcer.

Studies including patients with chronic limb-threatening ischemia [27] or/and infection were excluded. The panelists decided to exclude these patients who are at higher risk for adverse events with the use of offloading systems, as also recognized from the IWGDF guidelines. In fact, IWGDF recommends to "primarily address the infection and/or ischemia and use removable offloading interventions over no-offloading based on the persons' individual factors to promote healing of the ulcers" [1].

Offloading interventions were defined as interventions performed with the aim to reduce loading from the plantar region of the foot.

In question 1 as "plantar offloading" we considered all the removable and non-removable offloading devices. When used alone, the dressing was not considered as an offloading technique [14].

In question 2 for "removable offloading devices or therapeutic footwear" we included all offloading methods that can be removed by the patient as Removable Cast Walker (RCW); Custom Therapeutic Footwear (CTF) as accommodative footwear; modified footwear; half-shoes; healing sandals. "Conventional footwear" means no therapeutic (non-orthopedic) shoes.

In question 3 for "Total Contact Cast (TCC) or Non-Removable knee-high Walker (NRW)" we have included these types of offloading: TCC (custom made knee-high non-removable fiberglass or plaster cast with total contact with plantar surface and lower leg) and instant-TCC (iTCC, removable cast walker or walking boot wrapped with a cohesive). For "other offloading devices" we have included all the alternative offloading methods that can be removed by the patient as RCW and CTF.

In question 4 for "surgical procedure" we have considered all the offloading modalities implemented with surgical techniques as: Achille tendon lengthening; gastrocnemius aponeurosis recession; metatarsal head resections; joint arthroplasty; joint arthrodesis; digital flexor tenotomy; exostectomy; and other techniques described.

Search strategy and selection criteria

The present analysis includes all RCTs, with a duration of at least 12 weeks, enrolling diabetic patients or reporting subgroup analyses on diabetic patients comparing:

- any offloading device versus either no offloading device
- any offloading device versus conventional footwear
- removable versus non-removable offloading devices
- surgical procedure versus other offloading approaches

A Medline and Embase search using the following key words: "offloading and diabetes" were performed up to September 4th, 2023. Detailed information on search strategy is reported in Table 2S. Further studies were manually searched in references from retrieved papers.

Two independent reviewers (LM and CG) screened all titles and abstracts of the identified studies for inclusion. Discrepancies were resolved by a third, independent reviewer (MM).

Data extraction and collection

Titles and abstracts were screened independently by the authors, and potentially relevant articles retrieved in full text. 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.

Data extraction was performed independently by two of the authors (CG and LM), and conflicts resolved by a third investigator (MM).

The risk of bias in RCTs was assessed using the Cochrane recommended tool [28], 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.

Endpoints

Primary endpoint was ulcer healing. Secondary endpoints were time-to-healing, incidence of infections and new ulcerations during follow-up, major amputation (any resection proximal to the ankle), minor amputation (any resection through or distal to the ankle), all-cause mortality, post-surgical complications (only for question 4), pain, quality of life (any disease-specific tool), and back to walk previously decided (after voting) by the panel of the Italian Guidelines for the treatment of diabetic foot syndrome [24]. The high number of endpoints is due to the GRADE method used. The first step of the development of the present guidelines was the definition of clinical questions (PICO). For each question, the panel defined several clinical outcomes, judged potentially relevant for the choice of different clinical options. Each outcome was then rated (from 1 to 9) for its importance; those receiving a rating of 7 or higher were classified as "critical." For each critical outcome, the panel performed a systematic review of relevant studies, predefining search strategies and inclusion criteria, and performing meta-analyses whenever possible.

Statistical analyses

Heterogeneity was assessed by I^2 test. Heterogeneity in a meta-analysis refers to the variability observed among individual studies that are combined in the analysis. When conducting a meta-analysis, data from multiple studies are pooled to calculate an overall effect size. However, due to differences in study participants, interventions, outcomes, study designs, or risks of bias, there is inherent variation in the results of these studies. I^2 values > 50% indicate a high heterogeneity lowering the strength of the synthetic result obtained by pooling more studies. To reduce the risk of non-reliable results due to high heterogeneity, sensitivity analyses removing one study at a time for the primary endpoint and secondary endpoints are performed only if a heterogeneity-related bias cannot be completely ruled out.

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–Haenszel 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.

A post hoc analysis dividing trials performed on TCC and NRW has been performed in order to assess possible differential effects of these two devices on the principal outcome.

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 [25] 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.

A search of Medline and Embase databases (Table 2S) led to the identification of 176 records; 14 additional records were added after manually searching reference lists of retrieved papers. After removing duplicates, we retrieved a total of 184 records. Subsequently, 148 trials were excluded after reading titles and/or abstracts. For question 1, we retrieved 6 items, 4 studies [29–32] were excluded after reviewing the full text and 2 RCTs were included in the meta-analysis [33, 34]. For question 2 we retrieved 1 RCT [31] that was excluded after reviewing the full text. For question 3, we retrieved 23 items, 12 studies [29, 30, 33–42] were excluded after reviewing the full text, whereas 11 RCTs [31, 43–52] fulfilling the inclusion criteria were included in the meta-analysis. For question 4 we retrieved 8 items, 3 studies [53–55] were excluded after reviewing the full text, whereas 5 RCTs [56–60] fulfilled the inclusion criteria and were included in the meta-analysis.

Table 3S describes reasons for exclusion of selected studies for any individual clinical question.

The principal characteristics of the included studies for questions 1, 3 and 4 are reported in Table 4S of Supporting Information.

The quality of studies was heterogeneous, and all studies were open label (Fig. 2S and 3S of Supporting Information) with a relevant selection risk of bias.

Question 1 – In patients with non-infected neuropathic foot ulcers, is plantar offloading preferable to no plantar offloading device to reduce the risk of lower limbs adverse outcomes?

Only 2 studies [33, 34] fulfilled the inclusion criteria, enrolling 103 patients with diabetic foot ulcer (54 treated with plantar offloading and 49 with standard of care, respectively) (Table 4S of Supporting Information).

Plantar offloading was associated with a significantly higher ulcer healing (MH-OR: 3.13 [1.08, 9.11], $p = 0.04$, $I^2 = 0\%$; Fig. 1). The incidence of ulcer infection, observed during the study period, was lower in patients allocated to plantar offloading than in patients with no offloading. However, the difference did not reach statistical significance (MH-OR: 0.20 [0.04, 1.03], $p = 0.051$, I^2: 0%; Fig. 4S of Supplementary Materials).

No formal meta-analysis for all the other outcomes (time-to-healing, incidence of new ulcerations during follow-up, amputations, all-cause mortality, pain, quality of life, and back to walk) was possible, due to the lack of information.

For the primary endpoint, GRADE methodology [25] was used to assess the quality of the body of retrieved evidence, which was rated as "low" (Table 5S of Supporting Information).

Question 2—In patients with non-infected neuropathic foot ulcers, is the use of a removable offloading device or therapeutic footwear preferable to conventional footwear, to reduce the risk of lower limbs adverse outcomes?

No studies fulfilling inclusion criteria have been retrieved.

Question 3—In patients with non-infected neuropathic foot ulcers, is a total contact cast or nonremovable knee-high walker preferable to other offloading devices, to reduce the risk of lower limbs adverse outcomes?

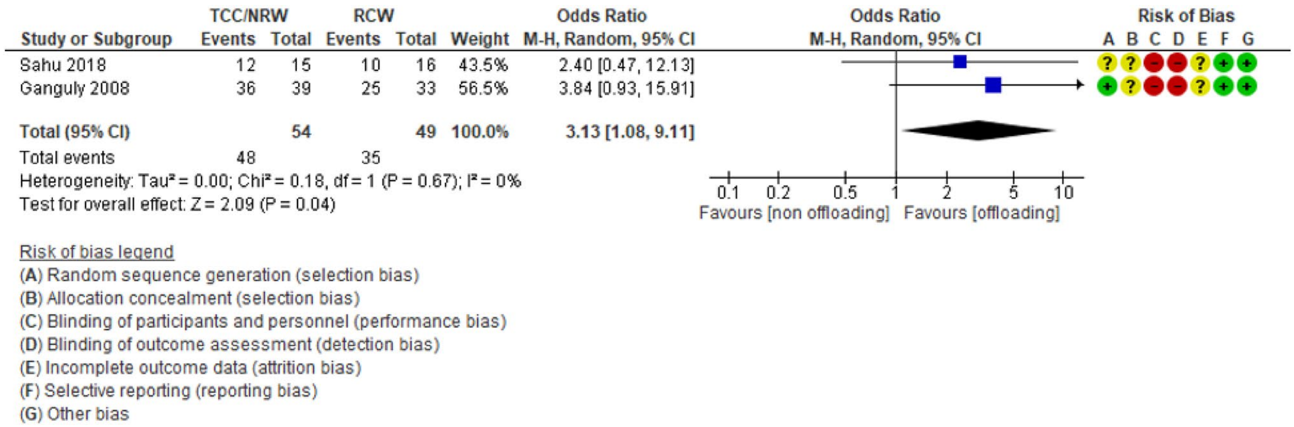

Fig. 1 Effects of plantar offloading on ulcer healing at the endpoint in comparison with no offloading (Question 1). *TCC/NRW* Total contact cast/non-removable knee-high walker, *RCW* removable cast walker

Of the 11 RCTs included [31, 43–52], the mean age was 58 years, the proportion of women 23% and the study duration 13 weeks (Table 4S of Supporting Information). The studies included in the analyses enrolled 574 patients with diabetic foot ulcer (281 with TCC/NRW and 293 with RCW, respectively).

All trials reported data on ulcer healing with a significantly higher ulcer healing rate (MH-OR: 2.64 [1.43, 4.89], $p = 0.002$, $I^2 = 51\%$; Fig. 2) and a significantly reduction of ulcer time-to-healing (n = 7 trials [31, 43, 44, 46–48, 50]; WMD -17.28 [-27.14, -7.41] days, $p = 0.0006$, $I^2 = 93\%$; Fig. 5S of Supplementary Materials) in favor of TCC/NRW. Two trials [45, 52] reported information on time-to-healing, without specifying standard deviations values, and one trial [51] did not provide information on this outcome and was, therefore, excluded from the analysis.

Funnel plot for ulcer healing rate (Fig. 6S of Supplementary Materials) did not suggest any publication bias.

A post hoc analysis dividing trials performed on TCC and NRW revealed no between-group differences (p for interaction: 0.17) in healing rate (Fig. 7S of Supplementary Materials).

TCC/NRW did not increase the risk of incident foot infection due to the type of intervention which showed a non-significant trend toward reduction of that risk in patients

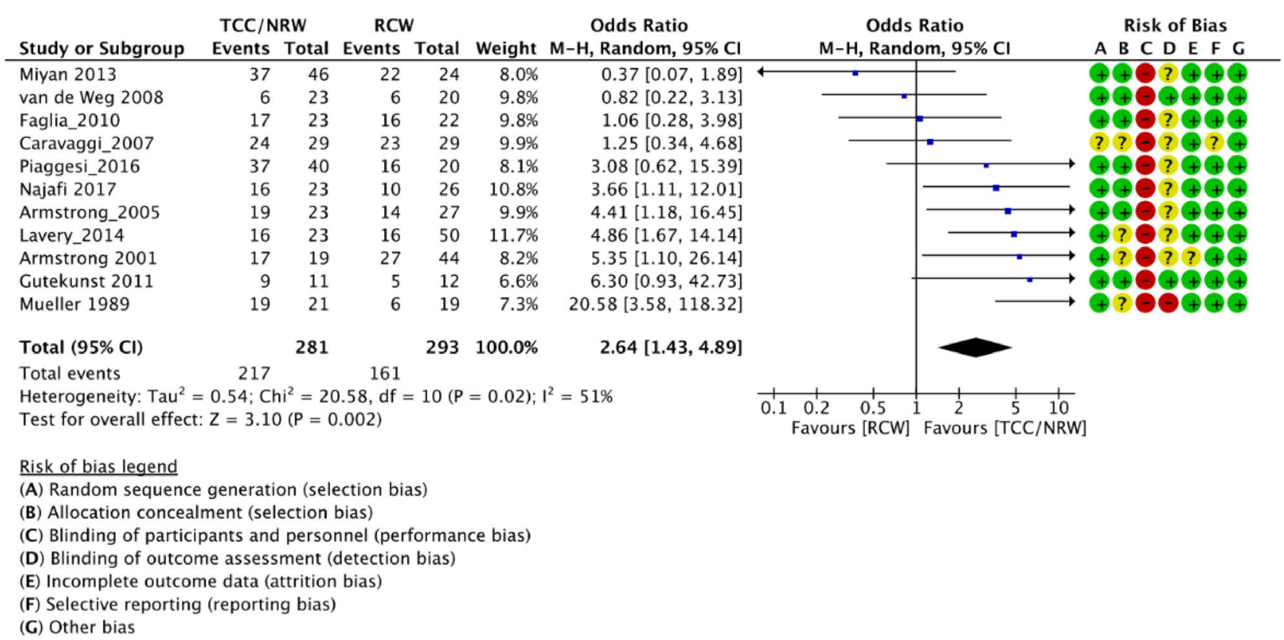

Fig. 2 Effects of TCC/NRW on ulcer healing at the endpoint in comparison with RCW (Question 3). *TCC/NRV* Total contact cast/non-removable knee-high walker, *RCV* removable cast walker

allocated to the TCC/NRW arm (MH-OR: 0.55 [0.29, 1.06], $p = 0.07$, $I^2 = 0\%$; Fig. 8S of Supplementary Materials).

Only one [31] and two [31, 47] studies reported information on major and minor amputations, respectively, with no major amputation and only 3 minor amputations (1 with TCC/NRW and 2 with RWC; MH-OR: 0.64 [0.04, 10.13], $p = 0.75$, $I^2 = 34\%$; Fig. 9S of Supplementary Materials).

Only one trial [47] reported a fatal event in patients allocated to TCC/NRW unrelated to the treatment. No studies reported information on falls and deep venous thrombosis.

For the primary endpoint, GRADE methodology [25] was used to assess the quality of the body of retrieved evidence, which was rated as “moderate” (Table 5S of Supporting Information). No formal meta-analyses for all the other outcomes (incidence of new ulcerations during follow-up, pain, quality of life, and back to walk) were possible, due to the lack of information.

Question 4—In patients with non-infected neuropathic foot ulcers, is the offloading obtained with surgical procedures preferable to that obtained with non-surgical interventions, to reduce the risk of adverse outcomes?

Only five studies fulfilled inclusion criteria [56–60] enrolling 171 patients with diabetic foot ulcer (88 ulcers allocated to surgical offloading arm and 88 ulcers to non-surgical plantar offloading arm) (Table 4S of Supporting Information).

Surgical plantar offloading was associated with a significantly higher ulcer healing rate (MH-OR: 6.77 [1.64, 27.93], $p = 0.008$, $I^2 = 0\%$; Fig. 3). Two trials [57, 60] reported information on time-to-healing without specifying standard deviations values and were therefore excluded from the analysis. The remaining three trials [56, 58, 59] showed no significant effect of surgical plantar offloading on time-to-healing (MH-OR: -14.52 [−46.38, 17.35], $p = 0.37$, $I^2 = 89\%$; Fig. 10S of Supplementary Materials).

The incidence of ulcer infection during the study showed no significant increased risk in patients allocated to plantar surgical offloading (MH-OR: 1.92 [0.37, 10.02], p = 0.44, $I^2 = 0\%$; Fig. 11S of Supplementary Materials). No effect on the incidence of new ulcerations was observed for surgical *vs* non-surgical plantar offloading (MH-OR 0.59 [0.10, 3.54]; $p = 0.56$, $I^2 = 52\%$; Fig. 12Sof Supplementary Materials). Only one fatal event and two falls were recorded in one study [58]; two rupture of Achilles tendon, one in gastrocnemius recession and one in percutaneous Achilles tendon lengthening [60] all in the surgical arm.

No formal meta-analysis for all the other secondary outcomes (post-surgical complications, pain, quality of life, and back to walk) was possible, due to the lack of information.

For the primary endpoint, GRADE methodology [25] was used to assess the quality of the body of retrieved evidence, which was rated as “low” (Table 5S of Supporting Information).

Discussion

Diabetic neuropathic foot ulcer formation is the result of multiple factors. Neuropathies lead to loss of protective sensation, foot deformities, altered biomechanics and skin dryness, promoting callus formation. Vertical pressure caused by minor repetitive traumas or acute damage due to high pressure on the callus can determine a skin ulceration. Plantar pressure relief, together with the removal of hyperkeratotic tissues, is therefore crucial in the prevention and management of neuropathic foot ulcers [10]. Plantar pressure relief and shear stress reduction can be achieved using different strategies, including several offloading devices, therapeutic footwear, and surgical offloading techniques.

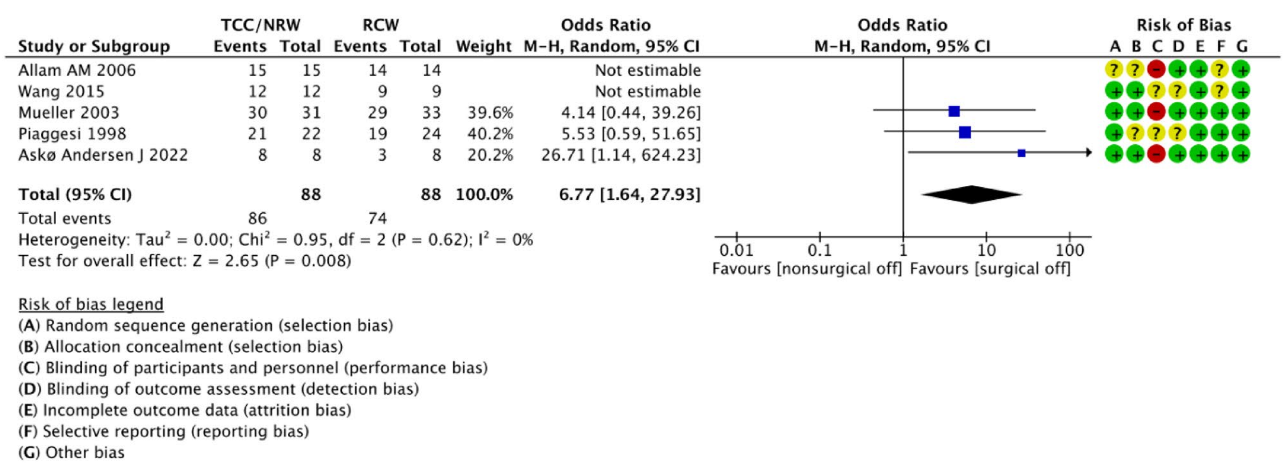

Fig. 3 Effects of surgical plantar offloading on ulcer healing at the endpoint in comparison with other offloading systems (Question 4). *TCC/NRV* Total contact cast/non-removable knee-high walker, *RCV* removable cast walker

We conducted a systematic review and meta-analysis of randomized control trials to evaluate the effectiveness and safety of different offloading methods for non-infected neuropathic foot ulcers. Based on the GRADE methodology, a series of clinical questions were pre-defined [25] using the PICO conceptual framework. For all questions related to any therapeutic intervention, only RCTs have been considered.

We addressed the following clinical questions:

- Is plantar offloading preferable to no plantar offloading device?
- Is the use of a removable offloading device or therapeutic footwear preferable to conventional footwear?
- Is a total contact cast or non-removable knee-high walker preferable to removable offloading devices?
- Is the offloading achieved with surgical procedures preferable to that obtained with non-surgical interventions?

As a result of our meta-analysis of available RCTs we can state that:

- Any plantar off-loading, when compared to the absence of plantar offloading device, is associated with a higher ulcer healing rate.
- A paucity of studies and no RCTs analyzed whether the use of a removable offloading device or therapeutic footwear is preferable to conventional footwear.
- Total contact cast or nonremovable knee-high walker, when compared to other offloading devices, is preferable. The use of total contact cast or non-removable knee-high walker was associated with higher ulcer healing rate. Moreover, the use of total contact cast or non-removable knee-high walker showed a reduction of ulcer time-to-healing.
- Surgical offloading for active ulcers, in combination with post-surgery offloading devices, achieves higher ulcer healing rate when compared to using other offloading devices alone, without an increase in incidence of infectious complications and new ulcerations.

Several limitations should be considered when interpreting the results of this meta-analysis. The first limitation to acknowledge is represented by the paucity of retrieved randomized control trials on off-loading in patients with DFU. Other authors [20], to increase the number of studies to meta-analyze, decided to also include non-controlled studies, pooling randomized and non-randomized studies together. We decided (as previously described elsewhere) to limit our analyses only to randomized control trials in order to reduce the heterogeneity and to comply with the pyramid of evidence that identifies RCTs as the most valid form of evidence beyond all else when considering either pharmacological or nonpharmacological treatments. The quality of a meta-analysis always depends on the number and quality of included parent studies. All studies fulfilling the inclusion criteria for each clinical question were open label, thus introducing a possible relevant selection bias. Moreover, high heterogeneity in many of the explored outcomes, mainly caused by different inclusion and exclusion criteria, study procedures, and endpoint definitions, suggests caution in interpreting the obtained results. Unfortunately, the scarce number of RCTs retrieved avoided the conduction of subgroup analyses which could have been of help in identifying possible moderators of efficacy and safety. Analyzing each individual question, considering the available clinical evidence, we can first state that offloading is considered in routine clinical practice an essential part of non-complicated neuropathic diabetic foot ulcers treatment. Any offloading device is likely to promote the healing of neuropathic foot ulcers in comparison with no offloading device or no therapeutic footwear.

Available studies on the offloading systems efficacy and safety have all been conducted on patients without ischemia/infections. However, it cannot be completely ruled-out the inclusion of ischemic patients in some of the included studies. In fact, exclusion criteria are not always fully described. Moreover, the exclusion of these patients limits the generalizability of the present recommendations only to patients with neuropathic noninfected ulcers. However, no controlled studies have been published on those patients and therefore, to comply with GRADE methodology [24, 25], we decided not to express any preference for the use of offloading systems. In fact, only three noncontrolled studies have been published on patients with infected/ischemic DFU even possibly reporting large increases in proportion of infected ulcers. Quite surprisingly, despite this adverse event without any clear beneficial effects of offloading on this subpopulation of patients, the IWGDF recommends the use of removable or nonremovable offloading for patients with mild/moderate infection and ischemia [6]. More studies on this frail subgroup of diabetic patients are needed in order to safely prescribe an undoubtedly useful tool for the treatment of plantar diabetic foot ulcers.

Among plantar offloading devices, non-removable offloading (TCC/NRW) should be preferred for the management of neuropathic foot ulcers. The panel of experts decided to consider these two offloading options equally effective in increasing the ulcer healing rate and reducing adverse events. In fact, to our knowledge, there are only two head-to-head comparison trials both reporting no between-group differences in healing rate and time-to-healing [35, 49]. We also retrieved one non-controlled study performed on few patients ($n=16$) suggesting lower peak pressures with TCC, but worse perceived walking comfort in comparison with NRW [61]. On the contrary, there are many studies suggesting a higher efficacy of both NRW and TCC in comparison with removable devices [44, 50]. The superiority of total contact cast or nonremovable knee-high walker is largely due to a forced patient compliance, because of its interference with the pathogenesis of ulcer formation, maintenance, and recurrence. Nevertheless, in the real world, the feasibility of knee-high non-removable devices does not always align with clinical indications. This discrepancy may be due to limited experience of healthcare professionals, supplies storage issue and patient intolerance. Patient tolerance is related to several factors, including age, unsteady gait, and the risk of falls. Postural instability can be explained with device-induced limb length discrepancy, resulting in knee, hip, and low back pains, as well as an antalgic gait [62]. We observed that our real-world population is somewhat older than the patients included in the RCTs. Moreover, knee-high non-removable devices are not recommended in the presence of moderate-to-severe infection, ischemia, heavy exudate, severe obesity, ataxia and blindness [1]. In clinical practice, for these patients, the use of removable devices, possibly knee-high but sometimes above-the-ankle-high, is therefore the only possible strategy for a valid plantar pressure relief. Knee-high removable devices are effective as long as they are worn, again in relation to patient compliance and with possible complications due to limb-length discrepancy, such as foot pronation and intrarotation of the tibia in the longer limb, pelvis anterior rotation, hyper-pressure on lumbar spine, increased peak pressure and risk of ulceration in the contralateral foot [62]. Clinicians should address these implications which might improve patient compliance.

Surgical offloading in combination with offloading devices may increase the rate of ulcer healing, although it demands specific surgical skills, and it is associated with higher hospitalization/procedure related costs and risks. Available RCTs on this subject are limited and highly heterogeneous because surgical procedures can be either prophylactic or curative in response to the presence of ulcers [63]. Additionally, the anatomical site (toes, sole/forefoot, and midfoot) and the underlying pathophysiology/causes of the ulcers (e.g., Charcot with bone pathology or post-amputation equinism of the forefoot) widely vary, similarly to the types of interventions proposed [64]. When healing can still be achieved without surgery, it is crucial to carefully consider the advantages and disadvantages of a surgical option. Offloading surgery may be considered in cases of no or partial response to optimized non-surgical offloading, as well as in situations of re-ulceration despite appropriate footwear with custom-made insoles.

Conclusions

In conclusion, addressing the PICO clinical questions for the Italian guidelines for the treatment of diabetic foot syndrome, the current evidence supports the assertion that any form of plantar offloading, when compared to the absence of a plantar offloading device, is associated with a higher ulcer healing rate. Furthermore, the use of a full-contact cast or a non-removable knee-high walker is preferable to other removable offloading devices, with no clear preference of one device over the other. Additionally, surgical offloading for active ulcers, when combined with postoperative offloading devices, yields a higher ulcer healing rate than using other offloading devices alone. However, such an approach should be adopted only for patients with severe plantar deformities. Unfortunately, there are no clear clinical features identifying the patients who are more likely to benefit from surgical offloading. To achieve a more comprehensive understanding of the role of offloading in the treatment and management of DFD, further studies with a larger cohort of patients and extended follow-up periods are necessary.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00592-024-02262-9.

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

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Declarations

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