Beyond the Monofilament for the Insensate Diabetic Foot

A systematic review of randomized trials to prevent the occurrence of plantar foot ulcers in patients with diabetes

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Foot ulcers in patients with diabetes lead to infections, amputations, and high costs, and their prevention is a stated goal of the American Diabetes Association. To assess the benefits of various interventions on the prevention of future diabetic foot ulcers, we searched for and reviewed all randomized clinical trials (RCTs) on the prevention of diabetic foot ulcers and evaluated their efficacy and scientific validity on the basis of an established systemic grading system. Only 13 RCTs were identified. All involved secondary prevention or a mixture of primary and secondary prevention. Most were small and of poor quality, with negative studies generally being of better quality than positive studies. Of all methods proposed to prevent diabetic foot ulcers, only foot temperature-guided avoidance therapy was found beneficial in RCTs, although this needs to be validated in other populations. These observations only apply to high-risk populations, and the benefits to the general population with diabetes are unclear.

Introduction

Diabetic foot ulcers are the cause of immense suffering and health system costs (1). The lifetime risk of a person with diabetes developing a foot ulcer may be as high as 25%, whereas the annual incidence of foot ulcers is as high as 2% (2–6). Multiple component causes, including peripheral neuropathy, peripheral vascular disease (PVD), foot deformity, and smoking, interact in the causal pathway to foot ulceration. In several cross-sectional and retrospective studies, the prevalence of PVD and peripheral neuropathy in patients was found to be as high as 40%. However, no prospective study clearly documented their relative contribution. This review is concerned primarily with clinical trials on the prevention of foot ulcers in the neuropathic, or insensate, foot.

Several physiologic measurements of the presence and degree of peripheral neuropathy have been shown to be predictive of the risk of future foot ulcer in diabetic patients (2), including *1*) sensation to the 5.07 (10 g) Semmes-Weinstein (SWM) monofilament, *2*) vibration perception threshold, *3*) sensation to the tuning fork, and *4*) formal nerve conduction studies. However, despite the ability to predict the risk of future occurrence of foot ulcers via the development of neuropathy, once neuropathy has developed, the prevention of foot ulcers remains a challenge. Indeed, although the graded SWM is widely used in practice to diagnose or screen for neuropathy, to document insensate feet, and to predict foot ulcers, repeated further testing with the SWM does not yield any useful information. Therefore, most patients with insensitive feet are referred for "preventive podiatry care" and specialized shoes, but no attempt is made to target more aggressive prevention in those highest risk individuals. It would be extremely valuable to be able to further stratify and predict the risk of a foot ulcer in the insensate foot (lost SWM perception) and devise methods of preventing future ulcer occurrence.

The goal of this review is to systematically assess RCTs regarding possible methods to prevent diabetic foot ulcers. This review does not evaluate articles on methods to simply predict the likelihood of future ulcers or on treatment approaches to pre-existing foot ulcers.

Research design and methods

A search was made for RCTs that described or reviewed methods to prevent the outcome of diabetic foot ulcers as the primary outcome in subjects deemed at risk. In addition, relevant references cited in these articles and in identified review articles were also reviewed. Both primary prevention and secondary prevention (subjects with a history of previous foot ulcers) were considered. Medline and PubMed were screened for relevant articles published between 1 January 1960 and 30 April 2010, using the combination of the terms "diabetes," "foot," and "ulcer." Additional searches were performed with the same search terms using the Clinical Trials section of the Cochrane Library, ClinicalTrials.gov, International Clinical Trials Registry Platform registry, and the Google databases. Unpublished registered studies were considered if study design, results, and validity criteria could be ascertained. Nonrandomized trials, prospective observational studies, and case-control studies were excluded from this review. The initial search was conducted by Y.A. and reviewed for completeness by V.F. Subsequently, two of the authors (Y.A. and V.F.) independently evaluated the articles that qualified on the basis of the selection criteria. The articles were then graded on the basis of the Amsterdam/Maastricht consensus list (10/5/2) system as initially described by Verhagen et al. (7) and accepted for use in the Cochrane commentaries system (8).

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This method of assessment of the quality of studies and the risk of bias follows the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.2* (9). All the authors reviewed the final selection and the accuracy of the grading scores. The criteria for grading the quality of clinical trials are listed in Table 1. Each item is graded as positive (+), negative (−), indeterminable (?), or not applicable (N). The final score is the sum of positive results. For the purpose of this article, the scores will be reported as (A/B/C) for absolute values for the three groups. To score a positive mark, the evidence for the specific item had to be stated or clearly implied (e.g., if the physician was the assessor of the end point and the same physician was stated to be blind), (A6) was presumed positive. When two items are listed in the criteria in Table 1, the score is 0, 1/2, or 1 based on the number of (+).

Results

The initial PubMed search, using the inclusive combination of the terms "diabetes" and "foot" and "ulcer," yielded 2,014 articles. Each abstract (or the full article if needed) was reviewed to determine eligibility, yielding 14 relevant review articles (2,8,10–21) and 11 RCTs (22–32) documenting the primary or secondary prevention of future foot ulcers as an end point. One additional RCT was found in ClinicalTrials.gov (K.R. Higgins, L.A. Lavery, K.A. Athanasiou, D.R. Lanctot, G.P. Costantinidis, C.M. Agrawal, and R.G. Zamorano, personal communication). No additional articles were identified via the Cochrane database or Google search. Review articles were extracted only to look for original articles, and no additional articles were found. The RCT included four studies on patient education and intensified monitoring (22–25), three studies on therapeutic footwear or insoles (26,27,33), one study on surgical bone debridement (28), one study on Achilles tendon lengthening (ATL) (29), and three studies on temperature-guided avoidance therapy (30–32). None of the studies was a true primary prevention study. Some used only subjects with a previous foot ulcer, whereas others used "high-risk group" combinations (neuropathy plus foot deformity, previous ulcer, or amputation).

Table 1—*Clinical trial evaluation criteria (7)*

A. Ten internal validity criteria
1. Random assignment/allocation concealed
2. Provider blinded
3. Cointervention avoided or comparable
4. Compliance acceptable
5. Patients blinded
6. Assessor of end points blinded
7. Outcome measurements relevant
8. Dropout acceptable
9. Timing of outcome measurements comparable
10. Analysis includes intention-to-treat analysis
B. Five descriptive criteria
1. Eligibility specified
2. Similar baselines
3. Intervention described
4. Side effects described
5. Short- and long-term measurements described
C. Two statistical criteria
1. Sample size described
2. Point estimates and measurements of variability presented for primary outcome measures

Table 2 describes the scoring for these studies. Note that because all the studies measured a binary variable, C2 was not applicable. Most of the studies did not describe a surgical or medication-base intervention, so B4 was usually not applicable. Also, none of the studies were blinded to the patients (A5). (These letter/number combinations are based on Table 1.)

Enhanced patient education and caretaker monitoring. The study by Malone et al. (22) enrolled 203 patients who had foot infection, ulceration, or prior amputation, excluding those requiring acute treatment. Patients in the active group received 1 h of education. The primary end point was a *combination* of subsequent limb amputation and recurrent ulcer or foot infection. Follow-up was by phone, letter, or physical evaluation. The authors reported a reduction of new events from 28% of limbs to 10% of limbs (no analysis per patient was provided) and a post hoc reduction of ulceration from 15 to 5%. The study was unblinded, and baseline characteristics were not described. It was scored as (4.5/2.5/1).

In the study by Litzelman et al. (23), patients received "usual care" (not defined) or a multifaceted intervention, including foot care education, behavior contract, and regular reminders. The providers of the intervention group were instructed to have patients remove their footwear, perform foot examinations, and provide additional foot care education. The care providers, who also assessed the end point, were blinded to assignment. Many baseline characteristics were not described (neuropathy, blood pressure, smoking among others), and only one third of eligible patients participated. Multiple end points (not prespecified in the protocol) were used without statistical penalties. Although the protocol seemed to improve self-care and provider care, the only significant difference in patient outcome (borderline, $P = 0.05$) was in "serious foot lesions" not further specified. The study scored (5.5/3.5/1).

The study by Lincoln et al. (24) randomized 172 patients with newly healed ulcers to receive targeted, one-on-one education or usual care. Randomization was concealed from the researcher. No difference in the subsequent incidence of foot ulcers in 6 or 12 months was noted despite better recommended foot care behavior in the intervention group. The study was graded as (5.5/3.5/1).

The study by McCabe et al. (25) randomized 2,001 patients into "control" and "index" groups. However, the index group was then subdivided and reallocated multiple times on the basis of *both* neuropathy and PVD, and only 127 high-risk subjects ultimately attended a diabetic foot clinic. It is not clear what end points were prespecified, how many patients had neuropathy versus PVD, whether the caretaker or assessors of end point were blinded, and what statistical methods were used. Ultimately, there was a decrease in major amputations but not minor amputations or ulcerations. The study scored (2/1.5/0).

Therapeutic footwear and insoles. Uccioli et al. (26) reported a small (69 subjects) prospective multicenter randomized follow-up of patients with previous foot ulceration. Patients were alternately (not randomly) assigned to wear their own shoes or therapeutic shoes. Baseline characteristics were poorly described, and caregivers were not blinded to assignment. After 1 year, there was a significant decrease in recurrence of ulcers (27.7 vs. 58.3%). The study was of poor design with a core of (3/1/1).

Reiber et al. (27) described a 2-year RCT of 400 patients with previous full-thickness foot lesions (presumably ulcers) or foot infections requiring antibiotics but without severe foot deformity. Patients were randomized into three groups: two types of insole inserts or own usual

Table 2—*Evaluation of studies on methods to prevent foot ulcers*

		Internal validity criteria										Descriptive criteria					Stat	
	Method	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	1	2
Malone et al., 1989	E	+/?	—	?	+	—	?	+	+	+	—	+	?	+	N	−/+	+	N
Litzelman et al., 1993	E	+/?	+	?	?	—	+	+	+	+	—	+	+	+	N	−/+	+	N
McCabe et al., 1998	E	?/?	?	?	—	—	?	+	—	+	—	—	?	+	N	−/+	?	N
Lincoln et al., 2008	E	+/?	—	?	+	—	+	+	+	+	—	+	+	+	N	−/+	+	N
Uccioli et al., 1995	F	—	—	?	?	—	?	+	?	+	—	?	?	?	N	−/+	+	N
Reiber et al., 2002	F	+/+	+	?	?	—	+	+	+	+	+	+	+	+	—	−/+	+	N
Piaggesi et al., 1998	D	+/?	—	?	?	—	—	+	?	+	?	+	?	+	—	−/+	+	N
Mueller et al., 2003	A	—/?	—	?	?	—	?	+	+	+	—	+	+	+	—	−/+	+	N
Lavery et al., 2004	T	+/?	+	+	?	—	+	+	+	+	+	+	—	+	N	−/+	+	N
Lavery et al., 2007	T	+/+	+	+	+	—	?	+	+	+	+	+	+	+	N	−/+	+	N
Armstrong et al., 2007	T	+/+	+	+	?	—	?	+	?	+	?	+	+	+	N	−/+	+	N

A, Achilles tendon lengthening; D, bony debridement; E, enhance education and patient monitoring; F, specialized footwear or insole; Stat, statistic criteria; T, temperature-guided avoidance therapy.

footwear. The use of the term "lesion" in the article was unclear, and a clear operational definition was not provided. The end point was somewhat ambiguous: "new cutaneous erosion extending into or through the dermis to deeper tissue or other cuts that did not heal within 30 days."

Only 400 of 763 eligible subjects participated. Other issues were that the study population was supposed to be high risk, but half of the subjects did not have neuropathy (only 58% were insensate to the 5.07 monofilament), probably accounting for the low overall recurrence rate. Caregivers were blind to assignment. Patients were similar at baseline. Withdrawal from the study was 16.5%. Otherwise, the study was well designed with a score of (8/3/1). There were no differences in the incidence of subsequent foot ulcerations among the three groups.

One additional study on footwear was found in ClinicalTrials.gov. Lavery et al. (K.R. Higgins, L.A. Lavery, K.A. Athanasiou, D.R. Lanctot, G.P. Costantinidis, C.M. Agrawal, and R.G. Zamorano, personal communication) conducted a National Institutes of Health-sponsored multicenter, RCT of 299 diabetic patients with severe neuropathy or history of previous ulcer or amputation, comparing a shear-reducing insole with standard therapy, which included extra depth shoes and vertical pressure-relieving molded insoles, podiatrist, neuropathy assessment, diabetes education, and vascular assessment (Lavery et al., personal communication, Clinical trial reg no. NCT00499356). The rationale for this study was based on the previous demonstration that this unique insole, constructed of two viscoelastic layers, with two intervening thin sheets of a low friction material as the middle layer, reduced peak shear force (but not vertical pressure) by 57%, compared with three other similar multilayer viscoelastic insoles that did not have the intervening layers (33). Among those with a previous ulcer (risk category 3), there was a relative 90% reduction in ulcers (13/38 vs. 1/40). Thus, at least in patients with a history of a foot ulcer, reducing shear stress in addition to standard reduction of vertical forces resulted in >90% reduction in foot ulcer recurrence. No benefit was found in patients without a previous plantar foot ulcer. The study scored (6/3.5/1).

Debridement. Only one randomized study comparing surgical bony debridement on the relapse of ulcers in 43 patients was found (28). The authors claimed reduction in foot ulcers from 8 to 3 ($P < 0.01$). The study was small and unblinded to both patients and the assessors of end points. No penalty was taken for multiple end points (total of 5). The study received a score of (2.5/2.5/1).

Achilles tendon lengthening. We found only one RCT of ATL (29), in which 64 patients with a history of forefoot ulcer were randomized to treatment with total-contact cast alone or to a combination of total-contact cast with ATL. There were two primary end points (ulcer healing and forefoot ulcer recurrence). Although it is stated that the study was randomized, approximately half the subjects in the ATL group were crossed over from the total-contact cast group before the start of the study. Early follow-up was via examinations. Subsequently, monthly follow-up was via phone, and the patients were to contact the study coordinator if they noted a skin breakdown. No data are provided on the success of phone contact attempts. Long-term verification of events was also via phone calls, but apparently without independent adjudication via examination or chart reviews. Recurrence of forefoot ulcers was significantly lower in the ATL group (15 vs. 59%). However, most of the effect was seen in the few weeks after healing with the Kaplan–Meier curves essentially parallel later on, suggesting that incomplete tissue healing may explain the difference. In addition, the rate of re-ulceration in the total-cast alone was high (59%) compared with control groups in other studies, for example, 17% by Reiber et al. (27). Of note, there was an increased rate of heel ulceration in the ATL group (13 vs. 0%). The study was terminated early because of perceived efficacy, but no prespecified stopping rules were described. No statistical penalty was taken for multiple time point observations. The study was scored (6/5/1).

Plantar foot temperature-guided avoidance therapy. Lavery et al. (30) reported an RCT of 85 subjects at high risk for foot ulceration (neuropathy and foot deformity or a history of ulceration or partial foot amputation). Standard therapy consisted of therapeutic footwear, diabetic foot education, and regular foot evaluation by a podiatrist. Enhanced therapy included the addition of infrared skin thermometer to measure temperature at six locations on the sole of the feet twice per day. When a difference of >4°F between the same locations of the two feet was noted, subjects were instructed to contact the nurse and reduce activity of the involved foot (higher temperature)

until the temperature gradient decreased to <4°F. During a 6-month period, new complications were found in 20% of the standard therapy group (seven ulcers and two Charcot fractures) versus 2% (one ulcer) in the intervention group (odds ratio 10.3, CI 1.2–85.3, $P = 0.01$). The study was single blinded (physicians). Relevant baseline values were not well described. It is possible that temperature monitoring led to more intense interaction with caretakers and thus better monitoring and therapy. Otherwise, the study was well designed with a score of (7.5/2.5/1).

A similar but larger study was subsequently reported by the same group (31). This was also physician blinded and a multicenter study of 173 individuals at high risk for foot ulcers. Randomization was computer-generated. To account for the possibility that effect of temperature monitoring may be due to more intense interaction with caregivers, the study was divided into three groups: *1*) standard therapy; *2*) structured foot examination twice daily by the patients using a mirror and a log book (The patient was instructed to call the nurse if any abnormality was noted.); and *3*) enhanced therapy group consisting of the addition of temperature measurements to standard therapy. If temperature increased by 4°F compared with the corresponding site on the other foot, patients were instructed to call the nurse and decrease activity until the gradient decreased to <4°F. After 15 months, the incidence of foot ulcer decreased from 30% in the first two groups to 8.5% in the plantar foot temperature-guided avoidance therapy. The study was well conducted and scored (8/3.5/1.5).

The study by Armstrong et al. (32) randomized 225 patients to two groups. Both groups received diabetic foot education and therapeutic footwear, and daily structured foot examinations were performed as described above. The intervention group also performed temperature-guided avoidance therapy as described above, although the patient's physician was blinded to the randomization compliance and dropout rates were not described. Furthermore, it is not clear whether the analysis was based on intent to treat. Overall incidence of subsequent foot ulceration was lower than in other studies (total of 8.4%). Nonetheless, the incidence of ulcers decreased by 62% (from 12.2 to 4.7%) in the group using temperature monitoring. The study scored (5/3.5/1.5).

Conclusions

It has now been 7 years since the position statement by the American Diabetes Association on preventive foot care in diabetes (34). Yet the quality of the data supporting the usefulness of such preventive care remains poor. Although there are many publications claiming efficacy based on retrospective studies, case-control studies, prospective observational, and nonrandomized studies, conclusions based on such studies are often discredited by later RCTs.

On the basis of our review, the evidence for most of the interventions to prevent a foot ulcer falls short. Clinicians lack guidance on what to do after a patient loses sensation. Anecdotally, many keep testing repeatedly with a monofilament, at scheduled intervals, although sensation rarely ever returns. The benefit of enhanced patient education or more intensive caretaker involvement, specialized footwear, surgical debridement of calluses, bone resection at pressure points, or decompression or neurolysis of the peroneal and tibial nerves is not supported by RCTs. The data for ATL seem enticing at first, in particular for prevention of forefoot ulcers. However, a closer look suggests that whatever benefit was seen was probably due to more complete tissue healing during the few weeks after apparent visual healing.

The data for plantar foot temperature-guided avoidance therapy are more compelling. Although no large-scale clinical trials have been reported, ~500 subjects have been involved to date in three randomized, controlled, and relatively well-designed studies (all funded by the National Institutes of Health) and the data have been remarkably consistent, documenting a large treatment effect (62–90% relative risk reduction). All three studies were blinded to the care provider who also assessed the end points and two specified intent-to-treat analyses; the study by Armstrong et al. (32) presumably used the same design but did not specify intent-to-treat analysis or describe the compliance and dropout rates. One confounder of these results is the possibility that using the temperature monitoring device altered patients' behavior such that they were more likely to examine their feet. However, it seems that the increased contact with the nurse in the temperature monitoring arm was mostly triggered by findings of elevated temperatures and not by visual or tactile detection of area of concern (31). It must also be noted that all three RCTs of temperature-guided avoidance therapy were performed by the same group of investigators, and this intervention has not yet been tested by an entirely independent group and needs to be validated in a different population.

Temperature monitoring could provide the next step in the hierarchy of steps to detect and prevent diabetic foot ulcerations. Evaluation would start with assessment of risk factors, such as severity and duration of the disease, blood pressure, lipids, poor diabetic control, smoking, evidence of peripheral artery disease and other vascular disease, weight and mobility, and engagement in activities that are more likely to result in injury, such as prolonged limb use. Subjective observation of progressive neuropathy, with loss of sensation and neuropathic pain, is followed by objective SWM monofilament testing. Finally, temperature measurement seems effective in identifying the subgroup of patients with insensate feet who are at risk for ulceration. When focal temperature differences >4°F are detected, reduced use of the involved foot, until the temperature returned to normal (usually 2–4 days but sometimes as long as 4 weeks), seems effective in reducing the likelihood of an ulcer.

Although the data do not support the use of therapeutic shoes or vertical stress-reducing insoles, shear stress-reducing insoles seem more promising. The reduction from 13 ulcers to one ulcer in the study (K.R. Higgins, L.A. Lavery, K.A. Athanasiou, D.R. Lanctot, G.P. Costantinidis, C.M. Agrawal, and R.G. Zamorano, personal communication) is intriguing, but the data have not been published and a larger RCT is clearly is needed. Furthermore, the special shear-reducing soles were beneficial only for patients who already had a foot ulcer or an amputation (there were no events in either of the lower-risk groups). A longer observation period may help to detect benefits in low-risk groups. It is notable, however, that the observed benefit was incremental to all other traditional prevention methods (extra depth shoes and pressure-relieving molded insoles, podiatrist, neuropathy assessment, diabetes education, and vascular assessment).

The observations regarding temperature-guided avoidance therapy are only applicable to similar populations, that is, high-risk diabetic patients with a history of foot ulceration or lower-extremity amputation or patients with peripheral sensory neuropathy with loss of protective

sensation, with a foot deformity such as hallux valgus or claw toes. They are not applicable to primary prevention or to patients not meeting these criteria. They are also not applicable to patients with severe PVD (ankle-brachial index <0.8), who were excluded. Temperature evaluation was only tested when SWM sensation was already lost, so data are needed regarding the benefit of temperature measurements in patients who have not yet lost the sensation to SWM sensation. When patients do qualify, intensive training in the proper use of the temperature measuring device and thorough discussion to increase motivation will be essential to ensure continuous use of the device.

Finally, any intervention may be associated with adverse effects. According to the Cochrane Handbook and The Adverse Effects Methods Group, if an intervention clearly does not work or has little potential benefit and is not widely used (such as in the first three methods described), it may not be worth devoting resources toward a detailed evaluation of adverse effects (35). In the case of ATL, adverse effects included a significant increase in incidence of heel ulcers (13 vs. 0%) and one local infection, further limiting the applicability of ATL. In the case of temperature-guided avoidance, adverse effects were not noted and are unlikely to be significant (perhaps with the exception of false-positive readings leading to unnecessary health care visits).

Once a patient has lost SWM sensation, self-measurement of sole temperature, followed by off-loading when temperature differences are detected, is currently the only scientifically supported tool for the prediction and prevention of diabetic foot ulcers in an insensate foot. Although the application of this concept for all patients with an insensate foot needs to be evaluated, it has the potential to reduce the risk of such patients progressing to ulcer development.

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