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SUPPLEMENT ARTICLE

A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable

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Abstract

Diabetic foot ulceration poses a heavy burden on the patient and the healthcare system, but prevention thereof receives little attention. For every euro spent on ulcer prevention, ten are spent on ulcer healing, and for every randomized controlled trial conducted on prevention, ten are conducted on healing. In this article, we argue that a shift in priorities is needed. For the prevention of a first foot ulcer, we need more insight into the effect of interventions and practices already applied globally in many settings. This requires systematic recording of interventions and outcomes, and well-designed randomized controlled trials that include analysis of cost-effectiveness. After healing of a foot ulcer, the risk of recurrence is high. For the prevention of a recurrent foot ulcer, home monitoring of foot temperature, pressure-relieving therapeutic footwear, and certain surgical interventions prove to be effective. The median effect size found in a total of 23 studies on these interventions is large, over 60%, and further increases when patients are adherent to treatment. These interventions should be investigated for efficacy as a state-of-the-art integrated foot care approach, where attempts are made to assure treatment adherence. Effect sizes of 75–80% may be expected. If such state-of-the-art integrated foot care is implemented, the majority of problems with foot ulcer recurrence in diabetes can be resolved. It is therefore time to act and to set a new target in diabetic foot care. This target is to reduce foot ulcer incidence with at least 75%. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords foot ulcer; prevention; recurrence; adherence; costs; classification

Introduction

Diabetic foot disease poses a heavy burden on the patient and the healthcare system. Nearly 600 million people worldwide are expected to have diabetes mellitus in 2035 [1], of which about 50% will develop peripheral neuropathy and 15–25% have been estimated to develop one or more foot ulcers [2,3]. Foot ulcers are a major risk factor for, and nearly always precede, foot infection and amputation. Furthermore, foot ulcers reduce patient mobility and quality of life. The estimated cost of treating a foot ulcer was approximately €10K in one large European study [4]. Therefore, by far the most effective way to prevent the heavy patient and economic burden is by preventing the foot ulcer. It is then rather disappointing to notice that foot ulcer prevention receives little attention, both in clinical practice and in scientific research. A shift in priority is needed.

Cost savings through prevention

Expenditure on diabetic foot care has been suggested to be about a third of total resource utilization for treatment of diabetes mellitus and its complications [5]. Of the total expenditure on diabetic foot care, ulcer prevention represents only a fraction of the costs incurred for treatment of the ulcer and its complications, in a ratio of approximately one to ten: for every euro spent on prevention, ten are spent on ulcer management [6,7]. If we consider one million patients with diabetes and an annual 2.2% ulcer incidence rate [8], total annual treatment costs for these foot ulcers are €220m. About half of the cost of ulcer treatment is spent on hospitalization and amputation treatment [4]. That means that if proper ulcer treatment would be able to prevent 20% of hospitalization and amputation (an effect size generally shown in wound healing studies) [9], total treatment costs would decrease to €198m (€220m $-$ 0.2 $\times$ €110m). However, if 50% of ulcers can be prevented with proper preventative care (an average effect size shown in 30 controlled studies on prevention) [10], costs for the same population of patients can be reduced to €110m (0.5 $\times$ €220m), a difference in saving of €88m per million persons with diabetes. In support of this, a cost-utility simulation based on Markov modelling showed that intensified preventative care would be cost-effective in at-risk patients if a 25% reduction in foot ulcer incidence is achieved [11]. In addition, an analysis of US Medicaid health cost data suggested that for each $1 saved by the elimination of low-cost preventative services provided by podiatric physicians, the associated increase in hospitalization charges was $48 [12]. These analyses clearly show the cost-saving potential of prevention.

Prevention underexposed in research

Of the 100 most recently published randomized controlled trials (RCTs) on the diabetic foot listed in PubMed as of 12 April 2015 (search terms 'Diabetic foot' and 'RCT'), 62 are on ulcer healing and only six on ulcer prevention (Figure 1). So, for every RCT on prevention, ten are conducted on healing. A further disparity is that trials on prevention are investigator initiated and most often include the comparison of an intervention with good-quality standard foot care, whereas trials on ulcer healing are mostly industry driven, often assessing the

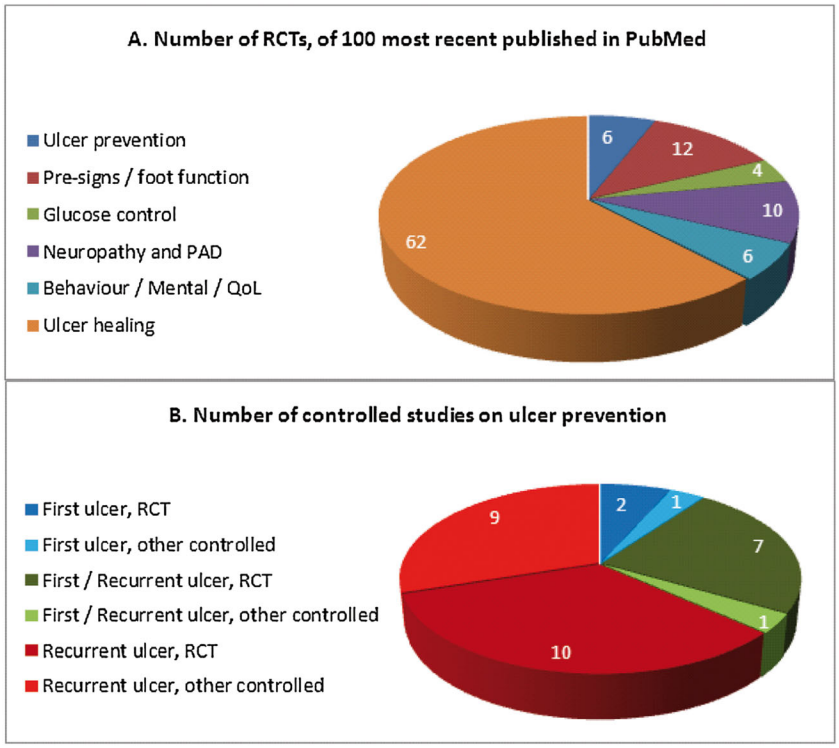

Figure 1. (A) Distribution of randomized controlled trials (RCTs) per outcome category among the 100 most recently published trials on the diabetic foot in the PubMed database, as of 12 April 2015; (B) number of controlled studies (i.e. RCTs and non-randomized controlled studies) on ulcer prevention, differentiated to first or recurrent ulcer as outcome, as identified in the 2015 International Working Group on the Diabetic Foot systematic review on ulcer prevention [10]. PAD, peripheral artery disease; QoL, quality of life

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efficacy of another wound-care product in addition to often badly defined foot care. Because the market introduction of wound-care products does not formally require proven efficacy, but only safe use, lower efficacy can be expected from trials on these products. Compared with prevention, this undermines the value for money invested in research and in diabetic foot care.

Also, within the research topic of ulcer prevention, a clear disparity is present: only three of the 30 controlled studies identified in the 2015 International Working Group on the Diabetic Foot (IWGDF) systematic review on ulcer prevention focus specifically on a *first* foot ulcer (Figure 1) [10]. Eight studies use a mixed population of patients with and without ulcer history, while 19 studies focus specifically on ulcer recurrence. This dominance of studies on recurrence may exist because (1) patients with ulcer history are at greatest ulcer risk, which increases the relevance to study these patients, and (2) trials on ulcer recurrence require fewer patients to demonstrate efficacy given the higher expected event rate. So, while screening and preventative treatment for patients without foot ulcer history is common practice in many settings, the evidence base supporting such practice is meagre.

Can we prevent a first foot ulcer?

In all prospective studies and risk classifications, persons with a previous foot ulcer are found to be at the highest risk for future ulceration [13]. Reported ulcer recurrence rates are 30–40% in the first year after an ulcer episode [14,15], compared with 7.5% annual incidence for patients with peripheral neuropathy and no ulcer history [8]. Thus, if the first ulcer is prevented or postponed, ulcer incidence rates will drop substantially. Because the evidence base for prevention of a first foot ulcer is practically non-existent [10], we need to ask ourselves if we can prevent a first foot ulcer in persons with diabetes.

A 'no' as an answer is rather unsatisfactory. It would mean that while millions of persons with diabetes are at risk for ulceration, we cannot intervene to prevent the problems awaiting them. This does not reflect current opinion and does not abide to consensus-based standards of good-quality care. For 'yes' as an answer, we have few clues as support. There are indications that home monitoring of foot temperature, therapeutic footwear, and advice within an education session that patients adhere to can help [10]. Yet, patients may be reluctant to accept such treatment considering they did not yet experience a foot ulcer, and cost-effectiveness may be an issue because ulcer incidence rates are relatively low. These few clues being unsatisfying on its own, we call out for action: healthcare providers and researchers should combine efforts to build up an evidence base on prevention of a first foot ulcer.

We need more insight in the effect of interventions and practices already applied globally in many settings. Some of these have been studied, such as foot screening, treatment of pre-signs of foot ulceration, advice on proper footwear, and patient education, and are listed in the IWGDF Guidance on Prevention [16], but the use of these interventions is based on low quality of evidence or expert opinion. A better understanding requires recording of interventions and outcomes in a systematic way, as a form of practice-based evidence, to initially progress our understanding on effective treatment. Furthermore, it requires well-designed large-sample studies on cost-effectiveness.

Recurrent foot ulcers: 75% are preventable

Because of the high risk involved, prevention of ulcer recurrence is one of the most important current topics in diabetic foot disease. But why is it so difficult to prevent a foot ulcer from recurring [17]? One reason is that patients consider themselves, or are considered by their caregiver, not to have a foot problem after they heal from a foot ulcer, while we know they have. We therefore agree with colleagues on a change in syntax in diabetic foot care, where prevention equals 'remission', to increase awareness for the foot problem and to promote the need for adequate follow-up and foot care [18]. Another reason is that many precipitating factors that caused the ulcer in the first place, such as peripheral neuropathy, foot deformity, and increased plantar barefoot pressure, have not been resolved after healing (unless the foot is operated on). A third reason is that the transition from a healing device such as a walker or total contact cast to a prevention modality such as therapeutic footwear likely increases plantar pressure at the healed ulcer location and therefore risk of recurrence. A fourth reason is professional non-adherence to provide recommended treatment, including foot care, therapeutic footwear, and patient education [19]. A final reason is patient non-adherence to follow advice on proper foot care or to wear therapeutic footwear [20]. All these reasons reduce efficacy in the prevention of ulcer recurrence.

The 2015 IWGDF systematic review on ulcer prevention [10] shows there is some evidence to support *integrated foot care*, consisting of a combination of professional foot care, patient education, and therapeutic footwear, in the prevention of ulcer recurrence. *Self-management* is

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considered important but has only been studied sufficiently and proven effective for the home monitoring of foot skin temperatures as a diagnostic method, in combination with proper follow-up when necessary. Studies on *patient education* show that while knowledge of foot problems and foot care behaviour can improve, ulcer recurrence is not prevented by limited (i.e. one or two sessions) education. There is now high-quality evidence to support the use of *therapeutic footwear* that has a demonstrated pressure-relieving effect and that is consistently worn by the patient. Finally, *foot surgery* can be effective in selected patients, but more well-designed studies are needed before definitive statements about safety and efficacy can be made.

Particularly interesting is to assess the potential *cumulative* preventative effect of these interventions. In Table 1, the median effect sizes for all identified controlled studies in the 2015 IWGDF systematic review on ulcer prevention [10] in each of the five aforementioned intervention categories are shown. Except for patient education, the median effect sizes demonstrate to be large, over 60% in three categories, showing their large potential for prevention. For integrated foot care, effect sizes found are <50%, but these are from studies that did not include state-of-the-art interventions. Therefore, one can imagine the effect that may be achieved when effective state-of-the-art single interventions are combined in an integrated foot care approach: a 75–80% reduction in ulcer recurrence incidence seems possible, although this should be demonstrated in properly designed randomized controlled trials. If confirmed, and if such a state-of-the-art integrated approach is implemented in diabetic foot care, the vast majority of foot problems after healing of the ulcer can be prevented, and with that the large burden of foot ulcer recurrence in diabetes.

Adherence

Treatment adherence has clearly been shown in the 2015 IWGDF systematic review on ulcer prevention to be a significant factor in outcome [10]. Each of a total eight studies that investigated the effect of adherence on ulcer prevention showed that patients who are adherent to advice given, to undergoing professional care, to monitoring their foot temperatures, or to wearing their therapeutic footwear, have significantly better outcomes than those who are non-adherent. Table 1 shows the mean effect sizes from these studies for the four intervention categories where adherence plays a role. Effect sizes are large in all categories, ranging from 58% to 98%. Interestingly, while the data on efficacy of patient education shows no general effect, positive outcomes are obtained for patients who are adherent to the advice given within the education program. Combining the effect sizes found on treatment adherence with those found on treatment efficacy further supports the large potential in preventative care. This strengthens the proposition that problems with foot ulcers and their complications can be mostly prevented when effective interventions are used in an appropriate way.

For this reason, non-adherence should be discussed with patients and should guide treatment choices in clinical practice, much more than is currently the case. It remains a challenge how we can achieve better adherence. It starts with knowing and understanding why a patient does not adhere to a given intervention. For the topic of footwear adherence, these reasons have been explored, but more effort is needed in this area [20,21]. We found no studies in the literature on the effect of interventions that aim to increase treatment adherence in the diabetic foot, and no current trials seem to be underway [10]. Therefore, investigations into factors that determine adherence and into interventions that aim to increase adherence are urgently needed.

Table 1. Effect sizes in foot ulcer risk reduction for five intervention categories as assessed for the 2015 International Working Group on the Diabetic Foot systematic review on ulcer prevention [10]

	Treatment efficacy			Effect of treatment adherence	
Intervention category	*n*	Median effect size[a] (%)	Range (%)	*n*	Mean effect size[b] (%)
Integrated foot care	5	33.3	9.1 to 100	3	83.0
Self-management	4	66.2	−5.4 to 90.0	1	98.0
Patient education	2	−13.4	−26.3 to −0.5	2	85.5
Therapeutic footwear	10	63.6	−14.6 to 92.9	2	58.1
Foot surgery	9	70.8	10.4 to 100	0	—
State-of-the-art integrated approach		75–80			

The treatment efficacy of the state-of-the-art integrated approach is an estimated range of what may be achievable based on the effect sizes of the single interventions if combined into a state-of-the-art integrated foot care approach.
n, number of controlled studies.
[a]Median effect size presented as the percentage foot ulcer risk reduction in the group of patients in the intervention arm compared with the control arm receiving usual care.
[b]Mean effect size, presented in percentage foot ulcer risk reduction in patients who are adherent to treatment, when compared with patients who are non-adherent to treatment.

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A new International Working Group on the Diabetic Foot risk classification

Persons with a previous foot ulcer are in the highest risk category of current risk classifications [2]; for the IWGDF risk classification, this is grade 3. However, in daily clinical practice, a large variation in disease severity exists within this risk group of patients. Some patients continuously recur, whereas others have only one ulcer episode in their life. Differentiation in disease severity within this risk category, with a corresponding differentiation in level of preventative care, seems indicated.

Factors that can be considered for more differentiation in risk are available from prospective studies on ulcer recurrence. These factors can be divided into foot-specific factors (e.g. previous ulcer location [22,23], presence of minor lesions [24], and amputation history [25]), biomechanical factors (e.g. barefoot peak plantar pressure [24,26] and in-shoe peak plantar pressure [24]), biomedical factors (e.g. presence of peripheral artery disease [22,23], HbA_{1c} [23], osteomyelitis of the healed ulcer [23], and elevated C-reactive protein [23]), and behavioural factors (most notably adherence [24]). While some prospective risk factor studies have combined several of these factors [24], a comprehensive multivariate analysis still remains to be conducted. Such analyses on large sample sizes can establish more certainty on the relative role of these factors and, subsequently, may help in developing a more detailed risk classification system.

An important aspect to be considered in any future study on recurrence is where the ulcer develops. In line with the IWGDF risk classification, we defined a 'recurrent ulcer' in the 2015 IWGDF systematic review on ulcer prevention as any ulcer after healing of a first ulcer, regardless of location on the foot [10]. Because none of the studies on recurrence provide specific information on whether the new ulcer developped at the same location as the previous one, another definition was not possible. Nevertheless, an ulcer that develops at a metatarsal head 6 months after healing of an ulcer at the very same location is clinically clearly different to an ulcer in the same patient that develops after 2 years on the dorsal side of the contralateral foot. To better understand foot ulceration and to better predict outcome in the highest risk group, we ought to take this difference into account. Investigations in this area require long-term recording of treatment provided, patient characteristics, and presence, location, and timing of a foot ulcer. Setting up such registries for such recording has proven possible for various aspects of medicine (e.g. surgical registries and cancer registries) and should therefore be possible for foot ulcers in diabetes.

What should we be doing?

To better inform clinicians and practitioners about effective treatment to prevent a *first foot ulcer*, we need large-scale registries on treatment in daily practice to establish a practice-based evidence base and, in addition, well-designed controlled studies in first line of care that take cost aspects into account.

To prevent *foot ulcer recurrence*, we need to (better) implement currently available state-of-the-art knowledge from well-designed RCTs. The new IWGDF Guidance on Prevention provides clinicians and practitioners with various recommendations on proper preventative care that can, if implemented, have a huge positive impact on the patient, economic, and social burden of diabetic foot disease [16].

We hope the following research agenda will guide researchers, clinicians, and funding bodies in prioritizing their limited resources.

- RCTs on the cost-effectiveness of interventions to prevent a first foot ulcer.
- Studies on the effect of interventions on incidence of first foot ulcer through a practice-based approach by setting up data registries in first-line foot care.
- RCTs on the (cost-)effectiveness of a state-of-the-art integrated foot care program to prevent foot ulcer recurrence.
- RCTs on the effectiveness of interventions to improve treatment adherence, and of improved adherence on foot ulcer incidence.
- Comprehensive analyses of predictive factors of foot ulcer recurrence from large-scale data registries that include biomedical, biomechanical, and behavioural factors.
- Studies on the effectiveness of using different time intervals for foot screening for risk factors, so as to determine the optimal time frequency for foot screening.

Conclusions

In this article, we have presented the cost-saving potential of preventative foot care, the gaps in our knowledge on ulcer prevention, the disparity in focus between ulcer prevention and ulcer healing, and the enormous potential in the prevention of foot ulcer recurrence in diabetes. We now need to shift priority in diabetic foot care and research to the prevention of foot ulcers. Two important actions in preventative foot care are a) to do what we say we should be doing, that is, to implement knowledge in daily foot care, and b) to improve treatment adherence. If we can achieve this, an enormous positive effect in ulcer prevention can be expected. International societies such as the

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International Diabetes Federation and IWGDF stress the burden of lower-extremity amputation in diabetes and have set goals to reduce amputation incidence by at least 50% [27]. It is now time to act and to set a new target in diabetic foot care. This target is to reduce foot ulcer incidence with at least 75%.

Conflicts of interest

The authors have none to declare.

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