RESEARCH ARTICLE

The future for diabetic foot ulcer prevention: A paradigm shift from stratified healthcare towards personalized medicine

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ABSTRACT

Prevention of diabetic foot ulcers is important to reduce the burden of diabetic foot disease. However, we found that ulcer prevention is underexposed in research and clinical practice. Barriers to explain this are seen in patient's goal-setting; in the lack of interdisciplinary teams for ulcer prevention; in sample sizes and funding for research; in industrial engagement; and in limited understanding of ulcer development. Rather than separately solving these barriers, we propose a paradigm shift from stratified healthcare towards personalized medicine for diabetic foot disease. Personalized medicine aims to deliver the right treatment to the right patient at the right time, based on individual diagnostics. Different treatment strategies should be available for different patients, delivered in an integrated, objective, quantitative and evidence-based approach. More than on the classical risk factors of peripheral neuropathy and peripheral artery disease, individual diagnostics should focus on modifiable risk factors for ulceration. This includes structured biomechanical and behavioral profiling, while new research with (big) data science may identify additional risk factors, such as geographical or temporal patterns in ulceration. Industry involvement can drive the development of wearable instruments and assessment tools, to facilitate large-scale individual diagnostics. For a paradigm shift towards personalized medicine in prevention, large-scale collaborations between stakeholders are needed. As each ulcer episode not prevented costs about €10,000 in medical costs alone, such investments can be cost-effective. We hope to see more discussions around this paradigm shift, and increasing investments of energy and money in diabetic foot ulcer prevention in research and clinical practice.

KEYWORDS
diabetic foot, foot ulcer, prevention, personalized medicine, stratified healthcare

[Correction added on 26 January 2020, after first online publication: the abstract title has been corrected and Figures 2 and 3 have been interchanged in this version.]
INTRODUCTION

Foot ulcers are the leading cause of hospitalization, amputation, reduced mobility, loss of social participation, and lower quality of life in people with diabetes. In fact, some people may fear loss of a limb more than death. Diabetic foot disease poses a huge cost burden to health care systems. The burden of diabetic foot disease is ranked in the top-10 of all medical conditions, and up to 34% of all people with diabetes are estimated to have a foot ulcer somewhere during their life. Prevention of foot ulcers and amputations is crucial to decrease this enormous patient, healthcare, and societal burden.

Four years ago, in the special issue of this journal related to the International Symposium on the Diabetic Foot, we argued that a shift in priority in care and research in diabetic foot disease was needed: more emphasis should be put on the prevention of foot ulcers, rather than on healing. The aim of the current article is to (a) assess the progress of this shift, (b) to describe barriers in prioritizing ulcer prevention in research and clinical practice, and (c) to discuss the potential of personalized medicine as the future of diabetic foot ulcer prevention.

ULCER PREVENTION IS STILL UNDEREXPOSED IN RESEARCH

In our previous article, we showed that for every randomized controlled trial (RCT) on prevention, 10 were conducted on ulcer healing (Figure 1A). We have repeated this search using the same search string, to assess the progress towards a shift in research priorities. We found that of the 83 RCTs on diabetic foot disease published between 2015 and 2019, only two were on ulcer prevention, and 72 were on ulcer healing (Figure 1B). So rather than a shift towards an increased research priority of prevention, the prevention to healing ratio in RCTs was only 1:36 in the last 4 y. With two published trial protocols and some ongoing trials identified from our systematic review of the trial registries, it is hoped that more than two RCTs on prevention will be published in the coming 4 y. However, the growing discrepancy over the last 4 y is concerning, and shows that diabetic foot ulcer prevention remains underexposed in research. We continue to urge researchers and funders to shift their priorities, given the large potential of prevention in reducing the enormous burden of the disease for patients, healthcare and society.

ULCER PREVENTION IS ALSO UNDEREXPOSED IN CLINICAL PRACTICE

Information on ulcer treatment in interdisciplinary clinics, and their results on amputation prevention, is widely available: from single center or regional studies, to national audits or databases. However, efforts on ulcer prevention are scarcely reported; and if they are, this is mostly indirect, through changes in ulcer incidence over time that might reflect some effect of preventative care. While this is at least partly the result of poor data availability on ulcer incidence, this also reflects in our opinion a limited attention for ulcer prevention in clinical practice. Prevention mostly takes place in community healthcare, often by individual healthcare providers. Pathways in treatment or referral may exist, but depend on local initiatives and are not clearly described in guidelines or other forms of written (scientific) publications. This is markedly different from elaborate specialist interdisciplinary foot care teams and pathways available for those who do ulcerate.

A possible reason can be found in national guidelines. Many guidelines provide predominantly recommendations on risk assessment in their chapter on ulcer prevention, with almost no actual treatment recommendations. And when recommendations on treatment are provided, these are mono-disciplinary and rather generic. While actual clinical practice may differ from guidelines, this underrepresentation in guidelines reflects in our opinion an underexposure of prevention in daily practice; it also creates an unwanted situation of potential regional differences in care depending on local initiatives and individual provider preferences, rather than an evidence-based care approach supported by guideline recommendations.
The exceptions are the guidelines from the International Working Group on the Diabetic Foot (IWGDF), who recommend integrated care for ulcer prevention. As authors of this guideline, we have argued that if such integrated care is state-of-the-art it may prevent 75% of the foot ulcers, based on the combined effect sizes found for ulcer prevention in adherent patients in trials on integrated foot care (effect size 83%), therapeutic footwear (58%), self-management (98%), prophylactic surgery (71%), and patient education (86%). However, such state-of-the-art integrated foot care does not seem to be widely implemented in clinical practice. Furthermore, even with these international evidence-based guidelines, the focus is almost entirely on the prevention of ulcer recurrence, not on preventing the first foot ulcer in a person with diabetes. This amplifies the problem of prevention in clinical practice.

4 | BARRIERS IN PRIORITIZING ULCER PREVENTION

Unfortunately, there are no published data or commentaries that explain the lack of importance seemingly given in research and clinical practice to diabetic foot ulcer prevention. Based on the discussions held with colleagues within IWGDF and within research collaborations, we describe five barriers that may explain this lack of priority.

1. Barriers with persons at risk of diabetic foot ulceration: The focus in ulcer prevention is on NOT getting a foot ulcer, thereby being a performance-avoidance goal. While remaining ulcer-free can be a strong motivation and positive outcome for some patients, avoidance goals are associated with negative self-esteem and depression, and ineffective disease problem solving. This is reflected in qualitative research on diabetic foot disease, describing that people at-risk have feelings of lack of control in preventing foot ulcers, limited knowledge, lack of perceived need for self-care, and negative views on therapeutic footwear. It is therefore understandably hard to keep up daily ulcer prevention self-care, which may explain the decreased self-care adherence frequently seen over time. This is opposite to ulcer healing, which is a performance-approaching goal (regaining an intact foot, staying out of hospital, reducing clinic visits, and regaining independence), and where patients describe their healing device as preferable after they understand its healing benefits. Redefining goal-setting in ulcer prevention probably requires a more psychosocial approach.

2. Barriers with clinicians: Clinicians who can commit the majority of their time to patients with diabetic foot disease, and thereby maximize both their expertise and outcomes, are those working in dedicated and specialized teams, mostly in university-based or tertiary hospitals. However, the primary focus in these teams is on ulcer healing. Once an ulcer heals, patients in most countries are discharged to community-based healthcare, where specialized focus on diabetic foot disease is often uncommon. It is therefore hard for clinicians to dedicate their career towards ulcer prevention.

3. Barriers with researchers: Support for research is limited in community settings where most foot care towards ulcer prevention takes place. This creates a gap between researchers and clinicians, as most researchers work within university medical settings and with diabetic foot teams that focus on ulcer management. Additionally, trials on ulcer prevention require large sample sizes to attain adequate statistical power (see for example), in particular in preventing a first ulcer because the event rate over time is relatively low. Large-scale collaborations between researchers and (community-based) clinicians are needed to overcome this barrier, for which significant funding (already a challenge) and carefully managed coordination are essential.

4. Barriers in industrial engagement: Similarly as 4 years ago, we found in our RCT search update that ulcer healing trials are mostly industry-driven, whereas ulcer prevention trials are investigator-driven. This might be explained by the lack of financial gain to be expected from preventative interventions, which is directly and indirectly associated with the lack of or minimal reimbursement. Perhaps because preventative interventions focus largely on behavior (eg, education, self-care, self-management), which is hard to monetize, or because the financial margins of products such as therapeutic footwear or temperature monitoring devices are much smaller compared to wound healing products. Furthermore, available robust technologies that have an evidence base to support their use, such as with plantar pressure measurements and temperature monitoring, are not used on a large scale in clinical practice, thereby missing opportunities to engage industry in this field. Investments are needed upfront (in ulcer prevention) to save money (for ulcer treatment) later on, but such “chain thinking” and proportionate financial payment of stakeholders has not yet become common in reimbursement policies in care for diabetic foot disease. Regardless of the underlying reasons, a lack of industrial engagement means limited investment in ulcer prevention.

5. Barriers in understanding ulcer development: From an epidemiological perspective, our understanding of ulcer development is limited at best. There are insufficient studies on the risk for and patterns of re-ulceration, and high-quality population-based studies on first ulcer development are not available, outdated or involving non-modifiable factors at best. As a consequence, ulcer risk stratification is based on limited information from predominantly irreversible variables. This is best seen in the highest risk stratum of ulceration according to the IWGDF risk stratification system, which is simply made up of all persons who have a history of foot ulceration. This oversimplifies “high risk”. For example: Figure 2 shows three patients, all at high risk, while their ulcer history pattern clearly differs. Better understanding of pathways of (re-)ulceration is needed, to better target preventative treatment.
Personalized medicine is a worldwide evolutionary process in healthcare, of which research and implementation is still in an early stage. This shift, when applied to diabetic foot disease, is depicted and exemplified in Figure 3 and its legend. One may argue that some form of personalized medicine is commonly seen already in daily practice, with clinicians making decision based on contextualizing a patient's situation and preferences. However, the evidence-base is very small, and quantitative and objective individual parameters are hardly obtained and used. As this may lead to arbitrariness in treatment, a paradigm shift to fully exploit personalized medicine is needed. This shift needs to take place in research and clinical practice, with changes going hand in hand, and evolving over time. We will describe the core elements here, as starting point for discussions, new research and changes in clinical practice towards personalized medicine in diabetic foot disease.

The key of personalized medicine is to deliver the right treatment to the right person at the right time. Personalized medicine is a worldwide evolutionary process in healthcare, of which research and implementation is still in an early stage. This shift, when applied to diabetic foot disease, is depicted and exemplified in Figure 3 and its legend. One may argue that some form of personalized medicine is commonly seen already in daily practice, with clinicians making decision based on contextualizing a patient's situation and preferences. However, the evidence-base is very small, and quantitative and objective individual parameters are hardly obtained and used. As this may lead to arbitrariness in treatment, a paradigm shift to fully exploit personalized medicine is needed. This shift needs to take place in research and clinical practice, with changes going hand in hand, and evolving over time. We will describe the core elements here, as starting point for discussions, new research and changes in clinical practice towards personalized medicine in diabetic foot disease.

The key of personalized medicine is to deliver the right treatment to the right patient at the right time. This still covers the cornerstones of ulcer prevention (education and self-management; adequate footwear; treatment of risk factors), but different treatment strategies within each cornerstone should be available for different patients (Figure 3). Such personalized treatment plans can reduce the self-care burden for people with diabetes, as they will only have to perform the care targeted to their situation, rather than all possible treatment options available. Furthermore, these plans should also incorporate outcomes beyond "not ulcerating," to assist in changes in goal-setting (barrier 1). A promising target outcome is safe physical activity levels. Physical activity is associated with various health benefits and quality of life improvements.
which means that performance-approach goals can be formulated. Ensuring this is done safely means providing people with diabetes with the tools to increase their (weight-bearing) physical activity without unnecessarily increasing their foot ulcer risk.\textsuperscript{30,31} Other performance-approach goals that are related to the reduction of foot ulcer risk and can be monitored using (wearable) smart technology are continuous low plantar pressures in the footwear worn, high adherence to the targeted individualized interventions, and a reduced number of abnormal temperature differences between the feet.\textsuperscript{19}

Personalized treatment should be delivered in an integrated approach, in line with current IWGDF recommendations.\textsuperscript{19} For this, specialized interdisciplinary ulcer prevention teams need to be set up. These teams should work hand in hand with the current interdisciplinary teams focusing on ulcer healing, with some professionals/clinicians (eg, podiatrists, shoe technicians, psychologists, and rehabilitation physicians) being part of both teams. At the same time, ulcer prevention teams should collaborate closely with community care, or be integrated in community care. Clear referral pathways should be made, to provide interdisciplinary care to those patients who need it most, while patients need to be transferred to community when the highest risk factors are safely negotiated or cared for, to ensure cost-effective organization of care. Creating such dedicated ulcer prevention teams will also aid in overcoming barrier 2.

To deliver such targeted personalized treatment, comprehensive individual diagnostics of people with diabetes are needed. More than on the classical risk factors of peripheral neuropathy and peripheral artery disease, individual diagnostics in personalized medicine should focus on modifiable risk factors. Based on currently available evidence

\textbf{FIGURE 3} Paradigm shift from stratified healthcare to personalized medicine in diabetic foot disease. IWGDF = International Working Group on the Diabetic Foot. IWGDF risk stratification is done according to.\textsuperscript{19} Three cornerstones of the IWGDF Prevention Guideline are depicted: education (green), footwear (brown), and risk factor treatment (blue). In stratified healthcare, a person would be screened for the five irreversible risk factors that determine someone’s risk status,\textsuperscript{19} and all guideline recommendations on education, footwear and risk factor treatment that are given for their risk stratum apply. In personalized medicine, specific recommendations on education, footwear and risk factor treatment are applicable to individual patients, depending on an individual assessment of multiple modifiable risk factors (eg, biomechanical and behavioral) and personalized treatment plans. For example, patient 1 (left) may get education on foot self-care via a smartphone application, custom-made footwear and corrective bone surgery to improve foot biomechanics, while patient 3 (right) is better off with home care support for her foot self-care, custom-made indoor footwear, and frequent callus removal by a home care nurse.
on ulcer development, this includes biomechanical and behavioral profiling of patients. For biomechanical profiling, barefoot and in-shoe pressure and tissue stress patterns are the most suitable candidates. Behavioral profiling includes assessing someone’s capacities, opportunities and motivation for preventative behavior, social and financial support, treatment adherence, and physical activity patterns. While clinicians may already be aware of these factors in their patients, personalized medicine should provide (currently hard-to-obtain) objective, quantitative and structured assessment thereof, and link outcomes with biomechanical and psychosocial treatment pathways.

It will be important that diagnostics are easily performed and results easily obtained, without requiring large resources per individual. Technological advancement and industry involvement can be expected to drive the development of affordable and reliable wearable instruments and (online) assessment tools, to facilitate large-scale individual assessment. When research can link the findings from diagnostics with clinical outcomes, understanding of (risk factors for) ulcer development will improve (barriers 3, 4, and 5).

Beyond biomechanical and behavioral profiling, new research with (big) data science may also find additional risk factors, for example in geographical and temporal patterns in ulceration, in linking such patterns with ethnicity or socioeconomic status, or in the role of (epi)genetics. Furthermore, artificial intelligence and machine learning may provide analyses and outcomes beyond state-of-the-art understanding of the relation between risk factors and foot ulceration. While some of these factors or relations then identified may not be modifiable on an individual level (e.g. geographical patterns or genetics), they do inform targeted treatment in ulcer prevention, and will thereby contribute to delivering the right treatment to the right patient at the right time.

To deliver on a paradigm shift to personalized medicine, large-scale collaborations between stakeholders are needed. These include the registration of foot ulceration in national databases, datasets with standardized core outcomes obtained via individual diagnostics, and subsequent (big) data linkage infrastructures. Such initiatives should include clinicians in community healthcare and tertiary care, and researchers working across settings. Setting up such collaborations will require significant efforts and resources from all stakeholders involved, especially with individualized diagnostics of the large and continuously growing number of people with diabetes. However, we argue that the current lack of knowledge and current efforts employed are even more expensive, as each ulcer not prevented costs €10,000 per ulcer episode in medical costs alone, with the additional societal burden in lost productivity and quality of life not even taken into account.

6 | CONCLUSIONS

Diabetic foot ulcer prevention is still underexposed in research and clinical practice, despite that all working in diabetic foot care agree that it is highly important. In this article, we identified a number of barriers that, in our opinion, prevent prioritizing ulcer prevention. To overcome these barriers, we propose a paradigm shift from stratified healthcare towards personalized medicine, to get the right treatment to the right patient at the right time. We hope to see more discussion around this paradigm shift, and increasing investments of energy and money in diabetic foot ulcer prevention in research and clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to the content of this article.

AUTHORS’ CONTRIBUTIONS

J.v.N. wrote the first draft of the article, based on numerous conversations between the three authors. S.B. and J.W. commented on the draft. J.v.N. adapted the draft accordingly. All authors approved the final version.

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