DFA Guides You Through

This year’s research in diabetic foot disease

Scientific and clinical developments between Diabetes Week 2016 and 2017
Introduction

Diabetic Foot Australia (DFA) aims to end avoidable amputations in a generation. DFA has engaged with multiple partner organisations across Australia to create a national body for people suffering diabetic foot disease. A multidisciplinary approach to the patient with diabetic foot disease is critical to the delivery of a gold standard of treatment. DFA also advocates a coordinated approach by health professionals, researchers, government and industry as critical to achieving our vision of ending avoidable amputations in a generation.

A key objective of DFA is supporting health professionals to improve clinical and quality of life outcomes for people with diabetic foot disease, and providing diabetic foot researchers with the infrastructure to accelerate high quality research. One method to achieve these aims is the “DFA Guides You Through” series. In this series, DFA summarizes and translates important diabetic foot disease research topics to help support clinicians and researchers.

The current “DFA Guides You Through” document, which is part of our Diabetes Week 2017 actions, discusses the latest scientific and clinical developments in diabetic foot disease. Since Diabetes Week 2016, we have seen a great variety of developments. Keeping track of what is out there and finding the time to read it seems a near impossible job at times. We therefore “guide you through” the most important developments between July 2016 and July 2017.

In this document, we follow the chapters of the International Working Group on the Diabetic Foot (IWGDF) Guidance. We start with research on epidemiology, and continue with the five chapters that make up the IWGDF Guidance: prevention, footwear and offloading, peripheral artery disease, diabetic foot infection and wound healing interventions.
Contents

1. Epidemiology ................................................................. 4
2. Prevention of diabetic foot ulcers ....................................... 6
3. Footwear and offloading ...................................................... 8
4. Peripheral artery disease ................................................. 10
5. Diabetic foot infection ....................................................... 12
6. Wound healing interventions ............................................. 14
Conclusion ........................................................................... 16
1. Epidemiology

Epidemiology is the backbone of many studies, as it accurately describes the problem of diabetic foot disease and the enormous burden it poses on people suffering from the disease, clinicians, and society. The last twelve months have seen various unique papers on this topic.

Armstrong, Boulton and Bus published one of the most important papers in the field of the last decade (1). They show, in the New England Journal of Medicine, that the lifetime incidence of foot ulceration in people with diabetes lies between 19% and 34%. For people with a healed foot ulcer, the one-year ulcer recurrence is a staggering 40%; this increases to 60% after three years. As advocated by the authors, by others and by DFA, this is further evidence that it is better to use the word “diabetic foot remission” when you talk with your patients, rather than telling them their ulcer has healed.

Another major document comes from the UK, where the second report from the National Diabetes Foot Care Audit England and Wales was published (2). Based on data from an impressive 11,073 patients, they conclude that “The longer it takes for someone with a new diabetic foot ulcer to reach expert assessment the more likely it is that the ulcer will be severe. It seems likely that pathways designed to shorten time to expert assessment would reduce the frequency of severe ulcers.” A conclusion any Australian clinician can use in their daily practice. At the same time, this report should stimulate us to implement the Australian Diabetic Foot Ulcer Minimum Dataset (3), so that we can discuss our own findings here in the future.

For the Australian situation, a large prospective population-based study identified the real burden of (diabetic) foot disease in our hospitals. Lazzarini and colleagues closely examined 733 inpatients from five hospitals, resulting in a sample representative for Australia (4). Overall, almost 10% had active foot disease. Of the people with diabetes (a quarter of all inpatients), almost 20% had active foot disease present. These results show that the burden of foot disease, both in people with but also in people without diabetes, is higher than expected.

Two papers report detailed findings on the costs of diabetic foot disease, always an important argument in discussions with health authorities or government. Based on a systematic review of all papers ever published on this topic (5), it can be estimated that an ulcer episode in Australia costs around 20,000 dollars, which increases to 35,000-70,000 when hospitalisation or amputation is needed. However, the majority of these costs are unnecessary, as shown by research from Queensland (6): 2.7 billion dollar can be saved in Australia when evidence-based care is implemented, because such care reduces ulceration rates as well as hospitalisation and amputations. What are we waiting for?
References:
2. Prevention of diabetic foot ulcers

The field of foot ulcer prevention is slowly growing, after having been the Cinderella in diabetic foot disease research for many years. Looking at last year’s research, it is probably the most exciting field for those with an interest in technology and other cutting-edge developments.

It has been shown many years ago that temperature home monitoring can prevent foot ulcers, yet this has not led to temperature measurements being implemented in clinical practice. This is probably the result of both poor, user-unfriendly, technology and questionable diagnostic accuracy. Smarter technology might solve both these problems. The most important new study on this topic comes from the US, where researchers and company representatives present a ‘temperature sensing bath-mat’, with new data on diagnostic accuracy (7). The bath-mat is an important improvement in usability, and able to accurately diagnose almost all foot ulcers before they occurred. However, this came at the cost of 57% false-positives, a number that needs to improve before temperature home monitoring can be widely used in clinical practice. The most likely cause of these false-positives is thermal asymmetry, as shown by UK researchers to exist in the general population (8). With the current technology (and with developments to be expected), these false-positives may be reduced by developing smarter algorithms. For that, however, more research and developments are needed.

The other target area in ulcer prevention are smart insoles and smart socks. ‘Smart’ is obviously a buzz-word, so some caution is needed when reading the studies on these technologies. Originally, the focus of smart insoles was put on continuous plantar pressure measurements and feedback, such as in the insoles in the study of Najafi and colleagues (9). These insoles seem to be one step closer to daily practice now, although questions on how to implement them still need to be answered. New developments include integrating plantar pressure measurements with temperature, range of motion, or vibration stimulation (e.g. (10)), but it is hard to see these making the step to clinical practice in the next year.

The most important aspect to keep in mind when reading of such technological developments is that they serve to support a purpose – foot ulcer prevention. While some technology is undoubtedly awesome, keep asking yourself whether it is also practical in clinical practice: can you integrate it in your clinic, or will it cost extra time that is not available? Will it lead to overtreatment, because of over-diagnosis (such as in the case of 57% false-positives following temperature monitoring), or will it lead to a false sense of security and therefore treatment delays? Which of your patients can actually use the technology, just the tech-savvy, or almost anyone? We cannot yet answer most of these questions. While this should not prohibit technological development, more and critical research is needed, and clinicians and patients would do well in providing their user perspective.
References:
3. Footwear and offloading

Even though this is one of the oldest fields in diabetic foot disease research, new evidence and new initiatives keep coming to the fore. Following seminal trials in the last few years, and new recommendations in the IWGDF Guidance, plantar pressure measurements are becoming a ‘must-have’ in clinical practice, rather than a nice-to-have. It is therefore now time to implement the footwear developments from the last years and implement them in clinical practice. First and foremost, plantar pressure measurements should become a routine measurement in daily clinical practice, but Australia has a long way to go. With this new publication on their implementation experiences, New Zealand is showing us the way forward (11).

In offloading for ulcer healing, some important gaps were filled last year. First, Anita Raspovic and colleagues from Melbourne studied felt padding (12). While knee-high devices are recommended in all guidelines, felt padding remains the most frequently used offloading intervention in clinical practice. However, felt padding had hardly been studied properly before this research. Two messages can be taken home from their findings: first, felt-padding does provide some plantar pressure reduction, but (inter)nationally recommended gold-standard offloading devices are much better in offloading a diabetic foot ulcer. Second, if felt-padding is the only available offloading method possible in a patient, it needs to be changed on a weekly basis to keep its offloading capacity.

Another important study is an extensive health technology assessment of lightweight fibreglass heel casts in the management of heel ulcers (13). Jeffcoate and colleagues from the UK investigated whether a simple, removable and lightweight fibreglass cast would speed up healing of heel ulcers, after having observed positive outcomes in a case series. Against their expectations, they conclude that “although the provision of a lightweight heel cast may benefit some individuals, this study found no evidence to recommend that this be adopted in routine clinical practice.” Unfortunately, and despite their great efforts, other offloading methods to improve outcomes of heel ulcer healing are needed.

Offloading with an adequate device is often not enough. When a device is removable, a patient needs to adhere to the treatment. While the importance of adherence is known from both clinical practice and secondary analyses, it has never received full attention in research. Technological advancement now create possibilities to objectively measure adherence, and the first results of such a study come from the US (14). Their study confirms our thoughts on the importance of adherence, as they show that greater adherence relates to better ulcer-related clinical outcomes. However, many questions on the intricacy of this relation remain unanswered, as well as the most important question of all: how do we improve adherence? Let’s hope some answers to that will come in the next year(s).
A final development in this field is the measuring of shear stress. Shear stress is the resultant of movement of a foot over the antero-posterior (forward-backward) and mediolateral (left-right) axes, which is different from the peak pressure measured along the vertical axis. Shear may be understood by the chainsaw comparison: a running chainsaw may easily cut the branch of a tree, while continuously applying pressure alone (i.e.: pressing the chainsaw against the tree) will not break this branch. While peak pressure has been measured for years, shear stress can now be measured with new sensors. Yavuz and colleagues had already shown that ulcers not always develop on the location with the highest peak plantar pressure, but also on locations where there’s no major plantar pressure but only high shear (15). They follow this up with a new study, showing that peak shear is significantly higher in people with a history of foot ulceration (16). A Japanese study looked at the ratio between plantar pressure and shear (17). Their findings indicate that high pressure might only lead to callus formation when it is accompanied by low shear; however, seeing the shortcomings in the study, this hypothesis needs more research before it can be safely and validly concluded. While measuring shear is an important development in offloading, there is much that we still do not know with regard to its role in ulcer development, and its direct application to clinical practice is uncertain. Whereas peak pressure has been investigated in large cohorts and preventative intervention trials, shear stress has (still) only been studied in small groups of patients, with varying results. This will hopefully change in the future, when shear pressure measuring equipment may become widely available.

References:
4. Peripheral artery disease

The big debates identified in the 2015 IWGDF Guidance on Peripheral Artery Disease (PAD) were endovascular treatment vs. bypass surgery; angiosome based treatment; and when not to revascularize. These have seen limited progress in the last year. However, some other interesting papers have been published last year.

An important development for surgeons is the Korean approach to “supermicrosurgery”. After a presentation at the International Symposium on the Diabetic Foot introducing the concept, a paper was now published describing the methods and results of this tiny surgical approach (18). The study concerns a retrospective review of 95 cases, so caution is needed when interpreting the findings. However, the authors describe a flap survival rate of 90.5% and limb salvage rate of 93.7% in a population with complex foot problems. This suggests that “supermicrosurgery” extends the possibilities for reconstruction in those with severe ischemic diabetic foot and limited revascularization options using current methods, some of your most difficult patients.

Other developments related to peripheral artery disease concern its diagnosis and classification. In 2014, Joseph Mills and colleagues presented the Wound, Ischemia, and foot Infection (WIfI) classification system (19). This classification system is more extensive than the University of Texas system. Even though it can be considered complex, it is still applicable in daily clinical practice (20). Two papers have been published last year externally validating this system (21,22). Both study show good findings. These studies not only increase the applicability of WIfI, it also shows the merit of validating existing classification systems, rather than inventing new ones. I would hereby challenge Australian clinics to collect data according to the Australian Diabetic Foot Ulcer Minimum Dataset (3), and use that to validate classification systems such as WIfI. Such an undertaking is immediately useful from both a clinical and a scientific point of view.

Three final papers that are worth mentioning point to an increasing importance of Toe-Brachial Index (TBI) measurements. In the IWGDF Guidance, TBI is only mentioned as a test to exclude PAD when values exceed 0.75. Australian research now shows that values <0.6 are associated with an increased risk of foot disease, which points at TBI as a potentially useful screening tool (23). Additional Australian research shows that it is feasible for podiatrists in busy clinical practice to perform these measurements (24). Finally, research from the US shows that TBI, as well as skin perfusion pressures, is among the most sensitive and cost-effective strategies to improve PAD identification (25). Combined, these suggests a move away from ABI towards more frequent TBI measurements in daily clinical practice.
References:


5. Diabetic foot infection

The most important development in the field of diabetic foot infection is the coming of age of new techniques. These techniques allow assessment of the microbiome in the wound that advances the culture-based sampling methods (either tissue or swab), and start to pave the way for new thoughts on how to treat these infections.

Various DNA-based techniques are available, and these are beautifully summarized in this review (26). Using such techniques, it is for example possible to investigate biofilms or fungi residing in the wound, or to examine the entire microbiome rather than the bacterial communities that respond better to culturing. The latter was investigated by Malone and colleagues, who showed that chronic diabetic foot ulcers have a highly polymicrobial microbiome, whereas ulcers with a duration less than six weeks only had one dominant species (27). However, antimicrobial treatment failure was not related to the microbiome. In another recent study by the same group, they used DNA-techniques to show all diabetic foot ulcers contained biofilms (28). It is not yet clear, however, if there is a causal link between the biofilms and a patient’s response to antimicrobial treatment. Further work continues on this interesting area, and can be expected in the coming year.

A study by Kalan and colleagues reported fungi to be prevalent, dynamic and associated with delayed healing (29). Unfortunately, they used swabs to obtain their samples for analyses, which means they may have included fungi that simply reside on wound surfaces as well. With further difficulties in fungi assessment, it is unlikely that this will soon become part of daily clinical practice. The same holds for the DNA techniques used by Malone and colleagues, which require enormous computer calculating power. However, with technological advancements, this might be in your clinic sooner than you expect. Keeping updated with the exciting new research in this area will hopefully help the transition to bring these advancements to daily practice.

Two papers with direct application to today’s clinical practice also deserve the attention. The first paper is an arduous study from the UK, trying to provide answers to the debate on wound swab vs. tissue sample (30). While a tissue finds more pathogens, it also brings a risk of pain or bleeding, and is harder to use. The authors refrain from an unequivocal answer, and provide four scenarios including a mixture of both methods (see here (https://www.diabeticfootaustralia.org/research-article/1433/) for a more extensive discussion of both methods). But if you would be forced to choose one option, this study underlines the IWGDF recommendation of doing a tissue sample, rather than a wound swab, when possible.

The other paper is a position paper on antimicrobial stewardship (31). The paper is written directly for clinicians dealing with wounds, where the use of antibiotics is common, and in cases unnecessary. The document provides guidance for clinicians on diagnosing infections, optimal
culture and specimen collection, and how to engage with antimicrobial stewardship. It is hoped by the authors that this will improve antimicrobial stewardship in the context of reducing the unnecessary use of antibiotics and the antibiotic resistance debate and potential worldwide threat. A must-read (and a well-written document) for anyone who sees potentially infected wounds on a weekly basis.

Finally, Queensland research reminds us of the scale of diabetic foot infections (32). Infections are not only present in new patients who enter your clinic, but the researchers found (in a very large and representative sample) that 4 patients out of 10 with uninfected ulcers will develop an infection before their ulcer is healed. This mostly occurred in patients with ulcers that took more than 3 months to heal. These Queensland findings confirm the importance of trying to speed up healing, and of continuous infection vigilance while the ulcer of your patient is still open.

References:
6. Wound healing interventions

Probably one of the most controversial topics in the field of diabetic foot disease, and for sure one of the most complex for scientific developments. Wound healing interventions concern dressings or technological interventions (such as negative pressure or hyperbaric oxygen), all with the aim of enhancing wound healing. But that’s exactly where the problems start in this field: how do you define ‘enhancing wound healing’? Should one dressing or one technological intervention improve wound healing by such an extent that it results in significantly more healed ulcers compared to standard care? Or is wound healing related to a myriad of factors, and should a dressing or technology only target (and improve) one of those?

The ‘healing’ approach is the traditional approach, where interventions aim to significantly improve wound healing. However, as the IWGDF notes in their Guidance, this has resulted in many trials with low evidence and poor design (33). The ‘one factor approach’ has seen products that target one specific factor (e.g. pain or ease of use), with better trials backing their statements. However, these studies often miss cost-effectiveness analyses. For more expensive products that only target a small part of the healing process, however, such information is needed before health authorities and clinicians can be expected to choose the more expensive solutions.

The debate in the field is growing, and some exciting developments are underway. For example, the Wound Innovations clinic in Brisbane is combining innovative healthcare with health economic cost-modelling studies. The first results of these developments can be expected in the coming year(s). For this current DFA Guides You Through, however, we can only present some more traditional new studies published in the last twelve months.

A new intervention kid on the block is continuous oxygen delivery. Two randomized controlled trials have been published on this intervention, both from experienced US researchers. Both trials had adequate sample size (122 and 100 participants), but the findings were markedly different. Driver and colleagues found 54% wound healing in oxygen treatment, versus 49% in the control group (34). They conclude that oxygen treatment does not offer any benefit. Niederauer and colleagues, on the contrary, report a clear benefit from oxygen therapy, with 46% vs. 22% wound healing (35). How can these differences be explained? A critical question to answer is: what care did the control group receive? The 22% wound healing in the second study seems very low, while the 49% by Driver and colleagues seems more realistic of current standard of care. This question can never be satisfactorily answered in the limited space of a scientific paper, but it is what clinicians should keep in mind. Looking at current standard practice in Australia, continuous oxygen therapy needs to be studied better and in comparison with appropriate (and preferably local) standard of care before it can make the step to daily practice.
The most scientifically rigorous paper from the last twelve months is a Cochrane review on topical antimicrobial agents, by Dumville, Lipsky and colleagues (36). Cochrane reviews are well-known for being very thorough, very extensive, almost impossible to read, and with a conclusion that is likely to state that more research is needed. Even though this is indeed the case with this review, the authors make some important statements for clinical practice. They suggest, based on low quality of evidence, that “use of an antimicrobial dressing instead of a non-antimicrobial dressing may increase the number of diabetic foot ulcers healed over a medium-term follow-up period.” However, before this conclusion is applied in clinical practice as a rationale to start using any antimicrobial dressing for all patients, some considerations are important. Various antimicrobial dressings are available at the market. The results of five studies were pooled to reach this overarching conclusion, but this does not mean that any specific product will work. This finding reflects the combination of those five products. Further, the reported effect was small (a Risk Ratio of 1.28). With the increasing costs of some dressings, cost-effectiveness is still an issue that needs to be solved. Duration of treatment and patient selection in relation to antimicrobial dressings or interventions could also not be answered based on this review. Regardless, this study is still an important step for antimicrobial treatments, showing some high-quality evidence pointing at potential increases in diabetic foot ulcer healing.

References:
Conclusion

The last twelve months have seen various interesting developments, both scientifically and clinically, in the field of diabetic foot disease. In this “DFA Guides You Through” we have described the most important developments in epidemiology, prevention, footwear and offloading, peripheral artery disease, infection and wound healing interventions.

For clinicians, we hope this document helps to keep track of the latest research in the field, and stimulate you to implement research findings in daily clinical practice.

For researchers, we hope this documents helps to show the gaps and point at relevant developments, to accelerate your diabetic foot disease research and innovation in Australia.

For everyone, we hope you enjoyed reading this, while we guided you through the scientific and clinical developments of 2016 and 2017. For those who cannot wait until our next yearly overview, remember that we publish various “latest research” posts every month on our website (https://www.diabeticfootaustralia.org/for-researchers/latest-research/). Keep a sharp eye out on our social media to read when a new one is online.

We look forward to further advancements in diabetic foot disease research and treatment in 2017 and 2018 that may contribute to ending avoidable amputations in a generation.