Factors associated with healing of diabetes-related foot ulcers: observations from a large prospective real-world cohort

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Diabetes-related foot ulcers (DFU) affect around 20 million people annually and are a leading cause of the global disability burden.(1) DFUs are complex to treat, take months to heal, result in poorer quality of life, and place patients at high risk of hospitalization and amputation. Thus, understanding the influence that different factors have on healing of DFU is vital.

Various demographic, comorbidity, limb, ulcer and treatment-related factors associated with healing of DFU have been identified from cohorts attending mostly metropolitan tertiary centers.(2-4) Yet, very few studies have prospectively investigated the influence that these and other factors have on healing in more real-world DFU cohorts attending geographically diverse secondary and tertiary centers. We therefore aimed to investigate the influence of 34 factors on healing in a large real-world DFU cohort.

We prospectively examined 4,832 consecutive patients with DFU(s) that presented for their first visit to one of 65 secondary or tertiary Diabetic Foot Services, across 15 of 17 regions in Queensland (Australia), between July 2011 and December 2017. A DFU was defined as a full-thickness wound below the ankle on a person with diabetes. For DFU clinical and research purposes, foot-related health professionals using the Queensland High Risk Foot Form (QHRFF) directly examined each patient clinically at their first (and subsequent) visit for four demographic, nine co-morbidity, six limb, three ulcer and twelve treatment factors.(5) For those with multiple DFUs we used the most severe score for each factor and the combined ulcer size from all DFUs.(5) Factors from the first visit were used as baseline. Subsequent visit examinations determined if the DFU(s) healed, defined as complete epithelialization of all DFU(s) without amputation, death or recurrence within one month. The QHRFF is valid and reliable for the direct capture of these factors by the foot-related health professionals that were trained with a QHRFF manual.(5)

DFUs healed within 3, and 12 months were the primary outcomes, as different factors have been reported to influence short- and longer-term healing. (2-4) All factors were analyzed at a univariable level, with those achieving $p<0.1$ entered into multivariable logistic regression models to examine for factors independently associated with each outcome. Before analysis, we excluded 123 patients lost to follow-up after baseline visit, excluded factors with >25% missing data, and used multiple imputation for factors with <25% missing data. All analyses were performed using Stata 16.1.

Of 4,709 included patients (median age 63 years (IQR: 54-72), 69.5% male, 91.0% type 2 diabetes, 10.5% Indigenous Australians), 1,956 (41.5%) healed within 3 months and 3,012 (64.0%) within 12 months. After entering eighteen factors into the multivariable models (Figure 1), seven were negatively associated with DFU healing within 3 and 12 months both, including younger age (<50 years), geographical remoteness, smoking, PAD, large ulcer sizes, deep ulcers, infection, while receiving knee-high offloading treatment at baseline was positively associated with healing (all, $p\leq0.05$). Other factors negatively associated with healing within 3 months were neuropathy, and healing within 12 months were previous amputation and recent surgical and medical specialist treatment (at baseline or prior week).

This prospective study of a large diverse real-world DFU cohort (equivalent to ~50% of ~9,000 people with DFU each year in Queensland(1)), firstly confirms previously reported limb and ulcer-related factors that negatively influence healing of DFU in cohorts attending mostly metropolitan tertiary centers, including neuropathy, PAD, previous amputation, larger ulcer size, deep ulcers and infection.(2-4) Secondly, it confirms the previously reported harmful effect of smoking on DFU healing from smaller tertiary center cohorts. Thirdly, and perhaps most importantly, we seemed to identify new factors positively (current knee-high offloading treatment), and negatively (younger age, geographical remoteness, recent specialist treatment) influencing healing of DFU.

Concerning these new findings, we suggest the negative influence of younger age to potentially be a surrogate for younger-onset type 2 diabetes, emerging as a more severe phenotype for (foot) complications. Geographical remoteness and recent specialist treatment are likely surrogates for delayed access and/or more severe presentation to specialist Diabetic Foot Services, reinforcing the impact of early access to these services on DFU healing. Knee-high offloading treatment confirms trial findings, and might be a surrogate for the positive influence of guideline-recommended treatment on DFU healing. Interestingly, we did not find Indigenous status, after controlling for geographical remoteness, to be associated with DFU healing.

Overall, these new findings confirm and extend our understanding of the influence that severity of DFU presentation, early access to Diabetic Foot Services and enacting guideline-recommended treatment have on healing DFUs.

Figure 1. Multivariable analysis of factors associated with healing of diabetes-related foot ulcers within 3 months and 12 months

DFU: Diabetes-related foot ulcer; OR (95% CI): Odds ratios (95% confidence interval).

[^]The results of the category of Yes is presented, with the category of No used as the reference group for this variable.

All included variables are those with $p<0.10$ on the univariable analysis.

Statistically significant ($p<0.05$) factors associated with lower likelihood to heal are highlighted in red, statistically significant factors associated with higher likelihood to heal are in green, and variables not found to be significant ($p>0.05$) are in grey.

Multiple imputation was used to impute variables with <25% missing data, including geographical remoteness, previous amputation, neuropathy, peripheral arterial disease, ulcer size, infection, deep ulcer, debrided ulcer, and knee-high offloading.

Multivariable logistic model for healing at 3 months was built including patients with at least 3-month follow-up (n=4,323); Multivariable logistic model for healing at 12 months was built including patients with at least 12-month follow-up (n=3,999).

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