Providing support for screening and strategic planning

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Welcome to another *Diabetes Digest* and I hope you enjoy the selection of papers that we have for you in this edition. Like last time, I want to draw your attention to two papers, both of which are topics that should be of interest to all.

I have commented on a couple of papers in the past regarding the Cinderella topic of peripheral painful neuropathy (PPN) and its treatment, which sadly is still a huge problem and often underreported or overlooked. A potentially exciting piece of research is about to be published in *Diabetes Medicine* looking at the relationship between vitamin D deficiency and PPN. Several studies have shown an association between vitamin D levels and diabetic peripheral neuropathy (DPP), however, none of these had differentiated between DPP and PPN, or accounted for seasonal sunlight exposure, daily activity and nerve fibre density. This study was designed to address these among other factors. Forty-five subjects were recruited with type 2 diabetes: 17 with PPN, 14 with DPP and 14 without peripheral neuropathy (HC). All subjects had seasonal sunlight exposure and daily activity measured, underwent a lower-limb skin biopsy and 25-hydroxyvitamin D levels measured between July and September. After adjusting for age, BMI, activity score and sunlight exposure, 25-hydroxyvitamin D levels were significantly lower in people with PPN compared with DPN and HC. Additionally, this also correlated with both lower cold detection thresholds (r=0.39, *P*=0.02) and subepidermal nerve density in PPN subjects. This paper, therefore, suggests there may be a causal link between Vitamin D deficiency and the pathogenesis of PPN. Although further studies are necessary, this could be very useful in preventative screening going forward.

The second paper that I want to draw your attention to is from the Scottish Diabetes Research Network group. Its aim was to investigate amputation-free survival in those categorised as being high-risk for diabetic foot ulceration. Additionally, to compare three different groups within this cohort of patients, namely those with no previous ulcer, those with an active ulcer or those with a healed previous ulcer, anyone with previous minor or major amputation were excluded from the cohort.

In all, 17,353 subjects were identified and included from the Scotland-wide diabetes register — SCi Di (*n*=247,278) between 2008 and 2011 with a 2-year follow up for each subject. The 2-year amputation-free survival rate in all high-risk foot subjects was 84.5% with 10% undergoing amputation (*n*=270), however, the paper does not distinguish between major and minor amputations in this figure.

Unsurprisingly, active and healed ulcers subjects had significantly lower 2-year amputation-free survival compared with ulcer-free subjects (*P*<0.0001). A shorter amputation-free time was also shown for subjects who were older, male, had longer duration of diabetes, higher HbA_{1c} level, a history of cardiovascular disease and an eGFR lower than 30 ml/min/1.73m^2. One-in-four healed ulcer subjects died within 2 years, compared with one in eight for ulcer-free subjects. Mortality in those who underwent amputation was 90% within the 2-year period and was 22.8%, 16% and 12.1%, those with healed, active or no ulcers, respectively. This paper shows the value of population-based data collection and is useful for strategic planning and service reviews. ■

Shillo P, Selvarajah D, Greig M et al (2018) Reduced vitamin D levels in pain-ful diabetic peripheral neuropathy. *Diabet Med* doi: 10.1111/dme.13798. [Epub ahead of print]

Vadiveloo T, Jeffcoate W, Donnan PT et al (2018) Amputation-free survival in 17,353 people at high risk for foot ulceration in diabetes: a national observational study. *Diabetologia* doi: 10.1007/s00125-018-4723-y. [Epub ahead of print]

Diabet Med

The development and validation of a multivariable prognostic model to predict foot ulceration in diabetes using a systematic review and individual patient data meta-analyses

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓

1 The authors set out to develop and validate a prognostic model of independent risk factors for diabetic foot ulceration by utilising all available individual patient data from cohort studies across the globe.

2 A systematic review and meta-analysis of individual patient data was conducted from 10 cohort studies of risk factors in the prediction of diabetic foot ulceration. Logistic regression created adjusted odds ratios (ORs) for foot ulceration by order of ulceration history, monofilament insensitivity, age, sex, absent pedal pulse and diabetes duration.

3 The chosen 10 studies had data from 16,385 participants and the largest ORs were found to be ulceration history [6.59 (95% CI 2.49 to 17.45)], insensitivity to a 10-g monofilament [3.18 (95% CI 2.65 to 3.82)] and any absent pedal pulse [1.97 (95% CI 1.62 to 2.39)].

4 In conclusion, the prognostic model of a history of foot ulceration, an inability to feel a 10-g monofilament and the absence of any pedal pulse compares positively with other approaches to foot risk assessment put forward in clinical diabetes guidelines.

Crawford F, Cezard G, Chappell M, PODUS Group (2018) The development and validation of a multivariable prognostic model to predict foot ulceration in diabetes using a systematic review and individual patient data meta-analyses. *Diabet Med* doi: 10.1111/dme.13797. [Epub ahead of print]

Diabetes Obes Metab

Remission in diabetic foot infections: Duration of antibiotic therapy and other possible associated factors

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 A clinical pathway for adult patients with diabetic foot infections (DFIs) was used by the authors when creating a cluster-controlled Cox regression model to determine the most appropriate duration of antibiotic therapy. Total amputations as a result of DFI and DFI episodes with a follow-up time of <2 months were excluded.

2 A total of 392 episodes of osteomyelitis were identified among 1,018 DFI episodes in 482 patients, while 626 soft tissue infections, 246 large abscesses, 322 episodes of cellulitis and 335 episodes of necrosis were identified. Patients experienced surgical debridement for 824 episodes (81%) with 596 (59%) requiring amputation; the median total duration of antibiotic therapy was found to be 20 days. Median follow-up was 3 years and 251 (24.7%) of the episodes were followed by ≥1 additional episode(s). The risk of recurrence was lower in those who underwent amputation, had type 1 diabetes or underwent revascularisation.

3 No optimal threshold for preventing recurrences was found after plotting duration of antibiotic therapy to prevent recurrences of DFI. These limited data may support shorter treatment duration for DFI patients going forward.

Gariani K, Lebowitz D, von Dach E et al (2018) Remission in diabetic foot infections: duration of antibiotic therapy and other possible associated factors. *Diabetes Obes Metab* doi: 10.1111/dom.13507. [Epub ahead of print]

Int J Low Extrem Wounds

Fungal osteomyelitis in diabetic foot infections: a case series and comparative analysis

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 There is currently a lack of studies in the literature dealing with fungal osteomyelitis (OM) in diabetic foot infections (DFIs). Therefore, this case series sought to examine the clinical characteristics of patients who were treated at a large tertiary academic centre for DFI with a causative agent of fungal origin in their bone on surgical intervention.

2 The authors conducted a prospective longitudinal analysis between July 2017 and March 2018, with data between bacterial and fungal OM cohorts analysed to determine both the differences and similarities in terms of both patient characteristics and outcomes.

3 Out of the 35 cases where OM was recognised through podiatric surgical intervention, five patients were identified with fungal OM. Some 40% of patients with fungal OM achieved healing, while oral fluconazole successfully treated *Candida* OM in those cases that achieved healing.

4 It is acknowledged that diabetes can increase the risk of *Candida* OM and, in DFIs, fungus can impede wound healing if not recognised and treated. Bone biopsy and mycological culture are both recommended for the definitive diagnosis and treatment of fungal OM.

Torrence GM, Schmidt BM (2018) Fungal osteomyelitis in diabetic foot infections: a case series and comparative analysis. *Int J Low Extrem Wounds* 17(3): 184–9

ACS Appl Mater Interfaces

Bioactive injectable hydrogels containing desferrioxamine and bioglass for diabetic wound healing

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Vascularisation poses problems for the healing of diabetic wounds. Previous studies have shown that desferrioxamine (DFO) can promote secretion of hypoxia inducible factor-1, which upregulates the expression of angiogenic growth factors and facilitates revascularisation.

2 The authors' study found that Si ions in bioglass (BG) can be used to upregulate vascular endothelial growth factor (VEGF) expression, promoting revascularisation as a result. They had hypothesised that BG and DFO in combination may promote VEGF expression and revascularisation, and so determined a DFO concentration range that had no apparent cytotoxicity on human umbilical vein endothelial cells (HUVECs). The optimal concentration of DFO was determined by cell migration and tube formation assays. It was shown that a combination of BG and DFO enhanced the migration and tube formation of HUVECs, compared to the use of either BG or DFO alone.

3 This study resulted in the authors creating an injectable hydrogel containing BG and DFO used to enhance the repair of diabetic chronic skin defects by taking advantages of the synergistic effects of BG and DFO in relation to the promotion of revascularisation.

Kong L, Wu Z, Zhao H et al (2018) Bioactive Injectable Hydrogels Containing Desferrioxamine and Bioglass for Diabetic Wound Healing. *ACS Appl Mater Interfaces* 10(36): 30103–14

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