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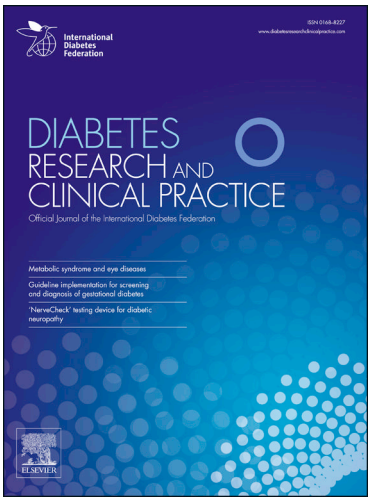

The impact of glycaemic variability on wound healing in the diabetic foot – a retrospective study of new ulcers presenting to a specialist multidisciplinary foot clinic

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Title:
The impact of glycaemic variability on wound healing in the diabetic foot – a retrospective study of new ulcers presenting to a specialist multidisciplinary foot clinic

Running Title
Glycaemic variability & wound healing in feet

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Duality of Interest: None declared

Keywords: glycaemic variability; diabetic foot; ulcer; healing

Abstract

Aims: Glycaemic variability – the visit-to-visit variation in HbA1c – plays a possible role in the development of micro and macrovascular disease in patients with diabetes. Whether HbA1c variability is a factor determining wound healing in diabetic foot ulcers remains unknown. We aimed to determine whether HbA1c variability is associated with foot ulcer healing time.

Methods: A retrospective analysis of patients presenting to our specialist multidisciplinary foot clinic between July 2013 and March 2015, with at least three HbA1c measurements within five years of presentation and more than two follow-up reviews. HbA1c variation was measured by magnitude of standard deviation.

Results: 629 new referrals were seen between July 2013 and March 2015. Of these, 172 patients had their number of days to healing recorded and sufficient numbers of HbA1c values to determine variability. The overall geometric mean days to heal was 91.1 days (SD 80.8 to 102.7). In the low HbA1c variability group the geometric mean days to heal was 78.0 days (60.2 to 101.2) vs 126.9 days (102.0 to 158.0) in the high Hb1Ac variability group (p=0.032). Those with low HbA1c (< 58 mmol/mol) and low variability healed faster than those with high HbA1c and high variability (73.5 days [59.5 to 90.8] vs 111.0 days [92.0 to 134.0], p=0.007). Additionally, our results show that time to healing is more dependent on the mean HbA1c than the variability in HbA1c (p=0.007).

Conclusions/interpretation: Our data suggest that there was a significant association between HbA1c variability and healing time in diabetic foot ulcers.

Key words: Glycaemic variability; HbA1c variability; ulcers; wound healing

Introduction

Foot ulcers are a common complication of diabetes and recent data has shown that across the UK, foot disease is the most common reason for a ‘diabetes specific’ acute hospital admission [1]. Previous work has suggested that up to 33% of ulcers fail to heal within 1 year [2,3], with a further 28% requiring lower extremity amputation within 2 years of initial presentation [4]. The 5-year mortality rate of people with diabetes related foot ulcers has been shown to be between 69-79%, with mortality increasing significantly if other comorbidities are present [5,6].

It is well recognised that chronic hyperglycaemia, as measured by HbA1c, is the key risk factor for the development of diabetes-related micro and macrovascular complications [7,8]. Several recent studies have suggested that there are relationships between the development of micro and macrovascular complications and the variation between HbA1c values at successive clinic visits [9,10,11,12,13,14]. These changes have been termed glycaemic variability. Besides visit-to-visit variation in HbA1c, other definitions of glycaemic variability include fluctuations in glucose concentrations or variability between daily glucose means [15].

To our knowledge, there are currently no data assessing the impact of glycaemic variability on the time taken to achieve wound healing in people with diabetes related foot ulcers. That was the aim of the present study.

Methods

We conducted a retrospective case note analysis of patients attending our specialist multidisciplinary foot clinic in Norwich (Norfolk, UK), between July 2013 and March 2015. Patients were included if they had at least three HbA1c values taken within the five years prior to their first presentation to our foot clinic with a diabetes related foot ulcer. In addition, they were only included if they had attended more than 2 follow-up reviews within the first year of their initial presentation with a foot ulcer. Patients were excluded if they had any of the following: Charcot neuroarthropathy, venous ulceration, dermatological conditions unrelated to their diabetes, or referral for other reasons (including, but not limited to, callus, nail care, or for provision of hospital footwear). Individuals were included in the analysis if they had sequential ulcers.

Baseline demographics and subsequent data were collected from the centralised hospital electronic clinic records, multidisciplinary clinic letters, and an electronic pathology database. Type, duration and management of diabetes were recorded. Data on HbA1c and renal function (estimated glomerular filtrate rate) prior to initial presentation to the foot clinic were collected. Previous history of foot diseases (ulcers and/or amputations), extent of peripheral arterial disease and history of revascularisation were also recorded. Data on the number of foot ulcers and their grade according to the University of Texas Wound Classification [4,16] were gathered. Patients were followed up for at least 1 year after their initial presentation. Ulcer healing was defined as complete wound closure with wound epithelisation and no recurrence at 6 weeks follow up.

This was a retrospective case notes analysis study and as such the Norfolk and Norwich University Hospitals NHS Foundations Trust audit department designated this as a service improvement exercise and ethical approval was deemed unnecessary.

Statistical Methods

Basic summary descriptive statistics have been reported comparing patients whose ulcers healed within 12 months versus those that did not heal, and also for time to healing. The variability in HbA1c was calculated as the standard deviation (SD) of all HbA1c observations over the 5 years prior to initial presentation, which had to have been recorded at least 30 days from their previous recorded observation. Only patients that had had 3 or more Hba1c measurements and had had their measurements recorded over a 1 year period had their HbA1c variability calculated. Low mean HbA1c was defined as those having a mean HbA1c less than or equal to 58 mmol/mol and high mean HbA1c as greater than 58 mmol/mol. The relationship between the mean HbA1c and the variability in HbA1c was analysed with variability classified as either low or high based on the median. Further analysis of the effect of HbA1c variability was conducted by discretising the SD of HbA1c into quartiles.

Basic Chi-square tests were performed to see what factors are associated with ulcer healing and logistic regression was performed to adjust for any potential confounding factors. The odds ratios for healing and their respective 95% confidence intervals were calculated. The secondary outcome variable, time to ulcer healing, was analysed on a log transformed scale by a 2 x 2 analysis of variance to see if it was dependent on

Hba1c variability or mean Hba1c. The number of days to heal were transformed back onto the natural scale and the geometric means reported with their respective 95% confidence intervals. The HbA1c variability quartiles were tested for a difference using Tukey's studentised range test.

Results

629 new patients were referred to our specialist multidisciplinary foot clinic between July 2013 and March 2015. 184 patients healed of whom 172 had their number of days to healing recorded and a sufficient number of HbA1c concentrations recorded to be included in the analysis. A further 117 patients had not healed by the end of the follow up period, of whom 116 had a sufficient number of HbA1c concentrations recorded to be included in the analysis. Thus 288 are included in the final analysis. The consort diagram is shown in Figure 1. The patient characteristics are shown in Table 1. For the purposes of this analysis we only included one ulcer per patient.

Our data suggest that there was a statistically significant association between HbA1c variability and time to healing. The overall geometric mean days to heal was 91.1 days (SD 80.8 to 102.7). In the low HbA1c variability group the geometric mean days to heal was 78.0 days (60.2 to 101.2) vs 126.9 days (102.0 to 158.0) in the high Hb1Ac variability group (p=0.032). However the mean HbA1c was also shown to have a more significant association with time to healing (p=0.007). Those with low HbA1c (< 58mmol/mol) and low variability healed faster than those with high HbA1c and high variability (73.5 days [59.5 to 90.8] vs 111.0 days [92.0 to134.0], p=0.007).

However, there was no association between the proportion of people who healed and HbA1c variability or the mean HbA1c over time.

The rate of ulcer healing was also shown to have a significant association with duration of diabetes ($p=0.028$), ulcer grade ($p<0.0001$), number of pulses ($p<0.0001$), Ankle Brachial Pressure Index (ABPI) ($p=0.021$) and a history of foot problems ($p=0.045$). ABPI was only recorded for 93 patients and was still significant.

The ulcer was more likely to heal if the diabetes had been present for more than 8 years. The odds ratio of healing for DM duration of 8-15 years was 2.72 (95 CI 1.33, 5.58) compared to having DM for less than 8 years. Additionally, people with medication treated type 2 DM had an odds ratio for healing of 2.6 (95% CI: 1.35 4.94) compared to people with either Type 1 DM or diet controlled type 2 DM

Discussion

Our data suggest that glycaemic variability, as measured by the magnitude of standard deviation in visit-to-visit changes in HbA1c, has a significant impact on time to wound healing in people presenting with diabetes related foot ulcers. However, the association between glycaemic variability and the likelihood of wound healing was not statistically significant – only the time taken to heal. In addition, that mean HbA1c was a stronger predictor of wound healing than glycaemic variability, with high HbA1c concentrations being associated with longer healing times.

High glycaemic variability is regarded as a reflection of poor health and unstable glucose control, which can also be a surrogate marker of patient adherence [17]. Many clinicians focus on individual HbA1c values – and indeed, primary care teams in the UK have, until recently, been incentivised to achieve low HbA1c values [18]. These targets are clearly important and are derived largely from the DCCT and UKPDS [7,8]. However, we feel that the added dimension of HbA1c variability could be considered as an addition to current practice. Recent work has also suggested an association between the combined effect of HbA1c variability and systolic blood pressure in the incidence of cardiovascular events amongst patients with diabetes [19], further emphasising the importance of regular monitoring modifiable risk factors for cardiovascular disease.

It has previously been suggested that variations in daily glucose concentrations or HbA1c may be independently responsible for diabetes-related complications [14,20,21]. This can be partly explained by the fact that fluctuations in glucose concentration increases the production of reactive oxygen species by the mitochondrial electron-transport chain resulting in endothelial and β cell dysfunction [22,23]. Other intracellular disturbances have also been described [24,25]. Moreover, large glycaemic variability over time has been shown to trigger greater levels of oxidative stress when compared to sustained hyperglycaemia [26]. Thus glycaemic variability has been proposed as part of the unifying mechanism for the development of end organ damage in diabetes [22]. These include chronic kidney disease [27,28,29,30], and retinopathy [31]. Furthermore, other studies have provided evidence supporting the association of glycaemic variability with macrovascular outcomes [32,9]. Previous work has shown that high glycaemic

variability was associated with an increased risk of developing ulcers and gangrene [12].

There are various methods proposed for measuring HbA1c variability. A systematic review by Eslami et al highlighted the use of thirteen differing methods that may be used to assess glycaemic variability; ranging from standard deviation to a glucose variability index [33]. We have used SD because it is a simple measurement for population data that is applicable to clinical practice. However, opinions differ towards defining glycaemic variability and its association with diabetes-related complications. There is also little discussion regarding possible influencing factors altering the validity and reliability of the methods. Thus, further work is required to establish a definitive method for measuring glycaemic variability.

To our knowledge, these are the first data assessing the relationship between HbA1c variability and the rate of wound healing in diabetes related foot ulcers. We have previously published data to show that patients attending our multidisciplinary foot clinic improve their overall glycaemic control whilst they are under our care [34]. The current data suggest that this is the most important ‘HbA1c related’ factor when considering wound healing and should remain a prime focus of clinicians looking after individuals with foot disease, but glycaemic variability clearly also requires more attention.

The reasons for glycaemic variability have not been explored, but would appear to be a measurable modifiable risk factor for the development of end organ damage in diabetes.

As with the development of other complication, an unknown factor is patient behaviour. It has been shown that people with foot ulcers do not comply with instructions when they are asked to wear offloading devices [35], and thus there may be an element of intermittent non-concordance with treatment accounting for the variability in HbA1c values. In addition, variable adherence with taking medication, or general self-management may have an impact [11,17]. However, further work needs to be done in this emerging area to better understand the causes of variability.

The data to show that the ulcer was more likely to heal if the duration of known diabetes was greater than 8 years is somewhat surprising because of the data from the UK National Diabetes Foot Audit that showed that a diabetes duration of less than 5 years was associated with increased likelihood of healing [36]. Previous authors have shown that glycaemic variability was greater when someone had a long duration of diabetes or with older age [37]. However, previous work from Sweden also showed that the odds ratio of an ulcer healing was marginally higher when the duration of diabetes was 8-15 years (1.8, [95%CI 1.17-2.77]), compared to a diabetes duration of 0-7 years (1.68, [95% CI 1.09-2.28]) [38]. Other data have shown that diabetes duration has no influence on ulcer outcomes [39].

We acknowledge that our data has limitations. We conducted a single centre study consisting of a relatively small number of participants, which could have affected the validity of the result, particularly given the small numbers of people in each quartile range for HbA1c variability. In addition, ours was a convenience sample. Our patient

population was primarily White Caucasians and this may limit the wider generalisability of our results. However, most baseline characteristics (diabetes type, gender, age, duration) were reflective of typical patient profiles in accordance with the latest UK National Diabetes Foot Audit data [36]. Furthermore, due to the nature of our retrospective observational study, our study was not designed to investigate whether the association was causal or not. By limiting our dataset to those who only had sufficient numbers of HbA1c values with which to calculate variability, we have, almost by definition, limited ourselves to a) those who turn up to the multidisciplinary foot clinic and b) agree to have a blood test. We have not looked at outcomes for those individuals who did not fulfil these criteria because that was not the focus of our investigation.

Lastly, our findings were limited by the different number of HbA1c readings available for each patient, ranging from 3 to 10 values. Consistent recordings would have allowed for a more detailed evaluation towards long-term glycaemic variation. In addition, because electronic records for HbA1c were only fully implemented in our institution in 2012 we were unable to fully access data from before this date. Furthermore, 10-15% of our case load came from other hospitals, and we were unable to access their electronic pathology databases to collect their data. This led to the exclusion of patients due to insufficient HbA1c values or providing a complete set of readings as per our inclusion criteria.

In summary, our data has shown that glycaemic variability, as measured by the standard deviation in visit-to-visit changes in HbA1c, has a significant impact on time to

wound healing in people with diabetes related foot ulcers. Wounds take longer to heal in people with diabetes with high glycaemic variability, with high HbA1c values also influencing the time to wound healing. Whilst in this dataset time to healing was more dependent on the mean HbA1c, further work is necessary to confirm the association with HbA1c variability. Finally, an analysis of which measure of glycaemic variability is the best predictor of outcomes needs to be carried out before it can be routinely included in any risk stratification tool.

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Author contributions

ELPW-PS, FYNL, JOSC, AYWY collected the data, did the initial background research and wrote the first drafts of the manuscripts. CG and KKD supervised the students and wrote the final version of the manuscript. IN did the statistical analyses and wrote the statistical section in the manuscript. All of the authors saw and approved the final submitted manuscript.

KKD acts as the guarantor for the paper. The authors received no financial assistance during this work. The authors declare no conflicts of interest. Some of these data were presented as an abstract at Diabetes UK Annual Professional Conference, Manchester UK 2017, and was presented at the Diabetic Foot Study Group Meeting, Porto, Portugal 2017.

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Legend to Figure and Table

Table 1. Patient characteristics

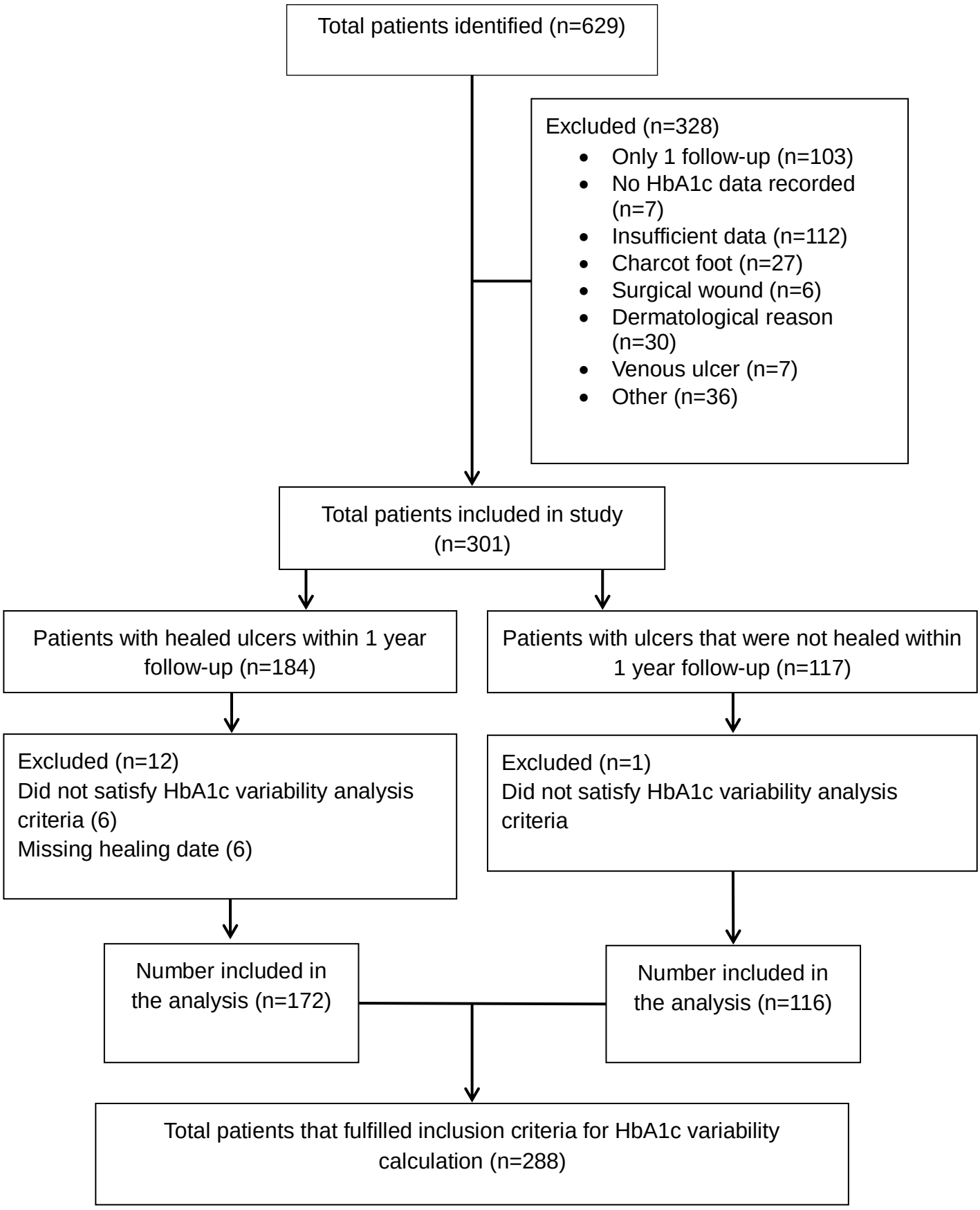
Figure1. Consort diagram to show patient selection process

Table 1 (NS – Not significant, SD – Standard deviation)

Demographics	**Healed within 1 year**	**Not healed within 1 year**	**p value**
Mean age at presentation (years) (±SD)	68.4 (13.8) (n=184)	71.6 (13.4) (n=117)	NS
Gender (M:F)	131:52 (n=183)	85:32 (n=117)	NS
% Smokers	30.9% (n=93)	19.3% (n=58)	NS
Type of diabetes			
Type 1	13.6 (n=25)	19.7 (n=23)	
Type 2	86.4 (n=159)	80.3 (n=94)	NS
Mean duration of diabetes (years) (±SD)	18.5 (13.2) (n=153)	16.7 (13.7) (n=95)	0.03
Mean number of HbA1c values measured in the 5 years prior to presentation (±SD)	6.71 (2.73) (n=184)	6.72 (2.62) (n=117)	NS
Percentage with established neuropathy at presentation	68.5% (n=126)	67.5% (n=79)	NS

Percentage with a history of revascularisation prior to presentation	7.0% (n=13)	9.5% (n=11)	NS
Mean estimated glomerular filtration rate at presentation (mL/min/1.73m^2) (±SD)	60.4 (24.5) (n=183)	60.0 (26.0) (n=117)	NS
Ankle Brachial Pressure Index			
Missing N (%)	136 (73.9)	75 (64.1)	
<0.5	5 (2.7)	4 (3.4)	
0.5-0.79	7 (3.8)	17 (14.5)	
0.8-1.12	17 (9.2)	14 (12.0)	
>1.12	19 (10.3)	7 (6.0)	NS
Ulcer Grade [Texas] N (%)			
A0 – C0	126 (68.5)	51 (43.6)	
C1 – D3	58 (31.5)	66 (56.4)	<0.0001
Number of Peripheral pulses N (%)			
None	51 (27.7)	61 (52.1)	
One	39 (21.2)	23 (19.7)	
Two	94 (51.1)	33 (28.2)	<0.0001

Figure 1


Total patients identified (n=629)
Excluded (n=328)
Only 1 follow-up (n=103)
No HbA1c data recorded (n=7)
Insufficient data (n=112)
Charcot foot (n=27)
Surgical wound (n=6)
Dermatological reason (n=30)
Venous ulcer (n=7)
Other (n=36)
Total patients included in study (n=301)
Patients with healed ulcers within 1 year follow-up (n=184)
Patients with ulcers that were not healed within 1 year follow-up (n=117)
Excluded (n=12)
Did not satisfy HbA1c variability analysis criteria (6)
Missing healing date (6)
Excluded (n=1)
Did not satisfy HbA1c variability analysis criteria
Number included in the analysis (n=172)
Number included in the analysis (n=116)
Total patients that fulfilled inclusion criteria for HbA1c variability calculation (n=288)

Highlights

Glycaemic variability – the visit to visit change in HbA1c – has been shown to be associated with the risk of developing complications in diabetes.

No work has been done looking at glycaemic variation in the time taken for diabetes related foot wounds to heal

Our data suggest that there was a significant association between HbA1c variability (as measured by magnitude of standard deviation) and healing time in diabetic foot ulcers.