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ORIGINAL RESEARCH

The Association of HbA_{1c} Variability with 12 Week and 12 Month Outcomes on Diabetes Related Foot Ulcer Healing

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ABSTRACT

Introduction: This study aimed to determine the relationship between HbA_{1c} variability and foot ulcer healing at 12 weeks and 12 months.
Methods: Using National Diabetic Foot Care Audit (NDFA) and hospital records, demographics, baseline ulcer characteristics and healing outcomes for subjects presenting with a foot ulcer between 2017–2022 were collected at 12 weeks and 12 months. Subjects had diabetes duration > 3 years and ≥ 3 HbA_{1c} recordings in the 5 years prior to presentation.
Results: At 12 weeks, factors associated with an active ulcer were presence on hind foot (adjusted odds ratios) (2.1 [95% CI 1.3–3.7]), ischaemia (2.1 [95% CI:1.4–3.2]), area > 1 cm^2 (2.7 [95% CI:1.7–4.2]) and diabetes duration > 24 years vs 3–10 (AOR 2.0 [95% CI 1.2–3.5]). After adjustment, HbA_{1c} variability 6–10 mmol/mol and > 14.5 mmol/mol had AOR of 1.76 (95% CI 1.1–2.8; $p = 0.0192$) and 1.5 (95% CI 0.9–2.6; $p = 0.1148$) of an active ulcer at 12 weeks vs variability < 6 mmol/mol. At 12 months, ischaemia (AOR 2.4 [95% CI 1.5–3.8]) and diabetes duration > 24 years vs 3–10 years (AOR 3.3 [95% CI 1.7–6.4] were significant factors. HbA_{1c} variability was not significant at 12 months.
Conclusion: In keeping with the national NDFA data, in our cohort ulcer characteristics, but not HbA_{1c} variability, were the key factors associated with ulcer healing at 12 weeks and 12 months.

PLAIN LANGUAGE SUMMARY

Diabetes complications occur more frequently when glucose control is not as good as it could be. For a long time, HbA_{1c}, or glycated haemoglobin, has been used as a measure of how well someone's diabetes has been controlled. However, another way of looking at diabetes control is to look at the changes of HbA_{1c} over time—this is called glycaemic variability. Diabetes-related foot disease is one of the most feared complications of the condition, and our group has previously shown in a small study that glycaemic variability was associated with ulcer healing at 12 weeks—with lower variability leading to better healing. However, it did not consider other variables known to be associated with not being alive and ulcer free at 12 months. In the UK, data are collected as part of the National

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Diabetes Footcare Audit (NDFA). This dataset collects a lot of information on new foot ulcers and their outcomes 12 weeks later. We have used our centre's data to look at factors not included in the NDFA dataset—in particular glycaemic variability—to determine whether this influences ulcer outcomes at 12 weeks, but also at 12 months. We found that low glycaemic variability is associated with greater chances of healing but that the greatest association is the presence of poor blood flow and diabetes duration.

Keywords: HbA_{1c} variability; Glycaemic variability; Ulcer healing; Diabetes-related foot ulcers

Key Summary Points
Why carry out this study?
Glycaemic variability as measured by visit-to-visit changes in glycated haemoglobin (HbA_{1c}) is becoming an increasingly important risk factor in the development of microvascular and macrovascular complications of diabetes
We have used a large single-centre database of people with diabetes with a foot ulcer to retrospectively assess whether glycaemic variability influences ulcer healing at 12 weeks and 12 months
What was learned from the study?
We show that at 12 weeks those who had the lowest variability had the greatest chance of healing, but at 12 months, only the presence of ischaemia and diabetes duration remained significant in predicting healing
The retrospective nature of our data analysis means that only associations, not causation, can be inferred

INTRODUCTION

Foot ulceration is an important and challenging complication of diabetes, with a lifetime risk reported of between 19–34% in people with diabetes [1, 2]. Following ulceration there is increased morbidity and mortality, with a high percentage of recurrence. Data from the most recent National Diabetes Foot Audit in the UK report a 15% mortality rate by 1 year in people presenting with severe ulcers [3]. Amputations remain a significant consequence, with approximately 84% being preceded by an ulcer and 3% of severe ulcers resulting in a major amputation by 1 year [1, 3–5]. In addition, not only do these ulcers impose a significant impact on quality of life, but management of these ulcers is very costly, accounting for up to 1% of the total NHS budget in England [3, 6]. It has recently been estimated that diabetes-related foot disease contributes to 2% of the global disease burden [7].

HbA_{1c} variability is a measure of long-term glycaemic control, which assesses the variation in HbA_{1c} values between visits over time. This has been shown to be associated with, and an independent risk factor for, the development of microvascular and macrovascular complications in type 1 and type 2 diabetes [8–15]. Lower extremity amputations also have a relationship to variability in HbA_{1c} concentration, potentially as an independent marker of future major and minor amputations [16]. With one study suggesting a relationship with minor amputations in people with type 2 diabetes-related foot ulcers [16, 17].

A previous small study has suggested a significant relationship between HbA_{1c} variability and healing of DFU [18]. However, as the first study of this kind, it had limitations, with no defined end point and a small sample size. Furthermore, it did not consider other variables known to be associated with not being alive and ulcer free at 12 months. It is already known that poor ulcer healing is influenced by a number of factors, in particular, the presence of ischaemia or infection, size and depth of ulceration, time to presentation at clinic and having multiple ulcerations [3]. The SINBAD (Site, Ischaemia, Neuropathy, Bacterial infection, Area and Depth)

classification uses these variables associated with poor ulcer healing to create a score that can be used for comparison of ulcers at baseline presentation [19]. Nationally, 12-week outcomes are used, in the National Diabetes Foot Care Audit and act as a consistent end point to measure the association of variables on foot ulcer healing, specifically whether a person is alive and ulcer free [3]. Twelve-month outcomes can also be used to assess the association with long-term healing.

This study aimed to determine whether HbA_{1c} variability influences 12-week and 12-month outcomes for DFU healing.

METHODS

Study Design, Setting and Patients

This was a retrospective study conducted using data collected routinely from the multidisciplinary diabetic foot clinic at the Norfolk and Norwich University Hospitals NHS Foundation Trust. People with diabetes who presented to the diabetic foot clinic between January 2017–December 2022 and whose data were included in the National Diabetes Foot Care Audit (NFDA) were selected for this study. Those with a diabetes duration > 3 years and who had at least three HbA_{1c} recordings in the 5 years prior to presentation were included in the analysis. Only the first ulcer presentation between 2017–2022 was included.

Data Collection

Data were collected using electronic hospital records, clinic letters and the NFDA reports. Data collected included sex, age at presentation, type and duration of diabetes. From the NFDA reports, the time interval to be first seen in clinic, the date of first presentation and 12-week follow-up dates were collected. Baseline retinopathy data were collected from the eye screening service. We used the highest stage between both eyes within 12 months of presentation.

Study Outcomes

Ulcer characteristics were recorded using the NDFA data and SINBAD classification. Using the NFDA definitions, a SINBAD score ≥ 3 was considered a severe ulcer. HbA_{1c} recordings were collected from presentation to 5 years prior. Healing was defined as alive and ulcer free. Active ulcers, any resultant amputations or deaths by 12 weeks and 12 months were recorded. Amputations were classified into major (above the ankle) or minor.

The project was registered with the audit department at our institution who deemed that ethical approval was not required because of the anonymised, retrospective nature of the data collection. Trust approval for the project was granted by the service director for diabetes and endocrinology.

Statistical Analysis

Summary statistics of the demographic and clinical characteristics were presented for all eligible subjects. Descriptive statistics were reported using means and standard deviations (SD) for continuous variables and frequencies and percentages were reported for categorical variables.

Univariate and multiple variable logistic regressions were performed and their odds ratios and respective 95% confidence intervals presented. For the multiple logistic regression only factors seen to be significant at the 10% level from the univariate analysis were included in the model. To compare ulcer healing across the different levels of adjusted HbA_{1c} variability (SD), the factors controlled for in the model were sex, age, ischaemia, ulcer area and depth, site of hind foot, SINBAD score ≥ 3 and diabetes duration.

As the number of individual visits (n) could influence the HbA_{1c} variability (SD) (with fewer visits likely to artificially inflate the SD), values

for HbA_{1c} SD were divided by sqrt($n/n-1$) to adjust for this possibility.

RESULTS

Using the NDFA database, 1100 subjects with diabetes were identified with presentation to the diabetic foot clinic between 2017–2022. Of these, 546 were included in the final analysis. Figure 1 shows the details on why people were excluded. No data were excluded because of deaths as only 21 subjects had died at 12 months.

The baseline characteristics of those included in the 12-week analysis are shown in Table 1. Of those included, 17 people (5.4%) who had an active ulcer at 12 weeks had a major or minor amputation compared with 3 people (1%) in those who did not have an ulcer. Figure 2 shows the factors that were and were not significant for having an active ulcer at 12 weeks. These were the presence of the ulcer on the hind foot (adjusted odds ratio 2.1 [95% CI 1.3–3.7]), ischaemia (AOR 2.1 [95% CI 1.4–3.2]) and area > 1 cm^2 (AOR 2.7 [95% CI 1.7–4.2]).

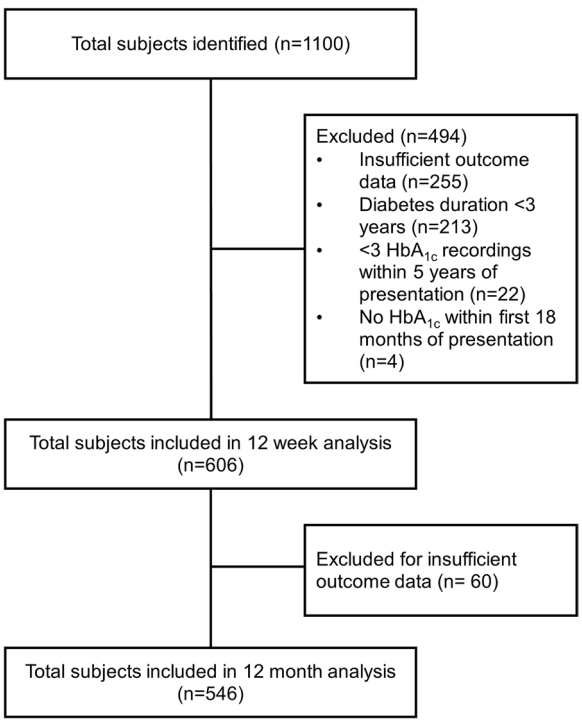

Fig. 1 Consort diagram to show patient selection

Duration of diabetes and HbA_{1c} variability, after adjusting for other factors, were not statistically significant ($p = 0.0754$ and $p = 0.0642$ respectively). Diabetes duration suggested a potential trend, with ulcer healing less likely to occur as diabetes duration increased. Those that had diabetes for > 24 years were more likely to have an active ulcer at 12 weeks compared with those for 3–10 years (AOR 2.0 [95% CI 1.2–3.5]). HbA_{1c} variability does not have the same monotonic trend as seen for diabetes duration. However, the subjects with lowest variability (< 6 mmol/mol) were at least risk of having an active ulcer at week 12. Those having HbA_{1c} variability between 6 to 10 mmol/mol and HbA_{1c} variability > 14.5 mmol/mol had higher risk than those with HbA_{1c} variability between 10 to 14.5 mmol/mol. Those having HbA_{1c} variability between 6 to 10 mmol/mol and HbA_{1c} variability > 14.5 mmol/l had AOR 1.76 [95% CI 1.1–2.8] ($p = 0.0192$) and AOR 1.5 [95% CI 0.9–2.6] ($p = 0.1148$), respectively, of having an ulcer at week 12 compared to subjects with HbA_{1c} variability < 6 mmol/mol.

Table 2 shows the characteristics of the subjects included in the 12-month analysis. Of those included, nine people (6.5%) who had an active ulcer at 12 months had a major or minor amputation compared with nine people (2.2%) in those who did not have an ulcer. Figure 3 shows the factors which were significantly and not significantly associated with ulcer healing at 12 months. After adjustment, type of diabetes, site of ulcer, area of ulcer, SINBAD score and HbA_{1c} variability no longer showed a statistically significant association.

Significant factors associated with amputation at 12 months before adjustment were mean HbA_{1c}, HbA_{1c} variability, ulcer depth and SINBAD score. However, after adjustment, the only significant factors were age at presentation, ischaemia (AOR 6.4 [95% CI 2.8–14.4]) and ulcer area > 1 cm^2 (AOR 2.3 [95% CI 1.0–5.4]). For every year increase in age, the odds of amputation were 0.97 (95% CI 0.94–0.99).

Sex and ischaemia were the factors associated with being alive at 12 months. The adjusted odds of being alive at 12 months were 2.7 (95%

Table 1 Baseline patient characteristics for those with 12-week data

	Active ulcer at 12 weeks (*N* = 315)	**No active ulcer at 12 weeks (*N* = 291)**
Male *n* [%]	235 [74.6%]	197 [67.7%]
Female *n* [%]	80 [25.4%]	94 [32.3%]
Age (years) mean [SD]	70.5 [13.0]	69.3 [13.8]
Interval to presentation 0–13 days *n* [%]	164 [52.4%]	168 [57.7%]
Interval to presentation ≥ 14 days *n* [%]	142 [45.1%]	114 [39.2%]
Self-presenting *n* [%]	8 [2.5%]	9 [3.1%]
Type 1 diabetes *n* [%]	65 [20.7%]	55 [18.9%]
Type 2 diabetes *n* [%]	246 [78.3%]	235 [80.8%]
Other/unknown diabetes *n* [%]	3 [0.9%]	1 [0.3%]
Duration of diabetes (years) mean [SD]	20.6 [13.4]	17.7 [11.6]
SINBAD < 3 *n* [%]	153 [48.6%]	219 [75.3%]
SINBAD ≥ 3 *n* [%]	162 [51.4%]	72 [24.7%]
Mean HbA_{1c} (mmol/mol) [SD]	71.4 [18.6]	69.7 [17.5]
Mean HbA_{1c} variability [SD]	10.2 [6.6]	9.7 [6.7]
	(*N* = 275)	(*N* = 266)
Retinopathy *n* [%]	186 [67.6%]	176 [66.1%]
	(*N* = 272)	(*N* = 267)
Maculopathy *n* [%]	50 [18.4%]	48 [18.0%]

n number, *SD* standard deviation, *SINBAD* site, ischaemia, neuropathy, bacterial infection, area and depth

CI 1.1–6.7) for male patients compared to female patients and 4.3 (95% CI 1.7–11.2) for those without ischaemia.

DISCUSSION

Our data showed that HbA_{1c} variability does not significantly influence the likelihood of DFU healing at 12 weeks or 12 months. After adjustment, ulcer site on the hind foot, ischaemia and area > 1 cm^2 were the factors which had the greatest association with ulcer healing at 12 weeks. Although glycaemic control was not a significant factor, our data did suggest that those with the lowest HbA_{1c} variability had the lowest risk of having an active ulcer at 12 weeks. At 12 months, ischaemia and diabetes duration were the only remaining significant variables related to ulcer healing in our cohort.

Unlike ulcer healing, visit-to-visit HbA_{1c} variability has already been reported as a predictor and a marker of lower extremity amputations in adults with type 2 diabetes, particularly in those with a diabetes duration > 3 years [16, 17]. A meta-analysis looking at people with type 2 diabetes suggested that HbA_{1c} variability is associated with micro- and macrovascular complications [11]. The authors reported that the risk of

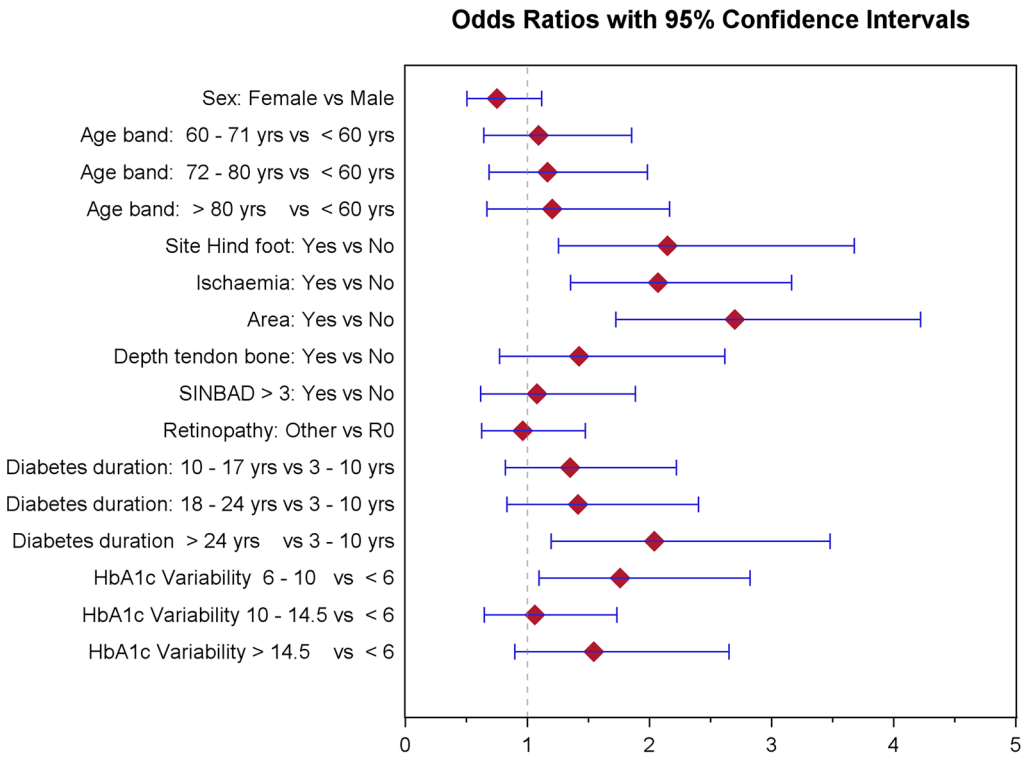

Fig. 2 Adjusted odds ratios for factors associated with having an active ulcer at 12 weeks

neuropathy in relation to glycaemic variability was not significant and diabetes-related ulceration was not assessed [11]. This link between HbA_{1c} variability and the increased risk of developing diabetes-related complications has previously been suggested to be explained by the hypothesis that glycaemic fluctuations correlate with oxidative stress along with interference of lipid peroxidation and cell membrane behaviour [20]. That our data did not reflect this may be due to a relatively small sample size. As mentioned, a meta-analysis of 23 studies with > 370,000 subjects suggested an association between HbA_{1c} variability and microvascular disease, but single-centre studies of just a few thousand such as the current study or others may not be able to replicate that [21].

Regarding DFU, a previous study suggested that glycaemic variability had a significant association with healing time. Those with low HbA_{1c} (< 58 mmol/mol) and low variability healed faster than those with high HbA_{1c} and high variability (73.5 days [59.5—90.8] vs 111.0 days [92.0—134.0], $p=0.007$) [18]. However, the link between glycaemic variability and likelihood of ulcer healing was not significant and, without a defined endpoint, it is difficult to compare the variables associated with ulcer healing. A recent retrospective study described the clinical characteristics of people with DFU according to glucose variability including the relationship between variability and DFU outcomes [22]. The study concluded that indices of glycaemic variability as coefficient of variation and standard deviation of glucose measurements were independent predictors of failure to heal DFU [22]. A significantly higher proportion of the low glucose variability group healed within 6 months compared with those having high glucose variability (65% vs 38%, $p<0.001$) [22]. Compared to the present study, these studies have suggested a significant relationship between glycaemic variability and ulcer healing. However, neither have assessed these variables at 12 weeks. In addition, our study looked at variability in HbA_{1c}, not glucose.

Table 2 Baseline patient characteristics for those with 12-month data

	Active ulcer at 12 months (*N* = 138)	**No active ulcer at 12 months (*N* = 408)**
Male *n* [%]	105 [76.1%]	287 [70.3%]
Female *n* [%]	33 [23.9%]	121 [29.7%]
Age (years) mean [SD]	69.2 [13.2]	69.4 [13.3]
Interval to presentation 0–13 days *n* [%]	76 [55.1%]	227 [55.6%]
Interval to presentation ≥ 14 days *n* [%]	58 [42%]	172 [42.1%]
Self-presenting *n* [%]	4 [2.9%]	9 [2.2%]
Type 1 diabetes *n* [%]	39 [28.3%]	72 [17.6%]
Type 2 diabetes *n* [%]	97 [70.3%]	333 [81.6%]
Other/unknown diabetes *n* [%]	2 [1.4%]	3 [0.7%]
Duration of diabetes (years) mean [SD]	21.8 [13.5]	18.4 [12.3]
SINBAD < 3 *n* [%]	70 [50.7%]	276 [67.6%]
SINBAD ≥ 3 *n* [%]	68 [49.3%]	132 [32.4%]
Mean HbA_{1c} (mmol/mol) [SD]	72.5 [18.3]	70.4 [18.1]
Mean HbA_{1c} variability [SD]	9.9 [6.2]	10.0 [6.7]
	N = 123	*N* = 372
Retinopathy *n* [%]	82 [66.7%]	248 [66.7%]
	N = 122	*N* = 373
Maculopathy *n* [%]	17 [13.9%]	75 [20.1%]

n number, *SD* standard deviation, *SINBAD* site, ischaemia, neuropathy, bacterial infection, area, and depth

Our data are consistent with those from the NDFA regarding variables associated with being alive and ulcer free at 12 weeks. Our study has showed that ulcer characteristics are the key factors which influence healing of ulcerations, in particular ischaemia, area and site on the hind foot. However, depth was not a significant factor in our dataset compared to the NDFA results [3]. Whilst the NDFA do not collect data beyond 12 weeks, a potentially surprising finding from our 12-month results was that the ulcer characteristics, with the exception of ischaemia, were no longer significant factors. There are many potential reasons for this finding. One suggestion for this may be that although these specific ulcer characteristics increase the healing time for DFU at 12 weeks, by 12 months many ulcerations have healed regardless of the initial characteristics of the ulcer or that the individuals may have died. More work needs to be done to try and explain these findings.

Although our study included many subjects, with the population being characteristic of people with DFU generally, we do recognise some limitations. We only included people from a single centre with a largely white population, which may impact the generalisability of the results. The COVID-19 pandemic also had an impact on our results, with some people taking longer to present to clinic and a reduction in

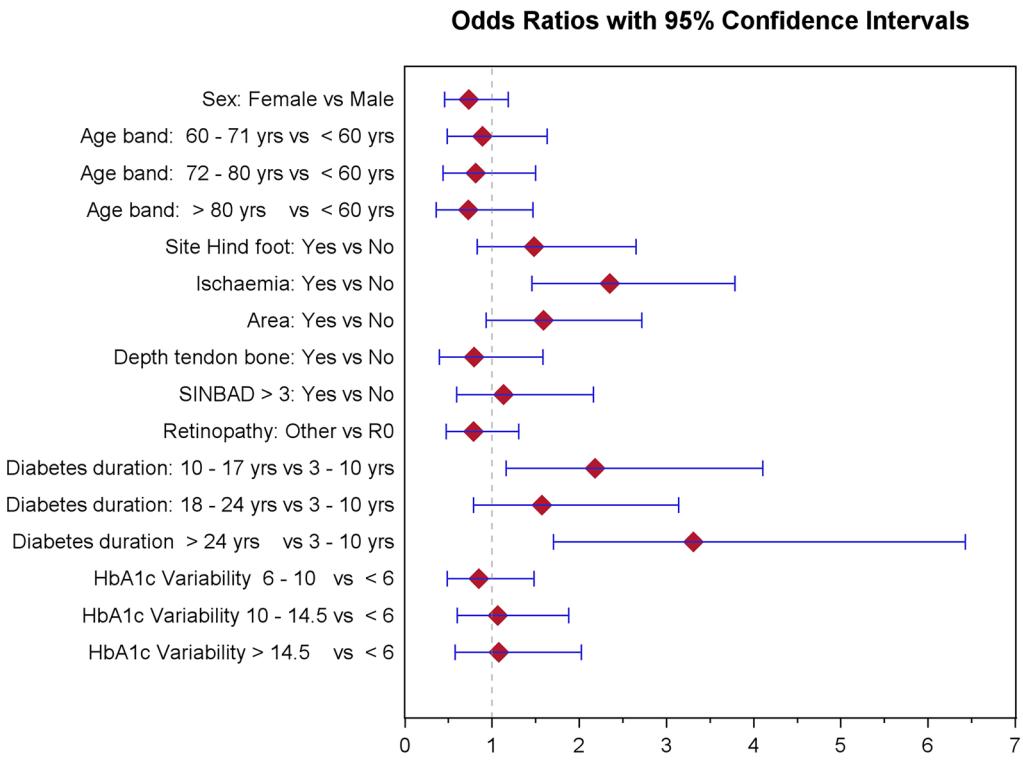

Fig. 3 Adjusted odds ratios for factors associated with having an active ulcer at 12 months

follow-up leading to missing outcomes in our dataset and exclusion of subjects from analysis. Data previously published by NHS England showed a reduction in amputation rates during the pandemic [23]. Due to the retrospective nature of the study, there were missing outcomes for some people, including those who died during follow-up, leading to exclusions in the patient selection process.

CONCLUSIONS

In summary, our data have shown that ulcer characteristics are the key variables associated with DFU healing at 12 weeks and 12 months, with diabetes duration also playing a role in the longer term outcomes. HbA_{1c} variability < 6 mmol/mol was associated with the least risk of an active ulcer at 12 weeks however was not a significant variable affecting the likelihood of ulcer healing at 12 months. Ischaemia was the only ulcer variable shown in our dataset to be associated with both 12 weeks and 12 month ulcer healing.

Author Contributions. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Georgia Thomason collected the data, did the initial data analysis and wrote the initial draft of the manuscript. Ian Nunney analysed the data. Ketan Dhatariya and Catherine Gooday conceived the study and wrote the final draft of the manuscript. All authors saw and approved the final draft. The authors accept that there was no patient and public involvement representation in the writing of this manuscript.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Ketan Dhatariya is an Editorial Board member of Diabetes Therapy and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Georgia Thomason, Catherine Gooday, and Ian Nunney have nothing to disclose.

Ethical Approval. The project was registered with the audit department at our institution who deemed that ethical approval was not required due to the anonymised, retrospective nature of the data collection.

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