Full Title:
Factors determining the risk of diabetes foot amputations - a retrospective analysis of a tertiary diabetes foot care service

Short Title:
Determining risk factors for amputation in the diabetic foot

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ABSTRACT

Aims: To identify which factors predict the need for minor or major amputation in patients attending a multidisciplinary diabetic foot clinic.

Methods: A retrospective analysis of patients who attended over a 27 month period were included. Patients had to have attended ≥3 consecutive consultant led clinic appointments within 6 months. Data was collected on HbA1c, clinic attendance, blood pressure, peripheral arterial disease (PAD), and co-morbidities. Patients were followed up for 1 year.

Results: 165 patients met the inclusion criteria. 121 were male. 33 patients had amputations. There was an association between poor glycaemic control at baseline and risk of amputation when adjusted for other factors, with those patients having HbA1c ≤58 at less risk of amputation with an odds of 0.14 (0.04 to 0.53) of amputation(p=0.0036). Other statistically significant factors predictive of amputation were: missing clinic appointments (p=0.0079); a high Charlson index (p=0.03314); hypertension (p=0.0216). No previous revascularisation was protective against amputation (p=0.0035). However PAD was not seen to be statistically significant, although our results indicated a lower risk of amputation with no PAD. Overall, 34.9% (n=58) of patients had good glycaemic control (HbA1c <58mmol/mol) at baseline & 81.3% (n=135) had improved their glycaemic control at their last follow up appointment.

Conclusions: In this cohort poor glycaemic control, poor attendance, previous revascularisation & hypertension were associated with higher risk of amputation, with PAD showing a trend. Moreover, we demonstrated benefits in glycaemic control achieved by attending this DFC, which is likely to translate to longer term diabetes related health benefits.

Keywords:

Diabetic foot; amputation; risk; clinic attendance; hypertension; co-morbidities

1.1 Introduction

Diabetic foot ulceration (DFU) is a common complication of diabetes, with a life time risk of developing an ulcer between 10 and 25% [1]. Foot ulcers frequently lead to lower extremity amputation and are a marker of premature mortality [2]. Previous work has suggested that ulceration is associated with a 50 fold increased risk of subsequent hospitalisation, and a 150 fold increased risk of lower extremity amputation, compared to patients with diabetes and no ulceration [3]. Whilst infection of the wound is one of the leading causes of amputation, several other risk factors have been implicated in further increasing this risk. These include peripheral arterial disease, poor glycaemic control, and the presence of other diabetes related co-morbidities [4-7].

It has been estimated that in England and Wales approximately 6000 people with diabetes have an amputation each year [8]. This equated to an overall expenditure on diabetes-related foot care and amputations of approximately £650million in 2010-2011[8]. Lower extremity amputation remains a major problem globally, and is associated with significant morbidity and mortality [9;10]. In addition, quality of life is substantially reduced, due to the social and psychological consequences of amputation and ulceration [11].

The UK National Institute for Health and Clinical Excellence (NICE) guidelines recommend using a multidisciplinary team (MDT) approach for patients with DFU [12]. This is because of the evidence base to show that the presence of multidisciplinary care with a well-designed team reduces rates of amputation and the length of hospital stay [12]. Few studies have examined what factors predict amputation, with most looking at prevention strategies [13]. Missing clinic appointments has been found to be associated with poor glycaemic control but to

date has not been investigated as an independent predictor of amputation [14]. Equally, whilst any patient undergoing amputation would be looked after in a secondary care environment, there are no data to evaluate outcomes according to different models of diabetes care – e.g. prior to amputation that the diabetes was managed exclusively in primary care – i.e. by the general practitioner and the practice nurse; or by the secondary care specialist diabetes team. However, it is accepted, that this may be because there are differences between these two groups with respect to severity, type and management processes for patients with diabetes, and local referral pathways.

We aimed to use our cross sectional data to establish which factors were associated with an increased risk of minor or major amputation in patients attending the tertiary care diabetic foot clinic at our institution and determine their predictive value. We aimed to create a risk score that can be used in clinical practice to predict amputation. Such a model may help clinicians identify high-risk patients in order to provide appropriate treatment and prevent morbidity and mortality in a targeted fashion. Furthermore, we aimed to determine if there were any significant differences in outcomes of patients managed in primary versus secondary care.

2.1 Subjects, Materials and Methods

We conducted a retrospective case note analysis of patients referred to the MDT diabetic foot clinic at the Norfolk and Norwich University Hospital between September 2009 and December 2011. The sole inclusion criterion was that patients must have attended at least 3 consecutive appointments in a consultant led clinic in which a diabetes consultant was always present, accompanied by either a vascular or orthopaedic surgeon. These patients had more complex foot complications, e.g. osteomyelitis, Charcot neuroarthropathy, significant peripheral vascular disease, or

had additional needs that could not normally be managed by the podiatrists alone. The diabetes consultant was also involved in the review of diabetes medicine management and this included improvement of glycaemic control facilitated by dietary and pharmacological advice – the latter being dose titration of both oral and insulin based treatments, management of painful diabetes neuropathy, and where indicated, perioperative diabetes management. Those with consecutive appointments that were greater than 6 months apart were excluded because they were deemed to have had foot disease that was not significant enough to require intensive input from a senior clinician. Patients seen solely by the specialist podiatrists were also excluded since glycaemic management was not done in this group of patients as part of their foot care. In our institution, whilst the podiatrists are non-surgical, they have extensive diagnostic and clinical skills in the management of diabetic complications and have the responsibility for the ongoing management of the majority of the patients referred to the diabetic foot clinic.

Baseline data was collected on previous revascularisation, co-morbidities, including hypertension and peripheral arterial disease (defined as the absence of both pulses in either foot) and was also reported as a Charlson Index score [15;16]. This is a previously validated scoring system that has been widely used to help predict mortality [17]. Hypertension was defined as a blood pressure of >140/80mmHg or being on an antihypertensive agent. In our clinic, whilst we routinely use a 10-gm Semmes Weinstein monofilament to check for the presence of neuropathy, to help identify the ‘at risk foot’, but in this dataset we did not include any measure of neuropathy. We documented whether the patients diabetes was managed by primary or secondary care at the time of referral. The number of times a patients attended a consultant led, clinic based care (months) and 3 consecutive clinic attendance rates (%) were recorded on our hospital appointment, patient

administration system. Baseline and subsequent information was collected from the clinic notes, the comprehensive letters generated from the specialist multidisciplinary foot clinics, and our electronic pathology database. The latter was used primarily for follow up because all HbA1c and other biochemistry and haematology results were reported here and any admissions for amputations were easily identifiable. Because of the retrospective nature of the study, the Norfolk and Norwich University Hospitals NHS Foundation Trust ethics committee classed this as a service improvement exercise and ethical approval was deemed to not be necessary.

2.2 Statistical methods

Amputation was modelled using a logistic regression model with forward stepwise model selection with a significance level of 5%. Unadjusted Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the effect size. Adjusted OR and 95% CI and P-values were from the likelihood ratio chi-square were reported based on the chosen logistic regression model. The SAS software (Version 9.3, 2011, SAS Institute Inc., Cary, NC, USA) was used to develop nomograms to estimate amputation probabilities and provide a visual aid for the model. The accuracy of the predictions was estimated by use of a bootstrap resampling technique as an independent dataset was not available.

Based on these results, each factor was allocated a score to produce the nomogram (Figure 1) that we believe can be used to predict individual risk of amputation.

3.1 Results

447 cases were identified as being referred to the clinic between Jan 2009 and December 2011. Of the 447 case identified, 282 were excluded because they failed to attend 3 consecutive consultant led foot clinics (including 23 patients who were

lost to follow up), leaving 165 eligible for analysis. Patients were followed up for a minimum of 1 year i.e. until 31st December 2012. Amputation was the primary outcome measure (minor or major), with secondary measures including mortality and glycated haemoglobin (HbA1c); the latter was recorded at referral and at 3-6 monthly intervals. Data from the patients who died during the follow up period were included in the outcome measures.

Of the 165 patients who were eligible for the study, 33 people (20%) underwent a total of 34 amputations. There were a total of 17 major amputations and 17 minor amputations, with 1 person having a minor and major amputation. As shown in Table 1, there were significantly more males and the majority of patients had type 2 diabetes mellitus. Table 2 shows the multivariable analysis highlighting factors that were independently associated with amputation. These were less than 100% attendance for 3 consultant led consecutive clinics, poor glycaemic control and hypertension. Patients who had undergone previous revascularisation or a low co-morbid status had significantly lower rates of amputation. Peripheral arterial disease (PAD) showed a strong trend towards increased risk of amputation but did not achieve statistical significance (p=0.0594).

Table 3 shows how patients who had their diabetes managed in primary care had statistically significantly lower glycated haemoglobin (HbA1c) at baseline ($p<0.05$). They also had lower rates of total amputations than those whose diabetes was managed in secondary care. However, this did not achieve statistical significance. The reduction in HbA1c for the whole cohort was 2.2mmol/mol (95%CI -0.4-4.8). For those people looked after initially exclusively in primary care, the mean decrease in HbA1c was 1.4mmol/mol (-2.8 to 5.7), and for secondary care the mean decrease was 2.6mmol/mol (0.7 to 5.9) (p=0.35). For those who did not undergo amputation

the mean decrease was 1.8mmol/mol (-1.0 to 4.6), and for those who had an amputation the decrease was 3.6mmol/mol (-3.1 to 10.3). Overall, 34.9% (n=58) of patients in this cohort had good glycaemic control (HbA1c <7.5% (58mmol/mol)), at baseline and 81.3% (n=107) had an improved glycaemic control at their last follow up appointment. Mortality rates between those patients whose diabetes was managed in primary or secondary care was not different.

4.1 Discussion

In this study we have found that poor glycaemic control, missing clinic appointments and hypertension were associated with increased risk of major and minor amputation. Previous revascularisation and low co-morbid status were associated with a lower risk of amputation. Figure 1 shows a nomogram derived from this data that acts as a basis for a predictive model for the risk for amputation.

A recent multicentre prospective study looked at factors predictive of lower-extremity amputation in patients with an infected diabetic foot ulcer using patients from the Eurodiale cohort [7]. Those authors developed a risk score for predicting amputation incorporating the following: peri-wound oedema, foul smell, (non) purulent exudate, deep ulcer, positive probe-to-bone test, pretibial oedema, fever and elevated CRP. In addition, a number of classification systems to predict lower extremity amputation have been developed but currently lack the evidence base and are not deemed to be ready for widespread clinical application [18]. Most of the classification systems investigated clinical factors attributed to the foot and limb. To date, only one study has used a combination of additional patient factors in conjunction with wound/limb related factors to produce a more complete predictive model of amputation risk [19]. However, the authors studied patients with concomitant infection and investigated some factors not included in our cohort and vice versa. In addition, they limited

themselves to hospitalised patients, who represent a small fraction of the total number of patients seen in a clinic. The lower extremity amputation risk score the authors produced consisted of additional factors such as male gender, albumin <2.8g/dL, white blood cell count >11x10^9/L. The present study provides support for some of the factors already identified by Lipsky et al, but our model also identifies additional factors that may need to be considered – including those pertinent to the outpatient population.

The improvement in glycaemic control we observed in 81.3% of the whole cohort is extremely encouraging, because poor glycaemic control has been showed to be a significant predictor of ulcer recurrence, in addition to contributing to the development of other micro and macrovascular complications [6;20].

Poor clinic attendance has been shown to be a major factor in the development of many diabetes related complications, such as retinopathy [21]. Our data are consistent with this, and from the work from the North West Diabetes Foot Care Study which looked at the risk of developing new ulcers. They showed that the risk was increased if patients had previously not attended podiatry appointments, foot deformity, and evidence of peripheral neuropathy or PAD [22]. However, other work has suggested that poor clinic attendance is not a factor when considering the risk of developing of diabetes related foot disease [23]. Attendance is an important factor, but clearly, this would be removed from any prediction model.

The majority of work around predicting amputation risk has been based on wound related factors, e.g. depth, infection or ischaemia [18]. The main strength of our study is that it used factors that have previously been overlooked to predict amputation risk.

We do acknowledge that our study has some limitations. We had a relatively small sample size, with only 165 eligible cases including 33 amputees. In order to strengthen our data, we plan on extending our collection period to 5 years. Larger, prospective studies will also be needed to validate these findings. It is worth noting that these patients were taken from a single centre in Norfolk, where 90% of the population are white British [24]. As a result, these results may not be generalisable to the wider population. By performing a sub-group analysis in patients from both primary and secondary care we have improved the external validity of our results although they do remain skewed towards those with more complex disease managed in secondary care. Another weakness of our study is the retrospective design in which we were reliant on accurate documentation, thereby increasing the possibility of information bias. Equally, the lack of randomisation increases the selection bias. In addition, we chose to only analyse patients seen in a consultant clinic at least 3 times, who, almost by definition had the most complex foot disease or were the most challenging patients. Through adjusting for the other variables we have attempted to minimise the effect of confounders, but some may remain. A possible barrier to implementing this model on a wider scale is the need for equipment to measure HbA1c. However, given the routine use of HbA1c to monitor glycaemic control in the management of diabetes mellitus this is unlikely to be a problem in clinical practice. We did not add infection to our list of potential risk factors, because this has already been shown to be strongly predictive of amputation [3]. We did not include a measure of neuropathy in our prediction model. Whilst the main reason for this was that we wished for the scoring system to be used in low resource environments, we also felt that because of the ongoing argument of 'how is neuropathy diagnosed?' [25], that this would lead to a greater generalisability of the findings without incurring controversy.

In conclusion, a cohort of patients attending our specialist MDT foot clinic, missing clinic appointments, hypertension and poor glycaemic control at baseline were associated with higher risk of amputation, with PAD showing a strong trend as well. Low co-morbid status and previous revascularisation were protective. Moreover, this case-note analysis demonstrated benefits in glycaemic control achieved by attending foot clinic, which is likely to translate to longer term diabetes related health benefits. We have used these results to develop a predictive model for amputation risk, although this needs to be validated with prospective studies done in different populations and a larger sample size.

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Legends to Figures and Tables

Table 1: Baseline characteristics of patients

Table 2: Factors associated with amputation in patients attending the multidisciplinary foot clinic

Table 3: Differences between patients managed in primary versus secondary care prior to referral

Figure 1: Nomogram derived from the data in the Tables that acts as a basis for a predictive model for the risk for amputation**.**

Table 1

Gender (M : F)				121 : 44
Type of Diabetes Mellitus T1DM:T2DM				31 : 134
		ANY AMPUTATION		
Amputation?		**YES**	**NO**	**TOTAL**
Number of patients (%)		33 (20)	132 (80)	165
Age	**< 50**	9 (32.1)	19 (67.9)	28 (16.9)
	50-54	4 (28.6)	10 (71.4)	14 (8.4)
	55-64	4 (13.8)	25 (86.2)	29 (17.5)
	65-74	8 (17.4)	38 (82.6)	46 (27.7)
	≥ 75	8 (16.3)	41 (83.7)	49 (29.5)
HbA1c at baseline ≤7.5% : >7.5% (≤58 : >58 mmol/mol)		8 : 25	50 : 82	
Peripheral arterial disease n (%)		14 (29.2)	34 (70.8)	
Hypertension n (%)		32 (24.4)	99 (75.6)	
Previous revascularisation n (%)		6 (60)	4 (40)	
Charlson index	**≤ 5**	7	62	
	6	13	32	
	≥ 7	13	39	
Renal function n (%)	**Normal (CKD 1)**	7 (21.2)	26 (78.8)	
	Mildly reduced (CKD 2-3)	16 (23.9)	51 (76.1)	
	Moderate and Severe (CKD 4-5)	4 (26.7)	11 (73.3)	
Duration of clinic care (months)	**< 3**	7	13	
	3 – 6	7	20	
	6 – 12	4	31	
	12 – 18	5	21	
	> 18	10	47	

Table 2

		Amputations (n=33)								
		No	**%**	**Yes**	**%**	**Total**	**Reference value**	**Unadjusted OR (95%CI)**	**Adjusted OR (95%CI)**	**Adjusted p value***
Attendance rate										
	<100%	54	72.0	21	28	75	100	2.56 (1.16-5.64)	3.84 (1.54-9.52)	0.0038
	100%	79	86.8	12	13.2	91				
Charlson Index										
	≤5	62	89.9	7	10.1	69	>5	0.31 (0.13-0.76)	0.32 (0.11-0.91)	0.0331
	>5	71	74	25	26	96				
Hypertension										
	No	33	97.1	1	2.9	34	Yes	0.09 (0.01-0.71)	0.078 (0.01-0.69)	0.0216
	Yes	99	75.6	32	24.4	131				
Peripheral Arterial Disease										
	No	98	83.8	19	16.2	117	Yes	0.47 (0.21-1.04)	0.89 (0.35-2.30)	0.811
	Yes	34	70.8	14	29.2	48				
HbA1c (mmol/mol)										
	≤58	50	86.2	8	13.8	58	>58	0.52 (0.22-1.25)	02.96 (0.10-0.84)	0.0227
	>58	82	76.6	25	23.4	107				
Previous revascularisation										
	No	128	82.6	27	17.4	155	Yes	0.14 (0.04-0.53)	0.08 (0.02-0.44)	0.0035
	Yes	4	40	6	60	10				
Type of diabetes										
	Type 1	21	15.9	10	30.3	31	Type 2	2.3 (0.96-5.52	3.15 (1.10-9.0)	0.0321
	Type 2	111	84.1	23	69.7	134				

*Likelihood Ratio Chi-square

Table 3

		Primary care	Secondary care	Chi-square p-value
Total number		62	104	
HbA1c at baseline (mmol/mol, %)	**≤7.5%(≤58)**	50%	26.2%	<0.05
	>7.5%(>58)	50%	73.8%	
HbA1c lower at last follow up (%)		77.4% (n=48)	83.7% (n=87)	0.319
Amputations	**Major**	4 (6.5%)	13 (12.6%)	0.207
	Minor	7 (11.3%)	10 (9.7%)	0.746
	All	11 (17.7%)	23 (22.1%)	0.350
Death		13 (21.3%)	19 (18.6%)	0.676