Preoperative blood glucose and prognosis in diabetic patients undergoing lower extremity amputation

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ORIGINAL ARTICLE

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Dan Med J 2016;63(4):A5216

ABSTRACT

INTRODUCTION: Previous work has shown that uncontrolled diabetes mellitus is associated with adverse surgical outcomes. The purpose of the present study was to establish if a high peri-operative random blood sugar (RBS) concentration among patients with diabetes with non-traumatic lower-extremity amputation (LEA) is a decisive factor behind post-operative outcomes (re-amputation/mortality) within three months after the first amputation.

METHODS: In this retrospective cohort study, the independent sample t-test, Pearson's chi-squared test and a Cox proportional hazards model were used.

RESULTS: A total of 270 patients underwent non-traumatic LEA of whom 105 had diabetes, whereas 81 patients were included for this study. The mean age was 71 years (standard deviation: ± 11.8). Mortality was 27% and 16% were re-amputated within three months after their first amputation. The median pre-operative RBS level was 8.6 mmol/l (range: 4.6-18.7 mmol/l) with tertile ranges as follows: Q1 4.0-7.0 mmol/l; Q2 7.1-11.0 mmol/l; Q3 > 11.0 mmol/l. For the Q3 tertile, the age-adjusted hazard ratio for re-amputation was 0.77 (95% confidence interval (CI): 0.16-3.62) and for mortality it was 1.90 (95% CI: 0.50-7.22), with the Q1 tertile as the reference group.

CONCLUSIONS: This study does not confirm that a high peri-operative RBS level can predict increased mortality or re-amputation among patients with diabetes who undergo non-traumatic LEA. Furthermore, based on our results, we cannot inform clinical decision-making about whether to delay or to avoid elective surgery in patients with a high RBS preoperatively. Further investigation is warranted.

FUNDING: none.

TRIAL REGISTRATION: This trial was registered with the Danish Data Protection Agency (record no. 01975 HVH-2012-053).

According to the Danish Diabetes Association, the prevalence of diabetes in Denmark was 5.7% (320,000) in 2012. By 2025, this number is projected to double, reaching over 10% (600,000 [1]. Diabetes and vascular disease are among the primary causes in the development of foot ulcers and subsequent non-traumatic amputation [2]. It has been demonstrated that having an amputation is a risk factor for subsequent amputation in the same limb, and the risk of amputation of the contralateral limb also increases [3]. Furthermore, amputation is associated with a significantly increased morbidity and mortality [4]. Over the past few years, the incidence of lower extremity amputation (LEA) has decreased [5]. However, a recent meta-analysis reported that in a consecutive series one-third of patients with non-traumatic LEA died within one month of their operation, and the risk increased among patients with one or more co-morbidities [6].

Previous prospective studies have shown an association between an improved control of glycated haemoglobin (HbA_{1c}) and a reduced incidence and slower progression of diabetes-related macro-vascular and micro-vascular complications [7, 8]. The Danish Endocrine Society advises that patients with poor glycaemic control, defined as an HbA_{1c} > 70 mmol/mol, should be referred to a specialist diabetes team for preoperative optimisation of glycaemic therapy [9]. The aim is a blood glucose concentration in the 7.0-11.0 mmol/l range. Nevertheless, HbA_{1c} measurement is currently not a standard element in the preoperative workup of either elective or non-elective amputation.

Previous studies have shown a relationship between preoperative HbA_{1c} and post-operative complications, including re-amputation [10, 11]. Correction of HbA_{1c} before amputation is not possible as amputations are performed within a few days from the established indication. Correction of blood glucose levels before amputation would be possible. The aim of the present study was therefore to investigate a possible association between high random blood glucose levels pre-operatively and an increased incidence of re-amputation and mortality within three months among diabetic patient with non-traumatic lower extremity amputation.

METHODS

Study population

In the present retrospective cohort study, we identified all patients undergoing non-traumatic LEA from the hospital surgery database at the Department of Orthopaedic Surgery, Hvidovre Hospital, Copenhagen, Denmark, from 1 January 2012 to 31 December 2013.

Medical records including surgical details were reviewed. Variables were stratified according to demographic and socio-economic status (age, sex, civil status (living alone or with a partner), housing condition (private/institution) and whether they needed domestic help (yes/no)), personal habits (alcohol consumption (yes/no) and smoking habits (never, former, current smoker)), previous medical history (hypertension (yes/no), dyslipidaemia (yes/no)). Patients on antihypertensive treatment, due to known hypertension or as renal protection, were considered hypertensive. Patients on lipid-lowering treatment were considered dyslipidaemic. Moreover, body mass index (BMI), laboratory data (HbA_{1c}, white blood cells (WBC)), amputation level (above knee, below knee and through knee), re-amputation within three months (yes/no) and mortality within three months (yes/no) were included. Finally, three random blood sugar (RBS) values were collected pre-operatively (before breakfast, before lunch and before dinner). RBS was measured at the bedside with a handheld glucometer, and values were tested and calibrated by the Department of Clinical Biochemistry.

TABLE 1

Descriptive statistics of study population: patients with diabetes (N = 81). Data presented as non-adjusted values.

Age, yrs, mean ± SD	70.7 ± 11.8
BMI, kg/m^2, mean ± SD	26.0 ± 7.4
Average RBS conc., mmol/l, mean ± SD	9.5 ± 3.4
HBA_{1c}, %, mean ± SD	9.6 ± 2.4
White blood cell conc., × 10^3/µl, mean ± SD	14.3 ± 6.0
Follow-up period, days, mean ± SD	60.2 ± 37.2
Gender, n (%)	
Male	47 (58.0)
Female	34 (42.0)
Hypertension, n (%)[a]	
Yes	49 (61.3)
No	31 (38.8)
Lipid lowering treatment, n (%)	
Yes	38 (46.9)
No	43 (53.1)
RBS conc. severity, n (%)	
Tertile Q1: 4-7 mmol/l	24 (29.6)
Tertile Q2: 7.1-11 mmol/l	35 (43.2)
Tertile Q3: > 11 mmol/l	22 (27.2)
Amputation level, n (%)	
Above knee	33 (40.7)
Below knee	35 (43.2)
Through knee	9 (11.1)
Above and below knee	4 (4.9)
Re-amputation, n (%)	
Yes	13 (16.0)
No	68 (84.0)
Mortality, n (%)	
Yes	22 (27.2)
No	59 (72.8)
Smoking habits, n (%)[a]	
Never smoker	31 (40.3)
Former smoker	23 (29.9)
Current smoker	23 (29.9)
Alcohol consumption, n (%)[a]	
Yes	34 (44.2)
No	43 (55.8)
Housing, n (%)[a]	
Private house	67 (84.8)
Institution	12 (15.2)
Civil status, n (%)[a]	
Living alone	48 (61.5)
Living together	30 (38.5)
Domestic help, n (%)[a]	
Yes	44 (56.4)
No	34 (43.6)

BMI = body mass index; HBA_{1c} = glycated haemoglobin; RBS = random blood sugar; SD = standard deviation.
a) Total < 81.

Statistical design

All statistical analyses were performed using PASW statistics Data Editor (version 18.0). Age, BMI, average RBS, HbA_{1c} and white blood cells were modelled as continuous variables; sex, civil status, housing condition, domestic help, alcohol consumption, smoking habits, patient on antihypertensive and antidyslipidaemic treatment, amputation levels, re-operation within three months and mortality within three months were fitted as categorical variables.

An independent sample t-test was conducted to compare diabetes with individual factors for continuous variables. We also used Pearson’s chi-squared test to compare diabetes with other independent categorical variables. A p-value < 0.05 was considered statistically significant. All significant values were categorised in three forms according to significance (p-value), i.e. < 0.05; < 0.01; < 0.001 and are presented in tables. Cox proportional hazards model was used to assess the relative contribution of RBS to re-operation and mortality within three months. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI).

Trial registration: This trial was registered with the Danish Data Protection Agency (record no. 01975 HVH-2012-053).

RESULTS

During the two-year study period, we identified 270 patients who underwent LEA. Among them, 105 patients (39%) were diagnosed with diabetes mellitus (type 1/type 2). A total of 24 diabetes patients were excluded due to missing values. Thus, the remaining 81 diabetes patients (30%) were included in this study. The majority of patients were male (n = 47, 58%). The median age of the whole cohort was 70 years (range: 35-92 years). Among the study population, 23 patients (30%) were current smokers, 23 were former smokers (30%) and 31 (40%) had never smoked. A total of 43 cases (56%) did not con-

TABLE 2

Prevalence and distributions of different risk factors in relation to re-amputation/mortality within 90 days in 81 patients. Data presented as non-adjusted values.

	Re-amputation (< 3 months)			Mortality (< 3 months)		
	yes (N = 13)	no	p-value	yes (N = 22)	no	p-value
Age, yrs, mean ± SD	68.1 ± 9.6	71.2 ± 12.2	0.390	76.1 ± 11.5	68.7 ± 11.4	< 0.05
BMI, kg/m^2, mean ± SD	26.7 ± 4.0	25.9 ± 7.9	0.731	22.8 ± 6.6	27.2 ± 7.4	< 0.05
Average RBS conc., mmol/l, mean ± SD	9.9 ± 3.8	9.4 ± 3.3	0.586	9.4 ± 3.1	9.5 ± 3.5	0.915
HBA_{1c}, %, mean ± SD	9.7 ± 2.4	9.6 ± 2.5	0.930	8.6 ± 2.1	10.0 ± 2.4	0.191
White blood cell conc., × 10^3/µl, mean ± SD	14.7 ± 3.7	14.2 ± 6.3	0.832	11.3 ± 5.6	15.2 ± 5.9	< 0.05
Gender, n (%)			0.132			< 0.05
Male	10 (12.3)	37 (45.7)		8 (9.9)	39 (48.1)	
Female	3 (3.7)	31 (38.3)		14 (17.3)	20 (24.7)	
Antihypertensive treatment, n (%)	10 (12.5)	39 (48.8)	0.205	13 (16.3)	36 (45)	0.943
Lipid-lowering treatment, n (%)	5 (6.2)	33 (40.7)	0.505	8 (9.9)	30 (37)	0.245
RBS conc. severity, n (%)			0.492			0.661
Tertile Q1: 4-7 mmol/l	4 (4.9)	32 (39.5)		9 (11.1)	27 (33.3)	
Tertile Q2: 7.1-11 mmol/l	6 (7.4)	21 (25.9)		9 (11.1)	18 (22.2)	
Tertile Q3: > 11 mmol/l	3 (3.7)	15 (18.5)		4 (4.9)	14 (17.3)	
Alcohol consumption, n (%)	9 (11.7)	25 (32.5)	< 0.05	7 (9.1)	27 (35.1)	0.242
Smoking habits, n (%)			0.691			0.684
Never smoker	4 (5.2)	27 (35.1)		10 (13)	21 (27.3)	
Former smoker	5 (6.5)	18 (23.4)		6 (7.8)	17 (22.1)	
Current smoker	4 (5.2)	19 (24.7)		5 (6.5)	18 (23.4)	
Civil status, n (%)[a]			< 0.05			0.450
Living alone	3 (3.8)	45 (57.7)		15 (19.2)	33 (42.3)	
Living together	9 (11.5)	21 (26.9)		7 (9.0)	23 (29.5)	
Domestic help, n (%)	5 (6.4)	39 (50)	0.153	16 (20.5)	28 (35.9)	< 0.05
Housing, n (%)			0.983			0.063
Private house	11 (13.9)	56 (70.9)		16 (20.3)	51 (64.6)	
Institution	2 (2.5)	10 (12.7)		6 (7.6)	6 (7.6)	
Amputation level, n (%)			< 0.001			0.166
Above knee	1 (1.2)	32 (39.5)		11 (13.6)	22 (27.2)	
Below knee	3 (3.7)	32 (39.5)		9 (11.1)	26 (32.1)	
Through knee	9 (11.1)	0 (0.0)		0 (0.0)	9 (11.1)	
Above and below knee	0 (0.0)	4 (4.9)		2 (2.5)	2 (2.5)	

BMI = body mass index; HBA_{1C} = glycated haemoglobin; RBS = random blood sugar; SD = standard deviation.
a) Total < 81.

sume alcohol. 56% of patients received domestic help and 62% lived alone. The median RBS level was 8.6 mmol/l (range: 4.6-18.7 mmol/l) with tertile ranges as follows: Q1 4.0-7.0 mmol/l; Q2 7.1-11.0 mmol/l; Q3 > 11 mmol/l. At three-month follow-up, 13 patients (16%) had undergone re-amputation and 22 patients (27%) had died. Seventeen (20.1%) of the fatalities occurred within one month (**Table 1**).

The patients who died within three months were older than those who survived; 76.1 ± 11.5 years versus 68.7 ± 11.4 years ($p < 0.05$); and the patients who were re-amputated within three months were younger, 68.1 ± 9.6 years versus 71.2 ± 12.2 years ($p = 0.39$). The patients who died had a lower BMI than those who survived; 22.8 ± 6.6 kg/m^2 versus 27.2 ± 7.4 kg/m^2 ($p < 0.05$). The mortality was higher among women: 14 deaths (17.3%) versus eight deaths (9.9%) in men

Severe gangrene of the foot. Extensive loss of tissue makes the foot unsalvageable even with re-vascularisation.

TABLE 3

Cox proportional analysis of re-amputation/mortality within three months in patients (N = 81) in relation to random blood sugar severity.

	Random blood sugar concentration		
	tertile Q1: 4-7 mmol/l	tertile Q2: 7.1-11 mmol/l	tertile Q3: > 11 mmol/l
Re-amputation < 3 months			
Events, n/N (%)	4/26 (15.4)	6/35 (17.1)	3/22 (13.6)
Models, HR (95% CI):			
Model 1[a]	1.0	1.31 (0.37-4.63)	0.90 (0.20-4.03)
Model 2[b]	1.0	1.37 (0.39-4.90)	0.77 (0.16-3.62)
Model 3[b, c]	1.0	1.65 (0.27-9.87)	0.97 (0.12-7.84)
Model 4[b, c, d]	1.0	6.47 (0.57-73.6)	3.68 (0.17-79.9)
Mortality < 3 months			
Events, n/N (%)	4/26 (15.4)	13/35 (37.1)	5/22 (22.7)
Models, HR (95% CI):			
Model 1[a]	1.0	2.79 (0.91-8.58)	1.47 (0.39-5.46)
Model 2[b]	1.0	2.42 (0.78-7.52)	1.90 (0.50-7.22)
Model 3[b, c]	1.0	3.71 (0.75-18.3)	5.06 (0.81-31.5)
Model 4[b, c, d]	1.0	4.07 (0.65-25.6)	10.9 (0.86-138)

BMI = body mass index; CI = confidence interval; HR = hazard ratio; WBC = white blood cell concentration.
a) Unadjusted.
b) Adjusted for age.
c) Adjusted for antihypertensive treatment, antidyslipidaemic treatment, WBC and BMI.
d) Adjusted for housing, domestic help, alcohol, smoking, and civil status.

($p < 0.05$). In our cohort, the majority of those who required an amputation had a through-knee procedure (nine cases ($p < 0.001$)). Neither HbA_{1c}, antihypertensive treatment, antidyslipidaemic treatment, smoking or alcohol habits was associated with a poor outcome (**Table 2**).

The Cox regression analysis demonstrated that a dysregulated or normal pre-operative RBS level was not associated with a poor outcome as our results were non-significant. For tertile Q3 (RBS > 11.0 mmol/l), the re-amputation HR after age adjustment was 0.77 (95% CI: 0.16-3.62), whereas in tertile Q2 (RBS: 7.1-11.0 mmol/l), the re-amputation HR was 1.37 (95% CI: 0.39-4.90) with tertile Q1 (RBS: 4.0-7.0 mmol/l) as the reference group. Similarly, for tertile Q3, mortality HR after age adjustment was 1.90 (95% CI: 0.50-7.22), whereas in tertile Q2, the mortality HR was 2.42 (95% CI: 0.78-7.52) with tertile Q1 as the reference group. The HR increased after further adjustment for confounders, but nevertheless remained non-significant (**Table 3**).

DISCUSSION

As previously described, it is estimated that the prevalence of diabetes in Denmark will rise in coming decades, and diabetes is considered one of the most important causes of non-traumatic amputation. We hypothesised that participants with dysregulated diabetes or a higher pre-operative RBS level would have poorer surgical outcomes within three months of the initial surgery. In this retrospective cohort study, we found that one-third of the patients had died within three months and approximately a fifth of the total cohort had died within one month of their initial operation. Among those who had died, almost half died within one month of their operation. These data are similar to those reported in a previous study conducted by Kristensen et al, who performed a meta-analysis at our institution. They reported that a third of the patients with non-traumatic lower limb amputation in a consecutive series had died within one month, and 44% had died within three months, and the probability of dying was increased among patients with one or more co-morbidities [6].

Hyperglycaemia and dysregulated diabetes mellitus are associated with an increased incidence of surgical and non-surgical complications such as systemic pulmonary embolus [12], wound infection [13] and a further increase in mortality [14]. Similarly, other studies have demonstrated that uncontrolled diabetes as measured by an elevated HbA_{1c} is directly associated with an increase in re-amputation and in the mortality rate.

According to Skoutas et al, there is a high risk of re-amputation in the diabetic foot, especially within six months of the initial amputation [15]. Other studies show that poor glycaemic control is an important predictor of amputation in patients with diabetes in addition to clinically detectable peripheral arterial disease and peripheral neuropathy [16, 17]. Our data did not support this finding as we found no statistically significant association between preoperative RBS and re-amputation and mortality within three months. Similarly, according to Kristensen et al, diabetes had no significant influence on mortality rates when patients with diabetes were compared with other patients [6]. Another study conducted by Fortington et al found no difference in mortality rates after lower limb amputation among patients with diabetes as compared with non-diabetics at any time point [18]. However, the Danish Endocrine Society has suggested a tight control of HbA_{1c} as standard preoperative workup to achieve a random blood sugar level in the 7-11 mmol/l range and recommends that a local endocrinologist is seen if HbA_{1c} exceeds 70 mmol/mol [9]. Nevertheless, HbA_{1c} measurement is currently not a standard element in the preoperative workup of either elective or non-elective amputation. The reason for the discrepancy between the uncontrolled diabetes as defined by HbA_{1c} or red blood cells (RBC) is unclear, but HbA_{1c} may reflect the overall host status, while RBC reflects the acute stress on the patients' immune system. It remains as a fact that in the majority of cases, HbA_{1c} cannot be adjusted in patients who are scheduled for amputation.

Even though the incidences of re-amputation and mortality have decreased, our focus should be on further improving outcomes. The idea behind routine control of the pre-operative RBS level remains ambiguous; and thus it is difficult to conclude whether to delay or avoid elective surgery in patients with dysregulated diabetes mellitus.

This retrospective study has several potential limitations. Firstly, the manner in which we routinely collected bedside RBS among patients with diabetes and further division as average RBS into tertile. Secondly, we could not include HbA_{1c} because of lacking data, and we focused on RBS. Thirdly, the sample size could be one reason why this study did not establish a difference in outcomes. According to Zhao et al, levels of blood glucose over a period of time (which can be assessed by HbA_{1c}) would have been a better predictor for lower-limb amputation among type 2 diabetes mellitus patients [19]. HbA_{1c} cannot be influenced at the time of amputation, but is often a marker of patient deterioration in the period leading up to a major amputation. The RBS levels can be and are regulated, but we did not collect data that could elucidate the reason why we observed high values. An intervention study focusing on correcting the elevated blood glucose values is needed to prove whether this has any benefits in relation to re-amputation or mortality.

CONCLUSIONS

This study showed that a high preoperative RBS level among diabetic patients with non-traumatic lower extremity amputation is not a decisive factor behind re-amputation or mortality within three months. Although uncontrolled diabetes has previously been associated with poor surgical outcomes, this study cannot inform clinical decision-making on whether to delay or avoid elective surgery. Further studies are warranted to explore the association between RBS and adverse surgical outcomes.

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ACCEPTED: 2 February 2016

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

ACKNOWLEDGEMENTS: The authors would like to thank *Ketan Dhatariya*, consultant in diabetes, endocrinology and general medicine and *Elsie Bertram*, Diabetes Centre Norfolk and Norwich University Hospitals, NHS Foundation Trust, for assistance and guiding in writing this paper.

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