Clinical Characteristics and Survival of Patients with Diabetes Mellitus following Non-Traumatic Lower Extremity Amputation

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ABSTRACT: **Background:** Diabetes mellitus-related lower extremity amputation is a major complication severely affecting patient survival and quality of life.

Objectives: To analyze epidemiological and clinical trends in the incidence and survival of lower extremity amputations among diabetes patients.

Methods: We conducted a retrospective observational cohort study of 565 consecutive diabetes patients who underwent their first non-traumatic lower extremity amputation between January 2002 and December 2009.

Results: Major amputations were performed in 316 (55.9%) patients: 142 above the knee (25.1%) and 174 below (30.8%); 249 (44.1%) had a minor amputation. The incidence rates of amputations decreased from 2.9 to 2.1 per 1000 diabetes patients. Kaplan-Meier survival analysis showed that first year mortality rates were lower among patients with minor amputations (31.7% vs. 39.6%, $P = 0.569$). First year mortality rates following below-knee amputation were somewhat lower than above-knee amputation (33.1 vs.45.1%, respectively). Cox regression model of survival at 1 year after the procedure found that age (HR 1.06 per year, 95% CI 1.04–1.07, $P < 0.001$), above-knee amputation (HR 1.36, 95% CI 1.01–1.83, $P = 0.045$) and ischemic heart disease (HR 1.68, 95% CI 1.26–2.24, $P <$ 0.001) significantly increased one year mortality risk.

Conclusions: In this population-based study the incidence rate of non-traumatic amputations in diabetes patients between January 2002 and December 2009 decreased slightly. However, one year mortality rates after the surgery did not decline and remained high, stressing the need for a multidisciplinary effort to prevent amputations in diabetes patients.

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Diabetes mellitus-related lower extremity amputation (LEA) is a major complication severely affecting patient survival and quality of life. Diabetic foot is a major cause of non-traumatic amputations that places a high economic burden on the health care system, but can be prevented [1,2]. Several risk factors have been found to be associated with LEA. Male gender, duration of diabetes (≥ 10 years), age at diabetes diagnosis, elevated levels of HbA1C (≥ 8%) or glucose (≥ 130), diabetes-related microvascular complications (neuropathy, nephropathy, retinopathy), insulin therapy [3], and prior amputation [4]. The risk of an individual with diabetes undergoing LEA in 2004 was 20.3 times that of an individual without diabetes and did not significantly change by 2008 [5].

Peri-operative mortality is affected by the site of the procedure. A higher mortality rate was shown for above-knee amputation compared to below-knee amputation [6]. Cardiac failure is a prevalent cause of death after surgery [7].

The rate of LEA varies greatly worldwide. While some studies suggest that the rates have been decreasing [8], others show a decrease only in major amputations (above the ankle), with rates of below the ankle amputation remaining stable [9,10]. Lopez-De-Andres et al. [11] found a decrease in both major and minor amputations among patients with diabetes mellitus type 1. In contrast, among individuals with type 2 diabetes the rate of major and minor amputations increased significantly [11]. Ideally, prevention of diabetic foot and its complications is the cost-effective strategy to reduce the amputation rate; this requires a multidisciplinary approach, with regular self-inspection of the feet, early diagnosis, and continual follow-up and treatment [12,13].

We sought to investigate the temporal trends in the incidence of low extremity amputations in diabetic patients and describe survival predictors and patterns.

PATIENTS AND METHODS

This retrospective observational study was conducted at Soroka University Medical Center, a tertiary, 1000-bed hospital. Located

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in Beer Sheva, the largest city in southern Israel, Soroka University Medical Center is the only medical center providing primary care facilities for approximately 700,000 residents in the southern district (2009, 14% of the country's total population) [14].

In 2002 there were approximately 35,000 individuals (5%) with diabetes in the southern district; by 2009 the diabetic population had doubled (70,460, 10%) with diabetes prevalence similar to that of the general population of Israel [14].

To identify diabetic patients who underwent related LEA between 1 January 2002 and 29 December 2009 we searched the computerized hospital database. In our search, we used the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes based on validation of a case definition for foot complications among hospitalized patients with diabetes studied by Harwell [15] (0.99 sensitivity, 0.93 specificity). Included were all adult patients (over 18 years old) with diagnostic codes for diabetes who had a first non-traumatic amputation and surgical debridement of the lower extremity distal to and including disarticulation of the hip (ICD-9 codes that were used to identify non-traumatic LEA are Z841, Z841-Z8419). We categorized the amputations as either below ankle (minor amputation) or above ankle (major amputation) with a subgroup of below-knee amputation (BKA) and above-knee amputation (AKA). First we extracted all the data on patients with the appropriate ICD codes from the general computerized hospital dataset, identifying 542 patients. We then manually reviewed the operating room patient lists, which yielded another 52 subjects. Therefore, we can assume 91% sensitivity and 100% specificity for ICD-9 amputation codes. We excluded patients with traumatic amputations and patients hospitalized with complications of a previous amputation. Comorbidity data were extracted from the same computerized database (ICD-9 codes) using the data from all patient admissions until the index hospitalization. All patients in our cohort were followed for at least 2 years or until death.

The study was conducted in accordance with the principles of the Helsinki Declaration of 1975 and the protocol was approved by the institutional ethical committee.

STATISTICAL ANALYSIS

One year all-cause mortality was the primary outcome of the analysis. The results are presented as the mean (SD) for continuous variables and proportions for categorical data. Student's t-test was used for comparing continuous variables and the chi-square test for categorical data, augmented by Fisher's exact test if needed. We used the Mann-Whitney test for the comparison of variables not distributed normally and presented as median and interquartile (IQ) range. Temporal incidence of amputation, adjusted and unadjusted for age, was assessed by using the population size data from the Central Bureau of Statistics. Kaplan-Meier survival curves were constructed for depicting long-term survival with calculated Kaplan-Meier rates. We used the Cox proportional regression model for assessing survival at one year. Initially, we included in the model age, gender, site of amputation, chronic ischemic heart disease, hypertension, dyslipidemia and smoking. Variable selection in multivariable modeling was based on clinical and statistical significance with the following variables: age, site of amputation, chronic ischemic heart disease and hypertension. We present a final parsimonious model. A two-tailed P value of < 0.05 was considered significant. The statistical analysis used SPSS version 18.

RESULTS

We assessed the data of 594 patients, 316 (53.2%) of whom had major amputations [142 (23.9%) with AKA and 174 (29.3%) with BKA], 249 (41.9%) had minor amputation, and 29 (4.9%) were excluded due to lack of data on the precise location of the amputation. Therefore, the study population comprised 565 consecutive patients who underwent their first lower limb amputation during the study period. Overall one year all-cause mortality following the procedure was 36.1% (204 patients). Median follow-up time was 35 months (IQ range 4–60).

Demographic and clinical data comparisons between patients who underwent major and minor amputations are presented in Table 1. First hemoglobin was lower among patients with major amputation as compared with patients who had minor amputation (10.76 ± 1.92 vs. 11.58 ± 1.84 respectively, $P < 0.001$) and white blood cells were higher (14.1 ± 6.15 vs. 12.26 ± 9.22 respectively, $P < 0.001$).

Among patients who underwent major amputations, 222 (87%) had low albumin levels (< 3.5 g/dl) vs. 122 (70.1%) patients who underwent minor amputation ($P < 0.001$). Estimated glomerular filtration rate (eGFR) of the cohort was 67.07 ± 36.74 and was significantly higher among patients with minor amputation (71.66 ± 35) compared to those with major amputation (63.73 ± 37.66) ($P = 0.028$). There was an association between the site of amputation and the degree of diabetes mellitus control, as indicated by HbA1C levels: 8.55% in the major amputation group vs. 8.01% in the minor amputation group ($P = 0.008$). HbA1c below 6.5% was not significantly different between the groups.

SURVIVAL ANALYSIS

Outcomes of the hospitalization and the subsequent year show that of the 204 patients (35.8%) who did not survive the first year after the procedure, 125 (61.3%) had major amputations. Above-knee amputation constituted 31.3% (39 patients) of the major amputations. Forty-eight patients (23.5%) died during their index hospitalization [Table 1].

Kaplan-Meier survival analysis [Figure 1] showed similar first year mortality rates among patients with minor and major amputation (31.7% vs. 39.6%, $P = 0.569$). Cox regression model for death within the first year after the procedure [Table 2] included

Table 1. Demographic and clinical data of patients who underwent major versus minor amputations

		All patients (n=565)	Minor amputation (n=249)	Major amputation (n=316)	*P* value
Gender	Female	225 (39.8)	101 (40.6)	124 (39.2)	0.750
Age (years, ± SD)		68.28 ± 12.32	67.39 ± 12.43	69.98 ± 12.2	0.127
Weight (kg, ± SD)		81.20 ± 16.37	80.06 ± 13.02	82.54 ± 19.76	0.552
Ischemic heart disease (n, %)		263 (46.5)	117 (47)	146 (46.2)	0.080
COPD (n, %)		30 (5.3)	7 (2.8)	23 (7.3)	0.074
Hypertension (n, %)		353 (62.5)	150 (60.2)	203 (64.2)	0.559
Dyslipidemia (n, %)		165 (29.2)	76 (30.5)	89 (28.2)	0.057
Smoking (n, %)		54 (9.6)	19 (9.5)	35 (11.1)	0.556
Laboratory results during admission	Systolic BP (mmHg, ± SD)	139.73 ± 63.51	146.92 ± 93.42	134.63 ± 25.92	0.335
	Diastolic BP (mmHg, ± SD)	72.64 ± 12.52	72.96 ± 12.63	72.42 ± 12.63	0.305
	First creatinine (mg/dl, ± SD)	1.71 ± 1.93	1.59 ± 1.79	1.80 ± 2.03	0.533
	Last recorded creatinine (mg/dl, ±SD)	2.04 ± 2.14	1.87 ± 1.97	2.16 ± 2.25	0.236
	First Hb (g/dl, ± SD)	11.10 ± 1.93	11.58 ±1.84	10.76 ± 1.92	< 0.001
	First WBC (g/dl, ± SD)	13.33 ± 7.64	12.26 ± 9.22	14.1 ± 6.15	< 0.001
	eGFR (ml/min/1.73 m^2, ± SD)	67.07 ± 36.74	71.66 ± 35	63.73 ± 37.66	0.028
	First albumin (ng/ml, ± SD)	3 ± 0.6	3.27 ± 0.53	2.81 ± 0.57	< 0.001
	First albumin < 3.5 g/dl (ng/ml, n, %)	344 (80.2)	122 (70.1)	222 (87.1)	< 0.001
	HbA1C (%) within 6 months (± SD)	8.26 ± 2.1	8.55 ± 2.08	8.01 ± 2.09	0.008
	HbA1C within 6 months > 10 % (n, %)	66 (19.2)	33 (21)	33 (17.7)	0.443
Hospital procedures and clinical outcomes	Length of hospitalizations (days) (Median, IQ range)	10 (5.5, 20.5)	10 (5,22.5)	10 (6, 19)	0.487
	Death during index hospitalization (n, %)	46 (8.1)	20 (8)	26 (8.2)	0.993
	Death within one year from index hospitalization (n, %)	204 (36.1)	79 (31.7)	125 (39.6)	0.054

COPD = chronic obstructive pulmonary disease, BP = blood pressure, WBC = white blood cells, eGFR = estimated glomerular filtration rate, IQ = interquartile

Table 2. Cox proportional hazards regression model for death within 1 year following the amputation

	Hazard ratio	95% confidence interval		*P* value
		Lower	Upper	
Age	1.055	1.040	1.069	< 0.001
Above- or below-knee amputation	1.358	1.007	1.833	0.045
Ischemic heart disease	1.678	1.259	2.236	< 0.001

the following risk factors: age [hazard ratio (HR) 1.07, 95% confidence interval (CI) 1.05–1.09, *P* < 0.001], major vs. minor amputation (HR 1.42, 95% CI 0.96–2.11, *P* = 0.083), and presence of chronic ischemic heart disease (HR 2.06, 95% CI 1.4–3.03, *P* < 0.001). A subgroup analysis of major amputations showed no significant change in mortality between AKA and BKA.

TEMPORAL TRENDS ANALYSIS

Figure 2 demonstrates amputation rates per 1000 patients with diabetes, with and without age adjustment, during the years 2003–2009. Age-adjusted annual amputation incidence rates show a minor decrease of 15.8% over the years. Age-adjusted rates during the study period declined by 27.6%, from 2.9 to 2.1 per 1000 diabetic patients.

One year mortality in the study population adjusted for age, site of amputation and chronic ischemic heart disease did not significantly change over the study period for both major and minor amputations: 39.5% to 37% and 35.7% to 30.8% in 2003 and 2009 respectively

DISCUSSION

This population-based study demonstrates that the incidence rate of non-traumatic amputations in patients with diabetes between 2003 and 2009 decreased by 27.6% (2.9–2.1 per 1000 patients with diabetes). The adjusted one year mortality rate following the amputation declined for both major and minor amputations. However, more than 60% (125 patients) undergoing major amputation and nearly 40% (79 patients) undergoing minor amputation did not survive the first post-surgery year.

Figure 1. Kaplan-Meyer comparison of survival rates between patients who underwent below-knee and above-knee amputation

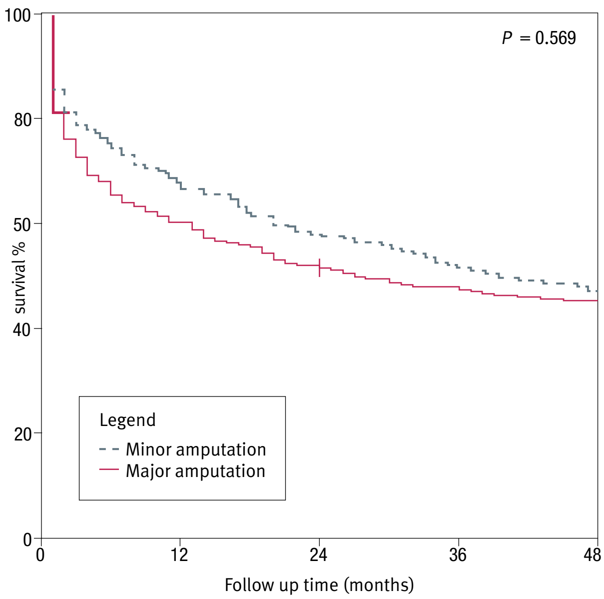
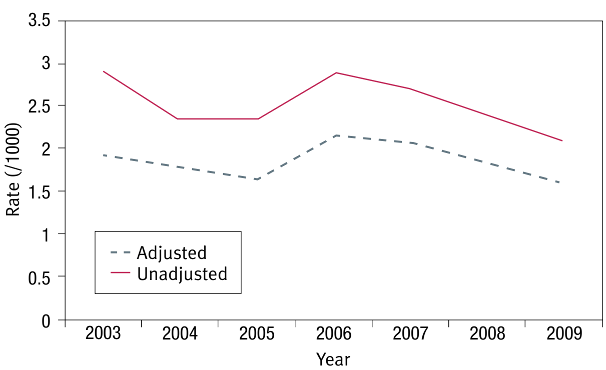


Figure 2. Age-adjusted and unadjusted incidence of amputation among patients with diabetes



During the last two decades, the reported incidence of LEA among patients with diabetes varies among different countries and type of amputation. Vamos et al. [5] reported the amputation incidence trends in England between 2004 and 2008. Among diabetes patients, a non-significant decrease of 9.1% was reported (2.75–2.50 per 1000 people with diabetes), while the total number of procedures increased due to the rising incidence of diabetes nationwide. In the United States, major amputations decreased by 45.9% when adjusted for gender and age [8]. In the Netherlands [16], the overall incidence rate of the number of patients who underwent LEA between the years 1991 and 2000 decreased over the years from 5.50 to 3.63 per 1000 patients with diabetes (34%). Similar results were found in Finland, with a decrease of 32% [17]. In contrast, a study in Ireland [18] showed a non-significant increase in the total incidence rate of amputations. In our study we noted a modest reduction in the amputation incidence rate of 27.6%, from 2.9 to 2.1 per 1000 diabetic patients. This rate is somewhat lower than found in other studies.

We examined the death incidence during hospitalization due to LEA. In our study 48 patients (8.5%) died during the hospitalization. Our findings are consistent with other studies (11% and 11.8%) [19,20]. However, first year post-LEA mortality data showed that death occurred in 35.8% of the cohort while 61.3% of patients undergoing major amputations died during the first year. By comparison, in a study conducted by Icks and colleagues [19], 31% of diabetic patients died during the first year after major LEA, and in a Swedish study [2], death occurred in 45% of diabetic patients with major amputations.

We found that the survival rate was 66.9% within one year after BKA and 54.9% after AKA. Similar rates were found by Aulivola et al. [21] in a U.S. population (1990–2001), with the first year survival being 72.5% among patients after BKA and 48% following AKA. In a somewhat different group of patients in Israel (2007–2010), Rosen et al. [22] showed first year survival rate for BKA of 64% and 43% for AKA. Higher rates observed in populations undergoing AKA are explained by a higher burden of co-morbidities and advanced age.

In our population we found lower first year survival rates as compared with other studies. This might emphasize the need for integrating aggressive treatment for cardiovascular risk factors as suggested by Schofield et al. [7] together with a comprehensive foot care approach including better screening and diagnosis of neuropathy. Treatment of infection by improving revascularization, debridement and dressing the wound, and better control of infection with systemic antibiotic therapy or topical treatment as well as hyperbaric oxygen therapy [23,24] are suggested therapeutic approaches.

We found that older age, above-the-knee amputation, ischemic heart disease and hypertension are risk factors that increase the probability of death within the first year post-amputation. These findings are consistent with the findings of Icks et al. [19]. The average age at the time of amputation is fairly similar across studies, including ours (64.5 ± 16.2 years); e.g., 69.9 ± 11.8 years in Scotland [7] and 73.0 ± 12.0 in Spain [4], while in developing countries the age is lower, as reported for Costa Rica [3] (60.6 ± 12.0 years) and India [20] (56.5 ± 10.3 years). This difference might be attributed to better screening and treatment, such as the presence of multidisciplinary foot care centers in developed countries.

The strength of our study is that it was conducted in a well-defined geographical area with only one hospital providing medical services to over 700,000 people. This enabled observation of the entire population of lower limb amputees among patients with diabetes mellitus in the region with virtually no loss during follow-up. Moreover, this geographic area is ethnically diverse and includes Bedouin Arabs, Russian Jews, Sephardic Jews, and others.

Our study had several limitations. First, we used ICD-9 codes that are based upon precise reports of amputation diagnosis and can have suboptimal validity (sensitivity and specificity). Therefore, we might have inaccurate estimates of amputation rates and sites, co-morbidities, treatment, and patients' lifestyle (e.g., smoking). Second, we used HbA1C levels reflecting glucose control during 3 months before the surgery and glucose levels at admission. Lastly, we did not have data on the post-amputation rehabilitation process and ambulatory care

CONCLUSIONS

Diabetes mellitus and its complications are the major cause of lower extremity amputations. In this population-based study, we found a moderate decrease in the incidence rate of non-traumatic amputations in patients with diabetes. However, the one year mortality rate after surgery did not decline and was found to be higher than in similar studies, stressing the need for a multidisciplinary effort to prevent low extremity amputations in patients with diabetes.

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"Architecture is inhabited sculpture"

Constantin Brancusi (1876-1957), Romanian sculptor, painter and photographer who made his career in France. Considered a pioneer of modernism, he was one of the most influential sculptors of the 20th century. His art emphasizes clean geometrical lines that balance forms

"Those who will not reason, are bigots, those who cannot, are fools, and those who dare not, are slaves"

Lord Byron (1788-1824), English poet, still widely read and highly regarded. He travelled widely across Europe and joined the Greek War of Independence fighting the Ottoman Empire, for which many Greeks revere him as a national hero. Flamboyant and notorious, he was both celebrated and castigated for his aristocratic excesses, including huge debts, numerous love affairs with more than one gender, rumors of a scandalous liaison with his half-sister, and self-imposed exile