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Impact of diabetes on clinical outcome in severely burned patients

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ABSTRACT

Introduction: According to the International Diabetes Federation, approximately 425 million people worldwide suffer from diabetes mellitus, a figure that will double in the next 20 years. Data on the ratio of treated diabetics in burn intensive care units remain scarce and the effects on the mortality rate are poorly defined.

Methods: Our retrospective, single-centre study aimed to evaluate differences in the risk factors due to diabetes mellitus, the clinical outcome and the patient population of diabetic patients after severe burn injuries over a time period of 21 years.

Results: Despite increasing numbers of diabetic patients, the ratio of burn patients suffering from diabetes remained stable during the study period. The risk factors for mortality were higher age (OR 1.03, 95% confidence interval (CI), 1.02–1.04, $p < 0.0001$), female sex (OR 1.56, 95% CI, 1.06–2.29, $p = 0.025$), higher % total body surface area (TBSA) (OR 3.88, 95% CI, 2.81–5.46, $p < 0.0001$), full thickness burns (OR 8.58, 95% CI, 3.84 – 23.60, $p < 0.0001$) and the presence of inhalation injuries (OR 4.68, 95% CI, 3.15–7.02, $p < 0.0001$) Patients with diabetes had a smaller extent of burned areas with a median TBSA of 30% (quartiles: 22–50%, $p = 0.036$) compared to non-diabetic patients (35% (25–55%)) but had a similar length of stay with a median of 29 (quartiles: 13–44) days vs. 23 (10–48) days. Outcome

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analysis showed an overall mortality of 35.6%. Diabetes was not associated with higher mortality rate after burn injury in a univariate model (OR 1.80, 95% CI 0.92–3.51). After correction for %TBSA, the effect of diabetes on mortality was significant (OR 2.80, 95% CI, 1.33–5.90).

Conclusion: Our data indicate higher mortality rates (50–100%) of diabetic patients with TBSA greater than 40% in severely burned patients compared to non-diabetic patients without a significant outcome due to the low number of cases in the subgroup analyses.

1. Introduction

Diabetes mellitus (DM) is a serious chronic disease affecting numerous systems of the body and potentially results in a variety of complications including limb loss, amaurosis, polyneuropathy and many more [1–11]. The number of patients suffering from DM is continuously rising. Data from the world health organisation (WHO) showed that in 2016 approximately 150 million patients are affected worldwide, and that this number may double by the year 2025. Much of this increase will occur in developing countries and will be due to population growth, ageing, unhealthy diets, obesity, and sedentary lifestyles [41]. In 2013, Statistics Austria counted 430,000 (6% of the population) diagnosed diabetic patients as well as 215,000 undiagnosed diabetic patients [42]. These numbers have risen to 800,000 diabetic patients in 2017, which amounts to 10% of the Austrian population [43].

Patients suffering from severe burn injuries are exposed to extreme levels of stress-mediated factors, a chronic persistence of hypermetabolism and hyperglycaemia [11–13]. These mechanisms weaken the immune system causing impaired wound healing and higher susceptibility to severe infections [14,15]. Burn severity generally directly correlates to the total body surface area (TBSA) of injured tissue. Above 20% TBSA, every burn trauma is considered as severe. The development of novel treatment options has made great strides in improving the patients' survival rates.

While, individually, each diagnosis already remarkably affects numerous immune systems, taken together, pre-existing DM combined with a severe burn trauma, might significantly affect patients' outcome. Several publications showed no significant effect on mortality in diabetic burn patients although higher risks of sustaining complications, e.g. infections, were described [15–19]. The aim of this study was to evaluate the impact of diabetes mellitus on the mortality of severely burned patients.

2. Materials and methods

The study was performed at the Division of Plastic and Reconstructive Surgery at the General Hospital of Vienna, a tertiary referral centre for bun injuries for the eastern part of Austria. Approval of the local ethics committee was obtained before commencing the study.

All patients admitted to the burn intensive care unit (BICU), who received surgical treatment due to a severe burn trauma from December 1993 to December 2014 were considered for inclusion. Patients with a TBSA under 20% were excluded to ensure the inclusion of only severely burned patients. Patients admitted due to other indications, e.g. Lyell-Syndrome, were excluded. Further exclusion criteria were patients younger than 18 years, patients receiving only non-surgical burn treatment and patients with frostbites. A retrospective analysis was conducted to evaluate our primary endpoint whether diabetes is predictive for in-hospital mortality. Subjects were labelled as diabetic if they had a diagnosis of diabetes documented in their medical records. Secondary endpoints included the association of DM with age, sex, BMI, length of stay, inhalation injury, survival, %TBSA, burn depth, causes of burn and circumstances of burn trauma. Patients were identified by an electronic patient data management system. Data were screened for completeness, consistency, and outliers before analysis. In case of missing values, alternative data sources, such as hospital records, were explored before inclusion was considered. In such cases, values were replaced.

2.1. *Statistical analysis*

Patients were stratified based on their DM status and descriptive analysis was used to compare the two groups. The analysed variables were DM status, age, sex, BMI, length of stay, inhalation injury, survival, %TBSA, burn depth, causes of burn and circumstances of burn trauma. Categorical data are characterised by frequencies and percentages and the Chi-square test was used for group comparisons. In case of expected frequencies less than 5 the Fisher's exact test was used for comparisons of categorical data. Normally distributed continuous variables are described by mean and standard deviation (SD) and compared between groups using the Student's t-test. In case of non-normal distribution, data are depicted as median (quartiles) and compared using the nonparametric Mann-Whitney U-test. In order to test for differences in the length of stay at the BICU between patient groups, the values of patients deceased at the BICU were set to the maximum observed value of 801 days and again the Mann-Whitney U-test was used. Survival at the BICU was considered as the primary endpoint of our analyses. Univariate and multivariable logistic regression models were performed to evaluate the influence of DM, age (in years), sex, %TBSA, inhalation injury and full thickness burns on the survival status. Two multivariable regression models were calculated: I.) adjusting the influence of DM only for the %TBSA presentation; II.) considering all six variables of interest to evaluate the independent potential influence of DM on mortality. To test for a potential TBSA-dependent changing

Table 1 – Demographic Data.

Variables	All patients (n = 489)	Diabetes (n = 37)	Non-Diabetes (n = 452)	p
Age (yr), mean/SD	50.1 / 19.3	66.1 / 13.7	48.8 / 19.2	< 0.0001[a]
Body mass index (kg/m²), mean/SD	27.4 / 5.4	31.8 / 7.4	27.0 / 5.0	0.001[a]
Gender (male/female)	324 / 165 (66.3%/33.7%)	14 / 23 (37.8%/62.2%)	310 / 142 (68,6%/31,4%)	0.0001[b]
Length of Stay (days), median (quartiles)	23.5 (10–48)	29 (13–44)	23 (10–48)	0.057[c]
Inhalation Injury	172 (35.2%)	14 (37.8%)	158 (35.1%)	0.739[b]
Survival	315 (64.4%)	19 (51.4%)	296 (65.5%)	0.084[b]
Non-Survivor	174 (35.6%)	18 (48.6%)	156 (34.5%)	
TBSA %, median (quartiles)	35 (25–53)	30 (22–50)	35 (25–55)	0.036[c]
maximum Depth of Burn Injuries 3°	412 (85.0%)	33 (89.2%)	379 (84.6%)	0.453[b]
2°a	249 (50.9%)	15 (40.5%)	234 (51.8%)	
2°b	420 (85.9%)	30 (81.1%)	390 (86.3%)	
3°	412 (84.3%)	33 (89.2%)	379 (83.8%)	
Cause of Burn	286 (58.5%)	26 (70.3%)	260 (57.5%)	0.077[d]
Flame	60 (12.3%)	5 (13.5%)	55 (12.2%)	
Scalding	36 (7.4%)	0	36 (7.9%)	
Electrical	8 (1.6%)	2 (5.4%)	6 (1.3%)	
Contact burn	97 (19.8%)	4 (10.8%)	93 (20.6%)	
Explosion	2 (0.4%)	0	2 (0.4%)	
Chemical				
Circumstances (%)	191 (39.1%)	22 (59.5%)	169 (37.4%)	0.052[b]
Home	82 (16.8%)	6 (16.2%)	76 (16.8%)	
Leisure time	76 (15.5%)	1 (2.7%)	75 (16.6%)	
Occupational	42 (8.6%)	3 (8.1%)	39 (8.6%)	
Suicide	98 (20%)	5 (13.5%)	93 (20.6%)	
Others				
Number of Operations, median (quartiles)	2 (1–3)	2 (1–3)	2 (1–4)	0.349[c]

[a] t-sample t-test.
[b] Chi-square test.
[c] Mann-Whitney U test.
[d] Fischer's exact test.

effect of DM on mortality, an interaction term was tested in both multivariable models. Due to the skew distribution, log2-transformed values of %TBSA were considered in the logistic regression models. Although patient numbers are too low to give conclusive answers, descriptive mortality subgroup analysis was performed to illustrate potential changes between diabetes and non-diabetes survival by dividing %TBSA into 5 groups (20–29%, 30–39%, 40–49%, 50–59%, > 60%).

3. Results

Between December 1993 and December 2014, 839 patients were treated at the BICU. 489 suffered from severe burns with a TBSA greater than 20% (Table 1). Out of these patients, 37 (7,6%) were diabetic according to their medical records upon admission to the BICU. The incidence of diabetes among the Austrian population has risen from 6% to 9% over the last years (2013–2016) [42,43]. The numbers and ratio of DM patients admitted to the BICU were evaluated from 1993 to 2014 (Fig. 1). Throughout the study period of 21 years, DM among the severely burn injured population (n = 37) did not increase but unexpectedly stayed consistent (0–10% per year).

Patients with a pre-existing diabetes were statistically significant older (66.1 years ± 13.7 vs. 48.8 ± 19.2; $p < 0.0001$), had a higher BMI (31.8 ± 7.4 vs. 27.0 ± 5.0; $p = 0.001$), and were more likely to be female (62.2% vs. 31.4%; $p = 0.0001$) than non-diabetic patients (Table 1). The majority of injuries occurred at home, during leisure time and at work in both groups and were mostly caused by flame (Table 1). Diabetic patients presented a smaller extent of burned areas with a median TBSA of 30% (quartiles: 22–50%, $p = 0.036$) compared to the non-diabetic group (35%,25–55%) but had a longer length of stay with a median of 29 (quartiles: 13–44) days vs. 23 (10–48 days, although this difference was not statistically significant. The depth of burn injuries was not significantly greater in the DM group (Table 1). Among the whole study cohort, 50.9% of the patients presented superficial partial, 85.9% deep partial and 84.3% full thickness burns. We also found no statistically significant differences between the diabetic and non-diabetic group for inhalation injuries (37.8% vs. 35.1%; $p = 0.739$). All patients included in this study underwent surgical procedures per patient due to their burn injuries whereas the number of operations, which amounted 1–14 procedures per patients, did not vary statistically significantly (2-times (1–3) vs. 2-times (1–4); $p = 0.349$) between the diabetic and non-diabetic group. (Table 1).

Outcome analysis showed an overall mortality of 35.6%. The mortality rate among DM patients was higher (48.7% vs. 34.5%), however this difference did not reach statistical significance in the group comparison (p = 0.084) nor in the univariate regression analysis (OR 1.80, 95% CI 0.92–3.51, p = 0.088). (Tables 1 and 2) Univariate regression analyses for risk factors of mortality in severely burned patients indicated

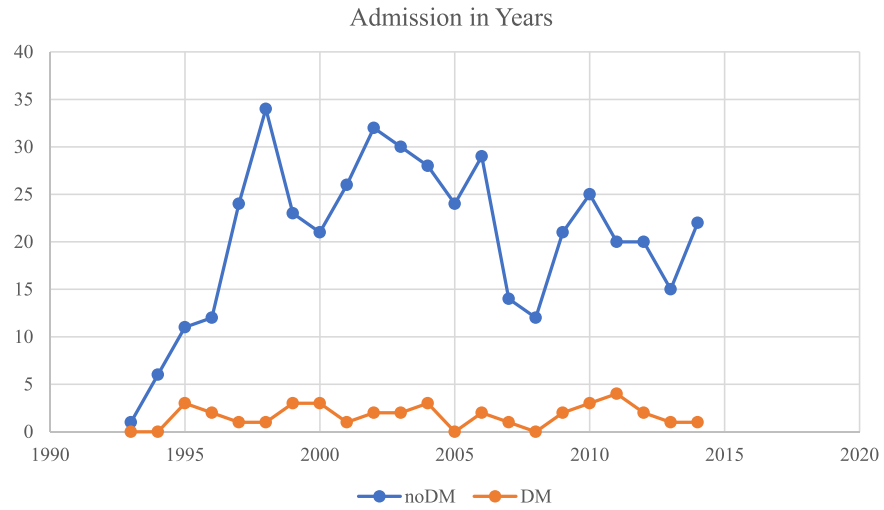

Fig. 1 – Admission of diabetic and non-diabetic burned patients at the burn intensive care unit in years: the number of treated severely burned patients with pre-existing DM at the BICU did not increase during the study period from 1994 to 2014 but stayed relatively consistent even though DM rates are rising among the general population of Austria.

Table 2 – Univariate logistic regression analyses of risk factors for survival after severe burns.

Variable	Univariate analysis		
	p	OR	95% CI
Age	< 0.0001	1.03	1.02–1.04
Sex	0.025	1.56	1.06–2.29
TBSA% (log2-transf.)	< 0.0001	3.88	2.81–5.46
DM	0.088	1.80	0.92–3.51
Inhalation Injury	< 0.0001	4.68	3.15–7.02
Full thickness burns	< 0.0001	8.58	3.84–23.60

that older age (OR 1.03, 95% CI, 1.02–1.04, p < 0.0001), female sex (OR 1.56, 95% CI, 1.06–2.29, p = 0.025), higher %TBSA (OR 3.88, 95% CI, 2.81–5.46, p < 0.0001), full thickness burns (OR 8.58, 95% CI, 3.84–23.60, p < 0.0001) and the presence of inhalation injuries (OR 4.68, 95%CI, 3.15–7.02, p < 0.0001) were statistically significantly correlated with higher rates of mortality (Table 2).

Multivariable analysis, considering all six variables of interest to evaluate a potential independent influence of DM on mortality did not reveal statistical significance (OR 1.36, 95% CI, 0.58–3.21, p = 0.479) (Table 3). Interestingly, the association of DM with higher rates of mortality adjusted only for the %TBSA was significant (OR 2.80, 95% CI, 1.33–5.90, p = 0.007) (Table 3). Neither of the two multivariable models revealed a statistically significant interacting effect of DM with the %TBSA level (p = 0.658, and p = 0.291, respectively). Nevertheless, we performed exploratory subgroup analyses with respect to the %TBSA level to descriptively compare mortality between DM and non-DM patients, and observed changes with increasing %TBSA (Fig. 2). While the first group (20–29%) showed no relevant difference, from the second group onwards the mortality curve rose markedly in DM patients. Patients in the second group had burns with a %TBSA 30–39 and presented a mortality rate among diabetic patients of 50% (4 of 8 patients) while non-diabetics had a mortality rate of 26.8% (30 of 112 patients). The third group %TBSA of 40–49% had a mortality rate of 100% for diabetic patients (2of 2), the fourth group with %TBSA 50–59% 50% (2 of 4 patients) and group 6 had 100% mortality rates with %TBSA greater 60% (6 of 6 patients) while non-diabetics had, in comparison, a low mortality rate of 38,5% in the third, 35,4% in the fourth and 65% in the fifth group (Table 4 and Fig. 2).

4. Discussion

The prevalence of DM in Austria is continuously rising and well-known complications include severe infections even in minor wounds and higher mortality rates in a variety of

Table 3 – Multivariable logistic regression models: factors affecting survival in burned patients.

Variable	Multivariable analysis I			Variable	Multivariable analysis II		
	p	OR	95% CI		*p*	OR	95% CI
Diabetes	0.007	2.80	1.33–5.90	Diabetes	0.479	1.36	0.58–3.21
%TBSA (log2-transf.)	< 0.0001	4.11	2.95–5.82	%TBSA (log2-transf.)	< 0.0001	8.22	5.10–13.78
				Age	< 0.0001	1.07	1.05–1.08
				Sex	0.757	1.09	0.64–1.85
				Inhalation injury	< 0.0001	3.40	2.09–5.58
				Full thickness burn	0.023	3.18	1.27–9.51

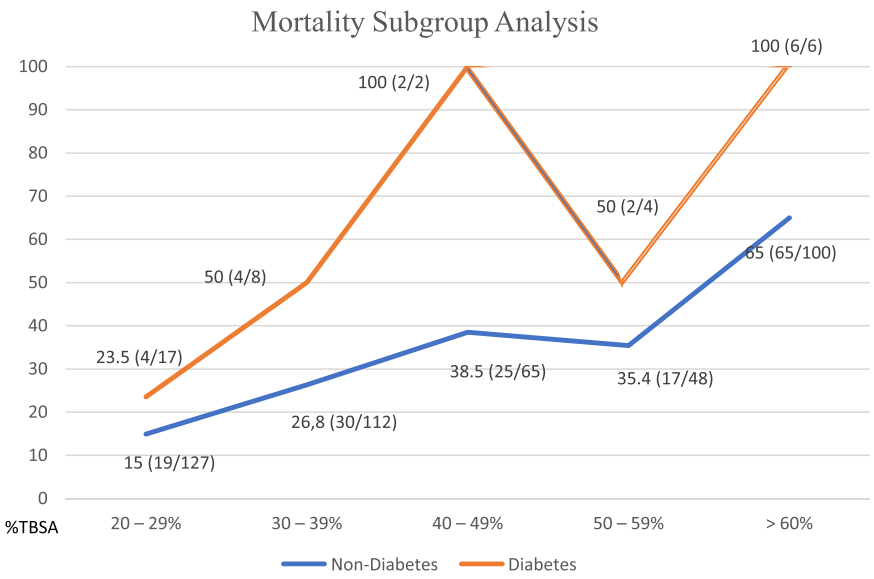

Fig. 2 – Mortality subgroup analysis: the effect of DM on mortality after correction for %TBSA found high mortality rates (50–100%) in DM patients with a TBSA of more than 40%.

Table 4 – Mortality subgroup analysis.

Variables	Diabetes (n = 37) *n*= 18 (non-survivor)	Non-Diabetes (n = 452) *n* = 156 (non-survivor)
TBSA groups		
20–29%	23.5% (4/17)	15.0% (19/127)
30–39%	50% (4/8)	26.8% (30/112)
40 – 49%	100% (2/2)	38.5% (25/65)
50 – 59%	50% (2/4)	35.4% (17/48)
> 60%	100% (6/6)	65% (65/100)

diseases [20,21]. The effect of DM on mortality after severe burn injuries compared to non-diabetic patients remains unclear. The aim of the current study was to evaluate the outcome of diabetic and non-diabetic severely burned patients with burn injuries greater than 20% TBSA who received surgical treatment at a single centre BICU.

In the presented study the number of treated patients with a pre-existing DM among the severely burn injured population did not increase during the study period from 1994 to 2014 but stayed relatively consistent. In Austria, the prevalence of DM has risen from 6% to 9% from 2013 to 2016 not accounting for the number of unreported cases. Even though DM rates are rising among the general population, this does not seem to affect the patient occurrence at the BICU. Most retrospective studies described pre-existing DM as a predictor for an increased length of stay [22–26]. We did not evidence a significant difference in length of stay between DM and non-DM patients. Although this effect may be biased by the smaller %TBSA in the DM group. A prolonged hospital stay can be expected since diabetes impairs several systemic metabolisms causing poor and delayed wound healing, altered perfusion, peripheral neuropathy and renal failure [26,27]. Univariate and multivariable analyses of variables on mortality showed that age is a significant risk factor. Lumenta et al. revealed a mortality rate of 30.6% among burn injured patients aged 65 and above [28]. Age is a decisive factor and older patients are the most vulnerable to the morbidity and mortality of burn injury, with an increased risk for adverse outcomes and disability [29,30]. These findings are similar to previous studies pointing out that DM burn patients are significantly older [23,28,31–33]. Given that most diabetic patients treated at our centre were of advanced age, burns resulted primarily from domestic incidents. This can be explained by the fact that workers in Austria normally retire at the age of 65 years. Work-related injuries were mostly observed in the non-diabetic group but did not present the leading cause of burn trauma as nowadays strict work safety precautions are well established.

Apart from age as a significant factor, female patients had a higher risk of death in the univariate analysis, but not in the multivariable regression model This finding confirms our prior published study that gender has no influence on mortality [34]. %TBSA is another crucially important and well-described parameter considerably affecting mortality [28,35–37]. Several studies described diabetic patients to be admitted with a lower [23,25] or a larger percentage of TBSA [31]. In contrast to previous studies, only patients with a TBSA > 20% were included to ensure inclusion of only severely burned patients with a systemic effect of the injury. The median %TBSA value observed in our study was lower in the diabetic group but the numbers of operations were equal in both cohorts despite the difference in the extent of burn injuries.

Mortality among DM patients was 48.7%. We found no significant difference between DM and non-DM patients (34.5%). Similar mortality rates in diabetic and non-diabetic patients were also observed in other studies [22,23]. However, we found an effect of DM on mortality after correction for %TBSA in a multivariable regression model. We further performed an exploratory subgroup analysis to illustrate a

potential difference in mortality rates between DM and non-DM patients and found high mortality rates (50–100%) in DM patients with a TBSA of more than 40%. However, the numbers of patients in these subgroups are too low to give conclusive answers and further research is needed. In a multivariable regression model with all variables of interest, DM had no significant effect on mortality.

Our data suggest a tendency towards higher mortality rates in patients with pre-existing DM and larger TBSA. The underlying pathomechanism remains speculative. Higher mean blood glucose levels and increased blood glucose variability during the BICU stay were observed in a previous study by Dahagam [33]. Prior studies revealed that a pre-diabetic status and a high glucose variability are associated with increased mortality in severely burned patients [38–40]. Kimball et al. also outlined a nearly two-fold increase in admission rates to the ICU and a higher likelihood of developing renal failure in the diabetic group compared to non-diabetics, although diabetics did not experience larger or more severe burns [26].

Limitations of this study include the lack of data on HbA1c since it was not routinely analyzed for each patient and therefore HbA1c values could not be included in the analysis. The low number of DM patients in the sub-analysis group is certainly another limiting factor. The width of the confidence interval for OR shows, despite the non-significant results in the multivariable model, that a relevant effect cannot be excluded.

5. Conclusion

Our data indicate a trend towards higher mortality rates (50–100%) of DM patients with TBSA greater than 40% in severely burned patients compared to non-diabetic patients without a significant outcome due to the low number of cases in the subgroup analyses, necessitating further clarification. In a multivariable model DM had a statistically significant effect on mortality after correction for TBSA.

Ethical approval

The study was approved by the institutional review board of the Medical University of Vienna and the Vienna General Hospital (protocol registration number 1165/2016).

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Author contributions

OA analysed the data and wrote the manuscript, AK analysed and interpreted the patient data, NS, IAE, SS retrieved the data, CR provided infrastructural support, SH analyzed the data and supervised the writing of the manuscript, RP designed the study. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

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