STATISTICAL AND CLINICAL ANALYSIS OF ALTERATIONS IN GLUCOSE VALUES AFTER BURNS

ANALYSE CLINIQUE ET STATISTIQUE DES ANOMALIES DE LA GLYCÉMIE CHEZ LES BRÛLÉS

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SUMMARY. The purpose of this study was to evaluate independent factors (mainly critical hyperglycaemic values on admission) with an impact on outcome in burn patients (sepsis and mortality) and analyse prevalence of critical hyperglycaemia on admission and during burn disease in adult and elderly patients with severe burns. This was an observational retrospective cohort study involving burn patients (≥ 20 years old) hospitalized in the ICU of the Burn Facility in Albania during 2010-2014. Patients were categorized as having euglycaemia, moderate or critical hyperglycaemia. Regression analysis, hyperglycaemia prediction test and risk measurement were performed for the population. Statistical significance for SIH was only found for glucose values on admission, presence of diabetes and BMI. Using 180 mg/dl as cut off for critical hyperglycaemia, we found that this test had a sensitivity of 66.67% (95% CI: 44.68% to 84.33%), specificity of 88.20% (95% CI: 84.16% to 91.51%), PPV of 29.63% (95% CI: 17.99% to 43.61%) and NPV of 97.26% (95% CI: 94.67% to 98.81%). Statistical significance was found for patients with critical hyperglycaemia on admission regarding relative and absolute risk measures for sepsis and mortality. Glucose values on admission, as one of the derangement features of burn shock, are prognostic factors in critical hyperglycaemia during disease, and have a close relationship with other outcomes (sepsis and mortality).

Keywords: hyperglycaemia, burns, sepsis, SIH

RÉSUMÉ. *L'objet de cette étude est l'analyse des facteurs indépendants (essentiellement l'hyperglycémie à l'admission) ayant un impact sur le devenir des patients (sepsis et mortalité) ainsi que l'étude de la prévalence de l'hyperglycémie à l'entrée comme en cours d'hospitalisation chez des patients adultes (avec un sous-groupe de patients âgés) sévèrement brûlés. Il s'agit d'une étude rétrospective concernant des patients de plus de 20 ans hospitalisés dans lez service de réanimation pour brûlés albanais entre 2010 et 2014. Trois catégories de patients ont été définies: glycémie normale, modérément élevée, fortement élevée. Une analyse par régression a été effectuée pour évaluer la corrélation entre le devenir du patient et ses glycémies. Une corrélation avec l'hyperglycémie de stress a été trouvée en cas de glycémie élevée à l'admission, en cas de diabète et avec l'IMC. Un seuil de 180 mg/dL pour la définition d'une glycémie fortement élevée permet d'obtenir une sensibilité de 66,67% (IC_{95} 44,68-84,33%), une spécificité de 88,2% (IC_{95} 84,16-91,51%), une valeur prédictive positive de 29,63% (IC_{95} 17,99-43,61) et une valeur prédictive négative de 97,26% (IC_{95} 94,67-98,81%). Il existe une association statistiquement significative entre l'hyperglycémie à l'entrée et la morbi-mortalité. Une hyperglycémie initiale est un facteur pronostic défavorable, en termes de complications infectieuses et de moralité, chez les patients gravement brûlés.*

Mots-clés: *hyperglycémie, brûlés, sepsis, hyperglycémie de stress*

Introduction

Physiological recovery of burn patients is seen as a continual process divided into three stages - resuscitative or critical, acute and long-term rehabilitation. Hyperglycaemia as a medical condition due to diabetes or other underlying conditions and sepsis as a life-threatening medical condition are two of the challenges faced during burn treatment. Patients with severe burns experiencing a kind of trauma undergo, among others, disturbances in glucose homeostasis, possibly leading to Stress Induced Hyperglycaemia (SIH).[1]

Control of glucose values with exogenous insulin has been found to be beneficial in treating critically ill burn patients despite previous diagnosis of diabetes (glucose targets differ depending on the presence of diabetes). Many professional organizations support the conclusions of Van Den Berghe and colleagues for tight glycaemia control; others support the NICE-SUGAR Study Investigators for conventional glucose control.[2,3,4] Surviving Sepsis Campaign (SSC) International Guidelines (2012) recommend a protocolled approach to blood glucose management in Intensive Care Unit (ICU) patients, commencing insulin dosing when two consecutive blood glu-

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cose levels are ≥180 mg/dl.[5]

Stress Induced Hyperglycaemia (SIH) during hospitalization after burns is characterized by hypo-metabolic ebb and a subsequent hyper-metabolic flow phase.[1] Burn patients exhibit increased gluconeogenesis and glucogenolysis (increase of glucose production) as well as insulin resistance, leading to decreased glucose uptake and reduced clearance.[6,7]

The purpose of this study was to evaluate other independent factors (mainly critical hyperglycaemic values on admission) with an impact on outcome in burn patients (sepsis and mortality) and analyse prevalence of critical hyperglycaemia on admission and during burn disease in adult patients with severe burns. We investigated whether testing for critical hyperglycaemia in the first 24 hours of admission in ED could help to predict a probable critical hyperglycaemic event during the disease course.

Materials and methods

Patients

This was an observational retrospective cohort study conducted in the Burns Facility of the University Hospital Centre "Mother Teresa" in Tirana (UHCT), Albania. UHCT is a tertiary level hospital and the only academic and research hospital centre in Albania. The study was approved by the Institutional Board.

We observed adult burn patients (≥ 20 years old) admitted to the ICU of the Burn Facility in the UHCT from 1st January 2010 to 31st December 2014. Children and non-burn related admissions (Stevens-Johnson/toxic epidermal necrolysis, necrotizing fasciitis and chronic wounds) were excluded from the study.

Patient management

Our Burn Facility consists of an Emergency Department (ED), Intensive Care Unit (ICU), a ward and operating theatres. Burns are classified according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD–9–CM) with codes 940-949; E890-E899 and E924.[8] Burn treatment in the ICU aims to complete management of the emergency period (resuscitation), providing surgical treatment (debridement, grafting and reconstruction), nutritional support, prevention and treatment of complications as well as psychosocial rehabilitation.

Patients are admitted to the ICU according to the American Burn Association (ABA) referral criteria.[9] They include patients with moderate burns who need fluid resuscitation monitoring. Before transfer, the referring physician must ensure adequate cardio-vascular and respiratory support as well as appropriate burn wound care. The patients are evaluated with specific laboratory measurements that help the physician to monitor fluid status and resuscitation. Blood tests in the Emergency Department include comprehensive metabolic panel (glucose, proteins, electrolytes, kidneys and liver tests), complete blood count, a clotting screen and blood typing.

Patient management for glucose control

Enteral and parenteral nutrition was implemented with glucose, amino acids and vitamins at 100 to 400 kcal/day for all patients in the study. Glucose measurements were done every day in the UHC Department of Laboratory Medicine. Hyperglycaemia was defined as BG values above the normal range. Patients were categorized as having euglycaemia (mean BG values ranging from 80-120 mg/dl), moderate hyperglycaemia (mean BG values <180 mg/dl) or critical hyperglycaemia (mean BG values ≥180 mg/dl).[10]

We implemented blood glucose control in all patients, adopting the goal of ≤180 mg/dl recommended in the SSC guidelines.[5] Patients with critical hyperglycaemia during burn disease were treated according to the insulin regimen: basal-bolus therapy with a correctional insulin scale, with a total daily dose of 0.3-0.5 unit/kg/day. Intensivists shortened measurement intervals and changed glucose/insulin doses more frequently if they judged it necessary. Stabilization of BG during the course of burn disease was followed by discontinuation of insulin.

Patient management for sepsis

Sepsis was defined according to the ABA Consensus Panel Publication for Infection and Sepsis.[10] In addition, Sequential Organ Failure Assessment (SOFA) score was calculated to evaluate degree of organ dysfunction in the patients studied, which was measured every day from the 3rd day after burn when acute resuscitation was over. SOFA is a six organ dysfunction/failure score that evaluates organ failure daily. Each organ is graded from 0 (6 considered normal as sum of each individual organ's score) to 4 (24 being the maximum organ failure score). During the calculation the highest scores for each parameter were used.

Variables

1. Patient clinical data and demographics:
   – Age (years);
   – Age groups: 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, >80 years;
   – Gender (male, female);
   – Body mass index – BMI (kg/m^2) divided in: <18.5 as underweight, 18.5-24.9 as normal, 25.0-29.9 as overweight, 30-34 as obesity class I, 35-39.9 as obesity class II, >40 as obesity class III;
   – Co-morbidities: presence of diabetes, cardiovascular, respiratory, gastro-intestinal, renal diseases (Yes/No).
2. Injury characteristics:
   – Burn Surface Area - BSA (%) grouped in the ranges: 0-10, 11-20, 21-40, 41-60, 61-80, 81-100;
   – Predomination of full-thickness burn (Yes/No);
   – Cause of burns (scalds, flame, electrical, chemical);
   – Presence of inhalation injury (Yes/No);
   – Surgical interventions (Yes/No).
3. For all patients:
   – BG values on admission (mg/dl);
   – BG values on admission grouped as: euglycaemia, moderate hyperglycaemia or critical hyperglycaemia;
   – BG values during burn disease grouped as: euglycaemia, moderate hyperglycaemia or critical hyperglycaemia;
   – Length of hospital stay - LOS (days);
   – Mean SOFA score (cumulative SOFA scoring divided by number of measurements);
   – SOFA categorization: organ dysfunction (7-12 points), organ failure (13-24 points).
4. Only for patients with critical hyperglycaemia during disease:
   – Glycated haemoglobin - HbA1c (%) grouped as: <5.7

as normal, 5.7-6.4 as pre-diabetes, >6.5 as diabetes;
 – Total daily dose - TDD (unit);
 – The day insulin was started (after hospitalization);
 – Period of treatment (days).
5. Outcome
 – Presence of sepsis during burn disease (Yes/No);
 – Mortality (survival/death).

Statistical Analysis

Data of patients with critical hyperglycaemia were compared with data of patients with moderate hyperglycaemia and euglycaemia. The normally distributed continuous data were analysed using one-way ANOVAs. The categorical data were expressed as frequency distributions and the Chi-square test was used to determine whether differences existed between groups.

In order to estimate any possible dependability of critical hyperglycaemia during burn disease on any of the variables (BSA%, depth of burn, age, glucose values on admission, presence of diabetes and BMI), we performed a logistic regression analysis.

To answer our clinical question, we designed a hyperglycaemia prediction test based on BG level in the first 24h of admission. We calculated test performance (sensitivity, specificity, prevalence, LR^+ [positive likelihood ratio], LR^- [negative likelihood ratio], PPV [positive predicted value], NPV [negative predicted value] and the accuracy of our test). Discrimination of the patients developing critical hyperglycaemia or not during burn disease is also graphically presented by the ROC Curve (Receiver Operating Characteristic curve) and AUC (Area Under the Curve).

As far as the magnitude of the relationship between exposure (critical hyperglycaemia on admission) and outcome (sepsis, mortality) is concerned, relative and absolute measure of the effect was calculated through relative risk (RR), odds ratio (OR), risk difference (RD) and "the number needed to treat" (NNT).

SPSS 22 was used for statistical analysis. Values were considered significant when $p<0.05$.

Results

A total of 785 patients including children were admitted to our facility over the period of study. Three hundred and forty-six (44%) were adults. Fifty of these 346 patients died. Overall mortality was 14.5%. Mean length of stay (LOS) in hospital was 14.1 ± 17.1 days.

Two hundred and thirty (66.5%) of the patients in the study were male. Mean age was 48.6 ± 16.9 years old and burn incidence peaked in the 40-49.9 years age group (84 patients or 24.3%) followed by the 50-59 years age group (62 patients or 17.9%). Categorization according to BMI revealed a normal distribution, peaking in the overweight group (BMI range 25-29.9 kg/m^2) with 154 patients (44.5%) while 17 patients had previously been diagnosed with diabetes. Mean BG values on admission were 149 ± 57.9 mg/dl. The number of patients with euglycaemia was 144 (41.6%), moderate hyperglycaemia 148 (42.8%) and critical hyperglycaemia 54 (15.6%) (data not shown).

In *Table I* we present the demographic and clinical char-

Table I - Demographic and clinical characteristics of adult and elderly patients with severe burns

VARIABLES	All patients (n=346)	Euglycaemia (n=204)	Moderate Hyperglycaemia (n=118)	Critical Hyperglycaemia (n=24)	P-value
Age, years, mean (SD)	48.6 (16.9)	46.2 (17)	51.5 (16.2)	55.8 (15.9)	0.002
Age group, years % (n)					0.025
20-29.9	17.3 (60)	24 (49)	8.5 (10)	4.2 (1)	
30-39.9	13.6 (47)	12.3 (25)	16.1 (19)	12.5 (3)	
40-49.9	24.3 (84)	25 (51)	24.6 (29)	16.7 (4)	
50-59.9	17.9 (62)	16.2 (33)	18.6 (22)	29.2 (7)	
60-69.9	13 (45)	10.3 (21)	16.9 (20)	16.7 (4)	
70-79.9	9 (31)	8.8 (18)	9.3 (11)	8.3 (2)	
80+	4.9 (17)	3.4 (7)	5.9 (7)	12.5 (3)	
Gender, male % (n)	66.5 (230)	65.2 (133)	70.3 (83)	58.3 (14)	0.437
Glucose values on admission, mg/dl, mean (SD)	149 (57.9)	129.4 (39.1)	162.7 (48.4)	248.4 (100.4)	<0.001
Glucose values on admission % (n)					<0.001
Euglycaemia	41.6 (144)	58.8 (120)	18.6 (22)	8.3 (2)	
Moderate Hyperglycaemia	42.8 (148)	35.3 (72)	59.3 (70)	25.0 (6)	
Critical Hyperglycaemia	15.6 (54)	5.9 (12)	22 (26)	66.7 (16)	
BMI % (n)					0.001
<18.5 (underweight)	0.3 (1)	0 (0)	0.8 (1)	0 (0)	
18.5-24.9 (normal)	32.1 (111)	35.3 (72)	29.7 (35)	16.7 (4)	
25-29.9 (overweight)	44.5 (154)	46.6 (95)	44.9 (53)	25 (6)	
30-34.9 (obesity class I)	19.7 (68)	15.7 (32)	22 (26)	41.7 (10)	
35-39.9 (obesity class II)	3.5 (12)	2.5 (5)	2.5 (3)	16.7 (4)	
Diabetes % (n)					<0.001
Diabetes (insulin)	3.5 (12)	0 (0)	0 (0)	50 (12)	
Diabetes (metformin)	1.4 (5)	0 (0)	3.4 (4)	4.2 (1)	
LOS, days, mean (SD)	14.1 (17.1)	11.2 (13)	16.2 (16.9)	28.9 (33.5)	<0.001
Mortality, deaths % (n)	14.5 (50)	8.3 (17)	24.6 (29)	16.7 (4)	<0.001
Abbreviations: BMI kg/m^2 (Body Mass Index)					

Table II - Burn related and clinical characteristics of adult and elderly patients with severe burns

VARIABLES	All patients (n=346)	Euglycaemia (n=204)	Moderate hyperglycaemia (n=118)	Critical hyperglyacemia (n=24)	P-value
BSA%, mean (SD)	31.8 (23)	26.3 (18.4)	39.8 (27.2)	39.3 (23.05)	<0.001
BSA % (n)					<0.001
0-10	12.1 (42)	16.2 (33)	6.8 (8)	4.2 (1)	
11-20	36.4 (126)	41.2 (84)	28.8 (34)	33.3 (8)	
21-40	28 (97)	27.9 (57)	29.7 (35)	20.8 (5)	
41-60	13.6 (47)	9.8 (20)	16.9 (20)	29.2 (7)	
61-80	3.8 (13)	2 (4)	5.9 (7)	8.3 (2)	
81-100	6.1 (21)	2.9 (6)	11.9 (14)	4.2 (1)	
Predomination of full-thickness (yes) % (n)	78.6 (272)	73.5 (150)	87.3 (103)	79.2 (19)	0.015
Cause of burns % (n)					0.252
scald	18.2 (63)	19.1 (39)	15.3 (18)	25 (6)	
flame	65.6 (227)	62.7 (128)	70.3 (83)	66.7 (16)	
electrical	10.7 (37)	13.7 (28)	6.8 (8)	4.2 (1)	
chemical	5.5 (19)	4.4 (9)	7.6 (9)	4.2 (1)	
Inhalation injury (yes) % (n)	22.5 (78)	15.7 (32)	34.7 (41)	20.8 (5)	<0.001
Surgical procedures (yes) % (n)	15.9 (55)	10.8 (22)	18.6 (22)	45.8 (11)	0.001
PRESENCE OF SEPSIS (yes) % (n)	26 (90)	15.7 (32)	37.3 (44)	58.3 (14)	<0.001
MEAN SOFA score % (n)					<0.001
SOFA 6-12 (organ dysfunction)	62.2 (56)	59.3 (19)	68.1 (30)	50 (7)	
SOFA 13-24 (organ failure)	37.7 (34)	40.6 (13)	31.8 (14)	50 (7)	

ABBREVIATIONS:
BSA % (burn surface area)
SOFA Score (sequential organ failure assessment) points/day is a six organ dysfunction failure score (from 0-24).

acteristics of the patients in the study. They were classified according to BG values on admission and during burn disease. Prevalence of critical hyperglycaemia in the burned adult population in our centre was estimated to be 15.6% on admission and 7% during burn disease.

The main age group of patients with critical hyperglycaemia during burn disease was different to that of the other groups (the most affected age group was 50.0-59.9 years compared with 40.0-49.9 for the euglycaemic and moderate hyperglycaemic groups), mean age was higher (55.8 versus 46.2 for the euglycaemic group and 51.5 for the moderate hyperglycaemic group) with statistical difference (p=0.002), BG values were higher on admission (p=0.001), and obesity classes I and II were predominant (p=0.005, p=0.001). All patients previously on insulin therapy belonged to this group (p=0.002). Observing the 24 patients who presented critical hyperglycaemia during burn disease, 2 (8.3%) of them had normal glucose values on admission; 6 (25%) had moderate hyperglycaemia on admission, while only 16 (66.7%) of them had critical values on admission. On the other hand, observing the 54 patients with critical hyperglycaemia on admission, 16 (29.6%) had critical BG values during disease, 26 (48.1%) had moderate BG values during disease and only 12 (22.3) had normal BG values during disease. A statistical significance was found when comparing LOS in the three groups (p=0.003).

In *Table II* we have presented burn-related, clinical characteristics and statistical comparisons of mean (SD) or population proportions of the three groups of patients. Patients belonging to the critical hyperglycaemia group had a mean BSA of 39.3 ± 23.05%, peaking in the categorization range of 41-60% with 7 patients (29.2%). There was a predominance of full-thickness burns in 19 patients (79.2%), while inhalation injury was present in 5 patients (20.8%) with statistical significance. Surgical interventions were performed in 11 of the 24 patients with critical hyperglycaemia (45.8%) with statistical significance. Sepsis occurred in 90 patients, and prevalence of sepsis in adult burn patients in our centre was 26%. Organ dysfunction was present in 56 patients (62.2% of the patients with sepsis) and 34 patients suffered organ failure (37.7%).

Negative cases b	322 (93.06%)
Null model -2 Log Likelihood	174.378
Full model -2 Log Likelihood	75.186
Chi-squared	93.563
DF	3
Significance level	P < 0.0001
Cox & Snell R^2	0.2369
Nagelkerke R^2	0.5985

COEFFICIENTS AND STANDARD ERRORS

Variable	Coefficient	Std. Error	Wald	P
GLUCOSE VALUES ON ADMISSION (mg/dl)	1.45076	0.49511	8.5859	0.0034
PRESENCE OF DIABETES	-5.23848	0.89944	33.9206	<0.0001
BMI	1.39224	0.40325	11.9203	0.0006
Constant	-0.8455			

Variables not included in the model
BURN SURFACE AREA BSA (%)
DEPTH OF BURN
AGE

ODDS RATIOS AND 95% CONFIDENCE INTERVALS

Variable	Odds ratio	95% CI
GLUCOSE VALUES ON ADMISSION (mg_dl)	4.2664	1.6166 to 11.2592
PRESENCE OF DIABETES	0.0053	0.0009 to 0.0309
BMI	4.0239	1.8255 to 8.8694

Fig. 1 - Logistic regression of glucose values during disease as dependent variable and other variables (BSA%, depth of burn, age, glucose values on admission, presence of diabetes, BMI).

Table III - Relative and absolute risk measures for sepsis and mortality:
- {with critical hyperglycaemia on admission (n=54)}
- {without critical hyperglycaemia on admission (n=292)}

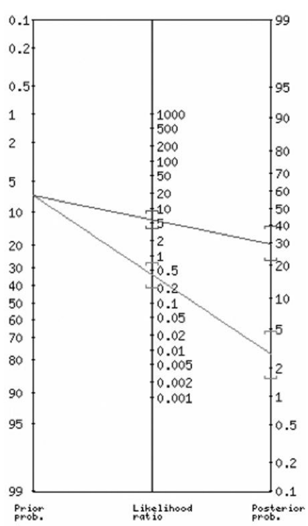
	Relative Risk (95% CI)	**p**	**Odds Ratio (95% CI)**	**p**	**Risk Difference (Absolute Risk Reduction)**	**Number Needed to Treat (95% CI)**
SEPSIS (23 out of 54) (67 out of 292)	1.85 (1.27 to 2.69)	0.0012	2.49 (1.36 to 4.56)	0.0031	0.20	5.09 (3.1 to 14.1)
MORTALITY (19 out of 54) (31 out of 292)	3.31 (2.02 to 5.4)	<0.0001	4.57 (2.33 to 8.94)	<0.0001	0.25	4.0 (2.9 to 6.8)

Of the 90 patients with sepsis, 32 (35.5%) had normal BG values during burn disease, constituting 15.7% of the euglycaemic group (n=204). Forty-four patients (48.9%) had moderate BG values, constituting 37.3% of the moderate hyperglycaemic group (n=118) while only 14 (15.6%) had critical values during burn disease. On the other hand, within the critical hyperglycaemic group 14 (58.3%) of the total (n=24) patients had sepsis.

In *Fig. 1* we present the results of logistic regression analysis relating variables like BSA%, depth of burn, age, glucose values on admission, presence of diabetes and BMI to the dependent variable 'blood glucose values during the course of disease'. BSA%, depth of burn and age are not included in the model since statistical significance was only found for glucose values on admission, presence of diabetes and BMI.

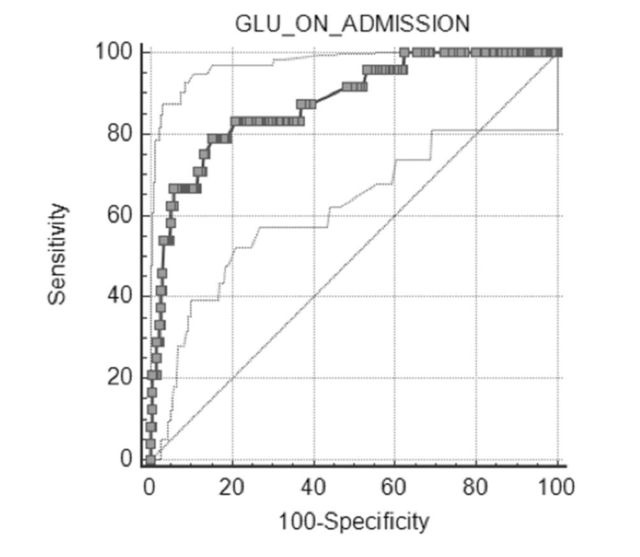
Analysing outcomes (sepsis and mortality) in patients with critical hyperglycaemia on admission (54 patients), we calculated RR, OR, absolute risk reduction and NNT. Relative risk for sepsis was 1.85 (P<0.001). The odds ratio was 2.49 (p<0.003). Risk difference (absolute risk reduction) was 0.20 and NNT was 5.5. Relative risk for mortality was 3.31 (P<0.001). The odds ratio was 4.57 (p<0.001). Risk difference (absolute risk reduction) was 0.25 and NNT was 4.0 (*Table III*).

Having proven that BG values on admission are predictors of BG during burn disease, we could further investigate if our test for predicting critical hyperglycaemia during disease based on critical hyperglycaemia on admission might be of clinical use. To do so, we present the test performance and ROC curve analysis (*Figs. 2 and 3*). Using 180 mg/dl as cut off for critical hyperglycaemia, we found that this test had a sensitivity of 66.67% (95% CI: 44.68% to 84.33%) and specificity of 88.20% (95% CI: 84.16% to 91.51%) as demonstrated in the



Statistic	Value	95% CI
Sensitivity	66.67%	44.68% to 84.37%
Specificity	88.20%	84.16% to 91.51%
Positive Likelihood Ratio	5.65	3.74 to 8.52
Negative Likelihood Ratio	0.38	0.21 to 0.67
Disease prevalence	6.94%	4.49% to 10.15%
Positive Predictive Value	29.63%	17.98% to 43.61%
Negative Predictive Value	97.26%	94.67% to 98.81%

Fig. 2 - Pre and post-test probability to predict hyperglycaemic event.



Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.878
Standard Error [a]	0.0378
95% Confidence interval [b]	0.839 to 0.910
z statistic	10.006
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988
[b] Binomial exact

Fig. 3 - Glucose values on admission (mg/dl) versus glucose values during disease.

Table IV - Characteristics of adults with critical hyperglycaemia during disease treated with insulin

VARIABLES	Patients with critical hyperglycaemia (n=24)		
	Patients previously diabetic (n=13)	Patients with stress induced hyperglycaemia (n=11)	p value
Age, years, mean (SD)	63.3 (14.9)	47 (12.8)	0.009
Gender, male % (n)	61.5 (8)	54.5 (6)	NS
BSA %, mean (SD)	33 (26.1)	46.8 (16.9)	NS
Predomination of full-thickness (yes) % (n)	76.9 (10)	81.8 (9)	NS
LOS, days, mean (SD)	11.1 (10.7)	50 (39.2)	0.002
PRESENCE OF SEPSIS (yes) % (n)	46.1 (6)	72.7 (8)	NS
Mortality, deaths % (n)	30.7 (4)	0 (0)	0.000
BMI % (n)			
<18.5 (underweight)	0 (0)	0 (0)	NS
18.5-24.9 (normal)	23.2 (2)	9.2 (1)	NS
25-29.9 (overweight)	46.1 (6)	0 (0)	0.03
30-34.9 (obesity class I)	30.7 (4)	54.5 (6)	NS
35-39.9 (obesity class II)	0 (0)	36.3 (4)	0.000
HbA1c % (n)			
<5.7 (normal)	0 (0)	45.6 (5)	0.02
5.7-6.4 (pre-diabetes)	7.7 (1)	36.3 (4)	NS
>6.4 (diabetes)	92.3 (12)	18.1 (2)	0.001
TOTAL DAILY DOSE units, mean (SD)	39.3 (14.1)	39.4 (18.3)	NS
DAY OF BEGINNING INSULIN, mean (SD)	1.3 (1.1)	7.2 (2.7)	0.0001
PERIOD, days, mean (SD)	11.3 (10.6)	28 (14.9)	0.004
ABBREVIATIONS: BSA% (burn surface area) BMI kg/m² (body mass index) HbA1c % (glycated hemoglobin)			

ROC curve. Having critical hyperglycaemic values with a prevalence of 7%, LR⁺ of 5.65 (95% CI: 3.74 to 8.52) and LR of 0.38 (95% CI: 0.21 to 0.67) we can identify post-test probability using Fagan's nomogram (*Fig. 2*).

Specifically, we have a PPV of 29.63% (95% CI: 17.99% to 43.61%) and NPV of 97.26% (95% CI: 94.67% to 98.81%). Accuracy of the test is 0.86. ROC curve is presented in *Fig. 3,* with AUC equal to 0.878.

Of the 346 patients hospitalized in the ICU for severe burns, only 17 or 5% were previously diagnosed with diabetes. Twelve were being treated with insulin and 5 were being treated with oral anti-diabetic drugs (*Table I*).

In *Table IV*, we present the characteristics of the adult patients with critical hyperglycaemia treated with insulin (n=24). We divided the group into patients previously diagnosed with diabetes (n=13) and patients with stress induced hyperglycaemia (n=11). Only one of the 5 patients needed additional insulin therapy during hospitalization.

A description and analysis of each group is as follows:

Adults with previously diagnosed diabetes: demographic characteristics of the first subgroup of patients show that the mean age was 63.3 years with a maximum of 85 years and a minimum of 39 years. 46.1% of the total number of patients in the subgroup were classified as pre-obese, and 30.7% as belonging to obesity class I. HbA1c levels were considered to be high in 92.3%. Sepsis was present in the majority of the patients while mortality was 7%. Prognostic factors (age, BSA%) as well as the presence of diabetes predispose these patients to a bad prognosis that is also accompanied by renal deterioration. LOS was 11.1 ± 10.7 with maximum 40 days and minimum 1 day. Patients needed a TDD of insulin of 39.3 ± 14.1 units with maximum 60 units/day and minimum 20 units/day, which is equal to the values for the second subgroup. Start of insulin therapy varied from the 1st to the 5th day after burn, with an average of 11.3 ± 10.6 treatment days, which corresponds with these patients' LOS.

Adults with stress induced hyperglycaemia (SIH): demographic characteristics of patients with SIH showed that mean age was 47 years with a maximum of 64 years and a minimum of 22 years. We noticed a younger population in this subgroup, and a higher rate of obesity class I (54%) and obesity class II (36.3%). Two patients (18.1%) were found to have elevated HbA1C levels, 4 patients (36.3%) were found to have HbA1C levels associated with pre-diabetes or risk of diabetes, and 5 patients (45.6%) had normal values. Sepsis was present in 72.7% of the total, while there were no deaths in this group. LOS was higher at 50 ± 39.2 days, with a maximum of 148 days and a minimum of 10 days. Patients needed a TDD of insulin of 39.4 ± 18.3 units, with a maximum of 70 units/day and a minimum of 8 units/day. Regarding the start of insulin, this usually corresponded with the 7th day after hospitalization (7.2 ± 2.7 days), the earliest was on day 4 and the latest on day 10 after burn. The duration of insulin therapy was more than double for this group, with an average of 28 ± 14.9 days and a maximum of 48 days of treatment. The period of insulin therapy was half of the mean LOS.

Discussion

Homeostasis is the maintenance of a stable internal environment in an organism through careful regulation of many parameters, including maintaining blood glucose levels within the narrow range of 60–120 mg/dl.

Patients with severe burns experience one of the most severe disruptions of homeostasis. Clinical situations associated with glucose homeostasis disorders are previous diagnosis of diabetes, SIH and relative deficiency of insulin in the preoperative period. Based on many studies, hyperglycaemia might have different biological or clinical implications and has been associated with an increased risk of adverse outcomes.[11,12,13]

A significant proportion of mortality and morbidity in severely burned patients with SIH is attributable to hyper-metabolic response.[7,14] Results of various studies researching altered metabolism and the role of insulin in the treatment of burn patients indicate that improvement in BG levels results in lower rates of hospital complications and mortality.[15,16,17,18,19,20]

Making the so-called point prevalence, which in our study is prevalence with respect to two main periods of burn disease, we observed higher values on admission than during disease. Our classification of hyperglycaemia is similar to the one of other authors based on American Diabetes Association recommendations.[21] In the GLUCEMERGE study, prevalence of hyperglycaemia on admission was 21% and patients were divided into three groups: patients with normoglycaemia, hyperglycaemia with a need for follow-up, and hyperglycaemia with the need for intervention where glucose values were at least 180mg/dl.[21] In our study the prevalence of hyperglycaemia on admission was 15.6% while during burn disease it was 7%, which corresponds with the patients who were treated with insulin therapy.

Emergency Department hyperglycaemia has been observed to be a strong predictor of in-hospital outcomes. Many studies emphasized the fact that SIH happened secondary to an increase in the levels of counter-regulatory hormones and that the phenomenon occurs in individuals with and without a history of diabetes.[7,21,22,23] Some authors have observed that conventional factors of disease severity, but not highest glucose value during the first 24 hrs after ICU admission, predict hospital mortality in the medical ICU.[24] Others concluded that hyperglycaemia is an independent risk factor only in patients without a diabetic history, specifically in cardiac, cardiothoracic and neurosurgical intensive care units.[25]

In this clinical and epidemiological study we have tried to assess the effect of critical hyperglycaemia on admission as a real forerunner on outcome (sepsis and mortality) in adult patients with severe burns. We concluded that outcome of patients hospitalized in our unit depends among other things on critical hyperglycaemic blood values, which in turn depend on BG values on admission. Based on this, we propose some possible starting points for the improvement of these pathology-dependent outcomes.

One of these starting points is critical hyperglycaemic values on admission. The clinical question we posed in this article was concerned with the possible relationship between critical hyperglycaemia on admission and during burn disease in burn patients. In 12 of the 54 patients experiencing hyperglycaemia on admission (22.3%), this was purely an expression of the shock phase after a burn, since their blood glucose values during disease were normal. In 16 patients (29.6%), there might have been a trigger for glucose homeostasis impairment, which could advance and result in hyperglycaemia needing insulin treatment. It is important to emphasize that patients with both moderate and critical hyperglycaemia during burn disease amounted to 42 or approximately 78% of all patients with critical hyperglycaemia on admission (n=54).

Based on our test results, we calculated a sensitivity of 66.67%, specificity of 88.2%, PPV of 29.63% and NPV of 97.2%. Specifically, a PPV of 29.63% means that 1 in 3 patients presenting critical hyperglycaemia on admission will manifest critical hyperglycaemia during disease. An NPV of 97.2% means that 9 out of 10 patients with glucose values <180 mg/dl in the first 24 hours will not have critical hyperglycaemia during disease. The value of this test is in its negative predicted value, which means that a patient showing no critical hyperglycaemia on admission will most likely not develop it during disease. AUC evaluates discrimination or the ability of the model to distinguish those with and without critical hyperglycaemia during burn disease. In our model, AUC value is 0.878 with a significance level of $p<0.0001$, which indicates very good discrimination for a diagnostic test.

The small positive predicted value (PPV=29.63%) of our test indicates that many of the positive results from this testing procedure are false positives. Most of the hyperglycaemic values on admission are the result of stress syndrome; however it is necessary to follow up these positive results with a more rigorous monitoring in the ICU for the presence of critical hyperglycaemia during burn disease.

Patients treated with insulin (in the group of patients with critical hyperglycaemia) had a better prognosis than patients with moderate hyperglycaemia. For the patients with no previously diagnosed diabetes, the mean day of beginning insulin was the 7th day after burn, which also corresponds with parenteral nutrition support. Treatment with insulin not only improved the prognosis of these patients but also made it possible to perform more surgical interventions because of their stabilized clinical situation. Insulin was discontinued after stabilization of glucose values with an average of 28 ± 14.9 days of treatment.

Patients with previously diagnosed diabetes had the worst prognosis after burn injury. A previous diagnosis of diabetes and BMI are independent factors that impact the occurrence of critical hyperglycaemia during disease that needs insulin treatment. Early diagnosis of diabetes or pre-diabetes in the emergency department will help both the emergency physician and the patient himself, since more attention will be paid to their condition and the treatment will be more accurate.

Measurement of Hba1c during periods of hospitalization allows us to differentiate patients with stress hyperglycaemia from those with diabetes who were previously undiagnosed. As we saw in our study group, the risk of developing critical hyperglycaemia was equal for patients with previously diagnosed diabetes and for those without diabetes. However, 4 patients (36.3%) in the latter subgroup had values of HbA1c that corresponded with pre-diabetes, while 18.1% had undiagnosed diabetes. The other 5 patients had normal values and SIH was mainly a metabolic response to the burn injury. Greater public awareness of these facts is required to detect diabetes and also treat these individuals early.

Clinical outcomes of a critical illness can be estimated from different perspectives (patients, medical staff, health managers and society). Staff-oriented outcomes differ from patient-oriented in the fact that in the former, short- and long-term outcomes are influenced by medical interventions as well as by directing medical attention and resources to those patients who are most likely to benefit from the decisions. On the other hand, society-oriented outcomes require making rational decisions using cost effectiveness and benefit. This analysis will help in the future to provide a more accurate prediction of morbidity in the ED.

In the following paragraphs, we discuss statistical data concerning patients grouped according to BG values and patient outcome (sepsis, mortality).

Analyzing sepsis and the risk of developing it in patients with critical hyperglycaemia on admission, we observed a relative risk of 1.8, meaning that the chance of sepsis is 80% higher if the patient presents with critical hyperglycaemia on admission. An OR of 2.4 indicates that the odds for sepsis are higher in the group with hyperglycaemia on admission (OR>1). In absolute values that would mean that the incidence of sepsis is 20% smaller in the group without critical hyperglycaemia on admission. In our test, the NNT or benefit was 5.0, which highlighted the need for very good monitoring and surveillance of the 5 patients with critical hyperglycaemia on admission to prevent one bad outcome (sepsis).

Analysing sepsis and its distribution in the three groups of patients, we noticed that sepsis (n=90) was present in 32 patients (35.6%) in the euglycaemic group, in 44 patients (48.8%) in the moderate hyperglycaemic group and in 14 (15.6%) in the critical hyperglycaemic group. We noticed that the majority of patients with sepsis (58 out of 90 patients or 64.4%) had hyperglycaemia during disease.

While analysing sepsis within each group, we noticed differences. In the euglycaemic group composed of 204 patients, there were 32 (15.6%) patients diagnosed with sepsis; in the moderate hyperglycaemic group of 118 patients, 44 (37.2%) had sepsis; and in the critical hyperglycaemic group of 24, 14 (58.2%) had sepsis. We noticed that sepsis was present in the majority of patients with critical hyperglycaemia, which is consistent with recent studies.[7]

Out of 24 patients in the critical hyperglycaemia group (26.6% of the patients with sepsis), 11 had SIH; there were no deaths but there was a greater presence of sepsis (8 or 72.7%). This compared with patients with diabetes: there were 13 deaths, and 6 (46.1%) had sepsis.

Analysing the risk of mortality in patients with critical hyperglycaemia on admission, we observed that the chance of a bad outcome was 3 times more likely to occur if the patient had critical hyperglycaemia on admission (RR=3). With an OR of 4.5, we concluded that the odds for a bad outcome were higher in the group with hyperglycaemia on admission (OR>1).

The absolute risk difference (absolute risk reduction) of deaths was 25%, meaning there was a smaller risk in the group of patients without critical hyperglycaemia on admission. An NNT or benefit of 4.0 suggested that very good surveillance of the 4 patients with critical hyperglycaemia on admission should be carried out in order to prevent one bad outcome.

Analysing mortality, we noticed that out of 50 deaths in total, 17 (34%) were patients with euglycaemia, 29 (58%) were patients with moderate hyperglycaemia and only 4 (8%) were in the critical hyperglycaemic group. If we look at mortality as the proportion of deaths within groups, we notice that the highest mortality 24.6% (29 deaths) was in the moderate hyperglycaemic group, followed by 16.7% (4 deaths) in the critical hyperglycaemic group and the lowest values, 8.3% (17 deaths), in the euglycaemic group.

Strengths and weaknesses of the study

Strengths

This study raises medical staff's awareness of the importance of evaluating hyperglycaemia in the first moments of trauma. It increases the efficiency of early treatment of hyperglycaemia but also serves as a screening for undiagnosed diabetes patients. The correct treatment of this syndrome significantly improves the prognosis of patients because they are reassessed dynamically. We think that hyperglycaemia should be included in the future burn scoring system to assess burn outcome.

Weaknesses

This study was performed in one burn centre only since there is only one centre for burns treatment in our country, suggesting the need to expand it through collaboration between regional centres. Some data elements like patient follow-up are not available because it is a retrospective study. The main outcome of patients of interest (diabetes patients after burn trauma) will be completed over a long period of follow-up.

Conclusions

The prevalence of critical hyperglycaemia in the burned adult population in our centre was estimated to be 15.6% on admission and 7% during disease. Glucose values on admission, as one of the derangement features of burn shock, are prognostic factors in critical hyperglycaemia during burn disease, and have a close relationship with other outcomes (sepsis and mortality).

By answering the clinical questions, we propose the need for a more detailed and accurate care trajectory during the evaluation of severely burned adult patients in the first 24 hours of hospitalization in the ED. Testing for critical hyperglycaemia in the first 24 hours of admission could help to predict a probable critical hyperglycaemic event during the course of burn disease.

Emergency Departments can play a vital role in the initial treatment of severely burned patients. Primary care physicians should obtain information about co-morbidities and assess the functional status of the patients. Their work can influence the patients' health-related quality of life.

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