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Diabetes mellitus and impaired glucose tolerance are underdiagnosed in intensive care units

Diabetes mellitus e intolerância à glicose são subdiagnosticados nas unidades de terapia intensiva

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ABSTRACT

Objective: To evaluate the presence of diabetes mellitus and impaired glucose tolerance in intensive care unit inpatients.

Methods: The study included patients in post-surgical care for elective and emergency surgery and excluded those patients with known diabetes mellitus. To diagnose prior serum glucose level disorders, we considered the value of glycated hemoglobin (HbA1c) at the time of admission, classifying the patients as normal (<5.7%), glucose intolerant (5.7-6.4%) or diabetic (>6.4%). During the first 3 days of the patient's hospital stay, glycemic control and clinical complications were assessed. Mortality was monitored for 28 days. For the statistical analyses, chi-square, ANOVA, student's *t*, Kruskal-Wallis or Mann Whitney tests were used.

Results: Thirty patients were included in the present study, 53% of whom were women; the patients had a mean age of

53.4±19.7 years and an APACHE II score of 13.6±6.6. The majority of patients were admitted for severe sepsis or septic shock followed by post-operative care for elective surgery, oncological surgery, multiple traumas and emergency surgery. When classifying these patients according to HbA1c, despite the absence of a prior history of diabetes mellitus, only 13.3% had a normal HbA1c level, 23.3% had levels compatible with the diagnosis of diabetes mellitus and 63.3% had levels compatible with impaired glucose tolerance. We found a significant association between the diagnosis of diabetes mellitus or impaired glucose tolerance and the use of vasoactive drugs ($p=0.04$).

Conclusion: A high prevalence of undiagnosed diabetes mellitus and impaired glucose tolerance was observed in inpatients at a general intensive care unit.

Keywords: Glucose metabolism disorders; Diabetes mellitus; Hyperglycemia; Intensive care; Hemoglobina A, glycosylated; Catecholamines

This study was conducted at the Intensive Care Unit, Disciplina de Anestesiologia, Dor e Terapia Intensiva, Universidade Federal de São Paulo - UNIFESP - São Paulo (SP), Brazil.

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INTRODUCTION

Intensive care unit (ICU) inpatients frequently present disorders of glucose metabolism and sometimes require the administration of insulin. These disorders have been ascribed to endocrine-metabolic stress related to acute disease and to the effects of the multiple medications that are used to treat the patients.⁽¹⁻³⁾ Several mechanisms are responsible for hyperglycemia, such as activation of the hypothalamic-pituitary-adrenal axis, the secretion of corticosteroids and the release of catecholamines.⁽⁴⁻⁶⁾

The importance of undiagnosed diabetes mellitus (DM) or impaired glucose tolerance in the pathogenesis of hyperglycemia in critical patients is still not well-established.⁽⁷⁾ Of the American population, 12.9% is diabetic, 40% of

whom are undiagnosed. A larger number of patients (29.5%) have underdiagnosed impaired glucose tolerance.⁽⁸⁾ Among inpatients, 12.4 to 25% are diabetic, many of whom do not have a prior diagnosis because the glycemia levels obtained during a hospital stay are not used to confirm the presence of DM.⁽⁹⁾

According to the American Diabetes Association (ADA),⁽¹⁰⁾ the levels of glycosylated hemoglobin (HbA1c) began being utilized as a criterion for the diagnosis of DM and impaired glucose tolerance in January 2010.

The goal of this study was to identify the presence of DM or impaired glucose tolerance among inpatients in a general ICU without a prior history of DM based on the HbA1c levels and the classification of DM according to the new guidelines established by the ADA in January 2010.⁽¹⁰⁾ Moreover, this study tested for the presence of correlations between high levels of HbA1c and the following events: hyperglycemic episodes, need for insulin administration, severe hypoglycemia, variability of glycemia and the incidence of clinical complications.

METHODS

Subjects

In this study, we prospectively included ICU inpatients older than 18 years who expected to stay at the ICU for at least 48 hours. All inpatients with a prior diagnosis of DM or impaired glucose tolerance, pregnant women and patients who were taking corticosteroids prior to admission to the ICU were excluded. The study was based on a convenience sample, and the inclusion of subjects was not consecutive. This ICU is within a public university hospital, and it admits highly complex patients sent by the Unified Health System (Sistema Único de Saúde - SUS).

The research protocol was approved by the Ethics Committee of the Universidade Federal de São Paulo (reference 0347/11; approved on April 15, 2011). All of the patients or their family members signed the informed consent form.

Protocol

At the time of admission to the ICU, a blood sample was collected to measure the HbA1c level. Demographic data were registered, and the *Acute Physiological Chronic Health Evaluation II* (APACHE II) score was calculated during the first 24 hours. Patients were monitored until their 3rd day at the ICU. Data for the fasting serum glucose (collected daily at 6 am as a routine procedure in this ICU) and capillary blood glycemic measurements were recorded, including the minimum, maximum and

median values for each day. Glycemic monitoring was conducted without interference from the study protocol according to the clinical protocol in the unit. Any clinical complications within the first 3 days of inpatient care were also registered. After that period, the electronic medical record was used to access 28-day mortality. Hypoglycemia was defined as glycemia <75 mg/dL, and hyperglycemia was defined as levels >150 mg/dL according to the protocol already established by the unit. The use of insulin, both subcutaneous and intravenous, and the total dose were recorded.

The HbA1c levels were measured at the hospital clinical laboratory using a Tosoh A1c 2.2 high performance liquid chromatograph (Tosoh, Tokyo, Japan), certified by the National Glycohemoglobin Standardization Program.

Complications, which were evaluated during the first 3 days of inpatient care, included the development of sepsis/severe sepsis/septic shock, the need for packed red blood cell transfusion, critical illness polyneuropathy, acute coronary syndrome, the need for dialysis and surgical complications. As the follow-up lasted for 3 days, the use of mechanical ventilation and the administration of vasoactive drugs, specifically, norepinephrine, epinephrine, dopamine and dobutamine, were evaluated at any time during this period.

In agreement with the ADA publication,⁽⁸⁾ patients were classified according to their HbA1c levels as normal (HbA1c<5.7%, Group 1), diabetic (HbA1c>6.4%, Group 2) or glucose intolerant (HbA1c between 5.7% and 6.4%, Group 3).

Statistical analysis

All quantitative variables were checked for normality using the Kolmogorov-Smirnov test. Normally distributed variables are expressed as the mean \pm standard deviation, and values with a non-parametric distribution are expressed as the median (25-75%).

Categorical variables were analyzed using the chi-square test or Fisher's exact test when appropriate. Quantitative variables were analyzed either with ANOVA and Student's t-test (normal distribution) or with Kruskal-Wallis and Mann-Whitney tests (nonparametric variables). The Müller Dunn post-test was performed for the Kruskal-Wallis test. To categorize continuous variables, the best cutoff point defined by the receiver operating characteristic curve was used.

For statistical analyses, we used the Statistical Package for the Social Sciences (SPSS), version 19.0 (SPSS Inc., Chicago, IL, USA), and SigmaStat. The results were considered to be significant when $p < 0.05$.

RESULTS

In the sample of 30 patients included in the present study, 53% were female; the mean age was 53.4 ± 19.7 years old, and the mean APACHE II was 13.6 ± 6.6 . The majority of the patients were admitted for severe sepsis or septic shock followed by post-operative care for elective surgery, oncological surgery, multiple trauma and emergency surgery (Table 1). The maximal length of hospital stay before the HbA1c measurement was collected was 15 days, and the lowest level of hemoglobin at collection was 7.2 mg/dL.

When classifying these patients according to their HbA1c levels, only 13.4% had normal HbA1c, 23.3% had undiagnosed diabetes and 63.3% had impaired glucose tolerance. These last two groups tended to have higher levels of blood glucose and a non-significant trend for greater variability (Table 2).

Among the complications studied, a statistically

Table 1 - Sample characterization

Variable	Result
Gender, women	16 (53)
Age (years)	53.4 ± 19.7
APACHE II	13.6 ± 6.6
HbA1c (%)	5.9 (5.7-6.2)
Reason for ICU hospitalization	
Severe sepsis/sepsis shock	9 (30)
Post-op care for elective surgery	6 (20)
Post-op care for oncologic surgery	5 (16.7)
Multiple trauma	4 (13.3)
Post-op care for emergency surgery	2 (6.7)
Stroke	2 (6.7)
Post-op care for liver transplantation	1 (3.3)
Other clinical complications	1 (3.3-2.5)

APACHE - Acute Physiological Chronic Health Evaluation; HbA1c - glycated hemoglobin; ICU - intensive care unit. Results are expressed the number (%), the mean \pm standard deviation or the median (25-75%).

Table 2 - Association between glycated hemoglobin and glucose control

	HbA1c<5.7%	HbA1c 5.7-6.4%	HbA1c>6.4%	p value
Serum glycemia D1	114 ± 28	143 ± 53	165 ± 36	0.25
Maximum glycemia D1	145 ± 11	178 ± 78	216 ± 60	0.47
Minimum glycemia D1	101 ± 10	105 ± 28	124 ± 19	0.33
Median glycemia D1	124 ± 12	130 ± 33	157 ± 28	0.21
Glycemia variation D1	44 ± 15	76 ± 78	89 ± 77	0.71
Serum glycemia D2	112 ± 7	144 ± 75	164 ± 36	0.22
Maximum glycemia D2	143 ± 11	204 ± 97	199 ± 45	0.73
Minimum glycemia D2	99 ± 22	95 ± 25	106 ± 15	0.68
Median glycemia D2	108 ± 19	126 ± 28	143 ± 31	0.22
Glycemia variation D2	44 ± 12	113 ± 10	97 ± 53	0.67
Serum glycemia D3	100 ± 15	109 ± 35	160 ± 67	0.31
Maximum glycemia D3	133 ± 10	158 ± 62	250 ± 137	0.27
Minimum glycemia D3	87 ± 2	98 ± 25	105 ± 24	0.52
Median glycemia D3	112 ± 16	124 ± 26	158 ± 46	0.23
Glycemia variation D3	46 ± 10	60 ± 57	145 ± 156	0.75

HbA1c - glycated hemoglobin. Results expressed in mean \pm standard deviation.

significant association was found between the change in the HbA1c level and the use of vasoactive drugs ($p=0.04$) (Table 3). Moreover, there was a higher frequency of vasoactive drugs administration among patients who were intolerant to glucose in comparison with diabetic patients.

Table 3 - Association between glycated hemoglobin and clinical variables

	HbA1c<5.7%	HbA1c 5.7-6.4%	HbA1c>6.4%	p value
Age	34.7 ± 14.9	55.7 ± 20.4	58.6 ± 15.4	0.11
APACHE II	15.5 ± 7.9	13.5 ± 6.6	12.6 ± 6.8	0.81
Men	2 (14.3)	10 (71.4)	2 (14.3)	0.55
RBC transfusion	1 (20)	2 (60)	1 (20)	0.82
Complications*	2 (20)	6 (60)	2 (20)	0.60
Use of vasoactive drugs	3 (18.7)	12 (75)	1 (6.3)	0.04
Days of mechanical ventilation	5 (4-5)	3 (0-5)	0 (0-2)	0.08
Insulin administration, day 1	0 (0)	5 (71.4)	2 (28.6)	0.46
Insulin administration, day 2	0 (0)	3 (60)	2 (40)	0.39
Insulin administration, day 3	0 (0)	3 (60)	2 (40)	0.26
28-day mortality	2 (33.3)	3 (50)	1 (16.7)	0.27

APACHE - Acute Physiological Chronic Health Evaluation; HbA1c - glycated hemoglobin. *Complications: sepsis/severe sepsis / sepsis chock development, need for packed red blood cells transfusion, polyneuropathy of critical patients, acute coronary syndrome, need for dialysis and surgical complications. Results are expressed as the number (%), the mean \pm standard deviation or the median (25-75%). Dunn test: $p<0.05$ for comparison between the HbA1c=5.7-6.4% group and the HbA1c<5.7% group.

DISCUSSION

In this study, the prevalence of DM and impaired glucose tolerance was assessed in a population of ICU inpatients. For this assessment, HbA1c was used to diagnose these conditions according to ADA standards. Our findings suggest a high prevalence of undiagnosed diabetes, especially impaired glucose tolerance, prior to hospital admission.

The measurement of HbA1c is widely used for the outpatient control of diabetic patients.^(11,12) In the literature, this level may also correlate stress hyperglycemia with the presence of undiagnosed DM.⁽¹³⁻¹⁸⁾ Silverman et al. analyzed patients who were admitted to the emergency department with acute diseases and had an episode of hyperglycemia; those patients with HbA1c $\geq 6.2\%$ were characterized as having undiagnosed diabetes.⁽¹³⁾ When analyzing trauma patients, Kopelman et al. considered values of HbA1c $\geq 6\%$ as indicating a "hidden" DM diagnosis.⁽¹⁴⁾ Husband et al. found that levels of HbA1c $>7.5\%$ indicated prior DM in patients with acute myocardial infarction (AMI).⁽¹⁵⁾

These different studies indicate that there has been no standardized HbA1c level for the diagnosis of DM. The ADA selected the value of 5.7% for HbA1c as a cutoff value for having an increased risk of

developing DM because this value reflects an average fasting blood glucose of 100 mg/dL over the past 2 to 3 months.⁽¹⁰⁾ A large prospective study showed that a HbA1c threshold of 5.7% has a sensitivity of 66% and specificity of 88% for identifying the incidence of DM in 6 years of follow-up.⁽¹⁹⁾ In addition, patients with an HbA1c level slightly below the previous mentioned cutoff value, ranging from 6 to 6.5%, have a high risk of developing DM, ten times higher than those patients with lower levels.⁽²⁰⁾

Interestingly, hospitalized patients with hyperglycemia but without a history of DM have a higher risk of adverse events, including increased hospital mortality, than patients with diabetes.⁽²¹⁾ In these patients, the diagnosis and treatment of hyperglycemia may have underappreciated.

The association between impaired glucose tolerance and the greater need for vasoactive drugs does not necessarily imply causation, and intolerance may simply represent a marker of severity. However, this association may represent greater hemodynamic instability in these patients due to increased susceptibility resulting from previously developed microcirculation changes. In an assessment of glycemic control in the intensive care setting, an association between glycemia and vasoactive drugs was identified. In that group of patients, the odds ratio of developing a glycemia level <40 mg/dL was 0.61 (0.52 to 0.71) ($p < 0.001$).⁽²²⁾ Another important factor is that capillary blood glucose levels may be overestimated in patients using vasoactive drugs. When comparing venous and capillary blood glycemia, Critchell et al. found that in 83% of patients, capillary blood glucose was higher than venous blood glucose, and 25% of these patients used norepinephrine.⁽²³⁾ However, in the present study, glucose was measured in blood collected from the arterial catheter, which was used to monitor blood pressure, for patients receiving vasoactive drugs; therefore, this study has no such bias.

This study has several limitations. The main one is the small number of patients, which can hinder some conclusions, especially regarding the analysis of associated factors. The small number of patients did not allow for a multivariate analysis. Moreover, this study includes only one center, and the patients were monitored for glycemic control and complications only during the first 3 days of ICU inpatient care. Nonetheless, this novel assessment

protocol for critically ill patients uses the HbA1c level to allow for the early diagnosis of DM and impaired glucose tolerance, which have been previously underdiagnosed in this population.

CONCLUSIONS

In this sample of patients who were admitted to a general ICU, we found a high frequency of diabetes or impaired glucose tolerance without prior diagnosis.

RESUMO

Objetivo: Avaliar a presença de diabetes mellitus e a intolerância à glicose em pacientes internados em unidades de terapia intensiva.

Métodos: Foram incluídos pacientes clínicos, em pós-operatório de cirurgias eletivas e de urgência, e excluídos aqueles com história de diabetes mellitus. Para o diagnóstico de alterações prévias da glicemia, utilizou-se a dosagem da hemoglobina glicada (HbA1c) na admissão do paciente, sendo classificado em normal (<5,7%), intolerante à glicose (5,7-6,4%) ou diabético (>6,4%). Durante os 3 primeiros dias da internação, foram avaliados o controle glicêmico e as complicações clínicas. A evolução para óbito foi acompanhada por 28 dias. Para as análises estatísticas, utilizaram-se testes do qui-quadrado, ANOVA, teste *t* de Student, Kruskal-Wallis ou Mann Whitney.

Resultados: Foram incluídos 30 pacientes, 53% do gênero feminino, idade de 53,4±19,7 anos e APACHE II de 13,6±6,6. A maioria dos pacientes foi admitida por sepse grave ou choque séptico, seguido por pós-operatório de cirurgias eletivas, oncológicas, politraumatismo e cirurgia de urgência. Ao classificar esses pacientes segundo a HbA1c, apesar da ausência prévia de história de diabetes mellitus, apenas 13,3% tinham HbA1c normal, 23,3% tinham níveis compatíveis com o diagnóstico de diabetes mellitus e 63,3% eram compatíveis com intolerância à glicose. Houve associação significativa entre o diagnóstico de diabetes mellitus ou intolerância a glicose e o uso de droga vasoativa ($p=0,04$).

Conclusão: Foi encontrada alta prevalência de diabetes mellitus e intolerância à glicose, sem diagnóstico prévio, em pacientes internados em uma unidade de terapia intensiva geral.

Descritores: Transtornos do metabolismo da glicose; Diabetes mellitus; Hiperglicemia; Terapia intensiva; Hemoglobina A glicosilada; Catecolaminas

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