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Dissertação de Mestrado

ASSOCIAÇÃO ENTRE PARÂMETROS GLICÊMICOS E DESFECHOS CLÍNICOS EM PACIENTES CRITICAMENTE DOENTES

PRISCILA BELLAVER

PORTO ALEGRE
2019

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PRISCILA BELLAVER

Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito para obtenção do título de Mestre em Endocrinologia.

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RESUMO

Alterações endocrinológicas são comuns em pacientes criticamente doentes internados em unidades de terapia intensiva. Entre elas, as alterações da glicemia são as mais frequentes. O estresse gerado pela doença crítica aguda desencadeia respostas simpáticas e hormonais, que culminam em hiperglicemia. A hiperglicemia é uma resposta mal-adaptativa que apresenta diversos efeitos deletérios, incluindo disfunções imunológica, endotelial e inflamatória. A hipoglicemia, por sua vez, também é deletéria, podendo ocorrer de forma espontânea ou associada ao uso de insulina. Sob essa perspectiva, muito tem sido discutido sobre o controle glicêmico ideal a ser buscado nessa população de pacientes graves, mas ainda existem muitas controvérsias com relação aos alvos específicos a serem atingidos em cada paciente. Tanto hiperglicemia quanto hipoglicemia aumentam a mortalidade em pacientes criticamente doentes, nos quais o controle estrito da glicemia é limitado pelo risco de hipoglicemia.

Portanto, o objetivo deste trabalho foi avaliar o impacto clínico de diversos parâmetros glicêmicos que poderiam ser úteis na definição individualizada dos alvos glicêmicos para cada paciente. Demonstramos nesta dissertação que tanto a hiperglicemia quanto a hipoglicemia associam-se de forma independente à mortalidade nessa população e que parâmetros como *gap* glicêmico, razão de hiperglicemia de estresse e variabilidade glicêmica também impactam em desfechos clínicos relevantes, incluindo tempo de ventilação mecânica, incidência de choque e necessidade de terapia substitutiva renal, embora não se associem à mortalidade.

ABSTRACT

Endocrinological changes are common in critically ill patients admitted at the intensive care unit. Among them, changes in blood glucose are the most frequent ones. The stress induced by the critical illness triggers sympathetic and hormonal responses, culminating in hyperglycemia. Hyperglycemia is a maladaptive response that has several deleterious effects, including immune, endothelial and inflammatory dysfunctions. Hypoglycemia, on the other hand, is also harmful, and may occur spontaneously or associated with insulin use. From this perspective, much has been debated about the optimal glycemic control to be achieved in this population of critically ill patients, but there are still controversies regarding the specific targets to be reached in each patient. Both hyperglycemia and hypoglycemia increase mortality in critically ill patients, in whom strict glycemic control is limited by the risk of hypoglycemia.

Therefore, the objective of this study was to evaluate the impact of multiple glycemic parameters in clinical outcomes, which may be useful to individualize glycemic targets for each patient. In this study, we demonstrate that both hyperglycemia and hypoglycemia are independently associated with mortality in this population and that glycemic parameters such as glycemic gap, stress hyperglycemia ratio and glycemic variability also impact clinical outcomes, including time on mechanical ventilation, incidence of shock and the need for renal replacement therapy, but not mortality.

LISTA DE FIGURAS

Capítulo II

LISTA DE TABELAS

Capítulo II

LISTA DE ABREVIATURAS

ATP	Adenosina trifosfato
CI	*Confidence interval*
DM	Diabetes *mellitus*
ECR	Ensaio clínico randomizado
FA-UTI	Fraqueza muscular adquirida na unidade de terapia intensiva
GLUT-1	*Glucose transporter 1*
GLUT-4	*Glucose transporter 4*
HbA1c	Hemoglobina glicada
HR	*Hazard ratio*
IC	Intervalo de Confiança
ICU	Intensive Care Unit
INSR	*Insulin receptor*
LOS	*Lenght of stay*
MV	*Mechanical ventilation*
OR	*Odds ratio*
RR	*Relative risk*
RRT	*Renal replacement therapy*
SAPS-3	*Simplified Acute Physiology Score 3*
SD	*Standard deviation*
SLC2A1	*Solute carrier family 2 member 1*
SLC2A4	*Solute carrier family 2 member 4*
SHR	*Stress hyperglycemia ratio*
UTI	Unidade de Terapia Intensiva

SUMÁRIO

Esta dissertação de Mestrado será apresentada no formato exigido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Ela é constituída de uma introdução em Português, um artigo em Inglês e considerações finais e perspectivas futuras em Português.

CAPÍTULO I

INTRODUÇÃO

Alterações endocrinológicas têm mostrado associação com prognóstico de pacientes criticamente doentes[1]. A hiperglicemia é desencadeada como uma resposta metabólica compensatória ao estresse agudo induzido por doenças graves em consequência do aumento de hormônios contrarreguladores da insulina e dos processos de glicogenólise e gliconeogênese. A presença de hiperglicemia reflete o desenvolvimento de resistência à ação da insulina a nível de receptor e pós-receptor, tanto no fígado quanto no músculo[2], sugerindo o desenvolvimento de uma resposta adaptativa a condições ameaçadoras da vida, o que garantiria uma oferta suficiente de glicose a tecidos vitais, como o cérebro, por exemplo, sendo um sinal de prognóstico desfavorável em pacientes criticamente doentes, tanto clínicos quanto cirúrgicos[3]. Estudos demonstram que a hiperglicemia pode associar-se à disfunção imunológica e endotelial, influenciando tanto a migração e a capacidade fagocítica de macrófagos quanto alterando o sistema do complemento e a produção de citocinas[4]. Além disso, estudos epidemiológicos encontraram correlação entre níveis glicêmicos elevados e mortalidade em pacientes com diabetes[5].

Controle glicêmico em pacientes criticamente doentes

Muito tem-se estudado sobre o manejo dos níveis glicêmicos de pacientes internados em unidade de terapia intensiva (UTI), porém estudos

com resultados controversos impedem que haja um consenso acerca do controle glicêmico ideal[6]. Diversos estudos avaliaram o controle glicêmico em pacientes criticamente doentes[7-13]. No primeiro grande estudo, Van den Berghe et al[7] avaliaram pacientes cirúrgicos internados em UTI, mostrando uma redução da mortalidade de 8% nos pacientes tratados com controle convencional (180-200 mg/dL) para 4,6% nos pacientes tratados com controle glicêmico intensivo (80-110 mg/dL). Os resultados desse estudo tiveram grande impacto internacional na época da sua publicação, determinando mudanças no tratamento da hiperglicemia neste grupo de pacientes. Os benefícios do controle glicêmico intensivo pareciam não estar apenas relacionados aos níveis mais baixos de glicemia, mas também aos efeitos anti-inflamatórios da insulina, levando à menor produção de radicais livres e à menor glicotoxicidade, com consequente proteção do metabolismo mitocondrial[14]. Porém, quando o mesmo grupo de pesquisadores conduziu um estudo com pacientes críticos não cirúrgicos, os benefícios na redução da mortalidade limitaram-se a pacientes com mais de três dias de permanência na UTI, apesar de o grupo randomizado para controle glicêmico intensivo ter apresentado menos disfunções orgânicas quando comparado ao grupo randomizado para controle convencional[8].

No entanto, estudos subsequentes não corroboraram os achados iniciais dos benefícios do controle glicêmico intensivo[9,10]. Por exemplo, Clayton et al[11] demonstraram alta incidência de hipoglicemia em pacientes com sepse grave (atualmente renomeada de sepse) que receberam controle glicêmico intensivo. Adicionalmente, outro ensaio clínico randomizado (ECR) que testava o impacto da prescrição de insulina em pacientes com sepse grave foi interrompido

precocemente em 2008, devido à elevada incidência de hipoglicemia (17% no grupo de tratamento intensivo versus 4% no grupo controle)[9]. Aqui, mais uma vez, o controle glicêmico intensivo era alvo de críticas, levantando dúvidas quanto aos benefícios de se buscar níveis glicêmicos estritos às custas do risco de eventos adversos potencialmente fatais.

Em 2009, a discussão sobre os alvos do controle glicêmico intensificou-se após a publicação dos resultados do estudo NICE-SUGAR, um ECR multicêntrico que randomizou 6.030 pacientes de UTIs mistas, incluindo pacientes clínicos e cirúrgicos, para receber controle glicêmico intensivo ou controle glicêmico convencional[12]. Os resultados do estudo não demostraram benefício do grupo de controle intensivo (80-108 mg/dL) em comparação ao grupo de controle convencional, que foi submetido a níveis glicêmicos moderados (144-180 mg/dL). Houve maior incidência de hipoglicemia no grupo intervenção (6,8%) em comparação com o grupo controle (0,5%). Além disso, houve aumento na mortalidade do grupo de controle intensivo (OR 1,14; IC 1,02-1,28; p=0,02).

Nessa mesma linha, o estudo Glucontrol[10] incluiu 1.108 pacientes em 19 centros e não evidenciou diferença na mortalidade entre pacientes tratados com controle intensivo da glicemia quando comparados a pacientes com tratamento convencional. Novamente, a incidência de hipoglicemia no grupo de tratamento intensivo com insulina foi maior do que no grupo controle (8,7% versus 2,7%). Além disso, a hipoglicemia foi um fator de risco independente para mortalidade (OR 2,2; 95%IC 1,4-3,5 para glicose <40 mg/dL)[10]. A metanálise que resumiu o resultado destes estudos não encontrou diferença na

mortalidade entre o controle glicêmico intensivo quando comparado ao controle convencional (OR 0,9; 95%IC: 0,85-1,03)[13].

Os estudos de Van den Berghe et al[7] e o estudo NICE-SUGAR[12] apresentam diferenças importantes, principalmente no que se refere aos alvos do controle glicêmico, ao manejo nutricional e às taxas de hipoglicemia. Porém, estes estudos apresentam em comum a desvantagem de não terem levado em consideração o controle metabólico prévio dos pacientes à admissão na UTI.

Além dos estudos sobre hiperglicemia e hipoglicemia em pacientes criticamente doentes, um outro parâmetro glicêmico que tem sido motivo de investigação na última década é a variabilidade glicêmica, que corresponde à diferença entre a maior e a menor glicemia das 24 horas. Estudos demonstram que incrementos na variabilidade glicêmica em valores tão baixos quanto 18 mg/dL associam-se a aumento do risco de morte em 5%[15].

Dessa forma, a pergunta que se impõe não é se o controle glicêmico deva ou não ser feito, mas sim como atingir alvos glicêmicos ótimos, que assegurem benefício com baixos índices de hipoglicemia. Além disso, parece haver vantagem na individualização dos alvos glicêmicos em populações distintas de pacientes criticamente doentes, havendo, por exemplo, benefício potencial de controle glicêmico intensivo em pacientes cirúrgicos. Por outro lado, pacientes sépticos parecem apresentar maior risco de hipoglicemia e assim beneficiariam-se de controle glicêmico mais permissivo[16].

A doença crítica e o diabetes

Um grupo particular de pacientes em UTI são os pacientes com diabetes *mellitus* (DM). A doença aguda grave cursa comumente com resposta

inflamatória sistêmica[17] e hiperglicemia[3]. A inflamação leva à ativação endotelial, dano mitocondrial e falência de múltiplos órgãos. Em um estudo retrospectivo publicado em 2013, Lanspa et al[18] analisaram 3.529 pacientes e compararam um protocolo de controle glicêmico intensivo (80-110 mg/dL) com um protocolo de controle moderado (90-140 mg/dL), demonstrando que o controle moderado associava-se a um maior risco de morte em pacientes sem DM, mas a um menor risco de morte em pacientes com DM. Tais achados sugerem que a presença de DM e o controle metabólico prévio à internação na UTI possam influenciar o efeito do controle glicêmico em pacientes criticamente doentes. Além disso, pacientes com DM costumam apresentar maior variabilidade glicêmica.

A hemoglobina é a proteína presente nas hemácias cuja função é transportar oxigênio aos tecidos. Tendo em vista que a glicação é um processo irreversível, a hemoglobina glicada (HbA1c) é um parâmetro representativo das glicemias médias diárias durante as últimas 12 semanas, tempo médio de vida dos glóbulos vermelhos[19]. A HbA1c tem a vantagem de não sofrer influências da doença aguda. A American Diabetes Association sugere que se proceda à dosagem de HbA1c em todos os pacientes com DM ou hiperglicemia admitidos em hospitais que não tenham realizado este exame nos últimos três meses[20].

Níveis mais elevados de HbA1c associam-se de forma independente à mortalidade hospitalar[21,22]. Valores acima de 6,5% associam-se à maior gravidade de disfunções orgânicas agudas e à maior mortalidade[23]. Além disso, Egi et al[24] avaliaram o nível de HbA1c de pacientes antes da admissão em UTI e demonstraram que pacientes com pior controle metabólico prévio (HbA1c >6,8%) apresentavam maior mortalidade quando submetidos a controle

glicêmico intensivo, sugerindo que, em pacientes com controle metabólico ruim prévio à admissão, deva-se permitir níveis glicêmicos mais elevados. Assim, os níveis de glicemia seguros e desejáveis para alguns grupos de pacientes podem não ser para pacientes com DM com controle metabólico prévio inadequado expostos à hiperglicemia crônica. Desta forma, a medida da HbA1c no momento da admissão do paciente na UTI pode ter um papel importante na definição dos alvos de controle glicêmico.

Além de ser um marcador de prognóstico durante a doença crítica, a HbA1c consegue discriminar os pacientes com DM daqueles que cursam com hiperglicemia aguda induzida pelo estresse da doença crítica. Neste sentido, tem surgido a discussão a respeito do valor prognóstico do *gap* glicêmico e da razão da hiperglicemia de estresse (do inglês, *stress hyperglycemia ratio* [SHR]), dois marcadores de hiperglicemia aguda induzida pelo estresse, em pacientes internados em UTI. Tanto o *gap* glicêmico quanto a SHR têm a finalidade de isolar o efeito da hiperglicemia aguda, separando dos efeitos da hiperglicemia crônica. O *gap* glicêmico é definido pela diferença entre a glicemia na admissão na UTI e a glicemia média estimada, determinada a partir do valor de HbA1c (glicemia média estimada= 28,7 x HbA1c – 46,7 mg/dL)[25]. O *gap* glicêmico tem sido estudado como um preditor de desfechos adversos em pacientes com infarto agudo do miocárdio[25] e pneumonia comunitária[26]. Além disso, valores de *gap* glicêmico acima de 80 mg/dL parecem associar-se à maior mortalidade hospitalar em pacientes críticos com DM[27]. A SHR, por sua vez, é definida como a razão entre a glicemia na admissão na UTI e a glicemia média estimada, determinada a partir do valor de HbA1c[27]. Estudos têm

demonstrado que a SHR se associa de forma independente a maior risco de desenvolver doença crítica e de necessitar de internação em UTI[28].

Frente ao exposto, nota-se que não há consenso sobre os níveis de controle glicêmico mais adequados para pacientes criticamente doentes. Evidências sugerem que a implementação de protocolos para controle glicêmico deva ser individualizada, principalmente levando-se em consideração se o paciente tem diagnóstico prévio de DM ou não e se tem controle metabólico adequado ou inadequado. Nesse sentido, a dosagem de HbA1c pode ter um papel importante na admissão de pacientes na UTI, individualizando as metas glicêmicas e permitindo a avaliação mais ampla de parâmetros glicêmicos, além da hiperglicemia, da hipoglicemia e da variabilidade glicêmica, incluindo *gap* glicêmico e SHR.

Dessa forma, esta dissertação tem como objetivo principal investigar a associação de múltiplos parâmetros glicêmicos (hiperglicemia, hipoglicemia, variabilidade glicêmica, *gap* glicêmico e SHR) com desfechos clínicos (mortalidade, tempo de ventilação mecânica, incidência de choque, necessidade de terapia substitutiva renal, tempo de permanência hospitalar e tempo de permanência em UTI) em pacientes criticamente doentes, com e sem DM, internados em UTIs clínico-cirúrgicas. Uma avaliação mais abrangente do estado metabólico do paciente crítico, incluindo múltiplos parâmetros glicêmicos simultaneamente, pode ser uma ferramenta auxiliar na escolha de alvos de controle glicêmico personalizados para cada paciente.

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CAPÍTULO II

ASSOCIATION OF MULTIPLE GLYCEMIC PARAMETERS AT INTENSIVE CARE UNIT ADMISSION WITH MORTALITY AND CLINICAL OUTCOMES IN CRITICALLY ILL PATIENTS: A PROSPECTIVE STUDY

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Association of multiple glycemic parameters at intensive care unit admission with mortality and clinical outcomes in critically ill patients: a prospective study

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Conflicts of Interest

The authors of this manuscript declare no conflicts of interest.

Keywords

Glycemic gap; hypoglycemia; hyperglycemia; glycemic variability; diabetes; critical illness.

Abstract

Objectives: Hyperglycemia is a compensatory response to acute stress and is associated with worse prognosis during critical illness. The aim of the present study was to investigate the association of multiple glycemic parameters at intensive care unit (ICU) admission with outcomes in critically ill patients.

Design and Settings: This prospective cohort study was conducted in a tertiary university hospital in Brazil from September 2017 to February 2018.

Patients: Critically ill adults admitted to ICU were included prospectively in the study and followed for 180 days until hospital discharge or death. Patients were assessed for glycemic gap, hypoglycemia, hyperglycemia, glycemic variability and stress hyperglycemia ratio (SHR).

Interventions: none.

Measurements and Main Results: A total of 542 patients were enrolled (30% with preexisting diabetes). Patients with glycemic gap >80 mg/dL had increased need for renal replacement therapy (RRT; 37.7% vs. 23.7%, p=0.025) and shock incidence (54.7% vs. 37.4%, p=0.014). Hypoglycemia was associated with increased mortality (54.8% vs. 35.8%, p=0.004), need for RRT (45.1% vs. 22.3%, p <0.001), mechanical ventilation (MV; 72.6% vs. 57.5%, p=0.024), and shock incidence (62.9% vs. 35.8%, p<0.001). Hyperglycemia increased mortality (44.3% vs. 34.9%, p=0.031) and the need for MV (66.1% vs. 55.7%, p=0.018). Glycemic variability >40 mg/dL was associated with increased need for RRT (28.3% vs. 14.4%, p=0.002) and shock incidence (41.4% vs.31.2%, p=0.039). SHR >1.1 was associated with increased need for MV (65.8% vs. 2.8%, p=0.001). Both hypoglycemia and hyperglycemia remained associated with mortality after adjusting for disease severity.

Conclusions: In this mixed medical-surgical sample of critically ill subjects, including patients with and without preexisting diabetes, glycemic gap, glycemic variability, and SHR were associated with worse outcomes, but not with mortality. Hypoglycemia and hyperglycemia were independently associated with increased mortality.

Keywords: glycemic gap; hypoglycemia; hyperglycemia; glycemic variability; diabetes; critical illness.

Introduction

In critically ill patients, hyperglycemia is an adaptive metabolic response to acute stress. Mechanistically, it reflects an increase in insulin resistance in an attempt to ensure a sufficient supply of glucose to vital structures during acute life-threatening conditions (1). Both hyperglycemia and hypoglycemia are independently associated with mortality in the intensive care unit (ICU) (2, 3).

Optimal glycemic targets in the ICU setting are controversial and seem to be related to previous patient metabolic status (3, 4, 5, 6, 7, 8, 9). As glycated hemoglobin (HbA1c) is not affected by the onset of acute illness, it can be used to estimate chronic glycemic control in critically ill patients (10). In patients with diabetes mellitus (DM), poor metabolic control with high levels of HbA1c is independently associated with in-hospital mortality (9, 10). In the intensive care setting, patients with higher HbA1c have higher mortality (11, 12). However, patients with poor chronic glycemic control have worse outcomes when treated with intensive glycemic control (13), suggesting that chronic hyperglycemia might be able to generate cellular mechanisms that protect against damage mediated by acute hyperglycemia during critical illness (14). Therefore, the question is more complex than selecting the "optimal glycemic target", as the interplay between multiple domains of glycemic control might be more relevant. In this sense, glycemic variability, which reflects the magnitude of glycemic excursions during the day, has been associated with unfavorable outcomes in critical illness, including higher mortality (15, 16). In the presence of the same mean blood glucose values, glycemic control can be quite different depending on the observed variability (17, 18).

In addition, to separate preexisting hyperglycemia from stress-induced hyperglycemia (elevated blood glucose that reverts to normal after disease and inflammation subsides), the glycemic gap and the stress hyperglycemia ratio (SHR)

have been proposed as predictors of adverse outcomes in the ICU. The glycemic gap, defined as the difference between blood glucose at ICU admission and the estimated mean blood glucose derived from HbA1c values, is associated with worse prognosis in specific populations of critically ill patients, such as patients with acute myocardial infarction, community-acquired pneumonia and hepatic abscess (19, 20, 21). Moreover, a glycemic gap above 80 mg/dL is associated with higher hospital mortality in critically ill patients with DM (22), but its value as a prognostic tool in mixed medical-surgical sample of critically ill subjects is unknown. The SHR is calculated by dividing the blood glucose on admission by the estimated average glucose derived from HbA1c. Studies suggest that an SHR > 1.1 is a better predictor for worse outcomes in critical illness than the absolute mean blood glucose (23).

Within this context, the aim of the present study is to investigate the association of multiple glycemic parameters at ICU admission with clinical outcomes in critically ill patients with and without diabetes. The primary endpoint was mortality. Secondary endpoints were need for renal replacement therapy (RRT), incidence of shock, need for mechanical ventilation (MV), time spent on MV, length of stay (LOS) in the hospital, LOS in the ICU, and need for ICU readmission.

Material and Methods

Patient population

This is a prospective cohort study. The study protocol was approved by the ethics committee at Hospital de Clínicas de Porto Alegre (project number 17-0386). Informed consent was obtained from patients or their legal representatives. From September 2017 to February 2018, critically ill adults (age >18 years) admitted to the

ICU were prospectively included in the study. The exclusion criteria were pregnancy, diabetic ketoacidosis, hyperosmolar hyperglycemic state, sickle cell anemia and other hemoglobinopathies. Blood samples were collected at study entry from all patients for random serum blood glucose and HbA1c quantifications, and clinical and laboratory data were recorded for all patients. Simplified Acute Physiology Score 3 (SAPS 3), ranging theoretically from a minimum of 0 points to a maximum of 271 points, with higher scores denoting higher severity (24), was used to score disease severity.

Hyperglycemia was defined according to the American Diabetes Association (ADA) proposed threshold for in-hospital hyperglycemia as any blood glucose measurement > 140 mg/dL (25, 26, 27) at ICU admission. Moderate hypoglycemia was any blood or capillary glucose < 70 mg/dL (ADA definition and same level from the NICE-SUGAR study) (25, 28) and serious hypoglycemia was <54 mg/dL (ADA definition) (25) during the first day in the ICU. Glucose variability was calculated as the absolute difference in capillary blood glucose during the first day in the ICU (15, 16, 17). In order to separate the effects of a chronically altered metabolic state from those of acute stress hyperglycemia, the glycemic gap and SHR were evaluated. The glycemic gap was calculated by the difference between the ICU admission serum blood glucose and the estimated mean blood glucose (serum blood glucose on ICU admission − estimated mean blood glucose) (19, 20, 21). HbA1c values were used to calculate the estimated mean blood glucose, using the following formula: (28.7 x HbA1c) − 46.7 mg/dL (29). The cutoff value of 80 mg/dL for glycemic gap was based on Liau et al (22). SHR was defined by the ratio between serum blood glucose at admission and the estimated mean blood glucose and the cutoff value of 1.1 based on Roberts et al (23). Diabetes was defined on the basis of previous diagnosis or when HbA1c was ≥6.5% (25).

The outcomes of interest were adjudicated by two unblinded researchers (P.B. and A.S) and included the following: mortality, need for renal replacement therapy (RRT), incidence of shock, need for mechanical ventilation (MV), time spent on MV, length of stay (LOS) in the hospital, LOS in the ICU, and need for ICU readmission. All patients were followed up for 180 days for survival analysis.

Biochemical measurements

Blood samples for glucose measurement were collected in tubes with sodium fluoride, centrifuged for 10 min at 3670 rpm, and analyzed by the hexokinase method in a Roche COBAS c702 system (Roche Diagnostics, Mannheim, GE). For HbA1c measurement, blood samples were collected in EDTA tubes, homogenized, and analyzed in BioRAD Variant Turbo II (BioRAD, Hercules, California, USA), processed by HPLC. Glucose values were expressed as mg/dL, and HbA1c values as percentage.

Statistical analysis

Categorical variables were expressed as percentages. Data were expressed as mean and standard deviation (SD) if normally distributed, or as median and interquartile range otherwise. Groups were compared using Student's *t*-test, the Mann–Whitney *U* test, or the chi-square test as appropriate. To assess relative risks of variables of interest and outcomes, linear regression or logistic regression models were constructed depending on the characteristics of the outcomes of interest. Cox regression analysis was used to study time to death and to calculate hazard ratios (HR), with variables adjusted for disease severity using SAPS 3 score. A sample size of 494 patients was calculated considering a power of 95% and an α-error rate of 5% to detect a difference in glycemic gap of 42 mg/dL between survivors and nonsurvivors. There was no

missing data. Values were considered statistically significant if $p < 0.05$. Statistical analyses were conducted in SPSS 20.0 (Chicago, IL, USA) and R version 3.5.2 (The R Foundation, version 3.5.1, 2018).

Results

Study population

A total of 542 consecutive patients admitted to the ICU were included in the study. Their main characteristics are summarized in Supplemental Digital Content Table 1. Briefly, 52.5% were male, and the mean age was 59±15 years; 42.4% were admitted to ICU from the emergency department. ICU admissions were for medical reasons in 84.3% and for surgical reasons in 15.7%, with acute respiratory failure as the leading cause (23.6%). The most common primary coexisting condition was hypertension (54%), followed by DM (30%). Mean serum glucose at admission was higher in nonsurvivors than in survivors (146 ± 73 vs. 132 ± 60 mg/dL, p=0.023), but HbA1c was not (5.8 ± 1.7 vs. 5.5 ± 1.4% p=0.058). The overall mortality rate was 38.2%. When analyzing patients with DM separately, the mortality rate was similar regardless of preexisting DM (43% vs. 38.2%; p=0.193). In these patients, mean blood glucose and HbA1c were similar in survivors and nonsurvivors (mean blood glucose: 166 ± 87 vs. 187 ± 96, p=0.16; HbA1c 6.8 ± 1.8% vs. 6.9 ± 2.4, p=0.705).

Glycemic parameters and mortality

The glycemic gap varied widely, from -159 to 400, with a median value of 11 (-15 to 42) mg/dL in the overall population and no difference between survivors and nonsurvivors was observed (Fig 1 a). When stratifying patients by a glycemic gap cutoff

of 80 mg/dL, a trend toward higher mortality was observed in subjects with wider glycemic gaps (49% vs. 37%; p=0.087). When analyzing patients with DM separately, the glycemic gap was 13 (-37 to 61) mg/dL, and no differences were observed between survivors and nonsurvivors (Fig 1 b). Similarly, in patients without preexisting DM, the glycemic gap was not different in survivors and nonsurvivors (Fig 1 c). More patients who died had hypoglycemia (54.8% vs. 35.8%, p=0.004) and hyperglycemia (44.3% vs. 34.9%, p=0.031) compared to survivors. In the participants, mean glycemic variability was 67 (41 to 112) mg/dL, with higher values in nonsurvivors (Fig 1 d). This difference is not demonstrated in patients with preexisting DM (Fig 1 e), but is clearly seem in patients without DM (Fig 1 f). Overall SHR was 1.1 (± 0.5), with no difference between survivors and nonsurvivors (Fig 1 g), independently or preexisting DM (Fig 1 h) or not (Fig 1 i).

Glycemic parameters and other outcomes

When comparing patients with glycemic gap above and below 80 mg/dL, the group with higher values had increased need for RRT and a higher incidence of shock (Table 1).

The presence of hypoglycemia within the first 24 hours of ICU admission was associated with increased need for RRT, increased need for MV and higher incidence of shock. Length of hospital stay was shorter in this population. The presence of hyperglycemia on admission was associated with increased need for MV. Glycemic variability during the first 24 hours of admission was associated with an increased need for RRT and a higher incidence of shock. These results are summarized in Table 2. SHR >1.1 was associated with greater need for MV, but with a shorter time spent on MV and

longer ICU stay (Table 1). Interestingly, no glycemic control parameters were associated with the need for ICU readmission (Tables 1 and 2).

Magnitude of the association between glycemic parameters and outcomes

Fig 2 presents the relative risks (RR) for outcomes according to each glycemic parameter. Data related to variability >60 mg/dL and >80 mg/dL are summarized in Supplemental Digital Content Table 2.

Glycemic gap >80 mg/dL was associated with an increased need for RRT and significantly increased the incidence of shock.

Mean blood glucose increased risk of death, but HbA1c did not. Hypoglycemia was the parameter with the highest RR for mortality, followed by hyperglycemia and glycemic variability. Hypoglycemia also yielded the highest RR for the need for RRT. Glycemic variability was also associated with an increased need for RRT. Besides glycemic gap >80 mg/dL, two other glycemic parameters significantly increased the incidence of shock: hypoglycemia and glycemic variability. Regarding the need for MV, hypoglycemia was associated with the highest risk, followed by hyperglycemia. Glycemic variability also increased the need for MV. No glycemic parameter was associated with risk of ICU readmission, as shown in Supplemental Digital Content Fig 1.

Separate Cox regression models with adjustment for SAPS 3 were calculated, with time to mortality as the dependent variable and glycemic parameters significantly associated with mortality on univariate analysis as the independent one. Hypoglycemia and hyperglycemia remained associated with mortality after adjustments (HR 1.68; 95%CI 1.16 to 2.44, p=0.006 and HR 1.37; 95%CI 1.04 to 1.81, p=0.026, for hypoglycemia and hyperglycemia, respectively) (Fig 3), but glycemic variability did not

(HR 1.14; 95%CI 0.86 to 1.51, p=0.366 for variability > 60 mg/dL and HR 1.25; 95%CI 0.95 to 1.64, p=0.104 for variability > 80 mg/dL).

Discussion

In this sample of unselected, prospectively followed critically ill patients, including those with and without preexisting diabetes, multiple glycemic parameters at ICU admission were associated with worse outcomes. Higher glycemic gap, a marker of stress-induced hyperglycemia, increased the need for RRT and incidence of shock, but had not impact on mortality. The presence of hypoglycemia in the first 24 hours of ICU admission was associated with the highest RR for worse outcomes, including increased mortality; a single episode of hypoglycemia doubled the risk of death and increased the incidence of shock and the need for RRT threefold. Additionally, hyperglycemia at ICU admission increased the risk of mortality by approximately 50%. Both hypoglycemia and hyperglycemia were independently associated with mortality.

Glycemic gap and SHR are markers of acute-stress hyperglycemia, as they are able to separate the effect of acute, critical illness-associated variations in blood glucose from the previous metabolic state. The present study was the first to analyze the role of glycemic gap and SHR in a general medical-surgical population of ICU patients. Unexpectedly, no increase in mortality was demonstrated in patients with high glycemic gaps or high SHR, even when patients with DM were analyzed separately, which stands in contrast to the findings of previous small studies of glycemic gap in very specific populations critically ill patients with diabetes (19, 20, 21). However, in our mixed population of surgical and medical critically ill patients, with and without DM, and with

very high disease severity scores, a high glycemic gap doubled the risk of shock and the need for RRT and SHR increased risk of the need for MV and the time spent on MV.

Some studies suggest that glucose variability during the 24 hours is a better predictor of outcomes in critical illness than mean blood glucose (15, 16, 17, 18). However, our results show that glycemic variability measured in the first 24 hours of admission was associated with worse outcomes, increased need for RRT and MV and higher incidence of shock, but only hypoglycemia and hyperglycemia were associated with increased mortality after adjustment for disease severity. Moreover, glycemic variability was not associated with higher risk of mortality in patients with DM, corroborating the idea that patients exposed to chronic hyperglycemia are adapted to glycemic excursions, possibly developing protective cellular mechanisms against wide blood glucose variations during the course of a critical illness (14). In our study, the mortality of patients with DM was similar to that of patients without DM, in agreement with the concept of the "diabetic paradox" in the ICU—i.e., the finding that DM is not independently associated with increased risk of mortality in heterogeneous populations of critically ill patients (30).

This study has limitations. First, glucose monitoring was not continuous, which raises the possibility that some extreme glucose values may have gone unrecorded. However, this is a conservative bias that might have decreased differences in outcomes, further corroborating our findings. Furthermore, glucometers are still largely used because they are practical and low cost. Second, accurate information on diet (including the amount of calories consumed) and on insulin doses administered was not recorded, thus precluding conclusions regarding the influence of carbohydrate intake or insulin therapy on outcomes. However, the association of at least one of the

outcomes evaluated herein, hypoglycemia, seems to be independent from insulin use, as suggested by the results of the NICE-SUGAR study (28).

The main strength of this study is its large, prospective cohort design, specifically selected to evaluate multiple glycemic parameters simultaneously in an unselected population of critically ill patients and their associations with clinical outcomes and mortality. Our findings reinforce that, besides mean blood glucose seems to be the most important predictor of outcomes, several other domains of glycemic control are relevant in critical illness. This might be especially important for research in glycemic control, as future trials should evaluate not only glycemic targets, but rather multiple glycemic parameters at the same time.

Conclusions

In summary, in this medical-surgical sample of critically ill subjects, including patients with and without previous diagnosis of diabetes, glycemic gap was associated with worse clinical outcomes, but had no impact on mortality. Hypoglycemia and hyperglycemia were independently associated with increased mortality and influenced other outcomes, such as incidence of shock and need for RRT and MV. Similarly to glycemic gap, glycemic variability and SHR also negatively affected outcomes, with no impact on mortality. It is common sense that optimal glycemic control should be pursued to reduce the risk of unfavorable outcomes. Then, further research is needed to personalize glycemic control targets in critically ill patients, focusing on a broader view of glucose dysregulation based in multiple parameters rather than in a single, in an effort to reduce the risks of iatrogenic adverse events.

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Authors' Contribution

PB participated in the study conception and design, data acquisition, analysis and interpretation of data, statistical analysis, drafting and revision of the manuscript. AFS participated in data acquisition and analysis. DPD participated in data acquisition. MVV participated in the study design, statistical analysis and revision of the manuscript. CBL participated in the study conception and design, interpretation of data, statistical analysis and revision of the manuscript. THR participated in the study conception and design, data acquisition, interpretation of data and revision of the manuscript.

THR is the guarantor of this work and, as such, had full access to all data and takes responsibility for the integrity of the data and the accuracy of data analysis.

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Figure Legends

Fig 1. Box plot demonstrating the effect of glycemic gap (**a, b, c**), glycemic variability (**d, e, f**), and stress hyperglycemia ratio (**g, h, i**) on mortality. **a, d, g**. Overall population. **b, e, h**. Patients with DM (diabetes mellitus). **c, f, i.** Patients without DM. Values are median and interquartile range; dots represent outliers.

Fig 2. Relative risks for outcomes according to each glycemic parameter. **a.** Mortality. **b.** Need for renal replacement therapy (RRT). **c.** Incidence of shock. **d.** Need for mechanical ventilation (MV). HbA1c: glycated hemoglobin. Hypoglycemia was defined as any serum or capillary glucose <70 mg/dL during the first ICU day. Hyperglycemia was defined as any serum glucose >140 mg/dL at ICU admission. Glycemic gap was calculated by the difference between serum glucose at ICU admission and the estimated mean blood glucose derived from HbA1c. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. SHR (stress of hyperglycemia ratio) was defined by the ratio between serum glucose at admission and the estimated mean blood glucose derived from HbA1c.Values are point estimates with 95% confidence intervals.

Fig 3. Cumulative survival at 180 days stratified by presence of abnormal blood glucose at ICU admission. **a.** Hypoglycemia (defined as any serum or capillary glucose measurement <70 mg/dL during the first ICU day). **b.** Hyperglycemia (defined as any serum glucose measurement >140 mg/dL at ICU admission). Hazard ratios are adjusted for SAPS 3 (Simplified Acute Physiology III) score.

Supplemental Digital Content Fig 1. Relative risks for ICU readmission according to each glycemic parameter. HbA1c: glycated hemoglobin. Hypoglycemia was defined as any serum or capillary glucose <70 mg/dL during the first ICU day. Hyperglycemia was defined as any serum glucose >140 mg/dL at ICU admission. Glycemic gap was calculated as the difference between the serum glucose at ICU admission and the estimated mean blood glucose derived from HbA1c. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. SHR (stress of hyperglycemia ratio) was defined by the ratio between serum glucose at admission and the estimated mean blood glucose derived from HbA1c. Values are point estimates with 95% confidence intervals.

Table 1. Effects of the stress-induced hyperglycemia on clinical outcomes.

Outcomes	Glycemic gap			SHR		
	<80 mg/dL (n = 489)	**>80 mg/dL (n = 53)**	**p**	**<1.1 (n = 267)**	**>1.1 (n = 275)**	**p**
Mortality (n, %)	181 (37)	26 (49)	0.087	96 (36)	111 (40)	0.247
Need for RRT (n, %)	116 (23.7)	20 (37.7)	**0.025**	62 (23)	74 (27)	0.287
Shock incidence (n, %)	183 (37.4)	29 (54.7)	**0.014**	96 (36)	116 (42)	0.112
Need for MV (n, %)	286 (58.4)	36 (67.9)	0.184	141 (52.8)	181 (65.8)	**0.001**
Time on MV (days)	4 (1 to 8)	4.5 (2 to 8)	0.117	3 (1 to 8)	2 (4 to 8.5)	**<0.001**
LOS, hospital (days)	20 (10 to 35)	20 (10 to 34.7)	0.585	19 (10.7 to 32.5)	21 (9 to 38)	0.263
LOS, ICU (days)	7 (3 to 12)	7.5 (4.25 to 11)	0.126	6 (3 to 11)	8 (4 to 12)	**0.005**
ICU readmission (n, %)	62 (12.6)	6 (11.3)	0.770	30 (11.2)	38 (13.8)	0.339

SHR: stress hyperglycemia ratio; RRT: renal replacement therapy; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit. Glycemic gap was calculated by the difference between the serum glucose at ICU admission and the estimated mean blood glucose derived from HbA1c. SHR was defined by the ratio between serum glucose at admission and the estimated mean blood glucose derived from HbA1c. Values are mean ± SD or median and interquartile range.

Table 2. Effects of hypoglycemia, hyperglycemia, and glycemic variability on clinical outcomes.

Outcomes	Hypoglycemia			Hyperglycemia			Glycemic variability		
	No (n = 480)	Yes (n = 62)	p	No (n = 350)	Yes (n = 192)	p	<40 mg/dL (n = 125)	>40 mg/dL (n = 417)	p
Mortality (n, %)	172 (35.8)	34 (54.8)	**0.004**	122 (34.9)	85 (44.3)	**0.031**	42 (33.6)	165 (39.5)	0.228
Need for RRT (n, %)	107 (22.3)	28 (45.1)	**<0.001**	81 (23.1)	55 (28.6)	0.158	18 (14.4)	118 (28.3)	**0.002**
Shock incidence (n, %)	172 (35.8)	39 (62.9)	**<0.001**	128 (36.6)	84 (43.7)	0.101	39 (31.2)	173 (41.4)	**0.039**
Need for MV (n, %)	276 (57.5)	45 (72.6)	**0.024**	195 (55.7)	127 (66.1)	**0.018**	64 (51.2)	258 (61.8)	**0.033**
Time on MV (days)	4 (2 to 8)	2 (1 to 6)	0.365	4 (1 to 8)	4 (2 to 7.7)	**0.014**	4.5 (1.2 to 9)	4 (1 to 8)	0.170
LOS, hospital (days)	21 (11 to 36)	14 (5 to 30)	**0.024**	21 (11 to 37)	17.5 (8 to 33.5)	0.498	22 (12 – 35)	19 (9 to 36)	0.575
LOS, ICU (days)	7 (4 to 12)	5 (2 to 8.5)	0.117	7 (3 to 12)	7 (4 to 11)	0.183	8 (4 to 12.7)	7 (3 to 11)	0.898
ICU readmission (n, %)	64 (13.3)	4 (6.5%)	0.123	41 (11.7)	27 (14)	0.430	14 (11.2)	54 (12.9)	0.604

RRT: renal replacement therapy; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit. Hypoglycemia was defined as any serum or capillary glucose <70 mg/dL during the first ICU day. Hyperglycemia was defined as any serum glucose >140 mg/dL at ICU admission. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. Values are mean ± SD or median and interquartile range.

Supplemental Digital Content Table 1. Baseline characteristics of patients.

Characteristics	Patients (n=542)
Age (years)	59 ± 15
Men (n, %)	285 (52.5)
BMI (kg/m^2)	27.2 ± 6.6
SAPS 3	57 ± 15
Coexisting conditions (n)	3.5 ± 2
Hypertension (n, %)	293 (54)
Diabetes (n, %)	163 (30)
Cancer (n, %)	108 (20)
Chronic kidney disease (n, %)	97 (18)
Ischemic heart disease (n, %)	97 (18)
Heart failure (n %)	76 (14)
COPD (n, %)	65 (12)
Other (n, %)	92 (17)
Reason for ICU admission	
Acute respiratory failure (n, %)	128 (23.6)
Shock (n, %)	122 (22.1)
Neurologic disorder (n, %)	94 (17.3)
Major surgery (n, %)	80 (14.7)
Cardiovascular disorders (n, %)	37 (6.8)
Other (n, %)	82 (15)
Sepsis (n, %)	351 (64.7)
Need for mechanical ventilation (n, %)	322 (59)
Use of vasopressors (n, %)	331 (61.1)
Need for renal replacement therapy (n, %)	136 (25)
Use of glucocorticosteroids (n, %)	231 (42.8)
Nutrition (n, %)	384 (70.8)
Enteral (n, %)	376 (69.4)
Parenteral (n, %)	8 (1.48)
Insulin therapy (n, %)	148 (27.3)
Long-acting insulin (n, %)	21 (3.9)
Short-acting insulin (n, %)	94 (17.3)
Both long and short-acting insulin (n, %)	33 (6.1)
Blood glucose (mg/dL)	137 ± 65
HbA1c (%)	5.6 ± 1.5
Hyperglycemia (n, %)	192 (35.4)
Hypoglycemia <70 mg/dL (n, %)	62 (11.4)
Hypoglycemia <54 mg/dL (n, %)	25 (4.6)
Glycemic variability (mg/dL)	67 (41 to 112)
Glycemic gap (mg/dL)	11.3 (-15.7 to 42)
Stress hyperglycemia ratio	1.1 ± 0.4

BMI: body mass index; SAPS 3: Simplified Acute Physiology III; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; HbA1c: glycated hemoglobin. Hyperglycemia was defined as any serum glucose >140 mg/dL at ICU admission. Hypoglycemia was defined as any serum or capillary glucose <70 mg/dL during the first ICU day; if <54 mg/dL, it was defined as serious hypoglycemia. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. Glycemic gap was calculated by the difference between the serum glucose at admission and the estimated mean blood glucose derived from HbA1c. Stress hyperglycemia ratio was defined by the ratio between serum glucose at admission and the estimated mean blood glucose derived from HbA1c. Values are mean ± SD or median and interquartile range.

Supplemental Digital Content Table 2. Effects of glycemic variability >60 mg/dL and >80 mg/dL on clinical outcomes.

Outcomes	Glycemic variability					
	<60 mg/dL (n = 235)	**>60 mg/dL (n = 307)**	**p**	**<80 mg/dL (n = 313)**	**>80 mg/dL (n = 229)**	**p**
Mortality (n, %)	78 (32.7)	129 (42)	**0.036**	107 (34.1)	100 (43.6)	**0.025**
Need for RRT (n, %)	39 (16.6)	97 (31.6)	**<0.001**	58 (18.5)	78 (34)	**<0.001**
Shock incidence (n, %)	80 (34)	132 (42.9)	**0.034**	108 (34.5)	104 (45.4)	**0.010**
Need for MV (n, %)	128 (54.4)	194 (63.1)	**0.040**	175 (55.9)	147 (64.2)	0.052
Time on MV (days)	4 (1 to 8)	4 (2 to 8)	0.077	4 (2 to 8.7)	4 (1 to 7)	0.176
LOS, hospital (days)	20 (11.5 to 36)	20 (9 to 35.2)	1	21 (10.2 to 38)	20 (9 to 34)	0.658
LOS, ICU (days)	7 (3.5 to 12)	7 (3 to 11)	0.602	7 (4 to 12)	6 (3 to 11)	0.569
ICU readmission (n, %)	28 (11.9)	40 (13)	0.698	42 (13.4)	26 (11.3)	0.473

RRT: renal replacement therapy; MV: mechanical ventilation; LOS: length of stay; ICU: intensive care unit. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. Values are mean ± SD or median and interquartile range.

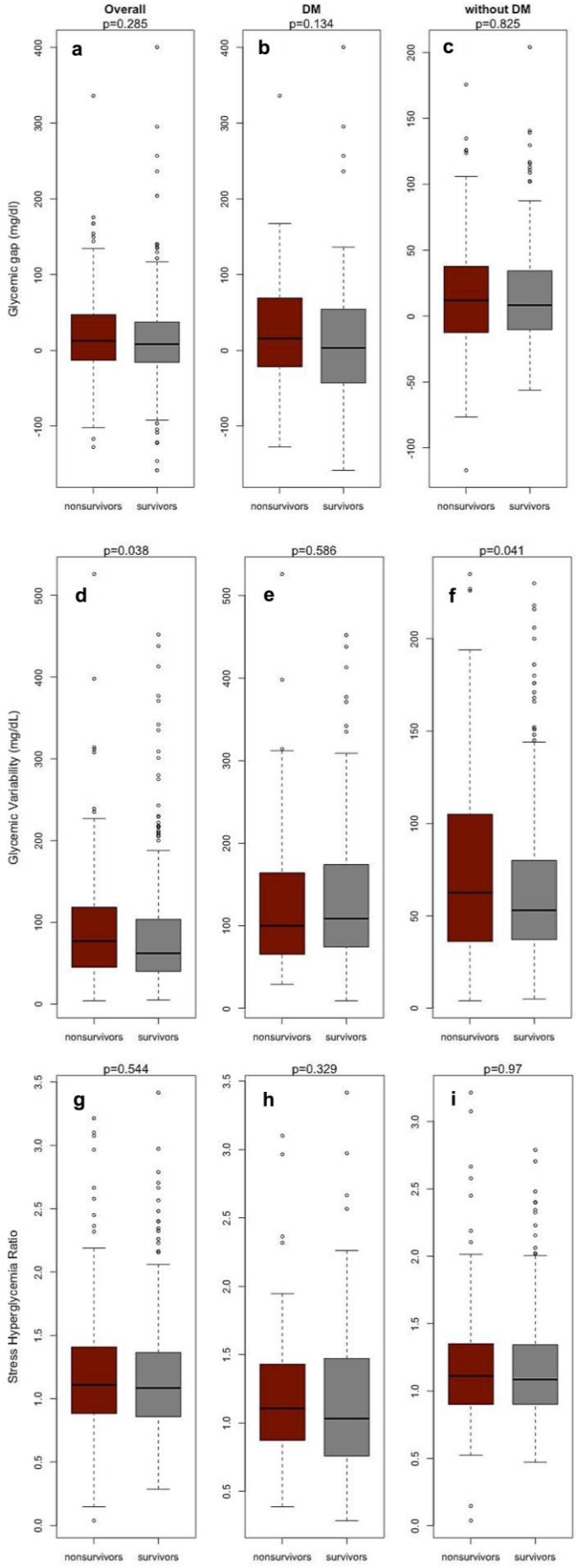


Fig 1. Box plot demonstrating the effect of glycemic gap (**a, b, c**), glycemic variability (**d, e, f**), and stress hyperglycemia ratio (**g, h, i**) on mortality. **a, d, g**. Overall population. **b, e, h**. Patients with DM (diabetes mellitus). **c, f, i.** Patients without DM. Values are median and interquartile range; dots represent outliers.

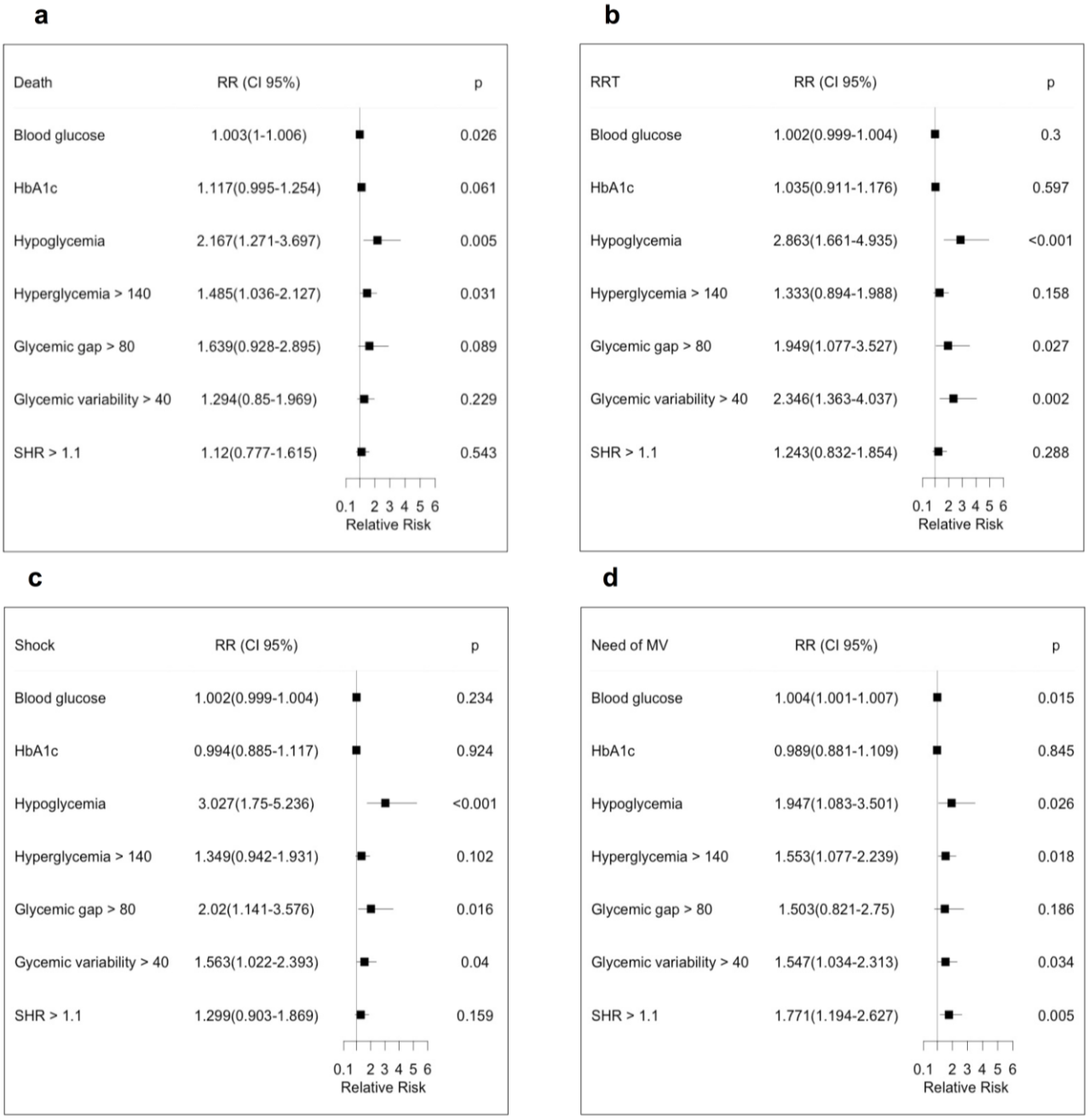


Fig 2. Relative risks for outcomes according to each glycemic parameter. **a.** Mortality. **b.** Need for renal replacement therapy (RRT). **c.** Incidence of shock. **d.** Need for mechanical ventilation (MV). HbA1c: glycated hemoglobin. Hypoglycemia was defined as any serum or capillary glucose <70 mg/dL during the first ICU day. Hyperglycemia was defined as any serum glucose >140 mg/dL at ICU admission. Glycemic gap was calculated by the difference between serum glucose at ICU admission and the estimated mean blood glucose derived from HbA1c. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. SHR (stress of hyperglycemia ratio) was defined by the ratio between serum glucose at admission and the estimated mean blood glucose derived from HbA1c.Values are point estimates with 95% confidence intervals.

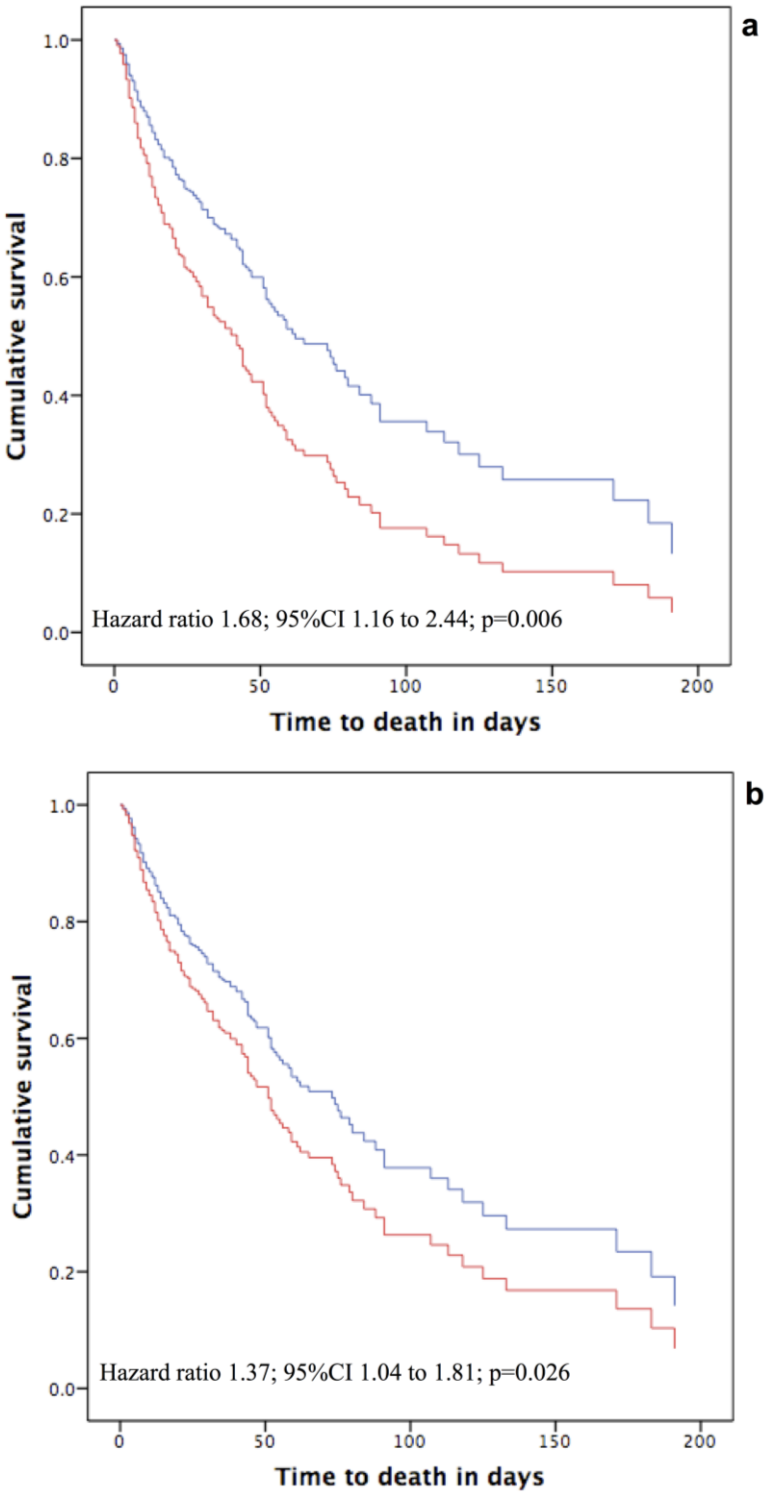
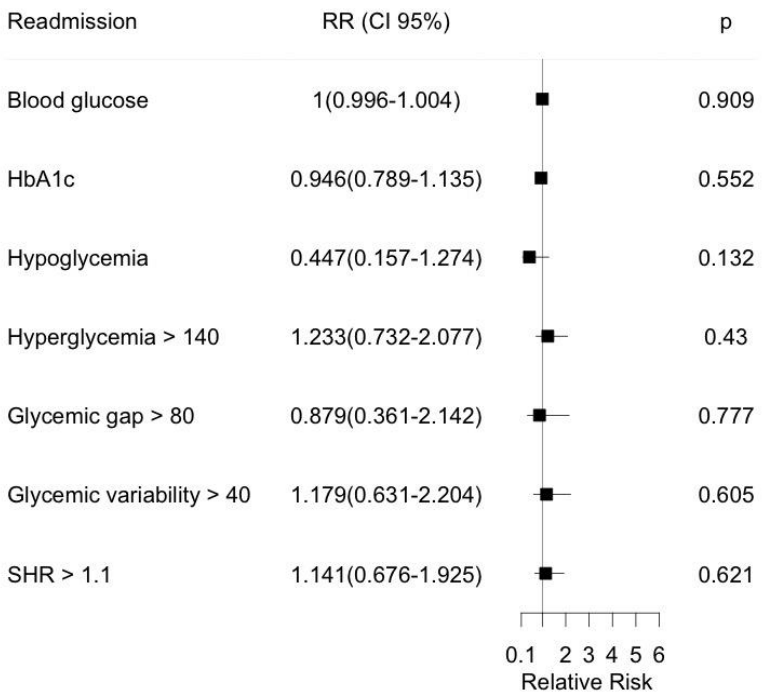


Fig 3. Cumulative survival at 180 days stratified by presence of abnormal blood glucose at ICU admission. **a.** Hypoglycemia (defined as any serum or capillary glucose measurement <70 mg/dL during the first ICU day). **b.** Hyperglycemia (defined as any serum glucose measurement >140 mg/dL at ICU admission). Hazard ratios are adjusted for SAPS 3 (Simplified Acute Physiology III) score.



Supplemental Digital Content Fig 1. Relative risks for ICU readmission according to each glycemic parameter. HbA1c: glycated hemoglobin. Hypoglycemia was defined as any serum or capillary glucose <70 mg/dL during the first ICU day. Hyperglycemia was defined as any serum glucose >140 mg/dL at ICU admission. Glycemic gap was calculated as the difference between the serum glucose at ICU admission and the estimated mean blood glucose derived from HbA1c. Glycemic variability was calculated as the absolute difference in capillary blood glucose during the first ICU day. SHR (stress of hyperglycemia ratio) was defined by the ratio between serum glucose at admission and the estimated mean blood glucose derived from HbA1c. Values are point estimates with 95% confidence intervals.

CAPÍTULO III

CONSIDERAÇÕES FINAIS E PERSPECTIVAS FUTURAS

Múltiplos parâmetros glicêmicos têm mostrado associação com desfechos clínicos em pacientes criticamente doentes, como relatado ao longo desta dissertação. Tão ou mais importante que demonstrar a associação das alterações da glicemia com desfechos clínicos é compreender os mecanismos pelos quais isso ocorre. Estudos demonstram que a hiperglicemia pode levar à disfunção imunológica e endotelial, influenciando tanto a migração e a capacidade fagocítica de macrófagos quanto alterando o sistema de complemento e a produção de citocinas[1]. Entretanto, os mecanismos fisiopatológicos do dano causado pela hiperglicemia ainda não são completamente compreendidos. Nesse sentido, parece ser relevante estudar os mecanismos moleculares que regulam a expressão dos genes dos transportadores de glicose e dos receptores de insulina.

O gene *INSR* (do inglês, *insuline receptor*) codifica uma proteína da família das tirosina-cinases. A ligação de insulina a este receptor ativa uma via de sinalização intracelular, culminando com a ativação de segundos mensageiros, como o *IRS1* e *IRS2*, que regulam a absorção e a liberação da glicose, bem como a síntese e o armazenamento de carboidratos, lipídeos e proteínas[2]. Alterações no gene *INSR* levam à resistência à ação da insulina e à hiperglicemia crônica. A proteína *SLC2A1* (do inglês, *solute carrier family 2 member 1*), também conhecida por GLUT-1 (do inglês, *glucose transporter 1*), é amplamente difundida pelos tecidos e responsável pela manutenção dos níveis

celulares basais de glicose[3]. O GLUT-1 possui alta capacidade de transporte e alta afinidade pela molécula de glicose, não tendo sua atividade mediada por insulina[4]. Já a proteína *SLC2A4* (do inglês, *solute carrier family 2 member 4*), também conhecida por GLUT-4 (do inglês, *glucose transporter 4*)[5], é regulada pela insulina. Na ausência de insulina, esta proteína integral da membrana está isolada dentro das células do tecido muscular e do tecido adiposo. Quando ocorre a estimulação pela insulina, o GLUT-4 é translocado para a superfície da célula, onde aumenta o transporte de glicose através da membrana celular, do exterior para o interior da célula. Alterações clássicas associadas a mutações nos genes codificadores dessas proteínas são o DM e a tolerância diminuída à glicose[6]. O transportador de glicose GLUT-4 é expresso em abundância nos músculos esquelético e cardíaco e no tecido adiposo. Processos inflamatórios, principalmente mediados pelo fator de necrose tumoral, diminuem a densidade dos GLUT na membrana, tornando o músculo mais resistente à captação de glicose. Em animais diabéticos, por exemplo, os níveis de GLUT-4 estão diminuídos, tanto em adipócitos quanto em células musculares cardíacas e esqueléticas[7].

Diferentes autores têm sugerido que a hiperglicemia crônica possa ser capaz de gerar um acondicionamento celular protetor contra o dano mediado pela hiperglicemia aguda durante a doença crítica[8], o que poderia explicar em parte o “paradoxo do diabetes” na UTI, já que DM não é um fator independente para mortalidade em pacientes criticamente doentes[9]. Esse mecanismo de acondicionamento celular consistiria na redução da expressão gênica (do inglês, *downregulation*) do *IRS2* (que participa das vias intracelulares sinalizadoras da insulina) e dos transportadores de glicose *GLUT-1* e *GLUT-4*

devido à exposição crônica à hiperglicemia. A análise da expressão desses genes pode esclarecer em parte o mecanismo relacionado às alterações da glicemia e do controle glicêmico em pacientes criticamente doentes. Com base nessa ideia, e a fim de compreender o mecanismo pelo qual a hiperglicemia causa lesão muscular, o nosso grupo de pesquisa propôs dois novos estudos, que apresentamos de forma sumária a seguir.

O primeiro deles tem o objetivo de avaliar a expressão do *IRS2* e dos transportadores de glicose no tecido muscular esquelético e sua relação com o estado glicêmico na admissão na UTI. No período de abril a agosto de 2018, cinquenta pacientes internados na UTI do Hospital de Clínicas de Porto Alegre foram submetidos a biópsias cirúrgicas do músculo vasto lateral da coxa. Essas amostras de tecido muscular estão armazenadas, aguardando as análises de expressão gênica, que serão realizadas até o final de 2019. O estudo pretende também avaliar se há diferença na expressão desses genes em pacientes com e sem diagnóstico prévio de DM.

Nessa mesma linha, a literatura mostra uma associação independente entre hiperglicemia e fraqueza muscular adquirida na UTI (FA-UTI)[10]. A FA-UTI consiste na fraqueza muscular generalizada que se desenvolve no curso da internação na UTI e para qual nenhuma outra causa pode ser identificada além da doença aguda e do seu tratamento. Ela pode ocorrer tanto por polineuropatia quanto por miopatia, ou pela combinação de ambas[11], e o seu desenvolvimento parece ter associação com os níveis glicêmicos[12-14]. A incidência de FA-UTI é alta, variando entre 26 a 67% dependendo do momento da avaliação e da gravidade da população estudada. Além disso, 36% dos pacientes apresenta FA-UTI no momento da alta hospitalar[15]. A polineuropatia

e a perda de musculatura esquelética, que acometem tanto a musculatura apendicular quanto a axial, tem impacto negativo no tempo de ventilação mecânica[16-18] e na mortalidade em cinco anos de pacientes com síndrome da angústia respiratória do adulto[19].

A fisiopatologia da FA-UTI é complexa e envolve alterações funcionais e estruturais de músculos e nervos. Os mecanismos do desenvolvimento tanto da neuropatia quanto da miopatia não são claros[11], mas a hiperglicemia parece desempenhar um papel importante, principalmente quando relacionada a quadros de inflamação sistêmica. A maneira como a glicose lesa os tecidos tem sido extensamente estudada. Por exemplo, a glicotoxicidade leva à apoptose das células beta, um dos mecanismos de morte celular no diabetes[20]. Além disso, altas concentrações de glicose resultam em estresse oxidativo, disfunção mitocondrial com redução da capacidade de síntese aeróbica de ATP, ativação de caspases e apoptose em neurônios[12]. Da mesma forma, estudos tem demonstrado ativação de caspases, degradação de proteínas miofibrilares e ativação da via de degradação proteica da ubiquitina em células musculares expostas a altas concentrações de glicose em cultura, sugerindo que a hiperglicemia ative vias sinalizadoras envolvidas na atrofia muscular. Um estudo de biópsias musculares de pacientes com baixa sensibilidade à ação da insulina mostrou redução da expressão do transportador GLUT-4 no sarcolema das células musculares, o que resultou na redução da captação muscular de glicose. Essa redução da expressão de GLUT-4 parece estar envolvida no desenvolvimento da FA-UTI[21]. Somado a isso, um fator de risco conhecido para o desenvolvimento de polineuropatia da doença crítica é a presença de inflamação sistêmica[22], que por sua vez predispõe à hiperglicemia, produzindo

um ciclo vicioso entre hiperglicemia e inflamação. Essa inter-relação entre hiperglicemia e inflamação parece promover a perda proteica muscular, especialmente de miosina, favorecendo a lise e reduzindo a síntese proteica, potencializando assim o risco de fraqueza muscular[11].

Assim, o papel da hiperglicemia em modular os processos de toxicidade muscular parece envolver múltiplos aspectos, como indução de disfunção mitocondrial, endotelial, inflamação e estresse oxidativo[12]. O entendimento sobre os mecanismos que levam à fraqueza muscular prolongada em pacientes críticos ainda é limitado. Acreditamos que o intrincado mecanismo que associa hiperglicemia, inflamação e FA-UTI deva ser melhor estudado em estudos mecanísticos, o que poderia reduzir o problema da falta de tratamentos específicos para uma patologia tão incidente em pacientes criticamente doentes. Com esse objetivo, o segundo trabalho foi desenhado. Atualmente, nosso grupo de pesquisa está desenvolvendo um estudo em colaboração com o *Laboratory of Exercise and Health do Swiss Federal Institute of Technology Zurich* (*ETH Zurich*), na Suíça. Neste projeto, serão realizadas biópsias musculares sequenciais em vinte pacientes, no primeiro e no quinto dia de internação na UTI. Nos cortes congelados dessas biópsias, serão avaliados tamanho e espessura da fibra muscular visando à quantificação da atrofia das fibras musculares, com determinação do tipo de fibra (tipo 1 ou tipo 2). Além disso, técnicas de imunofluorescência serão utilizadas para identificar mionúcleos, células satélite, progenitores/fibroblastos fibroadipogênicos e vasos sanguíneos. A avaliação da expressão gênica de *IRS2, GLUT-1* e *GLUT-4* também será realizada nessas biópsias. As peças de parafina e os cortes congelados para as análises moleculares serão enviados

para o *Laboratory of Exercise and Health*, da *ETH Zurich*, onde serão processados para as análises histológicas, imunohistoquímicas e moleculares. A presença de FA-UTI será definida clinicamente pela presença de fraqueza muscular flácida, difusa e simétrica da musculatura esquelética apendicular e respiratória, sem envolvimento de nervos cranianos[23]. Além disso, será realizada avaliação ultrassonográfica do tecido muscular esquelético nos mesmos dias das biópsias, para definição da estrutura muscular por meio da ecogenicidade do tecido.

Dessa forma, por meio destes dois estudos que estão em andamento, pretendemos compreender melhor os mecanismos fisiopatológicos e moleculares pelos quais a hiperglicemia causa lesão muscular esquelética. Além disso, será estudada a relação entre hiperglicemia e o desenvolvimento de FA-UTI, condição muito frequente e que resulta em desfechos desfavoráveis para os pacientes criticamente doentes a curto e longo prazos. Como não há opções específicas de tratamento da FA-UTI, esforços devem ser feitos para identificar, controlar e prevenir os seus fatores de risco, especialmente a hiperglicemia, a fim de reduzir sua incidência e suas consequências.

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