

Behavior of glycemic variability in hospitalized type 2 Diabetes Mellitus patients

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ABSTRACT

Introduction: Hyperglycemia may be present in up to 38% of hospitalized patients. Glycemic control is associated with better clinical outcomes. **Objective:** assess the behavior of glycemic variability in hospitalized patients with Diabetes Mellitus 2. **Methodology:** Cross-sectional study composed of hospitalized patients with and without diabetes, adults and elderly, of both genders, undergoing enteral nutritional therapy. Blood glucose was measured by capillary blood glucose tests and classified as normoglycemia, hyperglycemia, and glycemic variability, assessed from the glycemic standard deviation and glycemic variation coefficient. Biochemical data such as C-reactive protein were assessed. Two-way analysis of variance (ANOVA) was used to compare the groups, in addition to Spearman's correlation. **Results:** Eighty-five individuals with diabetes mellitus 2 (20%; n=17) and without diabetes mellitus (80%; n=68) participated in the study; 34% (n=29) were adults, and 66% (n=56) were elderly. Adults and elderly people with diabetes mellitus presented hyperglycemia concerning non-diabetic patients ($p < 0.01$), higher values of glycemic standard deviation ($p < 0.01$), and glycemic variation coefficient concerning patients without diabetes ($p = 0.03$); however, they were not classified with glycemic variability. The C-reactive protein values were correlated with the glycemic standard deviation ($R = 0.29$; $p = 0.0065$); however, the amount of carbohydrates infused in the enteral diet was not statistically correlated with glycemia or with the glycemic variability of patients ($p > 0.05$). **Conclusion:** hospitalized patients with or without diabetes mellitus 2 did not show glycemic variability, demonstrating glycemic control during hospitalization.

Keywords: Glycemia, C-reactive protein, Nutritional therapy.

INTRODUCTION

Throughout the day, hospitalized patients, mainly those with Diabetes Mellitus 2 (DM2), present glycemic alterations known as glycemic variability (GV), dysglycemia, lack of glycemic control, glycemic disorder, or glycemic fluctuations.^{1,2} Studies demonstrate that glycemic variability, mainly associated with severe hypoglycemia, it can be harmful in patients with or without diabetes.³

The etiological factors for the lack of glycemic control are related to the decrease or absence of glycemic self-regulation and the occurrence of glycemic drops due to the availability of insulin.⁴ Hyperglycemia, on admission, may result from stress-responsive to diseases, associated treatments, or due to DM when diagnosed during hospitalization.⁵ However, insulin therapy can be a target parameter for glycemic control and may be applied to all patients with Diabetes

Mellitus (DM) 1 and 2, hospitalized and without diabetes.³ Also, non-diabetic patients have fewer episodes of hypoglycemia; however, in surgical wards, they need to fast, and this can lead to mild hypoglycemia², and often do not receive treatment during hospitalization.⁶ In the hospital context, glycemic variability is a predictor of mortality and has been established as essential goals in the glucose management.³

Although there are recommendations for glycemic goals for the control of DM, it is essential to emphasize the need to individualize glycemic goals to avoid glycemic oscillations resulting from hyperglycemia alternating with hypoglycemia.¹ Hypoglycemia is correlated with morbidity and mortality, and it is recommended to assess the number of events and time spent in hypoglycemia as variables in glycemic monitoring.⁷ It is also associated with a prolonged hospital stay, increased demand for human resources and hospital costs, and worsening of the clinical outcome.⁸

The glucose standard deviation (GSD) is considered the preferred method to quantify GV, as it demonstrates the relationship between GV and outcomes such as mortality in hospitalized patients.⁹ According to the Brazilian Society of Diabetes (SBD), glycemic variability can be assessed by different parameters, with the GSD and the glucose variation coefficient (GVC) being the most important to analyze the risk factors related to glycemic variability.¹ The methods to assess GV are influenced by glycemic exposure (glucose excursion \times time) and slope (glucose excursion/time), being indicators of the rate of change in glucose.¹⁰

Given the inflammatory state of patients during hospitalization, C-Reactive Protein (CRP) is a marker produced by liver cells in response to increased concentrations of pro-inflammatory cytokines.¹¹ The increase in blood glucose contributes significantly to the production of reactive oxygen species, characterizing oxidative stress related to the pro-inflammatory state.¹²

Given the diet therapy approach of hospitalized patients with diabetes, the specialized enteral diet facilitates glycemic control and the need for insulin, which reduces the risk of hypoglycemia, and glycemic variability.¹³

In the long term, glycemic variability can establish a framework of risk factors for the development of complications related to DM, in addition to being associated with longer hospital stays, representing high public costs. Furthermore, glycemic variability is strongly associated with cardiovascular diseases and increased mortality in hospitalized patients². In this sense, a glycemic variability is an essential object of study, as it is a parameter used to optimize glycemic control and can be applied in hospitalized patients. Therefore, this research aims to assess the behavior of glycemic variability in hospitalized patients with Diabetes Mellitus 2.

METHODS

Type of study and ethical aspects

A cross-sectional, prospective, descriptive, and observational study, with a convenience sample

selected randomly, composed of hospitalized adults and elderly people, with or without diabetes mellitus 2, of both genders, on exclusive enteral nutrition. The study was carried out in a public hospital in the countryside of Rio Grande do Sul (RS) from August 2017 to December 2018.

The research project and the Informed Consent Term follow the Regulatory Guidelines for Research involving human beings (Resolution 466/12)¹⁴ of the National Health Council (NHC). The present work was approved by the Ethics and Research Committee under opinion number 1,369,154 and the Certificate of Presentation of Ethical Appreciation (CAAE) number 51109315.4.0000.5306.

Eligibility and exclusion criteria

Eligibility criteria were hospitalized patients with or without diabetes mellitus 2, on exclusive enteral nutritional therapy (ENT), lucid and/or with a companion.

Patients with another type of diabetes using ENT associated with another feeding route, such as oral or parenteral, were excluded from the study. In addition, patients on comfort measures and/or palliative care and patients and/or companions unable to sign the informed consent term were also excluded from the sample.

Study design

Data collection began at the time of admission of patients to the adult emergency care (AEC) or medical clinic unit, with monitoring for up to 72 hours after admission. For each patient, a form was filled out containing the following data: name, date of birth, age, gender, measurement of capillary blood glucose (CBG), CRP, type of diet in the ENT, the volume of enteral diet, total carbohydrates, and maltodextrin infused. Regarding the carbohydrate in the diets, the amount in grams of maltodextrin and total carbohydrate described on the formula labels was verified. Enteral diets were administered in a continuous system, with caloric density between 1 to 2 kcal/mL, and prescribed according to the nutritional status of the patients and their illnesses.

Regarding the values of CBG, a daily mean was performed during five days of hospitalization. CBGs were measured 3 to 6 times a day, every 4, 6, or 8 hours a day, according to medical prescription. Patients' blood glucose levels were classified according to the following categories: normoglycemia, hypoglycemia, hyperglycemia, and GV. According to the American Diabetes Association (ADA) and the SBD, hospital hyperglycemia is defined as values greater than 140 mg/dL.^{1,7} Hypoglycemia is considered when values are lower than 70 mg/dL, and values lower than 54 mg /dL are considered a severe and clinically important condition. Thus, patients who had at least, during the day, a CBG value that exceeded 140 mg/dL were considered hyperglycemic, and patients with CBG value lower than 70 mg/dL were considered hypoglycemic.^{1,7}

The SBD recommends GVC as a primary indicator of glycemic variability due to its relative sensitivity to hypoglycemia (compared to GSD) and easy calculation.¹ Thus, to classify the GV, the GSD and GVC calculations were used.

The glycemic standard deviation assesses the glycemic variability, which must be less than 50 mg/dL or, at most, 1/3 of the mean blood glucose.¹⁵ The glycemic variation coefficient was calculated by dividing the glycemic standard deviation by the mean of daily blood glucose levels and multiplying by 100, resulting in a percentage. The glycemic standard deviation and glycemic variation coefficient were calculated daily, considering the CBG of the patient's first five days of hospitalization.

Values of glycemic variation coefficient greater than 36% are associated with greater glycemic variability.¹⁶ In agreement with this assessment value, based on the results of the literature, the most stable glycemia is defined as GVC <36% (low glycemic variability), and unstable glucose levels are defined as GVC ≥36% (high glycemic variability).¹⁷ Therefore, patients who obtained GVC values above 36% were considered to have glycemic variability.

Statistical analysis

The data obtained were tabulated and stored in Microsoft Excel® software. Statistical analysis was performed using the Statistica program version 10.0. The Shapiro-Wilk test was performed to verify the normality of the sample. Patients were categorized into the following groups: with DM2 and without DM2, according to medical diagnosis, and according to age group, adults and elderly (over 60 years old). A two-way analysis of variance (ANOVA) was used to compare the groups. In addition, a Spearman correlation test was performed. The 95% confidence interval and p-value were considered. Data were considered statistically significant when $p < 0.05$ and were presented as mean \pm standard error.

RESULTS

Eighty-five hospitalized patients with exclusive ENT were assessed. Twenty-six patients were excluded for starting oral feeding associated or not with enteral nutrition, death, and hospital discharge before completing the follow-up period. The study patients were classified according to the presence of a medical diagnosis of DM2 (20%; $n = 17$) and without a medical diagnosis of DM2 (80%; $n = 68$), and 34 % ($n = 29$) were adults and 66% ($n=56$) elderly.

According to the blood glucose levels analyzed, the 2-way analysis of variance indicated significant differences only in patients with and without DM2 ($F= 26.4$; $P < 0.01$) but not concerning adults and the elderly ($F=0.54$; $P= 0.46$), as shown in Figure 1. It was observed that adults (207.1 ± 24.1 mg/dL) and elderly (200.5 ± 11.1 mg/dL) with DM2 had mean values higher blood glucose levels than adults (123.2 ± 8.1 mg/dL) and elderly patients (137.7 ± 6.4 mg/dL) without DM2. No patient assessed had hypoglycemia, according to the ADA (2019).⁷ The mean blood glucose of patients was 146.1 ± 50.1 mg/dL glycemic standard deviation.

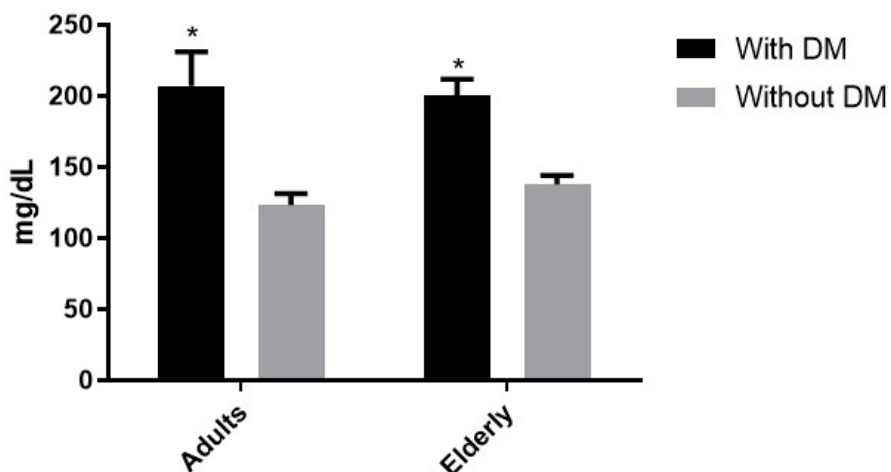


Figure 1: Mean blood glucose values in hospitalized patients with and without Diabetes Mellitus 2. *P < 0.05. Concerning patients without DM2. Analysis of variance (ANOVA).

According to the glycemic standard deviation, the analysis of variance showed significant differences only in patients with and without DM2 (F=21.5; P<0.01) but not in association with adults and the elderly (F=3.0; P= 0.08), as shown in Figure 2. It was observed that adults (43.1 ± 7.4 mg/dL) and

elderly (33.7 ± 3.4 mg/dL) with DM2 had higher GSD compared to adults (14.9 ± 2.5 mg/dL) and elderly (20.8 ± 2.0 mg/dL) without DM2 (Figure 2). Although patients with DM2 had higher GSD, they were not classified with glycemic variability according to the reference parameters (> 50 mg/dL).¹⁵

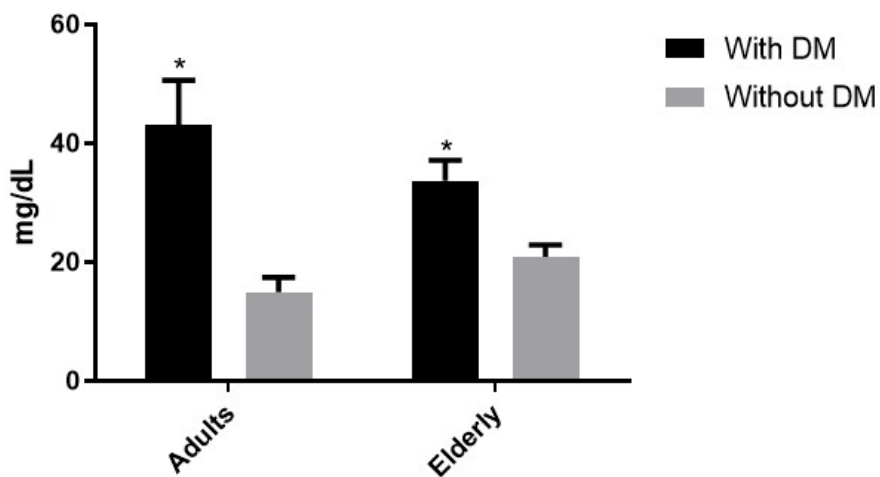


Figure 2: Mean glycemic standard deviation values in hospitalized patients with and without Diabetes Mellitus. *P < 0.05. Analysis of variance (ANOVA).

When analyzing the coefficient of glycemic variation, the analysis of variance indicated an effect in patients with and without DM2 in adults and the elderly (F=4.7; P=0.03), as shown in Figure 3. After ANOVA, the Post-Duncan's Hoc to

identify the pairs of means that differ statistically, and statistically higher values of the glycemic coefficient of variation were demonstrated in adults with DM2 (23.2 ± 3.9%) related to the elderly with DM2 (16.1 ± 1.8%; P=0.03), followed by the elderly

without DM2 ($15.2 \pm 1.0\%$; $P= 0.022$) and adults without DM2 ($12.2 \pm 1.3\%$; $P= 0.002$). However,

no group was classified as having high glycemic variability, according to reference values ($> 36\%$).

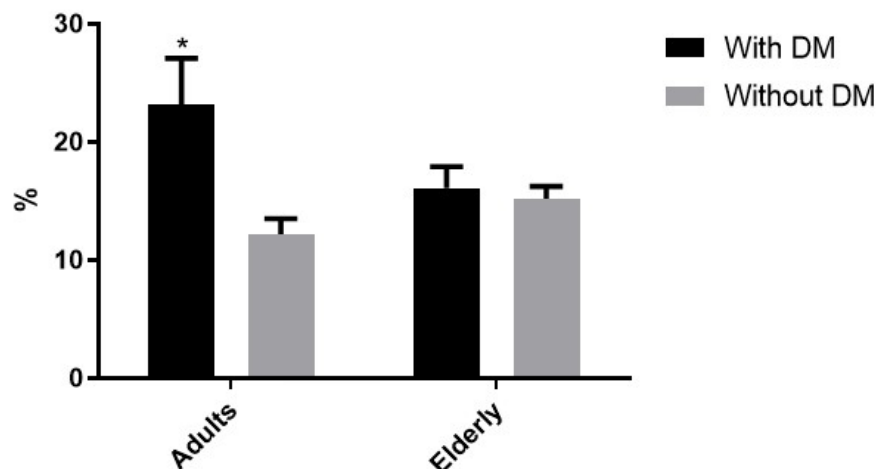


Figure 3: Mean values of the coefficient of glycemic variation in hospitalized patients with and without diabetes. * $P < 0.05$. Analysis of variance (ANOVA).

CRP did not indicate significant differences with the analyzed associations (adults and elderly, with and without DM) ($F=0.84$; $P=0.36$). Likewise, when the consumption of total carbohydrates and maltodextrin alone was assessed by the administration of enteral diets, no statistical differences were observed in patients with and without DM2, adults, and elderly ($F = 1.54$, $P = 0.22$; $F = 2.48$, $P = 0.12$, respectively).

When analyzing CRP, weak correlations were found with glycemic standard deviation, glycemic variation coefficient, and age of the patients; however, there was no correlation with the patients' blood glucose levels nor with the amount of total carbohydrate or maltodextrin (in grams), as shown in Table 1.

Table 1

Correlation analysis in hospitalized patients with and without Diabetes Mellitus 2.

Variables	Spearman-R	p-value
CRP x CBGT	0.16	0.130
CRP x glycemic standard deviation	0.29	0.006*

(Continuação)

Table 1

(Continuação)

Variables	Spearman-R	p-value
CRP x glycemic variation coefficient	0.21	0.044*
CRP x age	0.27	0.010*
Total CHO ENT x CBGT	-0.05	0.73
Maltodextrin ENT x CBGT	- 0.04	0.97
Total CHO ENT x glycemic standard deviation	- 0.05	0.68
Maltodextrin ENT x glycemic standard deviation	0.02	0.88
Total CHO ENT x glycemic variation coefficient	- 0.14	0.29
Maltodextrin ENT x glycemic variation coefficient	- 0.07	0.59

Legend: CRP = C-Reactive Protein; CBGT = capillary blood glucose test; CHO = carbohydrate; ENT = Enteral Nutrition Therapy. * $P < 0.05$. Spearman correlation test.

DISCUSSION

This research showed that hospitalized patients, with or without diabetes, were not

classified as having high glycemic variability, according to the classification of the glycemic standard deviation and the glycemic variation coefficient.¹⁵ However, according to the statistical analysis, it was observed that patients with DM2 presented hyperglycemia and higher values of standard deviation and glycemic variation coefficient concerning patients without DM2. In the group of patients without DM2, it can be seen that both age groups (adults and elderly) have normal glycemic means, according to the SBD.¹ Regarding the age group, no statistical differences were observed between adults and the elderly, with the exception of results of the glycemic variation coefficient, in which adults with DM2 had higher GVC related to the elderly with DM2.

The glycemic variation coefficient method confirms the absence of hypoglycemic events in the present study, as seen from the blood glucose means. Values greater than 36% are associated with a greater risk of hypoglycemia and greater glycemic variability.¹⁶ According to a retrospective cohort study, critically ill patients who experience a hypoglycemic event have greater glycemic variability during hospitalization.¹⁸ The present study allowed us to observe that patients hospitalized, even with DM2, but not critical, had glycemic control, not presenting hypoglycemia.

Among the factors that can lead to glycemic alterations, we highlight inadequate insulin administration, in addition to physiological stress, alteration of the nutritional regimen and medications,¹⁹ generating hypoglycemia or hyperglycemia during hospitalization. Furthermore, the type of carbohydrate present in the diets can change the glycemia of patients using ENT,²⁰ and therefore, the choice of the type of diet can benefit the patient, avoiding hospital complications. In the present study, the type of enteral diet did not statistically change the results of glycemia and glycemic variability. In view of this, the patients in this study seem to have received adequate adjustments in administration and insulin therapy, promoting adequate glycemic control.

Also, concerning glycemic changes, the hyperglycemic events observed, especially in patients with diabetes, may be a response to

increased hepatic gluconeogenesis caused by the action of counterregulatory stress hormones, such as corticosteroids and catecholamines. In addition, in response to stress, the release of pro-inflammatory mediators occurs, triggering the loss of sensitivity of peripheral tissues.²¹ The use of enteral and parenteral diets, dialysis solutions, glucocorticoids, and vasoactive substances are also mechanisms that can contribute to the hyperglycemia.⁹

CRP was positively correlated with glycemic standard deviation and glycemic variation coefficient, that is, with glycemic variability, but it was not associated with hyperglycemia in these patients. However, high CRP concentration may be associated with excess adipose tissue, which activates insulin signaling pathways, resulting in insulin resistance and hyperglycemia²² and endothelial dysfunction that triggers inflammatory reactions²³; however, this was not observed in this study. As CRP is a sensitive inflammatory marker, as it is responsive to a variety of stimuli and to various types of inflammation,²⁴ in the present study, it may be more associated with the reason for the hospitalization of these patients.

Another important result obtained was the correlation of CRP with the age of the patients, demonstrating an association with the senility of these patients. The increase in the inflammatory state with age is partly due to the accumulation of senescent cells that secrete pro-inflammatory cytokines and the remains of damaged cells that trigger the activation of macrophages and other innate immune cells.²⁵

The findings of the present study showed good glycemic control in hospitalized patients with or without DM. As a limitation of the study, there was the number of hospitalized patients analyzed. Many patients had to be excluded, as they did not remain hospitalized during the entire follow-up period. As a contribution of this study, it is suggested the creation of protocols that show, in a clearer way, to health professionals how to identify glycemic alterations in hospitalized patients during hospitalization. More studies are needed to assess the impacts of hyperglycemia and glycemic variability in hospitalized patients.

CONCLUSION

The patients in this study, even with diabetes, did not show glycemic variability, according to the glycemic standard deviation and glycemic variation coefficient analyzed, demonstrating glycemic control during hospitalization.

The care of the multidisciplinary team is essential for the glycemic control of patients, being able to minimize and avoid health problems and complications, improving clinical outcomes.

REFERENCES

- Pititto B, Dias M, Moura F, Lamounier R, Calliari S, Bertoluci M. Metas no tratamento do diabetes. Diretriz Oficial da Sociedade Brasileira de Diabetes (2022). DOI: 10.29327/557753.2022-3, ISBN: 978-65-5941-622-6.
- Akirov A, Shochat T, Dotan I, Diker-Cohen T, Gorshtein A, Shimon I. Glycemic variability and mortality in patients hospitalized in general surgery wards. *Surgery*. 2019; 166 (2): 184-192.
- Krishna SV, Kota SK, Modi KD. Glycemic variability: clinical implications. *Indian J Endocrinol Metab*, 2013; 17(4): 611-9.
- Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: The role of protein kinase C and NAD (P) H-oxidase activation. *Diabetes*. 2003; 52 (11): 2795-804.
- American Diabetes Association (ADA). Diabetes Care in Hospital: Standards of Medical Care in Diabetes – 2019. *Diabetes Care*. 2019; 42 (1): 173-81.
- Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.*, 2012; 97 (1): 16-38.
- Leibowitz J, Wisotky, DJ. 2294-PUB: Professional Continuous Glucose Monitoring Improves Glucose Control in Type 2 Diabetes. *Diabetes*. 2019; 68 (Supp. 1).
- Viana MV, Moraes RB, Fabbrin AR, Santos MF, Gerchman F. Avaliação e tratamento da hiperglicemia em pacientes graves. *Rev Bras Ter Intensiva*. 2014; 26 (1): 71-6.
- Siegelaar SE, Holleman F, Hoekstra JBL, Devries JH. Glucose variability: Does it matter? *Endocr Rev*. 2010; 31 (2):171-82.
- Service FJ. Glucose variability. *Diabetes*. 2013; 62 (5): 1398-404.
- Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J*. 1990; 265: 621-36.
- Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation*. 2000; 102 (11): 1296-301.
- Sanz-Paris A, Alvarez H, Ballesteros PMD, Romero FB, Sanz-León M, Palmero-Martín A et al. Evidence-based recommendations and expert consensus on enteral nutrition in the adult with diabetes mellitus or hyperglycemia. *Nutrition*. 2017; 41: 58-67.
- Brasil. Ministério da Saúde. Resolução nº 466, de 12 de dezembro de 2012 [Internet]. Ministério da Saúde; 2012 [citado em 10 de junho de 2018]. Disponível em: https://bvsms.saude.gov.br/bvs/saudelegis/cns/2013/res0466_12_12_2012.html
- Posicionamento Oficial SBD nº 02/2017. Conduta terapêutica no diabetes tipo 2: algoritmo SBD 2017.
- Monnier L, Colette C, Wojtusciszyn A, Dejager S, Renard E, Molinari N, Owena DR. Toward defining the threshold between low and high glucose variability in diabetes. *Diabetes Care*. 2017; 40 (7): 832-38.
- Kovatchev B. Glycemic Variability: Risk Factors, Assessment, and Control. *J Diabetes Sci Technol*. 2019;13 (4): 627-635.
- Kauffmann RM, Hayes RM, Buske BD, Norris PR, Campion TR, Dortch M, et al. Increasing blood glucose variability heralds hypoglycemia in the critically III. *J Surg Res*. 2011; 170 (2): 257-64.
- Silva, GG, Diabetes vs UTI. [monografia]. Cuiabá; Associação de Medicina Intensiva Brasileira. 2011. 30 p.
- Gosmanov AR, Umpierrez GE. Management of hyperglycemia during enteral and parenteral nutrition therapy. *Curr Diab Rep*. 2013;13 (1): 155-62.
- Hansen TK, Thiel S, Wouters PJ, Christiansen Berghe GVD. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab*. 2003; 88 (3): 1082-8.
- Phosat C, Panprathip P, Chumpathat N, Prangthip P, Chantratita N, Soonthornworasiri N et al. Elevated C-reactive protein, interleukin 6, tumor necrosis factor alpha and glycemic load associated with type 2 diabetes mellitus in rural Thais: a cross-sectional study. *BMC Endocr Disord*. 2017; 17: 44.
- Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006; 444 (7121): 875-80.
- Kaplan, MH. C-Reactive Protein: Relation to Disease and Pathological Significance. *Ann N Y Acad Sci*. 1982; 389: 419-22.
- Franceschi C, Garagnani P, Vitale G, Capri M, Salvioli S. Inflammaging and 'Garb-aging'. *Trends Endocrinol Metab*. 2017; 28 (3): 199-212.

Funding Source

This article has not received funding

Authors' contributions

DFM participated in the construction of the manuscript, the interpretation of data, and the review and approval of the final version; CD participated in the construction of the manuscript, the review and approval of the final version, MS, AG and DOS participated in the collection of data, construction of the manuscript, interpretation of data, and review and approval of the final version; JEB and MCC participated in data collection and review and approval of the final version; EC participated in the construction of the manuscript, interpretation of data and review and approval of the final version.

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Editor:
Prof. Dr. Paulo Henrique Manso

Received: jun 01, 2022
Approved: sep 12, 2022
