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Evaluation of the oxidative profile of critical patients hospitalized in adult intensive care unit

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ABSTRACT

The objective of this work was to evaluate and correlate the oxidative stress in patients with uncontrolled blood glucose levels (hyperglycemia or hypoglycemia) hospitalized in an intensive care unit (ICU). This was a cross-sectional study, performed with 26 patients in an ICU of a hospital in the Zona da Mata in Minas Gerais. Patients with uncontrolled blood glucose levels were evaluated in two moments: on the day of admission (T0) and one day after the uncontrolled glycaemia (DG1). The evaluation of the oxidative profile was determined by the dosage of serum total antioxidant capacity, based on the ability of ferric reduction, determination of enzymatic activity of Superoxide Dismutase, Catalase and Glutathione S-Transferase, lipid peroxidation products and carbonylated proteins. The levels of ferric reducing ability decreased significantly, whereas the activity of the Superoxide Dismutase enzyme increased significantly after uncontrolled glycaemia in relation to the initial time. Although the lipid peroxidation did not change between the times evaluated, the damage marker significantly reduced, shown by carbonylation of proteins after the uncontrolled glycaemia. The critical patients evaluated in this study present altered oxidative profile after the uncontrolled glycaemia, a common problem that imposes the worst prognoses.

Keywords: Critical Care; Oxidative Stress; Blood Glucose; Hyperglycemia; Hypoglycemia; Risk Factors

1 INTRODUCTION

The increased life expectancy in the last century reflected in the quality of life and the comorbidities presented by the population, aggravating and making

acute certain diseases. In this way, there has been a great demand for care with critically ill individuals. The Intensive Care Unit (ICU) aiming to treat severely ill patients who require complex care and close monitoring. This support is possible through high technological density, allowing professionals to control risks and enhanced support for decision-making, based on the clinical need of each patient (RODRIGUEZ; BUB; PERÃO; ZANDONADI; RODRIGUEZ, 2016).

One of the common complications in critically ill patients is the hyperglycemia, even in the absence of preexisting Diabetes Mellitus (VIANA; MORAES; FABBRIN; SANTOS; GERCHMAN, 2014). The constant variation of glycaemia entails various damage to these patients and increased susceptibility to infections, favoring sepsis, hydroelectrolytic disorders, thrombolytic conditions and intensified inflammatory response. The glycemic control and the risk factors associated with uncontrolled glycaemia (UG) (hypoglycemia and hyperglycemia) in intensive care are a challenge for health professionals, and have been subject of studies, because the maintenance of acceptable glycemic values in these patients is essential (BRINATI; TOLEDO; JANUÁRIO; DOMINGOS; CARDOSO; SALGADO, 2017; BRINATI, 2018). Some risk factors favor the GR in critical patients: diabetes, acute coronary syndrome, age, corticosteroids, carbohydrate enteral nutrition, vasoactive drugs, mechanical ventilation, duration of hospitalization, sepsis, APACHE II score and glycemic variability (BRINATI; TOLEDO; JANUÁRIO; DOMINGOS; CARDOSO; SALGADO, 2017).

The glycemic control in intensive care is important for the patient's prognosis, but, due to the strict glycemic control, events of severe hypoglycemia occur with greater frequency, due to treatment with insulin therapy of correction, negatively affecting prognosis and leading to uncontrolled glycaemia (SOCIEDADE BRASILEIRA DE DIABETES, 2011).

Hyperglycemia leads to an increased production of reactive species of oxygen (RSO) within the endothelial cells of large vessels (GOMES; FOSS; FROSS-FREIAS, 2014), suggesting that oxidative stress has an important role in this process.

The RSO are formed by aerobic metabolism, by means of phosphorylation that happens in the mitochondria, which may be facilitated by iron and copper. In this process, oxygen is transformed into water, consuming more than 95% of the total metabolic oxygen, and the remainder is not completely reduced, generating reactive oxygen species. Thus, the mitochondria, through electron transport chain is the main producing source of free radicals (TELES; MONTEIRO; OLIVEIRA; RIBEIRO-FILHO, 2015).

The main substances included in the RSO are free radicals, superoxide anion, hydroxyl and hydrogen peroxide (SOUZA, 2019). They have unpaired electrons, factor that causes high reactivity to these molecules, favoring the interaction with the body cells and causing oxidative damage that can result in cell death. This disorder in the organism is known as oxidative stress (TELES; MONTEIRO; OLIVEIRA; RIBEIRO-FILHO, 2015).

Oxidative stress is characterized by an imbalance between the formation of RSO and endogenous antioxidant ability. This oxidative modification predisposes to occurrence of insulin resistance, hypertension and metabolic syndrome. Free radicals can react with the body molecules, being the main the deoxyribonucleic acid (DNA) and lipid peroxidation and proteins, resulting in intracellular oxidative effects and causing cell death (MURE; YOSHIMURA; HASHIMOTO; MURAKI; OKA; TANAKA; *et al.*, 2015; FRANCISQUETI; CHIAVERINI; SANTOS; MINATEL; RONCHI; FERRON *et al.*, 2019).

In the production of free radicals, the RSO exceed the capacity of action of antioxidants, favoring the oxidation of biomolecules, releasing specific metabolites, used as oxidative stress markers that can be identified and quantified. Such markers derive from the oxidation of lipids, proteins and DNA, being the first and with greatest expression; another indirect way to evaluate the oxidative stress is through antioxidant capacity. The oxidative stress triggers implications on the development of the metabolic syndrome, thus, oxidative stress markers are an

important tool in the assessment of the effects of this process in the worsening and generation of diseases (BARBOSA; COSTA; ALFENAS; PAULA; MINIM; BRESSAN, 2010).

Therefore the glycemic control in acceptable values assists in good prognosis of critically ill patients, and the deregulation of this factor triggers oxidative stress that entails implications that culminate in the metabolic syndrome. Oxidative stress markers are extremely important to prove and study this process, in order to assess the effects of therapies that cause this process and its implications for the prognosis of critically ill patients (PINTO; OLIVEIRA, 2017; BARBOSA; COSTA; ALFENAS; PAULA; MINIM; BRESSAN, 2010).

Knowing that the variation of glucose levels can intensify inflammatory conditions and that the RSO can be generated in inflammatory processes, one questions whether critical patients with GR also have oxidative stress.

Thus, this study is justified in the fact that the oxidative stress generated in the body by glycemic disorder provokes intense inflammatory condition and may be an important cause of the worsening of these patients, compromising the safety and efficacy of the treatment.

Anchored in the aforementioned facts, the objective of this study is to evaluate and correlate if there is an association between the glycemic variation in patients hospitalized in an Intensive Care Unit and the oxidative profile generated in the body by this glycemic disorder.

2 METHOD

This is a cross-sectional study, conducted at an ICU for adult patients of a hospital located in the countryside of Minas Gerais. This ICU is composed of six beds, attends approximately 280 patients annually and is destined for hospitalization of critical patients, who require ongoing professional specialized care.

This study is part of a Masters study developed at the Federal University of Viçosa, titled: Risk factors associated with unstable blood glucose in critical patients. The study included adult individuals (≥ 18 years) with more than 24 hours of hospitalization in an adult ICU, who presented GR (< 70 mg/dl or > 180 mg/dl) during hospitalization. Individuals with GR at admission were excluded, since the factors that caused the problem could not be precisely identified, and the relationship between uncontrolled glycaemia in the ICU and oxidative stress could not be evaluated.

Twenty-eight patients met the inclusion and exclusion criteria; however, two samples presented insufficient volume for the laboratory tests and were excluded from the study, thus, the study sample comprised 26 patients.

This study is part of a cohort study in which patients were monitored during the period from March to July 2017. The patients included in the study were daily monitored, from admission until discharge/death/transfer. In the morning, 4 ml of blood were collected, which were conditioned in a Styrofoam box, protected from light and sent to the Biochemistry Laboratory of the Department of Medicine and Nursing of the UFV, where the analysis of the material was performed to identify the patients with uncontrolled glycaemia.

Subsequently, there was the serum evaluation of oxidative stress markers in the Immunology Laboratory of the Department of Cell Biology at UFV. The evaluation of the oxidative profile was performed with serum samples collected at two different times: on the day of admission (T0) and one day after the uncontrolled glycaemia (DG1).

The quantification of serum total antioxidant capacity was based on the method of ferric reducing ability of plasma (FRAP) (BENZIE; STRAIN, 1996). For this purpose, 10 µl of sample/standard were added to 220 µl of FRAP solution in polystyrene microplates, which were incubated in the dark for 30 minutes. As oxidizing agent, a Trolox solution was used, starting with a concentration of 2

mmol.l-1. The readings were performed in a Multiskan GO Microplate Spectrophotometer (Thermo Scientific) at wavelength of 570 nm. The relative concentrations were obtained from the standard curve and the results were expressed in µM.

The determination of the catalytic activity of SOD was performed through the pyrogallol method, based on the ability of the enzyme to catalyze the reaction of superoxide (O-2) and hydrogen peroxide (SARBAN; KOCYIGIT; YAZAR; ISIKAN, 2005). For this reason, 30 µl of sample were added to 99 µl of 0.1M phosphate buffer (pH 7.0), 6 µl of MTT (1.25 mm) and 15 µl of pyrogallol (100 µM) in 96-well plate and incubated for 5 minutes at 37ºC. The standard and the white paper were done in the same way, but, for both, without sample and using 129 µl and 144 µl of buffer, respectively. In the white paper, no pyrogallol was added. After incubation, the reaction was established with 150 µl of DMSO (1.25 mm) and the samples were submitted to reading at 570 nm in the plate reader (Thermo Scientific Multiskan™ GO). The enzymatic activity was expressed in SOD units per mg of protein.

The Catalase enzyme activity was evaluated by measuring the kinetics of decomposition of H2O2 (AEBI,1984). For this reason, 6 µl of sample, along with 600 µl of phosphate buffer (0.1 M and pH 7.0), were used as white paper for each sample, while for reading, the Phosphate buffer received H_2O_2 (30%). Thus, in a quartz cuvette, the samples were subjected to reading at 240 nm on a spectrophotometer, during 60 seconds, to monitor enzyme kinetics. The enzymatic activity was expressed in units of Catalase per mg of protein.

In the determination of enzymatic activity of Glutathione S-transferases in the serum of volunteers, the quantification of the product formed from the complexation of reduced glutathione (GSH) with 1-chloro-2,4-dinitrobenzene (CDNB) was carried out (HABIG; PABST; JAKOBY, 1974) and was calculated by the rate of oxidation of NADPH. Thus, in a quartz cuvette, 682 µl of phosphate buffer (0.1 M and pH 7.0) were pipetted together with 6 µl of CDNB (0.1 M), 6 µl of sample and 6 µl of GSH solution (0.1 M) and the reaction rate of the enzyme present in the

samples was monitored at 340 nm on a spectrophotometer, during 90 seconds, to monitor enzyme kinetics. A white paper was also performed for the experiment, which does not have the addition of sample and was used to check the rate of non-enzymatic reactions. The enzymatic activity was expressed as μmol min-1 g -1, where a unit of activity represents the quantity of enzyme that catalyzes the formation of 1 μmol of product per minute per gram of sample, under the test conditions.

To quantify the products of lipid peroxidation (lipid peroxides and aldehydes, malondialdehyde and other low-molecular weighted aldehydes), serum samples were submitted to the reaction with the thiobarbituric acid reactive substances (TBARS) (BUEGE; AUST, 1978). In this way, 200 μl of each sample were added to 400 μl of solution of TBARS (15% TCA, 0.375% TBA and 0.25M HCl), agitated on a vortex mixer for 10 seconds and placed in a water bath at 90ºC during 40 minutes. Then, after cooling, the thiobarbituric acid reactive substances were extracted, with the addition of 600 μl of n-butanol, followed by centrifugation at 3500 rpm for 5 minutes. Finally, after centrifugation, 200 μl of supernatant were carefully removed and submitted to reading at 535 nm. The values of TBARS were expressed in ηmols of malondialdehyde (MDA) per mg of protein.

The dosage of carbonylated proteins in serum was determined according to the methodology of Levine and colleagues (LEVINE; GARLAND; OLIVER; AMICI; CLIMENT; LENZ; *et al*, 1990). In this way, the precipitate obtained by centrifugation was re-suspended with 1 ml of phosphate buffer (0.1 M, pH 7.0) and this divided into two eppendorfs (samples and white papers), with 500 μl in each. Then, both were precipitated with 500 μl of TCA 10% solution and centrifuged at 5000 g for 10 minutes at 4ºC and the supernatant discarded. Subsequently, only the samples were incubated at ambient temperature for 30 minutes, with 500 μl of solution containing 2.4-dinitrofenilhidrazina 10mM 18 and 2M HCl Soon after, the samples and the white papers were again precipitated with TCA 10 % and centrifuged for 10

minutes at 5000 g. The precipitated were then washed twice with ethanol solution: ethyl acetate (1:1), and centrifuged at 10000 g for 10 minutes at 4ºC and the supernatant discarded. Finally, the precipitate obtained were re-suspended in 1 ml of 6% SDS solution, again centrifuged at 10000 g for 10 minutes at 4ºC and 200 µl of supernatant were carefully removed and submitted to reading at 370 nm in the plate reader (Thermo Scientific-Multiskan™ GO). The content of carbonylated proteins was expressed in ηmol of carbonylated proteins per ml of sample.

The data collected were scanned on Epi Info, version 7.2.1 and, after checking their consistency, the sociodemographic and clinical data were analyzed, using descriptive statistics, through the calculation of absolute and relative frequency.

The analyzed variables had a normal distribution on the Shapiro-Wilk test, thus, the parametric T test was performed. The results were expressed as mean ± standard deviation, with statistical significance when $p<0.05$. The statistical analysis was performed using the software GraphPad Prism 7.0.

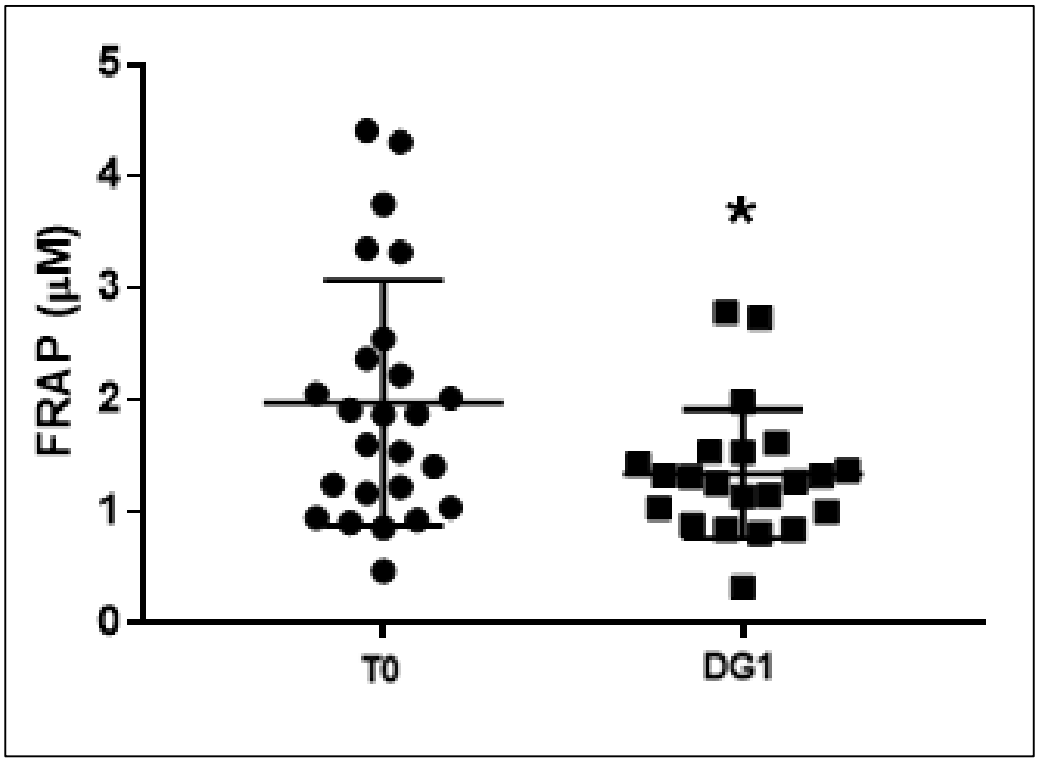
The study was submitted to the Human Research Ethics Committee of the UFV and obtained approval under number 1.913.394. All patients or companions previously signed the Informed Consent Form (ICF), after clarifying all their doubts.

3 RESULTS

The present study evaluated the oxidative profile of 26 adult patients who remained more than 24 hours in an ICU. Most patients were male (14-53.84%), and, of these, only 40% were over 60 years (6-40%), with a mean age of 56.14 years. Among the female patients (12-46.15%), the majority (9-60%) was over 60 years, with a mean age of 66 years. The outcome predominant among the male patients was discharge (9-64.28%); among the female patients, was death (6-50%).

The serum oxidative profile of patients in TO and DG1 was evaluated initially by determining the total antioxidant capacity (Figure 1).

Figure 1 - Total serum antioxidant capacity by iron reduction (FRAP), in patients with uncontrolled glycemia during hospitalization. T0: day of patient admission and DG1: one day after glycemic control

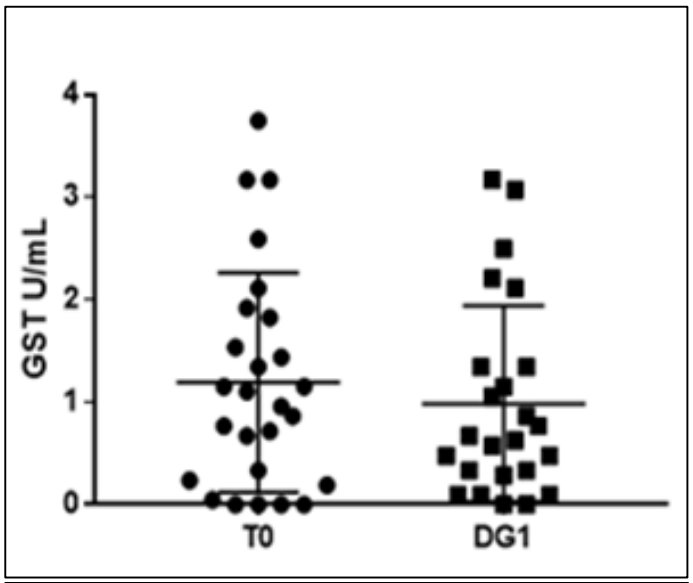


Source: Authors (2020)
In were: * p≤0.05 t- student test

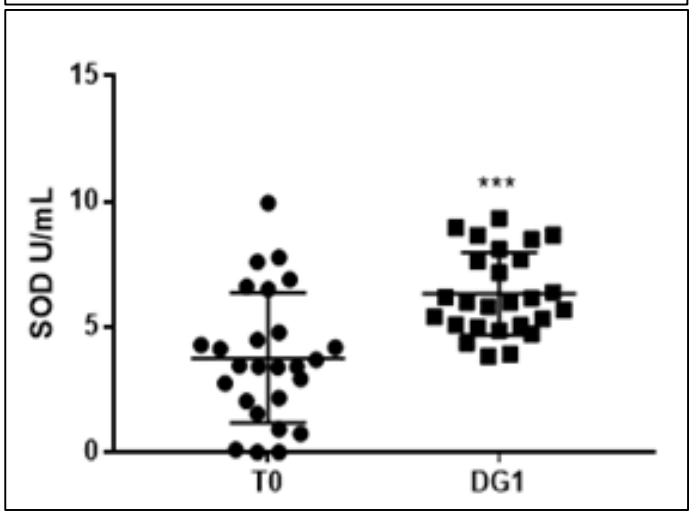
After the UG, the average total antioxidant capacity is significantly lower than the capacity at the initial time of evaluation. In the paired analysis, there was a FRAP-reducing biological trend after the uncontrolled glycemia with $p < 0.0980$.

For evaluation of the antioxidant enzyme activity in serum, the SOD, CAT and GST enzymes were evaluated. There was no difference in the level of enzymatic activity of GST at T0 in comparison to DG1 (Figure 2a). Nevertheless, there was a significant increase in the activity of SOD after the uncontrolled glycaemia in relation to the initial time of analysis (Figure 2b). The activity of CAT in the serum presented undetectable levels at both times evaluated.

Figure 2 - Detection of serum antioxidant enzymatic activity of GST (Figure 2a) and SOD (Figure 2b) in the serum of patients with glycemia during ICU stay. T0: day of patient admission and DG1: one day after glycemic control



(a)

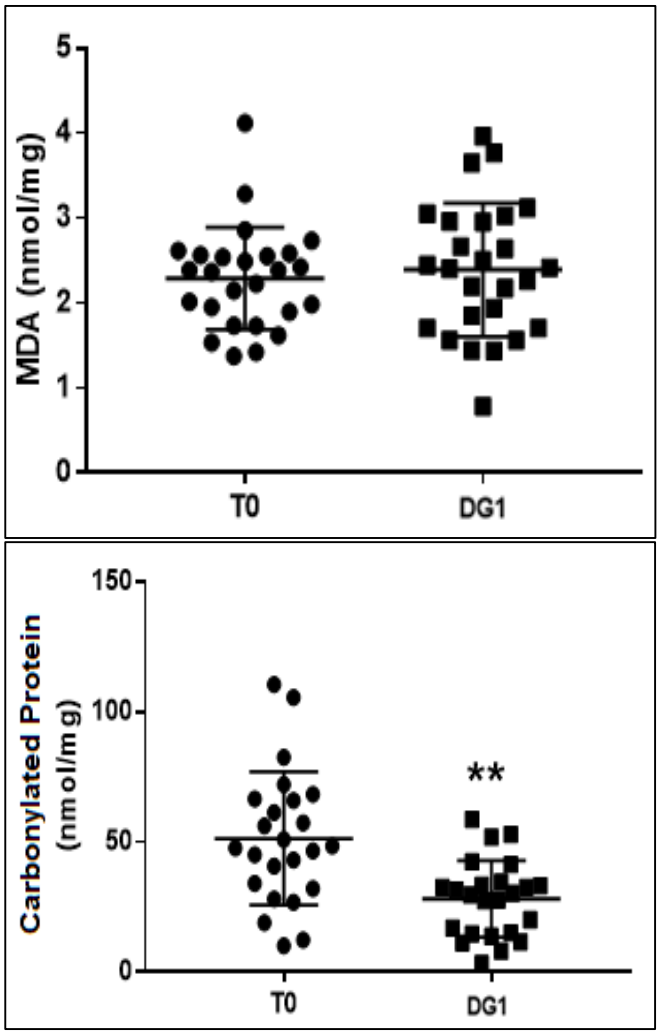


(b)

Source: Authors (2020)
In were: *** p≤0.005 t- student test

The markers related to the oxidative damage, lipid peroxidation (MDA) and carbonylation of proteins were subsequently evaluated. Although there was no difference in lipid peroxidation (MDA) between the two times assessed (Figure 3a), there was a significant reduction of the protein oxidation marker after uncontrolled glycaemia in comparison to the initial time of analysis (Figure 3b).

Figure 3 - Detection of oxidative damage markers MDA (Figure 3a) and carbonylated protein (Figure 3b) in the serum of patients with uncontrolled glycemia during ICU stay. T0: day of patient admission and DG1: one day after glycemic control



(a)

(b)

Source: Authors (2020)
In were: ** p≤0.01 t- student test

4 DISCUSSION

In relation to the characterization of the studied population aged between 18 and 89 years, most patients are males 14 (53.84%) (RODRIGUEZ; BUB; PERÃO; ZANDONADI, 2016). Among the 12 female patients (46.15%), the majority was over 60 years old (60%), the feminization of old age is a reality, women aged over 60 years are 56% of the population (LINS; ANDRADE, 2018).

The glycemic control is essential to favorable outcomes in critically ill patients. Maintaining normoglycemia requires continuous and multiprofessional efforts. Factors present in routines related to care with critical patients are risk for the patient develop uncontrolled glycaemia, such as: age, corticosteroids, parenteral carbohydrate, vasoactive drugs, hospitalization time, hindering the prognosis of critically ill patients (BRINATI; TOLEDO; JANUÁRIO; DOMINGOS; CARDOSO; SALGADO, 2017). Oxidative stress is defined as an increased formation and decreased removal of reactive oxygen species, i.e., reduced antioxidant capacity. The oxidative stress impairs the ability of the muscle to acquire glucose and decreases the secretion of insulin in pancreatic B cells (KIRAN; LAKSHMI; SRIKUMAR; REDDY, 2016).

The main advantage of the evaluation of serum total antioxidant capacity (FRAP) is the determination of antioxidant profile of a biological sample and not just isolated antioxidant compounds. Representing the sum of endogenous and exogenous non-enzymatic antioxidants that provide important protection against ROS. In the present study, there was a significant decrease in the mean total antioxidant capacity after UG in relation to the initial time. Demonstrating that this non-enzymatic marker was spent in the oxidative process, similar to another study on the evaluation of the oxidative stress in patients with metabolic syndrome and Diabetes Mellitus (KIRAN; LAKSHMI; SRIKUMAR; REDDY, 2016).

Among the enzymatic antioxidants evaluated, the Glutathione-S-Transferase enzyme importantly related to reduced toxicity of endogenous and exogenous agents showed no statistically significant difference between the initial time and UG (TSAI; HSIEH; TUNG; KUO; SHEN, 2012). Nonetheless, the SOD enzyme, which presents relevant participation in the control of oxidative stress by acting on the conversion of superoxide into hydrogen peroxide, was significantly increased after the UG in comparison to the initial time, in both the paired and non-paired analyses. The superoxide dismutase and the hydrogen peroxide promote a peroxidase reaction, with the objective of preventing its activity, controlling the enzyme activity

(MACHADO; CAMPOS; VINGERT; KIULKOSKI; PERASSOLO, 2016). The CAT enzyme was not detected in both times evaluated, which can be explained by the critical state of patients in intensive care. However, an increased SOD after UG along with FRAP consumption suggest that the uncontrolled glycaemia induces an oxidative condition, which can result in cell damage.

Among the stress-related oxidative damage markers, the carbonylated protein and lipid peroxidation are evaluated. The lipidic peroxidation is assessed by quantifying MDA. There was no significant difference in the quantification of serum MDA at the two times assessed. However, the detection of carbonylated proteins obtained by the method of quantification of carbonil radicals resulting from the ROS action in body proteins, there was a significant reduction after the UG in paired and non-paired analyses (KIRAN; LAKSHMI; SRIKUMAR; REDDY, 2016).

The results of this study demonstrate that critical patients present altered oxidative profile after the uncontrolled glycaemia, which is a common problem that imposes the worst prognoses. After the UG, there was the consumption of FRAP and increased serum SOD. Interestingly, after the UG, these patients showed a reduced carbonylation of proteins. Demonstrating that the oxidative process induced by UG resulted in consumption/activation of the antioxidant system, which was efficient in preventing oxidative damage.

This study presents limitations, such as the occasional periods of analysis of blood samples, being T0 and DG1. After the DG1, one questions whether these markers of oxidative profile were maintained and the possibility of cell damage after the hospital stay.

5 CONCLUSION

The present study evaluated, through laboratory tests, the correlation between the uncontrolled glycaemia and oxidative stress in critical patients assisted in an intensive care unit.

Most patients with UG were males with mean age of 56.14 years. Among the oxidative profile markers analyzed, after the UG, the FRAP reduced and the enzymatic activity of SOD increased. These two findings suggest, jointly, that the uncontrolled glycaemia changed the oxidative profile, leading to the consumption of FRAP and induction of expression of the SOD antioxidant enzyme. The oxidative damage marker, carbonylated proteins, was smaller after the uncontrolled glycaemia, demonstrating that the consumption of FRAP and activation of SOD were effective in the prevention of cell damage.

The analyzed data show that there is a correlation between the uncontrolled glycaemia and the oxidative profile, a fact that compromises the prognosis of patients hospitalized in the ICU and affects the effectiveness of health care. Therefore, it is important to identify the risk factors associated with the uncontrolled glycaemia by adopting preventive measures, in order to prevent oxidative stress in critically ill patients.

There is need for new studies on the theme in the ICU, since the glycemic control is a complex process that can affect the clinical evolution of critically ill patients.

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Authorship contributions

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