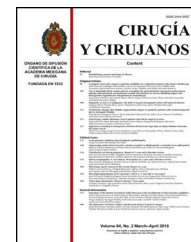




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GENERAL INFORMATION

Metabolic control in the critically ill patient an update: Hyperglycemia, glucose variability hypoglycemia and relative hypoglycemia[☆]



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KEYWORDS

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Abstract

Background: Metabolic changes of glucose in critically ill patients increase morbidity and mortality. The appropriate level of blood glucose has not been established so far and should be adjusted for different populations. However concepts such as glucose variability and relative hypoglycemia of critically ill patients are concepts that are changing management methods and achieving closer monitoring.

Objectives: The purpose of this review is to present new data about the management and metabolic control of patients in critical areas.

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PALABRAS CLAVE

Hiperglucemia;
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Control de la
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Conclusions: Currently glucose can no longer be regarded as an innocent element in critical patients; both hyperglycemia and hypoglycemia increase morbidity and mortality of patients. Protocols and better instruments for continuous measurement are necessary to achieve the metabolic control of our patients.

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Actualidades en el control metabólico del paciente crítico: hiperglucemia, variabilidad de la glucosa, hipoglucemia e hipoglucemia relativa

Resumen

Antecedentes: Las alteraciones metabólicas de la glucosa en pacientes críticamente enfermos pueden aumentar la morbimortalidad. El nivel adecuado de glucosa en sangre no se ha establecido hasta el momento y debe ajustarse para diferentes poblaciones. Sin embargo conceptos como la variabilidad de la glucosa e hipoglucemia relativa del paciente crítico son conceptos que están cambiando el manejo y logrando métodos de monitorización más estrechos.

Objetivo: El propósito de esta revisión es dar a conocer las actualidades en el manejo y control metabólico de pacientes en áreas críticas.

Conclusiones: En la actualidad la glucosa ya no puede considerarse como un elemento inocente para el paciente crítico; tanto la hiperglucemia como la hipoglucemia incrementan la morbimortalidad de los pacientes. Protocolos de actuación y mejores instrumentos de medición continua son necesarios para lograr el control metabólico de nuestros pacientes.

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Background

Hyperglycemia is common in critically ill patients, even in those who have not been diagnosed as having diabetes. There is evidence that developing hyperglycemia during an illness or acute surgery increases morbimortality, the number of days spent in the intensive care unit (ICU) and in hospital, as well as the number of days with mechanically assisted respiration.¹

Alterations in glucose metabolism arise during critical illnesses due to a range of factors, including increased insulin resistance, changes in the production of the said hormone and the activation of cytokines. A hypermetabolic state occurs in patients in a critical condition due to their disease, with intense activation of contraregulating hormones and cytokines, such as tumour necrosis factor alpha (TNF- α), interleukin 1 (IL-1) and interleukin 6 (IL-6), which are important insulin resistance mediators, thereby causing hyperglycemia. The great majority of the patients in an ICU will have stress-induced hyperglycemia, in the form of transitory hyperglycemia during the disease which is generally restricted to patients with no previous sign of diabetes.²⁻⁴

When they are admitted to hospital, patients without diabetes are at greater risk of mortality than those patients with a previous diagnosis of diabetes.¹

Hypoglycemia is significantly greater in patients with strict control of glucose by intensive intravenous insulin

therapy. The current recommendation is for strict glycemia control to focus on hyperglycemia secondary to critical disease, while at the same time avoiding hypoglycemia, so that management protocols have now been set in the majority of ICUs.⁵

The purpose of this review is to publish the latest developments in patient metabolic control and management in critical areas.

Methods

The aim of this review is to publish the latest developments in patient metabolic control and management in critical areas. PubMed was searched using the terms MeSH glycemia, metabolic control and critical, with 5-year filters in humans and including systematic reviews, reviews and clinical studies. 884 results were found, of which 59 fulfilled the search criteria and were included in this review.

Epidemiology

It is difficult to estimate the prevalence of hyperglycemia in critically ill patients as the diagnosis is variable. Approximately 75% of all patients, including diabetic ones, have blood concentrations of glucose higher than 110 mg/dl at the moment of admission to the ICU, while 12% of all patients have blood concentrations of glucose higher than

200 mg/dl.⁶ Another study showed that more than 60% of patients admitted to an ICU have blood concentrations of glucose higher than 110 mg/dl, 38% of patients have a glucose level above 150 mg/dl and 23% of patients have figures higher than 200 mg/dl.⁷

Pathology

Critical disease induced hyperglycemia was thought for a long time to be beneficial for patients, as an adaptive response to supply additional energy to the organs that predominantly depend on glucose as a metabolic substrate (the brain and blood cells).⁸ The factors that contribute to hyperglycemia in critically ill patients include the secretion of stress hormones such as glucagon, the adrenergic response, cortisol and an increase in gluconeogenesis, glycogenolysis and the use of medicines (exogenous glucocorticoids, vasopressors, lithium and beta blockers), the secretion of cytokines, over feeding, parenteral feeding, intravenous infusion of dextrose, dialysis solutions and antibiotics, which also contribute to it. Insulin insufficiency or depletion in volume may cause hyperglycemia.⁹ Bed rest, even in the absence of evident disease, leads to an alteration in glucose uptake by the skeletal muscles and stimulates insulin resistance. Gluconeogenesis is triggered to a greater degree by glucagon than it is by epinephrine and cortisol. TNF- α may prompt gluconeogenesis by stimulating glucagon production. Glycogenolysis is chiefly stimulated by the catecholamines and is perpetuated under the influence of adrenalin and cortisol.¹

The adverse effects of hyperglycemia

Hyperglycemia may lead to complications and poor progress. High concentrations of glucose in the blood are associated with an increase in the morbimortality of patients after burns, surgery, cerebrovascular accidents, acute coronary syndromes and head injuries. Hyperglycemia may cause neutrophil dysfunction, a reduction in intracellular bactericide activity and opsonisation, which plays a role in the increase in the incidence of infections. High glucose concentrations in the cells leads to mitochondrial dysfunction, activating inflammatory routes and modifying the innate immune system. It is associated with endothelial and microcirculatory damage due to the reduction in vascular reactivity and endothelial production of nitric oxide.^{1,10} Acute hyperglycemia also facilitates protein lysis, increasing the risk of cardiac and haemodynamic complications, as well as acute kidney failure and death.¹¹

Insulin therapy protocols

The efficacy of using a validated protocol to aid the maintenance of a suitable level of blood glucose has been proven by clinical studies of critically ill patients. The protocol must be developed by a multidisciplinary team that includes doctors, nurses, pharmacists and dieticians, supplying the guidelines for obtaining a specific level of glucose, adjusting the dose of insulin and detaining or reducing the speed of infusion

according to the glucose levels in serum of each patient together with their diet. The risks of complications such as hypoglycemia must also be covered.¹

Intravenous insulin therapy is suggested. The initial blood glucose level is checked every one or two hours until the speed of infusion has been set, after which it is checked every four hours once the blood glucose concentration has been stabilised. The advantages of using an algorithm or protocol include improved control of glucose, reduced treatment error, the capacity to keep control of glycemia close to the target or normal range and avoiding hypoglycemia.¹²

It is often necessary to convert intravenous insulin infusion into subcutaneous therapy, either before or at the moment of discharge from the ICU.¹³

Scientific evidence

The SPRINT study showed that strict control of glycemia to an average level of 108 mg/dl reduced organ failure in comparison with patients who were controlled conventionally at levels higher than 130 mg/dl.¹⁴

In the Leuven I study Van den Berghe demonstrated that patients with strict control of glycemia and a target level of blood glucose of from 80 to 110 mg/dl had a better result than critically ill surgical patients who were controlled conventionally. This showed a fall in surgical ICU mortality from 8% to 4.6%, a 34% fall in the risk of multiple organ failure, with 40% less infection and sepsis, a 41% fall in the incidence of acute kidney failure, a 44% fall in critical patient polyneuropathy, a 50% fall in the need for haemoderivative transfusions and a 50% fall in the need for prolonged mechanical ventilation. Based on the Leuven I study strict control of glycemia was adopted as the standard for critical patient care around the world.⁶

In the Leuven II study in a medical ICU the same author did not show any benefit in the survival of all critically ill patients with strict control of glycemia; nevertheless, the best results were found in the fall in the number of days patients spent with mechanical ventilation, as well as with fewer days of hospitalisation.⁵ The impact of strict glycemia control was not as significant as it was in the Leuven I study, and it was concluded that the large difference between the results in the medical ICU and surgical ones is due to the fact that a high percentage of patients in a medical ICU had organ damage on admission, so that this could not be prevented by any intervention.

Krinsley showed that patients whose blood concentrations of glucose were controlled at <140 mg/dl had higher survival rates than those whose blood concentrations of glucose were controlled at <200 mg/dl in medical-surgical ICUs.¹⁵

The efficacy study of volume substitution and insulin therapy in severe sepsis (VISEP), ($n = 537$), was a multicentre study designed to evaluate the efficacy of resuscitation with fluids (pentastarch 10% vs. Modified ringer lactate) and the control of glucose in serum (intensive management with insulin vs conventional management) in patients with severe sepsis and septic shock. Two glucose target levels were compared, in the intervention group (80–110 mg/dl) and the control group (180–200 mg/dl). The administration

of insulin and measurement of glucose in serum were standardised in the 18 participating centres. The study was halted early after 488 patients had been included because the incidence of hypoglycemia (12.1%) in the intensively managed group was considered to be unacceptably high.¹⁶

The GLUCONTROL study was multicentre and larger than the VISEP study ($n=1101$), with the participation of 21 medical-surgical ICUs. This study investigated whether strict control of glycemia (80–110 mg/dl) improved survival in a mixed population of critical patients in comparison with a moderate control target (140–180 mg/dl). This study did not standardise measurements of glucose in serum and the use of glucometers was permitted. This study was halted early as the target levels of glucose were not reached and the incidence of hypoglycemia was 9.8%. Hospital mortality did not differ between the intensively managed group (19.5%) and the control group (16.2%).¹⁷

Two studies undertaken in medical-surgical ICUs and which were smaller than the Leuven studies showed that there were no significant benefits in mortality.^{18,19}

The common denominator in the above-mentioned studies is that they were not statistically significant in the detection of a reasonable difference in mortality.

The multicentre NICE-SUGAR study included 6100 patients and compared strict control of glucose levels at below 108 mg/dl with an intermediate target level of 140–180 mg/dl. It reported a significantly higher rate of mortality (24.9% vs 27.5%) in the strict glucose control group. These deaths were attributed to cardiovascular causes and organ failures documented by the SOFA score, with no significant difference between the two groups studied. Additionally, the NICE-SUGAR study did not demonstrate a fall in the number of days with invasive ventilation or days of hospitalisation. Nor did it show a lower rate of kidney failure, replacement therapy, positive haemocultures or haemoderivative transfusions, although significantly higher rates of severe hypoglycemia were found.²⁰ In comparison with the Leuven^{5,6} studies, in which levels of glycemia up to 215 mg/dl were permitted in the control group, the intermediate target level of 140–180 mg/dl led to an improvement in control group mortality. This suggests that one benefit of the moderate control of glycemia, as shown in the control group with an intermediate level of glucose (110–150 mg/dl) was much better than a target glucose level above 150 mg/dl. Another of the aspects that influence the lack of benefit in terms of mortality in this study was the level of therapeutic determination as measured by the degree of success in achieving and maintaining target levels of glycemia in the intervention group; in the Leuven studies 70% of the strict control group patients reached the target glucose levels, while in the NICE-SUGAR study less than 50% reached this target. This is important, as a recent meta-analysis suggested that studies in which the target level of glucose were reached showed a fall in mortality, while in those studies in which this target was not reached no benefit was found and there was even an increase in mortality.^{21,22}

In a meta-analysis with a total of 8432 patients Wiener showed that hospital mortality did not differ between patients with strict control of glucose levels and those patients treated as usual.²³

Umpierrez reported that hyperglycemia diagnosed at the moment of patient admission is associated with a 16% rate of mortality, in comparison with a mortality rate of 3% in patients known to be diabetic, and a rate of 1.7% in patients without hyperglycemia.²⁴ The conclusion was that hyperglycemia during admission to the ICU had a more significant impact on the risk of mortality among non-diabetic patients than it did on diabetic patients.²⁵

Glycemia variability

Glycemia levels in critically ill patients fluctuate widely, even when continuous feeding and insulin infusions are used.²⁶

Glucose level variability is an independent mortality risk factor in the ICU^{27,28} and in septic hospitalised patients.²⁹

This variability is generally expressed as standard deviation (SD) from the mean glucose level or as the average amplitude of glycemic fluctuations.³⁰

Patients who do not survive a critical illness showed a higher SD and glucose variation coefficient (SD/average glucose level) during their time in the ICU. A level of glucose in the blood with a SD > 20 mg/dl is associated with a 9.6 times increase in mortality in comparison with a blood glucose SD < 20 mg/dl.³¹

In a retrospective study of 7049 critical patients, Egi reports that survivors experienced less variability in their glucose levels vs non-survivors. Additionally, in diabetic patients variability in glucose levels was a better predictor of mortality in the ICU than the absolute level of glucose in serum.²⁸

The authors of other retrospective studies also reported the importance of variability in glucose levels. When they classified patients according to their glucose control pattern, they identified a group which they described as the "high variability group". This group was found to be associated with higher rates of infection, longer stays in the ICU and hospitalisation, as well as with an increase in mortality compared with other glucose control patterns (low variability).³²

Krinsley found that the mortality rate among non-diabetic patients with an average glucose level of 70–99 mg/dl during their stay in the ICU was 10.2% for patients with a glucose variation coefficient (VC) <15% vs 58.3% for patients with a VC above 50%.³³

The idea that glycemia variability must affect mortality is biologically credible. Two patients are considered, both with an average glucose level of 130 mg/dl during their stay in the ICU. One individual had levels of 70 mg/dl, 80 mg/dl, 130 mg/dl, 180 mg/dl and 190 mg/dl (SD 55.2). The second individual had the following levels: 120 mg/dl, 125 mg/dl, 130 mg/dl, 135 mg/dl and 140 mg/dl (SD 7.9). The first patient was exposed to potentially harmful glucose levels, and several studies have shown that these have damaging effects on mitochondrial, endothelial, neuronal and immune system functioning.^{10,34}

Risso exposed human umbilical vein cells to sustained conditions of hyperglycemia or alternating conditions of euglycemia with hyperglycemia. He found higher rates of apoptosis in the cells exposed to the latter condition.³⁵

Qualiario used the same methodology to measure kinase C-beta protein, an oxidative stress marker associated with the microvascular lesion linked to hyperglycemia. Levels of kinase C-beta protein were significantly higher when glycemia levels fluctuated than they were with sustained hyperglycemia.³⁶

In a similar way, Monnier found that oxidative stress as measured by the excretion of 8-iso prostaglandin F2 alpha in the urine after 24h was high in patients with type 2 diabetes mellitus with greater fluctuations in glucose control than it was in a cohort subjected to sustained hyperglycemia.³⁷

These findings have important clinical implications. They suggest that specialists who implement glycemia management protocols in intensive care should pay as much attention to glucose variability as they do to the set target levels. Although there is no full agreement on glycemia target levels, it is clear that there is an important relationship between variability and mortality, so that implementing the measures necessary to prevent this variability would have a profound impact not only on mortality, but also on the length of time patients remain in the ICU.

Hypoglycemia

Severe or prolonged hypoglycemia causes arrhythmia, convulsions, coma and irreversible brain damage. While the most severe complications are easy to identify, more subtle neuroglycopenic manifestations such as cephalgia, fatigue, confusion and dysarthria, etc., may be hard or practically impossible to identify in a critical patient.³⁸

In the Leuven I⁶ study, two of the episodes of hypoglycemia recorded were accompanied by diaphoresis and agitation. In the Leuven II⁵ study the patients showed no symptoms during episodes of hypoglycemia.

In a cohort of 154 patients who experienced an episode of hypoglycemia, Vriesendorp reported one case of refractory convulsive crisis and two cases of coma in which the cause seemed to be hypoglycemia, although this causality was not fully established. It therefore seems that the majority of severe hypoglycemia episodes observed during the infusion of insulin in an ICU were solely "biochemical" hypoglycemia, i.e., without any clinical symptoms; nevertheless, it is possible that neurological signs may be masked by other situations (sedation, encephalopathy or another type of neurological deterioration not linked to hypoglycemia).³⁹

Different levels have been used to define an event of hypoglycemia, and they vary from <40 to <82 mg/dL.^{40,41}

In a study which recorded the lowest level of glucose detected in during the first 24h of stay in the ICU, the incidence of hypoglycemia varied from 13.8% with a cut-off point below 82 mg/dL to less than 1.5% with a threshold below 44 mg/dL.⁴²

"Severe hypoglycemia" is usually defined as a level of glucose in serum that is below 40 mg/dL.

The risk of hypoglycemia with intensive use of insulin increases from 0.8% to 5.1% in the study by Van den Berghe in a medical ICU, and from 3.1% to 18.7% in the study of a surgical ICU by the same author.^{5,6}

The patients in a medical ICU are more severe than those in a surgical ICU, with a higher rate of kidney and liver failure, meaning they have a higher susceptibility for the development of hypoglycemia. In particular, septic patients are at the greatest risk,⁴³ with an overall incidence of 11.4% (2.9% for conventional management and 19.6% for intensive management) vs 3.9% in non-septic patients (1.2% for conventional management and 6.8% for intensive management with insulin). Conventional management aims at keeping glycemia below 180–200 mg/dL, while intensive management aims to achieve control at below 110 mg/dL.

These episodes of "biochemical" hypoglycemia were not associated with obvious clinical events, and in fact did not cause early deaths or neurological sequelae in patients who survived hospitalisation in an ICU. Nevertheless, as the risk of hypoglycemia coincided with the risk of death (OR, 3.2 in the surgical ICU; OR 2.9 in the medical ICU) in both management groups (conventional vs intensive), it is impossible to completely rule out the possibility that hypoglycemia counterbalances the benefit in terms of mortality offered by intensive management with insulin.⁴³

The increase in the incidence of hypoglycemia in the intensively managed groups justified the interruption of two large-scale studies: VISEP and GLUCONTROL. In the first of these, the incidence of hypoglycemia (<40 mg/dL) reached 12.1% in the group managed intensively with insulin (versus 2.1% in the conventionally managed group), while in the second study the number of patients who experienced at least one episode of hypoglycemia amounted to 9.8% (versus 2.7% in the conventionally managed group). It is important to point out that in the GLUCONTROL study the rate of mortality increased significantly in the patients who experienced hypoglycemia, with similar severity scores (SOFA).^{16,44}

The study by Krinsley⁴⁵ describes the clinical characteristics of 102 patients extracted from a cohort of 5365 patients admitted to the ICU consecutively and who had at least one episode of hypoglycemia (glucose in serum <40 mg/dL). These patients had an average APACHE II of 27.7 and presented an early episode of hypoglycemia (after an average stay in the ICU of one day) and a high percentage had septic shock. 55.9% of the patients who had an episode of hypoglycemia died, in comparison with 39.5% who did not have hypoglycemia. Thus a single episode of severe hypoglycemia is an independent risk factor for increased mortality.

While the majority of studies have focussed on severe hypoglycemia, other researchers have shown that moderate hypoglycemia (<70 mg/dL) has a negative effect on survival in a mixed population of critically ill patients.

Egi⁴⁶ studied 4946 critically ill patients and identified 1109 patients (22.4%) who suffered at least one episode of hypoglycemia (glucose level <81 mg/dL). Mortality in hospital was 36.6%, compared with 19.7% of the patients in the control group (who did not suffer an episode of hypoglycemia). Even the patients with a glucose level of from 72 to 81 mg/dL had a higher mortality rate than the control patients (25.9 vs 19.7%, OR 1.42). Patients with a minimum concentration under 63 mg/dL had significantly higher mortality than those whose glucose levels were in the range from

63 to 81 mg/dl (50.2 vs 28.2%; OR 2.59). There was no significant increase in mortality for patients with levels below 63 mg/dl.

Krinsley⁴⁷ carried out a study with the aim of evaluating the association between hypoglycemia (defined as a glucose concentration below 70 mg/dl) and hospitalisation time in the ICU in three different cohorts of critically ill patients. He recruited a total of 6240 patients, and the patients who had no hypoglycemia stayed in the ICU for 1.8 days, while those who had a single episode spend 3 days in the ICU. A very strong positive correlation was found between the number of episodes of hypoglycemia and the time spent in the ICU in all three cohorts.

There are at least 3 possible explanations for the association between hypoglycemia and the increase in morbimortality that has been detected:

1. The severity of hypoglycemia may be associated with the degree of severity of the illness.
2. Hypoglycemia may be a biomarker for imminent death, although the study by Egi⁴⁶ found that hypoglycemia is present at an average of 105 h before death in the ICU or after discharge from this unit. Hypoglycemia is therefore still an independent risk factor for mortality.

Hypoglycemia has harmful biological effects in critically ill patients. For example, episodes of hypoglycemia increase the systemic inflammatory response, induce neuroglycopenia, inhibit the glucocorticoid stress response, reduce the sympathetic autonomic response and cause cerebral vasodilatation by means of mechanisms which are still not known.⁴⁸ These studies suggest that low and even moderate levels of hypoglycemia should not be tolerated. Appropriate and continuous monitoring of glucose levels in the ICU is needed to prevent hypoglycemia or detect it at an early stage.

Glycemia control targets

Major doubts still exist regarding the optimum and desirable glucose levels in ICU patients. The upper limit for blood glucose during treatment with insulin has yet to be precisely determined in critically ill patients.

VanVught⁴⁹ evaluated the association between glucose levels at the moment of admission and 15 relevant sepsis biomarkers, as well as mortality after 30 days in a large cohort of critically ill patients with sepsis. Based on levels of glucose at the moment of admission, patients were classified as euglycemia (71–140 mg/dl), mild hyperglycemia (141–199 mg/dl), or severe hyperglycemia (>200 mg/dl).

The authors showed that severe but not mild hyperglycemia at the moment of admission was associated with higher risk of death in diabetic and non-diabetic patients. It is important to point out that significant differences exist in the basal characteristics of the groups, and that the authors simply show that there is an association between blood glucose levels at the moment of admission and their outcome; this does not imply a cause and effect relationship. Nevertheless, a more interesting finding of this study was that inflammation markers, endothelial lesion and activation of

coagulation are attenuated in patients with stress hyperglycemia.

This finding supports the idea that stress hyperglycemia is a beneficial adaptive response. Finally, the meta-analysis published by Yamada⁵⁰ showed that strict control of glycemia in critically ill patients has no benefit in terms of mortality, although it did show that hypoglycemia was five times more likely to be present than it was for mild or very mild control.

Conclusion

It is now not possible to consider glucose to be an innocent element in the ICU; hyperglycemia as well as hypoglycemia increases patient morbimortality. The correct level of blood glucose has yet to be determined, and it has to be adjusted for different populations of patients. Current efforts must be towards controlling variability in glycemia. Protocols for acting and better continuous measuring instruments are necessary to achieve metabolic control metabolic of our patients, keeping a treatment threshold at a level of >180 mg/dl and a target glucose level of from 140 to 180 mg/dl in ICU patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interests

The authors have no conflict of interests to declare.

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