

Corticosteroid-induced hyperglycemia

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Abstract

Glucocorticoids are medications of wide medical use, notably due to their known anti-inflammatory effects. Furthermore, fluctuations in glycemic indexes stand out as risk factors for clinical and surgical complications, mortality and increased hospital stay. The study consists of an integrative and descriptive literature review, through the PUBMED platform with the following keywords: “Hyperglycemia”, “Glucocorticoid” and “Induce”, in the last 12 years and aims to gather and unify information regarding the understanding and clinical and therapeutic management of hyperglycemia induced by the use of corticosteroids and corticogenic diabetes. The fluctuation in glycemic indexes with the use of corticosteroid therapy is an imbalance between the increase in insulin resistance and the inhibition of insulin production and secretion at the pancreatic cellular level. Screening for Diabetes Mellitus in patients on corticosteroid therapy is based on consensus in the literature with a plasma glucose level above 125 mg/dL, any capillary measurement above 200 mg/dL, HbA1c > 6.5% or oral tolerance test glucose above 200mg/dL after 2 hours. The main glycemic target is capillary blood glucose between 108-180 mg/dL and in cases of initiating therapeutic approaches for hospital management of glycemic fluctuations, the use of insulin therapy is chosen. Hyperglycemia induced by the use of corticosteroids is a topic that has been gaining prominence in the medical scenario, despite the lack of studies that uniformly protocol the approach to patients when this scenario is confirmed, with the aim of reducing the risks associated with hospitalization.

Keywords: Hyperglycemia; Diabetes Mellitus; Adrenal cortex hormones.

Resumo

Glicocorticóides são medicações de amplo uso médico, destacadamente, por seus efeitos conhecidos de ação anti-inflamatória. Acresça-se que, destaca-se as oscilações dos índices glicêmicos como fatores de risco para complicações clínicas e cirúrgicas, mortalidade e aumento da permanência hospitalar. O estudo consiste em uma revisão de literatura integrativa e descritiva, por meio da plataforma PUBMED com as seguintes palavras-chaves: “Hiperglicemia”, “Glucocorticoid” e “Induce”, nos últimos 12 anos, e tem como objetivo reunir e unificar as informações acerca do entendimento e do manejo clínico e terapêutico sobre a hiperglicemia induzida pelo uso de corticosteroides e a diabetes corticogênica. A oscilação dos índices glicêmicos com uso de corticoterapia é um

desbalanço entre o aumento da resistência insulínica e a inibição da produção e da secreção da insulina em nível celular pancreático. O rastreio de Diabetes Mellitus em pacientes em corticoterapia é feito a partir de consenso entre literatura com nível de glicose plasmática acima de 125 mg/dL, qualquer medida capilar acima de 200 mg/dL, HbA1c > 6,5% ou teste oral de tolerância à glicose acima de 200mg/dL após 2 horas. A principal meta glicêmica é uma glicemia capilar entre 108-180 mg/dL e nos casos de iniciar condutas terapêuticas para manejo hospitalar das oscilações glicêmicas opta-se pelo uso de insulino terapia. A hiperglicemia induzida pelo uso de corticoesteroides é um tema que vem ganhando destaque no cenário médico, apesar de carecer estudos que protocolam uniformemente a abordagem dos pacientes quando esse cenário for confirmado, com o objetivo de diminuir os riscos associados ao internamento.

Palavras-chave: Hiperglicemia; Diabetes Mellitus; Corticoesteroides.

Resumen

Los glucocorticoides son medicamentos de amplio uso médico, especialmente por sus conocidos efectos antiinflamatorios. Además, las fluctuaciones en los índices glucémicos se destacan como factores de riesgo de complicaciones clínicas, quirúrgicas, mortalidad y aumento de la estancia hospitalaria. El estudio consiste en una revisión integrativa y descriptiva de la literatura, a través de la plataforma PUBMED con las siguientes palabras clave: “Hiperglicemia”, “Glucocorticoide” e “Induce”, en los últimos 12 años, y tiene como objetivo reunir y unificar la información sobre la comprensión y el manejo clínico y terapéutico de la hiperglicemia inducida por el uso de corticosteroides y la diabetes corticogénica. La fluctuación de los índices glucémicos con el uso de la terapia con corticosteroides es un desequilibrio entre el aumento de la resistencia a la insulina y la inhibición de la producción y secreción de insulina a nivel celular pancreático. El cribado de Diabetes Mellitus en pacientes en tratamiento con corticoides se basa en el consenso de la literatura con un nivel de glucosa plasmática superior a 125 mg/dL, cualquier medición capilar superior a 200 mg/dL, HbA1c > 6,5% o prueba de tolerancia oral a la glucosa superior a 200 mg/dL después 2 horas. El principal objetivo glucémico es la glucemia capilar entre 108-180 mg/dL y en los casos de iniciar abordajes terapéuticos para el manejo hospitalario de las fluctuaciones glucémicas se opta por el uso de terapia con insulina. La hiperglicemia inducida por el uso de corticoides es un tema que viene ganando protagonismo en el escenario médico, a pesar de la falta de estudios que protocolen de manera uniforme el abordaje de los pacientes cuando se confirma este escenario, con el objetivo de reducir los riesgos asociados a la hospitalización.

Palabras clave: Hiperglicemia; Diabetes Mellitus; Corticoesteroides.

1. Introduction

Glucocorticoids are very common medications in medical practice, that is, they are widely used due to their known anti-inflammatory effects, especially prescribed for patients with COPD (Chronic Obstructive Pulmonary Disease), Asthma and inflammatory respiratory diseases, inflammatory bowel disease, adrenal insufficiency, transplantation (assisting in the immunosuppression process to reduce the risk of solid organ transplant rejection), vasculitis and inflammatory vascular diseases, cancer treatment, among other very prevalent conditions (Baldwin et al., 2012; Ferrelli et al., 2014; Grommesh et al., 2016; Li et al., 2016; Johal et al., 2023). The main associated risk factors are high body mass index (BMI), presence of injuries or reduced glucose tolerance and high previous doses of corticosteroid therapy (Baldwin et al., 2012; Gerads et al., 2015; Leiter et al., 2021; van Bommel et al., 2018).

Hyperglycemia in hospitalized patients can exist for different causes, for example, previous undiagnosed diabetes mellitus, psychological stress, glucocorticoids or a combination of these factors. Furthermore, there is already a consensus in the literature that glucocorticoids can cause type 2 diabetes mellitus or decompensate previously undiscovered DM2, due to peaks of hyperglycemia, since these mechanisms cause increased insulin resistance, increased gluconeogenesis and dysfunction of the beta cell (Merkofer et al., 2022). This mechanism occurs due to increased basal hepatic glucose production and reduced insulin resistance mediated, especially in skeletal tissues that are permissive to glycogenic metabolism (Baldwin et al., 2012; Merkofer et al., 2022; Whyte et al., 2021).

These aforementioned data are corroborated by a review of previous studies, for example, a study with 617 patients admitted to a university hospital who were hospitalized for approximately 1 month with a minimum treatment of 2 days with doses >40mg/day of prednisone described that 64% had blood glucose above 200 mg/dL, only 50% had a previous history of diabetes. Reaffirming the danger and need for screening for hyperglycemia in glucocorticoid therapy, there is a 10% increased

risk of death for each sustained increase above 18 mg/dL in the blood glucose reference value (Baldwin et al., 2012; Low et al., 2016; Merkofer et al., 2022;). In addition, 50%-70% of hospitalized patients prescribed moderate to high doses of corticosteroid therapy developed hyperglycemia (Whyte et al., 2021).

Fluctuations in high levels of hyperglycemia increase the risk of clinical and surgical complications, mortality and longer hospital stays. Therefore, protocols and monitoring of blood glucose levels are urgently needed in the face of hospital use of corticosteroids, with a high level being considered when blood glucose levels (GS>180 mg/dL) using corticosteroid therapy doses >10mg of prednisone or equivalent dose (Gerads et al., 2015; Grommesh et al., 2016; Leiter et al., 2021; Low et al., 2016; Merkofer et al., 2022).

The present study aims to gather and unify information about the understanding and clinical and therapeutic management of hyperglycemia induced by the use of corticosteroids and corticogenic diabetes, since corticosteroids are widely used drugs and knowledge about their complications there is little attestation in medical practice, especially its propaedeutic conduct.

2. Methodology

The study consists of a narrative review based on the literature (Rother, E.T; 2007; Snyder, H.; 2019) focused on evaluating the increase in the glycemic index following treatment with corticosteroid therapy. The bibliographic research took place through the PUBMED platform with the following keywords: “Hyperglycemia”, “Glucocorticoid” and “Induce”, in addition to the time limitation of the last 12 years (2012-2023). 484 articles were analyzed, 23 articles were included in the study and 460 articles that did not contain keywords in the title and those that had limited online access were excluded from the study.

3. Results and Discussion

3.1 Pathophysiology

The decompensation or abnormal oscillation of glycemic indexes in association with corticosteroid therapy is better understood in view of an imbalance between the increase in insulin resistance and the inhibition of insulin production and secretion at the pancreatic cellular level (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

Understanding the metabolic aspects of glucose absorption and its systemic repercussions is essential for a better understanding of the action of corticosteroids on this process. Initially, plasma glucose levels fluctuate constantly, compensated within a normal range by hepatic mechanisms called gluconeogenesis and glycogenolysis. Corticosteroids increase blood glucose levels through the mechanism of gluconeogenesis in the phosphoenolpyruvate carboxykinase and glucose-6-phosphatase pathways, antagonizing the insulin action of the process, especially in muscle and adipose tissues where glucose sensitization is greater (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

Corticosteroids establish their relationship with the induction of insulin resistance by blocking the removal of plasma glucose by muscles and fatty tissues. Therefore, this fact occurs due to the GLUT 4 receptors in the muscles, which are sensitive to insulin and are responsible for capturing this glucose, but their action is inhibited in the presence of corticosteroids in the blood circulation (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

From this perspective, this blockade of muscular action in glucose uptake especially harms postprandial glycemia, since its action is essential for the normalization of plasma glucose levels after meals, therefore maintaining sustained hyperglycemia and damaging the production cascade. insulin. Furthermore, corticosteroids also affect muscle protein

degradation itself, releasing an excess of amino acids into the plasma that cause double physiological damage, as it causes muscle atrophy, thus reducing the volume of active muscle for glucose absorption, as well as decreasing protein synthesis. , which represents an active gain in the process of energy expenditure through glucose, thus being a factor for the persistence of high glycemic levels (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

In parallel, changes in tissue damage also occur in fatty structures, for example, in adipose tissue the process of lipolysis occurs, which increases the release of non-esterified fatty acids into the plasma circulation in large quantities, directly interfering in two mechanisms to induce hyperglycemia , the first, fatty acids are attracted to muscle cells so that they start to accumulate in them, disrupting the glucose absorption process, the second, is the direct interference in the action of plasma insulin (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

In this context, in addition to muscle and adipose changes, corticosteroids also structurally alter the secretion and production of insulin in pancreatic β cells that are sensitive to systemic chemoreceptors regulating plasma glucose levels. Currently, the knowledge is well established that after 4 to 5 days of use of corticosteroid therapy, that is, acute treatment, depending on the dose, time and form of application (intravenous or oral in high doses), there is structural damage to physiology regulation of pancreatic β cells, especially when related to the apoptotic and reducing effects of insulin biosynthesis due to cell failure secondary to the sustained high level of hyperglycemia (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

In situations of chronic use of corticosteroid therapy, the induction of lipolysis with lipotoxicity due to the accumulation of fatty acids also in the pancreas is added, aggravating structural changes and corroborating the systemic picture of insulin resistance and sustained hyperglycemia, which can potentiate the factors of risk and pathophysiological effects inducing type 2 Diabetes Mellitus (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

Pharmacodynamic aspects are extremely relevant for understanding the risk factors related to the use of corticosteroid therapy, for example, the use of this therapy has greater action, especially within 4 hours postprandial, due to the mechanisms previously explained. Thus, hyperglycemia due to the use of corticosteroids depends on the formulation of the drugs, such as prednisone or methylprednisolone, which have a peak between 4 and 6 hours, or long-acting corticosteroids, such as dexamethasone, which has a peak of up to 24 hours, potentiating higher glycemic levels. for almost the entire day (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

In view of this, the pathophysiological understanding of the process of hyperglycemia secondary to the use of corticosteroids is well founded to better define a strategy for diagnosis, prognosis and treatment of patients, especially during hospitalization, based on prior knowledge about the patient's profile. , presentation of the current disease, established basic conditions, previous blood glucose levels and monitoring method, race and therapeutic options for corticosteroids based on time of action, dose used, time of use of the drug, since they are essential therapeutic strategies in the hospital context as they are potent anti-inflammatories. Therefore, with this basis it is possible to prevent, understand and manage conditions related to worsening prognosis, increased risk of infections due to hyperglycemia, reduced complications and prolonged hospital stays (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

3.2 Diabetes Mellitus Screening and Glycemic Control Goals

Screening for Diabetes Mellitus in the international consensus determines persistent plasma glucose levels above 125 mg/dL, any capillary blood glucose measurement above 200 mg/dL, HbA1c>6.5%, or oral glucose tolerance test above 200mg /dL after 2 hours. These concepts are important in view of the pathophysiology of corticosteroid therapy, since there is the factor of insulin resistance, influence of gluconeogenesis and structural pancreatic damage involved, therefore, the ideal is not

to perform OGTT in patients who use corticosteroids, given the postprandial mechanisms of medication (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

Furthermore, HbA1c is only ideal for screening when you have had more than 2 months of treatment with corticosteroid therapy, as this glycemic parameter analyzes an average of the last 60 to 90 days of glycemic levels, therefore it does not reliably assess the possibility of establishing corticogenic diabetes. (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

Therefore, capillary blood glucose is the main form of analysis and monitoring with some caveats, including that any value above 200mg/dL is already decisive for DM due to steroids, especially if it is postprandial from lunch due to corticosteroid therapy with a single dose in the morning, as this way the peak of action of the drug reduces its interaction, or alternatively, the pre-prandial capillary glycemia of dinner, with less sensitivity. Therefore, patients who use medium to high doses of corticosteroids in the morning should be monitored with serial blood glucose measurements throughout the day, essentially post-prandial at lunch and pre-prandial at dinner (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

This screening during corticosteroid therapy should be even more precise and assertive when the patient presents risk conditions for Type 2 Diabetes Mellitus, since they already have physiological and systemic stressors that can enhance the decrease in pancreatic function and regulation of glucose levels. plasma. Even so, there are no parameters established in the literature that determine the diagnostic conditions of diabetes after the use of steroids, therefore, attention should be paid to pre-prandial glycemia at dinner above 140 mg/dL, and post-prandial glycemia at lunch above 200 mg /dL, as an alarm signal for better control, avoiding hyperglycemia and hypoglycemia (Baldwin et al., 2012; Liu et al., 2014; Merkofer et al., 2022; Perez et al., 2014; Whyte et al., 2021).

3.3 Diagnosis and Screening Goals

Before diagnosing steroid-induced diabetes, we must remember some risk factors that may predispose to this condition, for example, the patient has type 1 or type 2 diabetes mellitus (DM), a positive family history of this disease, impaired glucose tolerance, obesity, women with polycystic ovarian disease and those who have had gestational diabetes, in addition to ethnic minority groups, previous history of glucocorticoid-induced hyperglycemia (IGH), smoking, systemic arterial hypertension and advanced age (Hwang et al., 2014; Nakamura et al., 2020; Roberts et al., 2018).

GIH (glucocorticoid-induced hyperglycemia) is the increase in blood glycemia resulting from the short and long-term use of glucocorticoids (GCs), including methylprednisolone pulse therapy, in diabetic or non-diabetic patients. The diagnosis of GIH occurs equally with other types of diabetes, using the criteria established by the American Diabetes Association (ADA), which are: fasting blood glucose ≥ 126 mg/dL, after 2 hours another fasting blood glucose measurement or the Oral Test Glucose Intolerance (OTGI) with levels ≥ 200 mg/dL (11.1 mmol/l), glycated hemoglobin (Hb1Ac) $\geq 6.5\%$ or random blood glucose ≥ 200 mg/dL (11.1 mmol/l) with the patient presenting signs and symptoms of hyperglycemia or hyperglycemic crisis (Aberer et al., 2021; Hwang et al., 2014; Litty et al., 2017; Nakamura et al., 2020; Uchinuma et al., 2020).

However, it is important to remember that this diagnosis is not so easy, as fasting blood glucose can be normal, especially when short or intermediate-acting GC is used in a single dose in the morning. Furthermore, Hb1Ac is normally used when the patient has been using the medication for a few weeks or to differentiate patients with pre-existing DM from those without diabetes, as this measurement detects a glycemia parameter from a few weeks prior, being bad for patients on treatment. of recent onset (Aberer et al., 2021;). Therefore, a study concluded that the detection of hyperglycemia is best during the 3rd day of treatment with glucocorticoids and 2 hours after lunch and dinner, thus being able to help with the diagnosis (Nakamura et al., 2020;). Control of corticosteroid-induced hyperglycemia. When the diagnosis of HIG is confirmed,

patients must be monitored so that there is adequate control of this hyperglycemia, thus avoiding future complications. However, control goals vary in the hospital and outpatient environment, in addition to the type of patient, whether they are those with a pre-existing diagnosis of DM or those without a pre-existing diagnosis of DM. The Joint British Diabetes Societies, in the outpatient setting, mentions that all patients with an existing diagnosis of DM1 or DM2 should monitor their blood glucose up to 4 times a day with the aim of maintaining glycemic levels between 108 to 180 mg/dL (6 to 10 mmol/L). Patients without previous DM treated with glucocorticoids who obtained glucose levels above 180 mg/dL on two different occasions with or without signs and symptoms of hyperglycemia are also recommended to monitor their blood glucose daily. Furthermore, it is necessary to educate these patients, especially those who are at higher risk of developing type 2 diabetes, regarding self-medication, baseline blood glucose levels, therapeutic regimens when necessary and symptoms of hypo and hyperglycemia (Aberer et al., 2021; Litty et al., 2017). In the hospital environment, the Endocrine Society recommends constant glucose monitoring in all patients using GCs, with or without a history of diabetes mellitus (Litty et al., 2017; Nakamura 2020).

The blood glucose targets for hospitalized patients are between 108 and 180 mg/dL (6 to 10 mmol/L), with a range of 4 to 12 mmol/L (Robertes - 2018). However, in patients without diabetes who have blood glucose levels below 140 mg/dL for more than 24 hours and without using insulin, monitoring may be discontinued (Litty et al., 2017).

3.4 Treatment of corticosteroid-induced hyperglycemia

Hyperglycemia induced by glucocorticoids has a high occurrence, ranging from 30 to 64% of patients, depending on the clinical scenario, comorbidities and the therapeutic dose used. It has an important impact on increased mortality in hospitalized patients, risk of complications and longer hospital stays (Low et al., 2016). Glucocorticoids are widely used in clinical practice and frequently cause new-onset hyperglycemia in patients without a previous history of diabetes or cause significant hyperglycemia in patients with previous diabetes. They are used to treat almost the entire body, such as cerebral edema, airway compromise, respiratory failure, inflammatory bowel disease, joint inflammation, adrenal insufficiency, transplant rejection and vascular collapse (Baldwin et al., 2012). Given this, there are risk factors for the development of glucocorticoid-induced diabetes, which are age, body mass index, presence of impaired fasting glucose/glucose tolerance, higher doses of glucocorticoids and coagulation problems (Baldwin et al., 2012, Li, P et al., 2016).

In this context, it presents a mechanism of action that is mediated by the cytosolic glucocorticoid receptor (cGR). It is worth noting that steroid-induced hyperglycemia is mediated by decreased β -cell insulin production, increased insulin resistance, and increased gluconeogenesis. In what happens, changes in the immune system, inflammatory mediators, the coagulation cascade and endothelial function (McDonnell et al., 2020).

Glucocorticoids are widely used in clinical practice and have an important association with hyperglycemia; there is not much study on the prevention of glucocorticoid-induced hyperglycemia and its consequences for patients' health. Furthermore, little is known about the pharmacodynamics of glucocorticoid-induced diabetes and which treatment has the best glycemic control (Liu et al., 2014, Gerards et al., 2015). Glucocorticoid-induced transient hyperglycemia. Glucocorticoids have a variety of uses, as potent anti-inflammatory and immunosuppressive drugs for the treatment of various illnesses. However, they are related to several side effects, including the development of glucocorticoid-induced hyperglycemia. The predominant mechanism responsible for glucose intolerance after drug therapy is insulin insensitivity (Liu et al., 2014).

The fluctuation in blood glucose levels during glucocorticoid therapy depends on the type, dose and administration regimen of the formulation used. Hyperglycemia due to medication is useful to distinguish whether the treatment of this side effect will be temporary, which is the most common, or indefinite (Liu et al., 2014).

The management of glucocorticoid-induced hyperglycemia with multiple daily doses of glucocorticoids or dexamethasone varies according to glycemic control to prevent errors or inappropriate conduct. Oral hypoglycemic agents are promising for treatment, requiring high potential, which can begin with high initial doses and be gradually reduced as the clinical condition improves. However, there are limitations to this drug, such as slow onset of action or very limited titration. Insulin is the most commonly used drug in the treatment of glucocorticoid-induced hyperglycemia due to its efficacy, rapid onset of action and can be easily titrated.

3.5 Patients with blood glucose > 200 mg/dl

Insulin therapy is widely used for the treatment of glucocorticoid-induced hyperglycemia and needs to be adapted to the pharmacodynamics of the administered glucocorticoid. It is worth noting that the initial dose will depend on the patient's weight, then the insulin dose will be adjusted according to capillary blood glucose levels (Paredes et al., 2016). The type of insulin and the regimen to be used depend on the presence or absence of previous insulin therapy. When the patient has not used previous insulin therapy, intermediate-duration glucocorticoid therapy is indicated, which is one of the measures that can be administered in the morning and before lunch using NPH/NPL/biphasic insulin, as its action profile accompanies the hyperglycemic effect of the glucocorticoid, avoiding hyperglycemia in the afternoon and before dinner to avoid hypoglycemia before lunch since the peak of action is 4-6 hours and the duration of action is 12-15 hours. Another option would be to apply an intermediate dose greater than or equal to two administrations per day (Paredes et al., 2016).

Taking NPH insulin, subdividing it into an estimated dose as follows: 2/3 before lunch and 1/3 before dinner. In the morning, they should monitor the insulin dose adjustment and monitor changes in the glucocorticoid dose at night, as an insulin dose adjustment is necessary before dinner (Paredes et al., 2016). Long-acting or intra-articular glucocorticoid therapy involves insulin glargine in a single administration or insulin detemir in two administrations. Insulins follow the duration of the glucocorticoid, providing better correction of hyperglycemia throughout the day. To carry out intra-articular administration, care must be taken when discontinuing insulin administration, and it is recommended two to three days after the last infiltration (Paredes et al., 2016). In patients with a previous insulin regimen, it is necessary to calculate the additional insulin dose necessary to carry out the therapy associated with the insulin doses already used (Paredes et al., 2016).

In this context, the glucocorticoid that is administered in the morning with the intermediate duration can be a regimen of NPH insulin at night or insulin glargine or determined by adding a dose of NPH insulin calculated before lunch. The patient who uses NPH insulin twice daily needs to add the extra dose in the morning. If the usual therapy is a basal-bolus scheme, it is important to maintain the previous basal insulin dose and add the equivalent of the estimated bolus NPH insulin dose, for example 20% before breakfast, 40% before lunch and 40% before dinner (Paredes et al., 2016).

Medium-term glucocorticoid treatment with two daily dosages, if the patient usually takes NPH insulin at night or twice a day, the estimated dose of NPH insulin should be added, dividing it into 2/3 before breakfast and 1/3 before dinner. If the patient regularly takes insulin glargine or detemir, the additional dose of insulin required should be calculated and distributed as follows: 2/3 should be administered as NPH insulin before breakfast; the remaining 1/3 should be added to the usual dose of insulin glargine or dosed, to be administered before dinner. If the patient routinely follows a basal-bolus insulin regimen, they need to combine the insulin calculated at 25% in the basal insulin format and 75% in the bolus format, being divided into every meal (Paredes et al., 2016). In medium-term treatment with glucocorticoids in doses starting from twice a day. If the patient usually takes NPH insulin at night or twice a day, the estimated dose of NPH insulin should be added and divided into 2/3 before breakfast and 1/3 before dinner. If the patient is regularly taking insulin glargine or detemir, the next required dose of insulin should be calculated and divided as follows: 2/3 should be administered as NPH insulin before breakfast; the remaining 1/3 should be added to the usual dose of insulin glargine or administered before dinner with intra-

articular or long-acting glucocorticoids (Paredes et al., 2016). If the patient usually takes NPH insulin once or twice a day, the estimated dose of NPH insulin should be added, dividing 2/3 into the dose before breakfast and 1/3 into the dose before dinner. If the patient usually takes insulin glargine or detemir, the estimated basal dose of insulin should be added to the usual regimen. If the patient is generally on a basal-bolus insulin regimen, an estimated dose of insulin should be added, 25% as basal insulin and 75% as bolus, divided equally into the three main meals (Paredes et al., 2016).

3.6 Management of hyperglycemia induced by prolonged treatment with glucocorticoids

Firstly, it is important to highlight that there is a lack of clear guidelines regarding the management of patients with glucocorticoid-induced hyperglycemia. It was agreed among a group of endocrinologists based on evidence and their practical management experiences that the earliest possible approach and clinical stratification of the patient's risk are fundamental in their approach (Shah et al., 2022).

OGTT and glycated hemoglobin are not indicated for monitoring and screening patients who develop hyperglycemia induced by acute diabetes, unless otherwise indicated (Barker et al., 2023). The glycated hemoglobin test is of great importance before starting treatment in patients with a high chance of developing hyperglycemia and to exclude pre-existing diabetes (Barker et al., 2023; Nakamura et al., 2020;). Diabetic patients must check their blood glucose 4 times a day, whereas non-diabetics are recommended to check their blood glucose only once, unless their blood glucose levels are above 200mg/dL, thus changing the indication to 4 daily measurements. A blood glucose target between 108 mg/dL and 180 mg/dL is recommended for hospitalized patients. In groups at high risk of hypoglycemia or vulnerable to harm from hypoglycemia, milder glycemic targets can be used, aiming for levels between 108mg/dL and 270mg/dL (Aberer et al., 2021; Barker et al., 2023; Litty et al., 2017).

In patients without diabetes, it is recommended to measure blood glucose once a day, the ideal measurement being in the early afternoon, during which the morning dose of glucocorticoid will induce an increase in blood glucose. However, evidence shows that measurements in the 2-hour postprandial period are also safe (Barker et al., 2023). When treating with insulin, several factors must be taken into consideration, such as the agent being used as a glucocorticoid, the time of use of the medication and its dose. The insulin dose adjustment must be made in accordance with the glucocorticoid adjustment, with half the change made in the steroid being indicated for the change in insulin (Aberer et al., 2021).

The preferred pharmacological treatment for patients with corticosteroid-induced hyperglycemia is a single daily dose of gliclazide of 40 mg, which can be increased to 240 mg if necessary. If glycemic control is not achieved with this action, a new dose of gliclazide can be introduced. night together with a medium-acting insulin (Barker et al., 2023). When glucocorticoid therapy is discontinued, it is important to consider the need to regularly monitor glucose levels and review ongoing treatment for hypoglycemia. It is recommended to reduce the doses of sulfonylurea and insulin along with decreasing the dose of glucocorticoids in order to avoid episodes of hypoglycemia (Barker et al., 2023).

Glucose monitoring should be continued until glucose levels are within the normal range. For hospitalized patients discharged while still on glucocorticoids, it is advisable to continue monitoring glucose at least once daily after discharge. If hyperglycemia persists after discontinuing glucocorticoids, glucose monitoring should be continued, and after three months, formal testing to detect the presence of diabetes is recommended (Barker et al., 2023). Newly diagnosed patients may need continuous glucose monitoring devices after discharge and receive appropriate educational guidance on glucose monitoring, including safety net advice if there is persistent hyperglycemia or hypoglycemia (Barker et al., 2023).

Oral antihyperglycemic drugs such as Metformin and Pioglitazone are not indicated in hospitalized patients with acute glucocorticoid-induced hyperglycemia due to an increased chance of kidney damage, hypoxia and fluid accumulation. Insulin

secretagogues, if used with caution to avoid hypoglycemia, can be effective in hospitalized patients with mild conditions who receive only a daily dose of glucocorticoids (Aberer et al., 2021).

4. Conclusion

Hyperglycemia induced by the use of corticosteroids is a topic that is gaining greater relevance in the medical scenario, but there is still a lack of sufficient studies to be able to understand its development in an ideal way and discuss it.

It is believed that this lack of knowledge about the nuances of the pathology is the main aggravating factor in its development, especially in scenarios where health professionals underestimate or are unaware of such clinical repercussions, which can be common in several hospital and outpatient cases.

Therefore, blood glucose screening should be considered in patients using medium or high dose glucocorticoids to avoid long courses of hyperglycemia in patients. If developed, its treatment must be adjusted to the individual's level of hyperglycemia. To manage glucocorticoid-induced hyperglycemia, it is important to regularly monitor blood sugar levels, adjust medication as needed, and adopt healthy lifestyle measures such as a balanced diet and exercise. In some cases, it may be necessary to initiate or adjust therapy with insulin or other hypoglycemic medications to adequately control blood glucose.

It is essential that patients taking glucocorticoids talk to their doctors about the risks of hyperglycemia and follow medical advice to minimize adverse effects and ensure adequate blood sugar control during treatment with these medications.

Furthermore, it is observed that, within the scientific community, there are few works addressing this subject, of paramount importance, in a concise and didactic manner. Given this context, more scientific productions are necessary with the aim of simplifying and explaining this topic for both healthcare professionals and the general public, thereby providing greater understanding and, consequently, better management of corticosteroid-induced hyperglycemia.

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