

REVIEW

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# Dexamethasone in the era of COVID-19: friend or foe? An essay on the effects of dexamethasone and the potential risks of its inadvertent use in patients with diabetes

Janine Alessi<sup>1,2,5\*</sup>, Giovana B. de Oliveira<sup>3</sup>, Beatriz D. Schaan<sup>1,4,5,6</sup> and Gabriela H. Telo<sup>2,3,6,7</sup>

## Abstract

**Background:** The disclosure in the media of a benefit with the use of dexamethasone in patients with COVID-19 infection sets precedents for self-medication and inappropriate use of corticosteroids.

**Methods:** This is a critical interpretive synthesis of the data available in the literature on the effects of the use of corticosteroids and the impact that their indiscriminate use may have on patients with diabetes. Reviews and observational and experimental studies published until June 18, 2020 were selected.

**Results:** Corticosteroids are substances derived from cholesterol metabolism that interfere with multiple aspects of glucose homeostasis. Interactions between corticoid receptors and target genes seem to be among the mechanisms responsible for the critical functions of glucocorticoids for survival and anti-inflammatory effects observed with these medications. Corticosteroids increase hepatic gluconeogenesis, reduce peripheral use of glucose and increase insulin levels. Previous studies have shown that glucocorticoids have a pro-adipogenic function, increasing deposition of abdominal fat, and lead to glucose intolerance and hypertriglyceridemia. In addition, these drugs play a role in controlling liver metabolism and can lead to the development of hepatic steatosis. Glucocorticoids reduce the recruitment of osteoblasts and increase the number of osteoclasts, which results in increased bone resorption and greater bone fragility. Moreover, these medications cause water and sodium retention and increase the response to circulating vasoconstrictors, which results in increased blood pressure levels. Chronic or high-dose use of corticosteroids can, by itself, lead to the onset of diabetes. For those who were already diagnosed with diabetes, studies show that chronic use of corticosteroids leads to a 94% higher risk of hospitalization due to diabetes complications. In addition to the direct effects on glycemic control, the effects on arterial pressure control, lipids and bone metabolism also have a potential for severe consequences in patients with diabetes.

**Conclusion:** Fear and uncertainty toward a potentially serious infection may lead people to self-medication and the inappropriate and abusive use of corticosteroids. More than ever, it is necessary for health professionals to be alert and able to predict damages related to the use of these drugs, which is the first step to minimize the potential damages to come.

**Keywords:** Corticosteroids, Diabetes mellitus, COVID-19 pandemic, Metabolic effects, Dexamethasone

## Background

The saga in search of a drug capable of changing the natural history of the coronavirus disease 19 (COVID-19) experienced a new chapter: dexamethasone emerges with

\*Correspondence: janinealessi@gmail.com

<sup>5</sup> Endocrinology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Full list of author information is available at the end of the article



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the aim of reducing mortality in hospitalized patients. However, before its emergence, other treatments arrived with the promise of miraculous achievements and stayed behind, remaining only adverse effects and lack of medications access for clinical conditions that would truly benefit from their use. In this context, the dimensions of self-medication and drug misuse are currently alarming. An example of this is hydroxychloroquine: in the same week of the release of a small study that showed a potential effect on reducing the viral load of infected patients, the drug's stocks ran out in pharmacies in Brazil, putting patients with lupus and rheumatoid arthritis at risk because of its unavailability [1, 2]. Although subsequent studies refuted the benefits of its use, the consumption of hydroxychloroquine in Brazil remained high. In the first week of June 2020, the country imported more than two million doses of this drug despite all recommendations against its routine use from international organizations and scientific community [3–5]. Similar expectations were experienced by azithromycin, ivermectin and, now, dexamethasone.

In the past few days, promising results from the use of dexamethasone in patients with COVID-19 infection have been published. The results of the RECOVERY study (Randomised Evaluation of COVID-19 Therapy) showed a potential reduction in mortality of up to one-third (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI 0.51 to 0.81) in patients on mechanical ventilation and up to one-fifth (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI 0.72 to 0.94) in patients using oxygen [6]. The rapid dissemination through the media of the effects of dexamethasone opens the door to the indiscriminate use of this medication and puts us on the brink of an unprecedented clinical collapse. For professionals who care for patients with diabetes mellitus, more than ever it is necessary to keep in mind the impact that the use of corticosteroids may have on glycemic control and other metabolic parameters. Moreover, individuals with obesity, insulin resistance and pre-diabetes may experience the change of their disease state to overt diabetes by the use of these drugs.

Training health professionals to predict damages related to the use of these drugs and to publicize the need for cautious and rational use of dexamethasone is the first step to minimize the potential damages to come. Based on this, the present study aimed to review the mechanism of action of corticosteroids, their metabolic effects and the possible consequences of their indiscriminate use, especially in patients with diabetes. A practical summarized guide of considerations prior to its use, treatment of exacerbated hyperglycemia and strategies for corticosteroids withdrawal will be provided.

## Methods

This is a critical interpretive synthesis of the data available in the literature on the effects of the use of corticosteroids, potential risks and benefits of their administration and the impact that their indiscriminate use may have on patients with diabetes. In addition, practical issues on glucocorticoid use and withdrawal in diabetes are also provided. An iterative search strategy was carried out, with a review of articles indexed on the PUBMED platform, as well as a manual review based on the main articles' reference list when appropriate. The key words for the search were "corticosteroids AND mechanism of action", "corticosteroids AND pharmacology", "corticosteroids AND diabetes", "corticosteroids AND COVID-19", "corticosteroids AND hyperglycemic AND treatment", "corticosteroids AND withdrawal". Reviews and observational and experimental studies *in vitro* and *in vivo*, including either animals or humans, published until June 18, 2020, addressing aspects related to the effects of the use of corticosteroids were selected. A screening based on the title and abstract of the articles that would be included in the analysis was carried out during the iterative search. After that, the full text was read. The research was conducted by two independent researchers (J.A. and G.B.O.), who were responsible for reviewing specific content and synthesizing the information considered relevant in order to offer an overview on the subject and discuss its insertion in the current context. All authors reviewed and agreed with the final content of the synthesis.

## The role of corticosteroids

Corticosteroids are substances derived from cholesterol metabolism that share three 6-carbon hexane rings and one 5-carbon pentane ring in their structure. The term corticosteroid is used clinically to describe agents with glucocorticoid activity and includes molecules that have two carbons at position 17 on the pentane ring and methyl groups at the carbon position 18 and 19 [7]. Cortisol, which is an endogenous glucocorticoid, is produced by the adrenal cortex and its release depends on the proper functioning of the hypothalamic–pituitary–adrenal axis, which is essential for the maintenance of vital functions. Under non-stressed conditions, the human body produces approximately 20 mg of cortisol during the day. Situations of physical or psychological stress, such as infections, trauma or surgery, can result in a physiological increase in serum cortisol levels up to 150–200 mg [8, 9]. In some circumstances associated with intense inflammation, such as sepsis, the adrenal gland's ability to produce cortisol may be insufficient to maintain vital function, a situation described as relative adrenal insufficiency [10].

The critical functions of glucocorticoids for survival involve the presence of receptors for these molecules in the regulation of gene transcription processes. The glucocorticoid receptor can function at least at three levels: first—recruitment of the general transcription machinery; second—modulation of transcription factor action through direct protein–protein interactions; and third—modulation of chromatin structure to allow the assembly of other gene regulatory proteins and the general transcription machinery on the DNA [11]. Interactions between corticosteroid receptors and target genes, especially the ones related to the immune system, seem to be among the mechanisms responsible for the anti-inflammatory effects observed with pharmacological doses of these medications [12].

In addition to the genomic effects, glucocorticoid have non-genomic actions of significant therapeutic relevance. From what is known so far, these effects are mediated by three different mechanisms: physicochemical interactions with cellular membranes, membrane-bound glucocorticoid receptor-mediated effects and cytosolic glucocorticoid receptor-mediated effects [13]. Although the mechanisms are not yet fully understood, the non-genomic actions of glucocorticoids may play a role in the management of inflammatory diseases [14].

Since 1950, when cortisol was first synthesized, several studies have been carried out with the aim of synthesizing a steroid with a specific anti-inflammatory action. It quickly became clear that it was possible to alter the steroid molecule so that the glucocorticoid or mineralocorticoid activity was intensified. However, the increase in anti-inflammatory activity is intrinsically associated with the increase in other glucocorticoid actions, which determines a significant metabolic effect [15]. Dexamethasone belongs to this group: higher glucocorticoid potency and minimal mineralocorticoid activity, generating greater hypothalamic–pituitary–adrenal axis suppression and more metabolic side effects than other corticosteroids.

### Metabolic effects of glucocorticoids

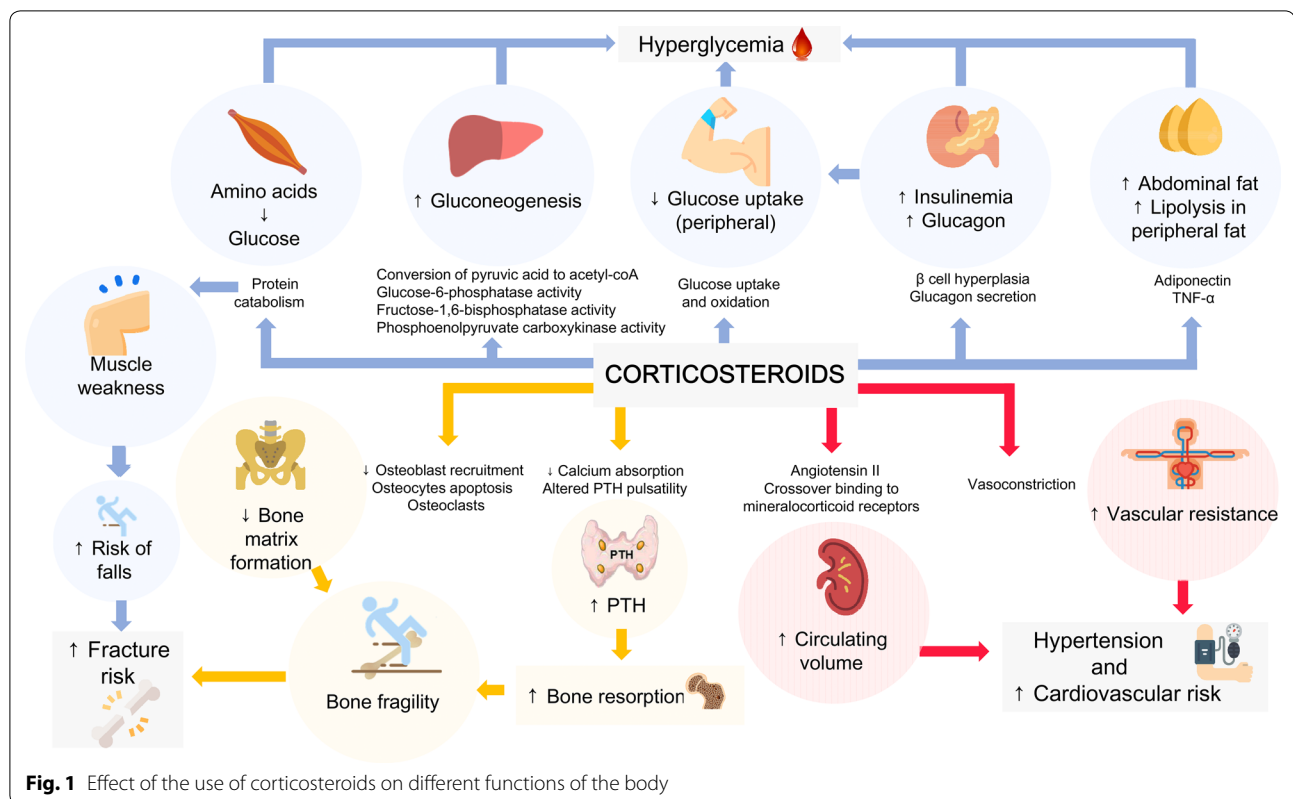
The administration of glucocorticoids causes a significant change on the metabolism of carbohydrates, which can lead to insulin resistance, hyperglycemia and glycosuria. One of the first well-elucidated effects of this drug was its role in increasing hepatic gluconeogenesis, which seems to be related to the inhibitory effects of glucocorticoids on the conversion of pyruvic acid to acetyl-coenzyme A, leading to an accumulation of pyruvic acid and resulting in glucose resynthesis [15–17]. Increased induction of enzymes related to gluconeogenesis, such as glucose-6-phosphatase, fructose-1,6-bisphosphatase and phosphoenolpyruvate carboxykinase contribute to this effect [18]. An increase in hepatic glycogen deposition can

be observed from three to twenty-four hours after the administration of glucocorticoids [19]. In addition, the use of glucocorticoids plays an important role by augmenting glucose production and decreasing peripheral glucose utilization, maintaining high serum glucose levels [20]. This action, which in physiological situations is fundamental for maintaining euglycemia during periods of fasting, may be exacerbated with the administration of exogenous corticosteroids, leading to hyperglycemia (see Fig. 1).

The chronic use of corticosteroids also increases fasting insulin levels [21]. This effect is related to a metabolic response of the pancreatic beta cells to hyperglycemia, which results in reduced peripheral sensitivity to insulin [22, 23]. In addition, glucocorticoids also alter insulin secretion by reducing the effect of incretins, even though this action has not yet been fully understood [21, 24, 25].

Experimental studies have shown that glucocorticoids have a pro-adipogenic function. The lipogenic effect of these drugs seems to be mediated by the genetic expression of pathways that lead to the maximization of insulin effects [35]. When evaluating animal models after exposure to the use of corticosteroids, high levels of these drugs in adipose tissue were associated with increased deposition of abdominal fat, reduced glucose tolerance and hypertriglyceridemia. Moreover, there was a reduction in adiponectin levels and an increase in serum tumor necrosis factor alpha (TNF- $\alpha$ ) levels, which are related to insulin sensitivity and resistance, respectively [26–30]. Glucocorticoids also have a lipolytic action, especially pronounced in peripheral fat. This function is mediated by the induction of transcription factors that regulate the function of lipases, increasing the action of these enzymes [27, 31–34]. However, the acute and long-term effects of corticosteroids on lipolysis are still not entirely clear.

Glucocorticoids play a role in controlling liver metabolism mediated by the genomic regulation of glucocorticoids receptors. More than 50 target genes for this regulation have been identified so far [27, 36]. These genes codify enzymes responsible for lipogenesis and triglyceride synthesis, and the consequences of the activation of these enzymes can lead to the development of hepatic steatosis even before the establishment of insulin resistance in the metabolic syndrome [27, 37–40]. In relation to other lipoproteins, *in vitro* and *in vivo* studies have demonstrated that animals treated with dexamethasone showed an increase in serum very-low density lipoproteins (VLDL) and high-density lipoproteins (HDL). This effect is believed to be due to increased production of apolipoprotein B (ApoB), associated with increased synthesis of triglycerides and apolipoprotein A-I (ApoA1) respectively, which are stimulated by the use of



corticosteroids [41–45]. In the case of low-density lipoproteins (LDL), the analyses so far are not conclusive, and further studies are needed to determine what the effect would be on these molecules [27].

Protein metabolism is also significantly affected by corticosteroids, which have shown to stimulate catabolism, resulting in inhibition of growth, osteoporosis, muscular atrophy, reduction in skin thickness and reduction in the amount of lymphoid tissue. Protein catabolism is the process by which proteins are broken down to their amino acids. Consequently, a greater uptake of amino acids in the liver occurs. These amino acids will be predominantly deaminated and converted to glucose or, less frequently, transformed into new proteins [15, 26].

Regarding calcium metabolism, glucocorticoids have a direct and indirect effect on bone remodeling [46]: they inhibit the formation of the bone matrix, which seems to be related to the reduction of the osteoblast's recruitment and to the accelerated apoptosis of osteocytes [47]. Another effect that can be observed is the increase in the expression of receptor activator of nuclear factor-κB ligand (RANKL), which leads to increases in the number of bone-resorbing osteoclasts. This condition may be accompanied by other changes, such as reduced muscle mass, which can be present due to protein catabolism, and with cataract-related visual impairment, which

is more prevalent in corticosteroid users. These three factors combined result in a significant increase in the risk of falls and fractures even before observation of bone mineral density reduction. Other indirect effects that can be observed are the reduction in calcium reabsorption in the kidney, changes in sex hormones and changes in the parathyroid hormone pulsatility, factors that are fundamental for adequate bone homeostasis [46, 48].

Water and sodium retention and the reduction in serum potassium are complications of the use of corticosteroids, especially those with mineralocorticoid action and when high doses are administered [15]. There are currently several formulations available with a predominance of glucocorticoid effect and practically negligible mineralocorticoid effect, with dexamethasone as an example of this category. Despite this, the effect on water regulation remains, regardless of the mineralocorticoid effect. Glucocorticoids act indirectly in the proximal tubule, increasing the cellular response of sodium transporters stimulated by angiotensin II. In the distal tubule, the effect is more direct and seems to be related to crossover binding to mineralocorticoid receptors. As a result, there is an increase in sodium and water retention, increasing the circulating volume and causing an increase in blood pressure levels [48, 50]. Another indirect effect of glucocorticoids that results in arterial hypertension

is the magnification of the circulating vasoconstrictors' response, since it acts upregulating the expression of receptors to many vasoconstrictors and downregulating the effects of potential vasodilators [51–55]. Thus, glucocorticoids have the potential to alter both circulating volume and vascular resistance [49].

### Corticosteroids and COVID-19

Since December 2019, when a series of cases of severe pneumonia caused by the SARS-CoV-2 coronavirus were described in China, several studies have sought to evaluate the effect of corticosteroids on the natural course of the disease [56–58]. The rationale for the use of dexamethasone in patients with severe infection is based on this premise that the damage caused by the disease is strongly related to the aggressive inflammatory response triggered [59]. Thus, the use of drugs with a potent anti-inflammatory effect could reduce the catastrophic effects generated by the overactivation of the immune system, helping to speed up the recovery of these patients [60]. The results published so far are, however, contradictory and inconclusive.

A study *in vitro* by Matsuyama et al. investigated the effect of inhaled corticosteroids on the replication of the SARS-CoV. This study suggested that ciclesonide interacts with the newly mapped coronavirus protein NSP15 during biogenesis and suppresses viral replication of SARS-CoV-2. Inhaled ciclesonide is expected to reduce viral replication and host inflammation in the lungs, with decreased immunosuppressive effects compared to systemic corticosteroids, as ciclesonide primarily remains in the lung tissue [61]. Later, a series of case reports by Iwabuchi et al. using this medication was published, showing favorable results [62].

Another study conducted by Wang et al. included 46 hospitalized patients with severe COVID-19 pneumonia, who were divided into two groups based on whether they received or not corticosteroid treatment. The first group received methylprednisolone (1–2 mg/kg/d for 5–7 days), and the second group received standard therapy without methylprednisolone. The first group achieved faster improvement in clinical symptoms (fever and peripheral oxygen saturation) and lung lesions detected by imaging. However, there was no improvement in mortality or in laboratory parameters [63].

A meta-analysis carried out by Lee et al., published in April 2020, evaluated studies from January 2002 to March 2020 that included patients with severe coronavirus pneumonia, and found an increase in mortality, duration of hospitalization and rates of associated secondary bacterial infection in patients treated with corticosteroids [64]. Other meta-analyses carried out later showed similar results [65, 66]. Despite that, all meta-analyses

included studies of other coronavirus outbreaks, and there was still a lack of robust and quality work that specifically assessed the impact of these medications on serious SARS-CoV-2 infections.

The RECOVERY (Randomised Evaluation of COVID-19 Therapy) study, first large clinical trial conducted to assess the impact of the use of dexamethasone on COVID-19 infection, was published in July 2020. This study analysed 2104 patients who received 6 mg dexamethasone daily compared to participants who received usual care. A reduction in mortality of up to one-third (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI 0.51 to 0.81) in patients on mechanical ventilation and up to one-fifth (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI 0.72 to 0.94) in patients receiving only oxygen was found. There were no benefits in patients without the need for ventilatory support [6]. Although it was recently published, the results already have great repercussion in the media and social networks. The impact it will have on the general population is still unknown.

The results of the RECOVERY trial must be looked at carefully. It is important to notice that the patients that benefited most from the use of dexamethasone, which were the ones receiving invasive mechanical ventilation, were on average 10 years younger than those not receiving any respiratory support and had a history of a longer duration of symptoms (an average of 7 days longer) [6]. Also, despite the promising results related to the reduction of mortality in cases of severe COVID-19 infection, this study has methodological limitations that should be critically considered. Changes in inclusion criteria, such as expanding the age limit during the course of the study, were not anticipated in the clinical trials' protocol. The withdrawal of patients from the trial after the randomization in case the dexamethasone was unavailable generates a margin for bias. In addition, the short follow-up time (28 days) makes interpretation difficult in relation to hospitalized and severely ill patients who still had an uncertain prognosis at the end of this period. In relation to patients with diabetes, this population appears to have been adequately sampled in the study, with a co-prevalence of diabetes and COVID-19 similar to that described in the literature. It is an important limitation of the study not to describe the occurrence of hyperglycemia at different times during and after the use of dexamethasone, considering the potential risks of this complication in patients with diabetes.

It is necessary to remember that the use of corticosteroids in critically ill patients is still controversial. Several systematic reviews carried out on the topic have shown contradictory results on the benefits of hydrocortisone in mortality in shock situations [67–70]. Taking this into account, the Surviving Sepsis Campaign 3 guideline

suggests against the use of corticosteroids to treat septic shock in patients with adequate resuscitation with fluids and vasopressors. The use of hydrocortisone at a dose of 200 mg per day would be indicated only for refractory cases, but with a weak recommendation [71]. The controversial results also apply to the use of corticosteroids in patients with acute respiratory distress syndrome, on which different meta-analyses carried out in recent years have presented divergent results, making this difficult to value for clinical practice [72–75]. So far, the use of corticosteroids in critically ill patients, regardless of etiology, remains restricted to cases in which there is refractoriness in shock or in which the ventilatory pattern reflects bronchial hyperreactivity [76]. There is still a long way to go before the validation of the presented results and the incorporation of these medications in the care of the patient infected with the coronavirus, if appropriate.

The possible inadvertent consumption of dexamethasone after the release of the results of the RECOVERY study could be catastrophic. The effects of mass dissemination of these results will soon be apparent to our population. Fear and uncertainty in the face of a potentially serious infection may lead lay people to desperate decisions when looking for a “magic pill”. This feeling may lead to self-medication and the inappropriate and abusive use of corticosteroids, similarly to what happened after the disclosure of other drugs. This concern is especially relevant in countries where some corticosteroids can be dispensed without a medical prescription, such as Brazil.

### **Corticosteroids and diabetes**

Chronic or high-dose use of corticosteroids can, by itself, lead to the onset of diabetes, especially in previously insulin-resistant or obese individuals. Changes in carbohydrate metabolism, including insulin resistance and reduced peripheral glucose uptake related to its use, may explain the increased risk of diabetes. Epidemiology data on predisposing factors and the prevalence of corticosteroid-induced diabetes are not well known; however, it is estimated to occur in up to 20 to 54% of people treated with corticosteroids [77, 78]. It is postulated that patients who have a predisposition, such as the presence of Langerhans B cells with latent dysregulation or some alteration in previous peripheral sensitivity, are at greater risk of developing diabetes. Some of the risk factors for corticosteroid-induced diabetes are the same as those for type 2 diabetes: age, family history of diabetes, previous gestational diabetes, and abdominal obesity. It is known that the drug use duration and the cumulative dose used are direct predictors of higher risk for diabetes [79].

Even more damaging is the effect of glucocorticoids on patients who already have the diagnosis of diabetes.

Studies show that hyperglycemia and insulin resistance enhanced by the use of glucocorticoids results in uncontrolled diabetes in a dose-dependent manner [80, 81]. In addition to all the complications already known of inappropriate glycemic control, especially regarding the presence of micro and macrovascular complications, another study also demonstrated that elderly patients with diabetes on chronic use of high daily doses of corticosteroids had a 94% higher risk of being hospitalized due to diabetes complications [82].

In addition to the direct effects on glycemic control, the other previously mentioned effects on arterial pressure control, lipid and bone metabolism also have a potential for severe consequences in patients with diabetes. Hypertension, obesity and diabetes are diseases that are intrinsically connected in patients with metabolic syndrome. The vasoconstrictor effects and the increase in circulating volume, resulting in uncontrolled blood pressure, as well as the redistribution of fat, resulting in increased incidence of hepatic steatosis, can be especially harmful in this group. In addition, changes in bone mineral and muscle mass in patients who already have bone fragility related to diabetes can result in an increased risk of falls and fractures [83, 84]. Lastly, the use of high doses or the long-term use (more than seven days) of corticosteroids would lead to hypothalamic–pituitary–adrenal axis suppression. Drug withdrawal should be carefully done in order not to induce an iatrogenic adrenal crisis.

In patients with either a steroid-induced diabetes or a previous diagnosis of diabetes using corticosteroids, it will be required to pay close attention to blood glucose monitoring, and an early intervention may be necessary to prevent prolonged symptomatic hyperglycemia. There is no consensus on which glycemic targets are ideal for patients using glucocorticoids. In patients without a previous diagnosis of diabetes but who are at high risk of hyperglycemia (family history of diabetes, previous gestational diabetes, pre-diabetes, polycystic ovary syndrome, obesity), we suggest considering assessment of glycemic control daily for those who use doses greater than the equivalent of 40 mg of prednisone daily for periods greater than 7–14 days, although one guideline suggests a more frequent glycemic verification [85]. In case of blood glucose levels greater than 180 mg/dL, consider a more frequent observation routine, which should be individualized for each case. For patients with a previous diagnosis of diabetes, it is suggested to reinforce the testing routine before meals during the treatment with corticosteroids [85]. We recommend, according to Suh et al., that the treatment for hyperglycemia be discussed and possibly considered when the preprandial and postprandial capillary glucose levels are  $\geq 140$  and  $\geq 200$  mg/dL,

respectively [86]. Treatment adjustments should be made according to guidelines for the treatment of diabetes.

There is no treatment strategy that is ideal for all patients, and the choice of the regimen to be used will depend on which corticosteroid is in use, its potency and the duration of its action. For short-acting corticosteroids, such as prednisone, the plasma peak occurs in four to six hours after administration, but the pharmacological actions can last throughout the day [85]. It is common for patients who use only morning doses to experience glycemic oscillations throughout the day, with a tendency to normalize blood glucose levels at night [85]. For long-acting corticosteroids, such as dexamethasone, or for regimens using multiple doses, glycemic changes can last longer, affecting also fasting glucose [87, 88].

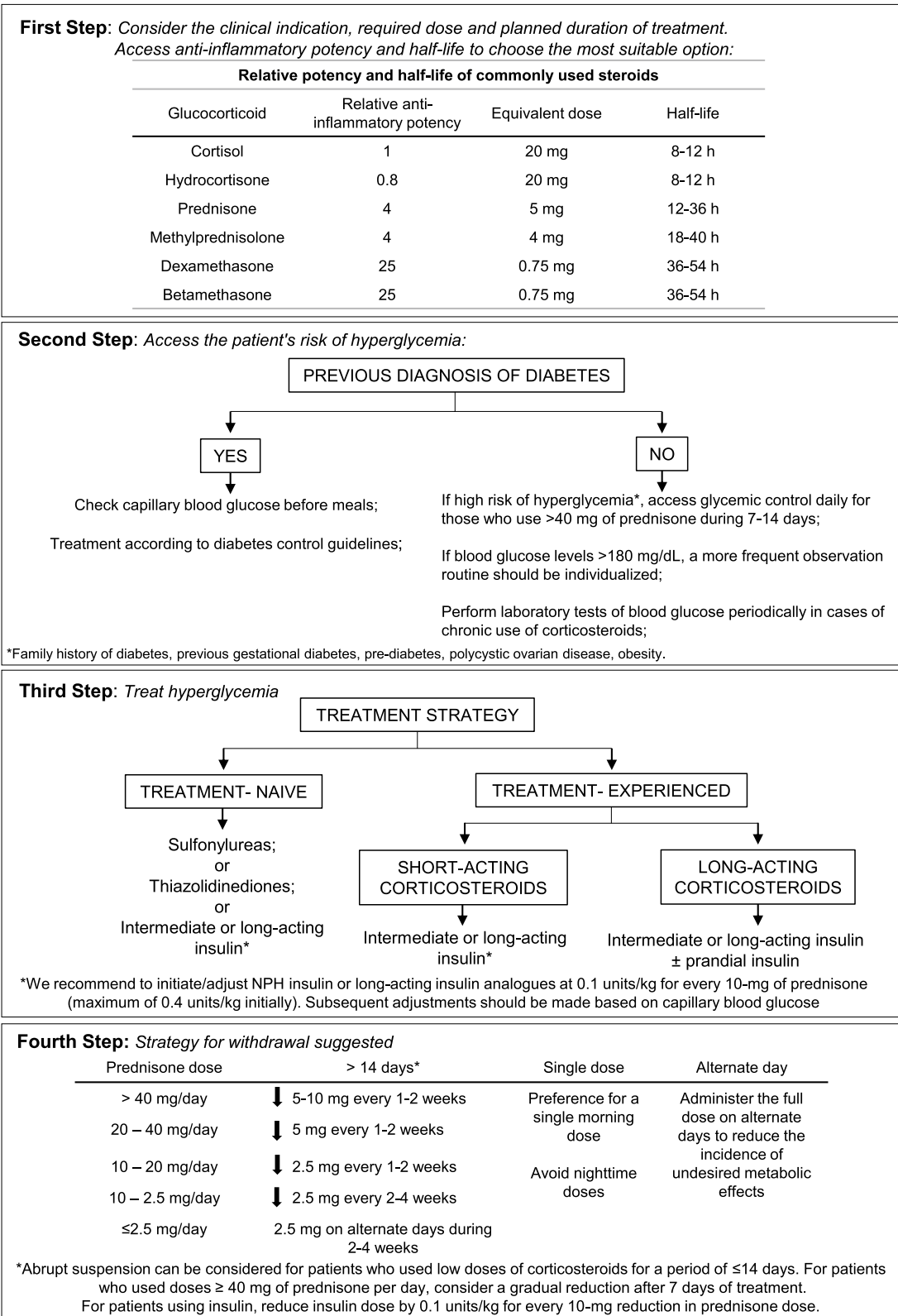
The American Diabetes Association recommends the use of insulin to correct glycemic oscillations in patients using corticosteroids. For patients receiving only single morning doses of short-acting corticosteroids, the use of intermediate or long-acting insulin analogues is usually the standard approach. For long-acting glucocorticoids, multidose or continuous glucocorticoid use, long-acting insulin may be required to control fasting blood glucose. For higher doses of glucocorticoids, a basal bolus insulin approach is often needed [89]. One recommendation is to initiate or to adjust weight-based NPH insulin at 0.1 units/kg for every 10 mg of prednisone up to a maximum of 0.4 units/kg initially [90]. Other treatment options, especially for treatment naive patients, include using sulfonylureas and thiazolidinediones considering their effects on prandial blood glucose and improvement in insulin sensitivity via PPAR agonism, respectively. It is necessary to keep in mind the risks of these medications, considering that sulfonylureas carry a risk of hypoglycemia, while thiazolidinediones are associated with fluid retention [91]. Evidences for glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors or sodium-glucose co-transporter 2 inhibitors in corticosteroids use are still limited.

Planning to withdraw corticosteroids treatment should also be part of the approach in cases where there is a prolonged use of these drugs. The most feared complication in corticosteroid withdrawal is the suppression of the hypothalamic–pituitary–adrenal axis, which can result in secondary adrenal insufficiency [92, 93]. Symptoms of chronic adrenal insufficiency include abdominal pain, nausea and vomiting, postural hypotension, drowsiness, anorexia, weakness, myalgia, arthralgia and depression [93]. More severe cases can manifest with vomiting, diarrhea, fever, acute dehydration, hypotension, shock and coma, characterizing an acute adrenal insufficiency, which is a life-threatening situation [94]. Studies show that patients who use corticosteroids for more than

14 days are at risk of developing adrenal insufficiency and need to gradually reduce the dose of the medication [95, 96]. Considering that COVID-19 is a self-limiting infectious disease, it is possible that the use of corticosteroids occurs for a shorter period of time, without causing any major concerns regarding the suppression of the hypothalamic–pituitary–adrenal axis. However, for patients who require prolonged use, gradual withdrawal strategies should be considered.

There are several different protocols for the gradual reduction of the corticosteroids; however, only a few have been tested in clinical trials, with no conclusive results. Currently, there is no evidence to support the use of one over the other. Some characteristics are associated with a lower chance of developing adrenal insufficiency in corticosteroid removal. The use of the total dose in the morning, avoiding night doses, may be a good strategy, considering that the night dose can block the peak of morning ACTH, increasing the chance of blocking the hypothalamic–pituitary–adrenal axis [97]. The administration of the total dose on alternate days is another strategy, and the rationale for its use is based on the theory that the anti-inflammatory effect persists longer than the undesired metabolic effects, making this an alternative for a lower incidence of adverse effects.

According to Axelrod et al., for patients who used corticosteroids for a period of less than or equal to 7 days, medication withdrawal can be done abruptly, without risk of adrenal suppression [95]. More recent references suggest that, when used for less than 14 days, there would be a low risk of hypothalamic–pituitary–adrenal axis suppression [96]. We suggest that the time for abrupt suspension should be assessed individually, and can be considered for patients who used low doses of corticosteroids for a period of less than or equal to 14 days. For those who used higher doses (greater than or equal to the equivalent of 40 mg of prednisone per day) for more than 7 days, we suggest a gradual dose reduction. When treatment is carried out for a longer period than 14 days, a gradual reduction according to the total dose administered is usually recommended. We suggest, for patients using a daily dose greater than 40 mg of prednisone (or equivalent), to start with a reduction of 5 to 10 mg every 1 or 2 weeks. When the daily dose is between 20 and 40 mg of prednisone (or equivalent), we suggest a reduction of 5 mg every 1 or 2 weeks. When the daily dose is between 10 and 20 mg of prednisone (or equivalent), we suggest a reduction of 2.5 mg every 1 or 2 weeks [98]. When the daily dose is less than 10 mg of prednisone (or equivalent), we suggest reducing 2.5 mg every 2 to 4 weeks and then administer 2.5 mg of prednisone on alternate days during 2 to 4 weeks until complete suspension. It is important to remember that, for patients using



**Fig. 2** Rational assessment for the initiation, maintenance and withdrawal of corticosteroids



insulin, dose adjustment should be performed during the corticosteroid removal. Wallace et al. recommends reducing insulin dose by 0.1 units/kg for every 10-mg reduction in the prednisone dose [91]. A summary of the suggested approach is shown in Fig. 2.

## Conclusion

The presence of hyperglycemia, increased insulin resistance and increased blood pressure levels are some of the effects that may clinically decompensate the patient with diabetes who decides to use corticosteroids without medical supervision or those being prescribed by physicians not aware of how to handle this situation. In the long run, the effects on liver metabolism, leading to hypertriglyceridemia and steatosis, and on bone metabolism, leading to a reduction in bone matrix, may lead to even more serious consequences. Although it is well known that these effects are dose dependent, it is unknown how the use of this medication, without medical supervision, will occur. However, it may occur in an erratic or lasting way. The risks of adrenal insufficiency after abrupt withdrawal of dexamethasone or Cushing's syndrome with continuous and prolonged use should always be suspected. More than ever, it is necessary for health professionals to be alert and able to predict damages related to the use of these drugs, which is the first step to minimize the potential damages to come. It is essential that, at this time, patients be offered guidance on the danger of inappropriate use of corticosteroids and self-prescription without adequate medical monitoring. Inexperience and recklessness in the use of medications such as dexamethasone have the power to transform a friendly drug into a potential foe of our health.

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## Authors' contributions

JA and GBO performed the literature review and wrote the initial manuscript. BDS and GHT supervised the work, reviewed and edited the final manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

Since it is a narrative review, availability of data and materials does not apply.

## Ethics approval and consent to participate

Since it is a narrative review, consent to participate does not apply. All authors agreed with the responsible use of the data used.

## Consent for publication

All authors have reviewed the final version of the manuscript and agree with the publication of the information presented here.

## Competing interests

No potential conflicts of interest relevant to this article were reported.

## Author details

<sup>1</sup> Medical Science Program: Endocrinology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. <sup>2</sup> Internal Medicine Department, Hospital São Lucas-Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil. <sup>3</sup> School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil. <sup>4</sup> School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. <sup>5</sup> Endocrinology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. <sup>6</sup> National Institute of Science and Technology for Health Technology Assessment (IATS), CNPq, Porto Alegre, Brazil. <sup>7</sup> Medicine and Health Sciences Program, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil.

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