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Review Article

Overview and Management of Glucocorticoid-Induced Hyperglycemia in Pulmonary Diseases: Insight into the COVID-19 Pandemic

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ABSTRACT

Background: Glucocorticoids are potent anti-inflammatory agents that have become an integral component of the standard of care for numerous pathologies. Their wide-ranging uses and efficacy in different treatment pathways are not without important adverse events to consider. Glucocorticoid-induced hyperglycemia remains a prominent issue but the optimal management is understudied. Pulmonary diseases represent a large disease group in which glucocorticoids have shown clinical benefits. Glucocorticoid-induced hyperglycemia in pulmonary disease has been associated with adverse patient outcomes. The coronavirus disease 2019 (COVID-19) pandemic has now introduced a novel indication for glucocorticoids and has further highlighted that hyperglycemia results in increased mortality.

Methods: Here we review literature-based epidemiology, clinical outcomes, and treatment of glucocorticoid-induced hyperglycemia in chronic obstructive pulmonary disease, asthma, and most recently, COVID-19. Lastly, we provide a comprehensive review of the outcomes related to hyperglycemia, implications of glucocorticoid treatment, and treatment approaches to hyperglycemia in the COVID-19 pandemic.

Conclusion: Management of people with diabetes requiring glucocorticoid therapy can be complex and require aggressive treatment. Awareness of the prevalence of hyperglycemia, attention to insulin and glucocorticoid action profiles, and treatment options can assist in improving glycemic outcomes.

KEYWORDS

Glucocorticoid-induced hyperglycemia, Glucocorticoids, Steroid-induced diabetes, Diabetes, Chronic obstructive pulmonary disease, Asthma, COVID-19.

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Introduction

Systemic glucocorticoids (GC) are implemented in the treatment of a variety of inflammatory and autoimmune pathologies, with new uses being implemented often including most recently in the treatment of severe coronavirus disease 2019 (COVID-19) [1,2]. While there are many important benefits to GC use, GC-induced hyperglycemia remains a prevalent issue among hospitalized patients with consequential health outcomes, including slower recovery from illness and longer hospitalizations [3,4].

GC-induced hyperglycemia is defined as the abnormal elevation in blood glucoses associated with GC administration [5]. Similar to other types of diabetes mellitus, diagnosis is made with either a fasting glucose > 126 mg/dL (7.0 mmol/L), glucose > 200 mg/dL (11.1 mmol/L) after a two hour 75-gram oral glucose tolerance test, hemoglobin A1c (HbA1c) > 6.5% (48 mmol/mol), or with a random glucose > 200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia [6].

Hyperglycemia secondary to high doses of GC is known to occur in patients with and without diabetes. It occurs in the majority of patients receiving this type of treatment with rapid onset, usually occuring within 24-48 hours of initiation [7-9]. Risk factors for GC-induced hyperglycemia include pre-existing diabetes, impaired glucose tolerance, family history of diabetes, abdominal obesity, high BMI, higher GC doses, longer treatment duration, and older age [10-12]. Despite the wide spectrum of use for GC and their widely known adverse effects, the optimal management of GC-induced hyperglycemia has not been established. Further, the management may vary according to the particular treatment indication and dose schedule.

Here we will review GC use in chronic obstructive pulmonary disease (COPD), asthma, and COVID-19, the impact of GC-induced hyperglycemia on patient outcomes, as well as the available hyperglycemia treatment methods in the literature.

Pathophysiology of Glucocorticoid-Induced Hyperglycemia:

Systemic GC induce insulin resistance and lead to elevated blood glucoses through several mechanisms. GC promote the release of energy precursors including glucose, amino acids, and fatty acids by increasing hepatic gluconeogenesis, skeletal muscle protein breakdown, and lipolysis, and by decreasing glucose uptake and consumption [13,14]. GC induce hepatic glycogen storage, reduce hepatic and peripheral tissue insulin sensitivity, and increase glycogenolysis in skeletal muscle [13,15]. The summation of these complex pathways results in insulin resistance and significant hyperglycemia. GC drive hyperglycemia further through their direct inhibition of insulin release from pancreatic beta cells [16,17]. In the short-term, GC-induced insulin resistance can cause beta cell hyperplasia resulting in excess insulin secretion to maintain euglycemia [13]. With chronic GC exposure, however, this balance fails resulting in persistent hyperglycemia [13]. Over time, GC excess leads to abdominal obesity and dyslipidemia, thus increasing the risk for chronic cardiovascular comorbidities [14].

Epidemiology of Glucocorticoid-induced Hyperglycemia:

With the growing number of indications for GC use in hospitalized patients, it is imperative that clinicians are cognizant of the risk of associated hyperglycemia. This prevalence varies according to the population examined in the literature. Donihi et al. investigated the prevalence of GC-induced hyperglycemia in hospitalized general medicine patients receiving ≥ 40 mg/day prednisone or equivalent steroid doses with glucoses ≥ 200 mg/dL (11.1 mmol/L). The authors showed that hyperglycemia was found in the majority of patients regardless of diabetes history [7]. Many other studies have corroborated these findings and have shown that 33.5 to 70% of hospitalized patients receiving GC develop hyperglycemia [7,9,18].

Morbidity and Mortality Associated with Glucocorticoid-induced Hyperglycemia:

Inpatient glycemic variability is widely known to be associated with adverse patient outcomes. It is linked to prolonged hospitalizations and increased mortality regardless of diabetes status or other risk factors [3,4]. Glycemic excursions have been also associated with increased cardiovascular mortality in patients with type 1 and type 2 diabetes, likely through inducing increased oxidative stress and endothelial dysfunction [20]. Hyperglycemia in hospitalized patients is very common and undertreated, including in patients without pre-existing diabetes [21]. GC treatment exacerbates the risk of new hyperglycemia in hospitalized patients [18]. Adverse events associated with GC-induced hyperglycemia include increased risks of adverse cardiovascular events and infections compared to normoglycemic patients [18].

Hypoglycemia is also very common among hospitalized patients regardless of diabetes history. Systemic GC impose an increased risk for hypoglycemia, which occurs in about 10% of patients undergoing GC treatment [22]. Hypoglycemia secondary to systemic steroids is associated with an increased risk of death after one year [18,22]. Hypoglycemia in general has been associated with increased mortality and clinicians must be aware of the increased risk with GC use [23].

With the clear evidence of increased morbidity and mortality associated with dysglycemia, diligence is needed to reduce glycemic variability when treating patients with GC. Inpatient treatment guidelines for GC-induced hyperglycemia, however, are not well established, outcome data for different regimens are limited, and there are no large head-to-head trials [24-26]. While basal-bolus insulin therapy is routinely recommended, optimal treatment regimens are not clearly described often leading to inadequate insulin dosing [24,25,27]. COPD and asthma represent common inpatient indications for GC, but hyperglycemia treatment guidelines are limited. The COVID-19 pandemic has introduced a novel indication for systemic GC with recent literature reporting increased mortality related to hyperglycemia [2,28]. An urgent need persists for insulin dosing and titration protocols that can be easily and widely adopted for GC-induced hyperglycemia.

Pulmonary Disease and Glucocorticoid-induced hyperglycemia:

Chronic Obstructive Pulmonary Disease:

GC are an essential component of therapy in acute severe exacerbations of COPD in hospitalized patients. GC rapidly improve oxygenation and symptoms of dyspnea, improve forced expiratory volume in one second (FEV1), reduce treatment failure, and shorten hospitalizations [29-32]. Shorter courses of lower doses of oral GC are recommended to achieve these outcomes while minimizing

any adverse outcomes associated with their use [33,34]. The landmark REDUCE trial demonstrated that a 5-day course of GC was noninferior to a 14-day course [33]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Science Committee now recommends 5 to 7 days of oral prednisone 40 mg [35].

Hyperglycemia is commonly observed with GC treatment during acute COPD exacerbations, however data describing the overall incidence and prevalence is variable. This is likely due to the diverse steroid regimens and differing diagnostic criteria for hyperglycemia used in studies [31]. The REDUCE trial described glycemic outcomes as well. New or worsening hyperglycemia was identified in more than 56% of patients in both treatment groups [33]. The prevalence of GC-induced hyperglycemia in hospitalized COPD patients has been reported to be as high as 80%. Steroid use in acute COPD is associated with a significantly higher risk of hyperglycemia, with a trend towards increased hyperglycemia as steroid doses are escalated [32,36,37]. Further details on these studies reporting glycemic outcomes in COPD are listed in Table 1.

Hyperglycemia is associated with adverse outcomes in acute exacerbations of COPD. Diabetes mellitus is a common comorbidity in COPD patients occurring in 22 to 36% of patients and has been linked to prolonged hospitalizations and increased mortality [34,38,39]. Chakrabarti et al. described an association between admission hyperglycemia and negative sequelae in 88 COPD patients admitted to critical care. Baseline hyperglycemia was defined as serum glucose > 126 mg/dL (7 mmol/L) prior to initiation of non-invasive ventilation (NIV). Hyperglycemia occurred in 50% of patients, with NIV failure occurring in 34% of the hyperglycemic patients compared to just 2% in the euglycemic group (p=0.003) (Table 1) [40]. A retrospective study by Baker et al. examining 433 hospitalizations assessed clinical outcomes of COPD patients treated with steroids according to blood glucose quartiles. Higher blood glucoses were associated with an increased risk of death and longer length of stay compared to participants in the lowest blood glucose group. The relative risk of death was highest in the participants with the greatest level of blood glucose elevations (Table 1) [41]. More recently, continuous glucose monitoring (CGM) has been utilized to demonstrate that hyperglycemia associated with acute COPD exacerbations prolongs inpatient hospitalizations. Results from a study using CGM in 47 participants illustrated an association in which length of stay was extended by 10% or 21 hours for every 18 mg/dL (1 mmol/L) increase in mean glucose (Table 1) [42].

Treatment of hyperglycemia associated with acute COPD exacerbations is understudied and optimal management remains unclear. Metformin as well as dapagliflozin have been studied in COPD patients, however these agents have not shown notable improvement in inpatient glycemic control [43,44]. The most appropriate insulin regimen has not been identified in acute COPD. A small randomized study in Spain compared once-daily insulin glargine to meal-time NPH insulin in 53 patients with type 2 diabetes receiving high doses of GC. There were no statistical differences in mean glucose, time in range (80-180 mg/dL or 4.44-10 mmol/L), measures of glycemic variability, or rates of hypoglycemia between the groups [45]. Details of the studies describing hyperglycemia treatment in COPD are included in Table 3. Further studies are ultimately needed to determine the optimal treatment of GC-induced hyperglycemia in COPD.

Asthma

Asthma affects 8% of adults in the United States and caused more than 3300 deaths in 2019 [46]. Guidelines recommend using oral GC in patients with severe asthma who experience persistent respiratory symptoms despite adherence to standard therapies including high-dose inhaled corticosteroids and bronchodilators [47,48]. Similar to COPD treatment, a short course of prednisone 40 to 50 mg/day for 5 to 7 days is typically used [47]. The lifetime cumulative GC exposure can be very high in patients with chronic severe asthma [49].

The prevalence of hyperglycemia in asthma was described by Koskela et al. Of the 89 patients with asthma but no history of diabetes, 79% experienced hyperglycemia during their admission, with 67% experiencing fasting hyperglycemia and 53% experiencing postprandial hyperglycemia (Table 1) [36]. Another study reported an increased risk of developing diabetes in patients with severe asthma during 8-year follow-up compared to patients who were not treated with systemic glucocorticoids (HR 1.20, 95% CI: 1.11-1.30) [48]. Diabetes is reported in 10% of patients with severe asthma, which is likely due to chronic glucocorticoid exposure, and is comorbid in approximately 25% of all asthma patients [50,51]. Diabetes is also known to be a risk factor for recurrent asthma exacerbations [51-53].

Hyperglycemia associated with GC use may be a risk factor for prolonged hospitalizations in acute asthma exacerbations. Wytrychowski et al. compared two glycemic target ranges in asthma patients receiving IV methylprednisone using an intensive IV insulin regimen with glucose target of 81 to 130 mg/dL (4.5 to 7.2 mmol/L) versus a target of 130 to 180 mg/dL (7.2 to 10.0 mmol/L) using a subcutaneous prandial insulin regimen. Regardless of the type of insulin regimen, hyperglycemia was associated with a prolonged length of stay compared to patients without diabetes or baseline hyperglycemia (Table 1) [54]. Although the link between hyperglycemia and asthma exacerbations has been described before, further studies describing GC-induced hyperglycemia's impact on clinical outcomes, as well as the ideal treatment, are sparse. Diabetes medications, such as metformin and glucagon-like peptide-1 receptor agonists, have been studied in the management and prevention of asthma symptoms but the management of hyperglycemia in the setting of asthma exacerbations has not been studied [55,56]. This may be an opportune patient cohort that could benefit immensely from algorithmic inpatient treatment protocols.

COVID-19

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was identified in December 2019 in Wuhan, China after several patients presented with severe

pneumonia [2,57]. As of May 2021, there have been more than 161 million cases of COVID-19 worldwide with more than 3.3 million deaths [58]. GC have become an essential component of inpatient treatment for COVID-19-related lung injury. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial published in 2020 led to some standardization of GC use in hospitalized COVID-19 patients. This study compared dexamethasone 6 mg daily for up to 10 days to standard of care and showed that dexamethasone led to reduced 28-day mortality in patients requiring mechanical ventilation or oxygen supplementation, shorter hospitalizations, and lower risk of mechanical ventilation [2]. GC have become the new standard of care in hospitalized patients with COVID-19 who require ventilatory support. As a result, hyperglycemia has moved to the forefront of management concerns for inpatient endocrinology.

COVID-19 causes diffuse alveolar damage, pulmonary edema, and the development of hyaline membranes in the lungs, which are features indicative of acute respiratory distress syndrome (ARDS). ARDS is a syndrome characterized by acute respiratory failure, lung inflammation, and increased vascular permeability [59,60]. ARDS is responsible for a significant proportion of mortality in COVID-19 patients [61,62]. Severe COVID-19 infection and the subsequent development of ARDS and multiorgan failure is thought to be driven by T cell overactivation and the proinflammatory cytokine storm that develops [63-66]. Systemic GC were introduced as a method to suppress this severe inflammatory response and prevent the devastating pulmonary damage often seen in COVID-19 patients [62,66].

Hyperglycemia has been frequently reported since the beginning of the COVID-19 pandemic [68]. Due to the relatively new use of GC in severe COVID-19 treatment, the prevalence and morbidity associated specifically with GC-induced hyperglycemia has not yet been described in the literature. Diabetes, however, is a common comorbidity in severe COVID-19 and has become an active area of research. In March 2020, diabetes mellitus was present in 10.9% of all confirmed COVID-19 patients and in 32% of all ICU admissions [69]. Table 2 provides a review of several recent studies on the impact of diabetes and hyperglycemia on the hospital course of patients with COVID-19. Several studies reported a higher incidence of ICU admissions and death in people with diabetes [70-73]. Furthermore, early hyperglycemia has been associated with an overall increased mortality risk [74]. A multicenter study published by Klonoff et al. showed that severe hyperglycemia on days 2 to 3 of non-ICU hospitalizations or at the time of ICU arrival is associated with increased mortality compared to patients with well-controlled glucoses (Table 2) [75]. These findings suggest that achieving early glucose control in COVID-19 patients could impact outcomes. Additionally, Bode et al. reported on the glycemic outcomes of COVID-19 patients with and without diabetes.The mortality rate of the diabetes and/or uncontrolled hyperglycemia group was 28.8%, which was significantly higher than that of the group without diabetes or hyperglycemia, where the mortality rate was 6.2% ($p<0.001$) (Table 2) [28]. Other studies have described an increased risk of ARDS, acute kidney and cardiac injury, septic shock, and disseminated intravascular coagulation in patients with diabetes [76,77]. Risk factors for increased COVID-19-related morbidity and mortality in diabetes include uncontrolled hyperglycemia, elevated HbA1c, obesity, renal dysfunction, longer history of diabetes, male sex, and older age [70,78,80].

Hyperglycemia in the setting of COVID-19 infection has been characterized, but the pathophysiology is not yet fully understood. Potential mechanisms explaining hyperglycemia include impaired insulin secretion, adipose tissue dysfunction, insulin resistance, diminished glucose utilization, and acute beta cell injury [81-84]. Hyperglycemia may support viral replication and proinflammatory cytokine expression, predisposing hyperglycemic individuals to a higher risk of COVID-19 [85]. With the increased use of systemic GC in severe COVID-19, the well-known effect of steroids on glycemic control, and the negative outcomes associated with diabetes in this novel virus, hyperglycemia must be urgently addressed.

Although there is growing evidence of negative outcomes associated with hyperglycemia in COVID-19, optimal management of inpatient hyperglycemia, especially with the addition of high doses of GC, has not yet been firmly established. No randomized controlled trials in this area have taken place, so recommendations have been based on observational data and expert opinion. In general, HbA1c, blood glucose levels, and venous blood gas should be checked upon admission for patients with known history of diabetes [86]. Most non-insulin diabetes medications should be stopped during treatment of COVID-19 due to risks of adverse effects such as hypoglycemia, acute kidney injury, or dehydration [86,87]. Insulin is the treatment of choice in patients requiring hospitalization for COVID-19 [86]. Subcutaneous basal, prandial, and correction insulin regimens have been recommended for hemodynamically stable COVID-19 patients, but the most ideal regimen is unknown [88-90]. Patients may require more than 1 unit/kg/day of insulin during acute infection, which is more than the typical inpatient recommended starting doses [91]. Anecdotal experience from the pandemic has been reported such as adding an arbitrary dose of 20 to 30 units of NPH insulin to standing insulin orders when glucocorticoids are given to offset the hyperglycemic effect [92].

In terms of glycemic targets in COVID-19 management, the evidence is variable. Results from Klonoff's study suggest that aiming for glucoses between 141 to 180 mg/dL (7.83 to 10 mmol/L) within 2 to 3 days of non-ICU hospitalization while avoiding hypoglycemia may reduce mortality (Table 2) [75]. These glycemic targets are not different from current inpatient diabetes management guidelines [89]. Zhu et al. reported better clinical outcomes in patients with glucoses between 70 to 180 mg/dL (3.9 to 10 mmol/L), compared to patients with glucoses >180 mg/dL (10 mmol/L) (Table 2) [77]. Ultimately avoiding hypoglycemia and hyperglycemia will benefit patients with diabetes who are confronted with COVID-19.

Protocols of insulin dosing in COVID-19 may aid clinicians in

achieving early glycemic control. The National Diabetes Inpatient COVID-19 Response Group in the United Kingdom published a guidance document for inpatient glycemic management in May 2020, aiming for glucoses to fall within 108 to 180 mg/dL (6 mmol/L to 10 mmol/L). The general guidance is to start the patient's home insulin regimen or to start weight-based basal insulin if there are more than two glucoses >216 mg/dL (12 mmol/L) with insulin titration instructions and correction doses based on glucose ranges [93,94]. Gianchandani et al. published their institution's hyperglycemia treatment algorithm in October 2020; their protocols aim for glucoses between 150 to 180 mg/dL (8.3-10 mmol/L). Results of these algorithms have not been reported yet [95]. Details of these treatment guidance articles are listed further in Table 3.

Conclusion

Hyperglycemia induced or worsened by GC remains a prevalent, undertreated aspect of inpatient care regardless of a patient's diabetes history. Treatment recommendations vary and may be vague often resulting in inadequate glycemic control. Major pulmonary diseases such as COPD and asthma often involve treatment with GC, and as a result, hyperglycemia becomes closely intertwined with the clinical outcomes of these pathologies. The new threat of COVID-19 has reinforced that diabetes and hyperglycemia should be treated aggressively to avoid unnecessary morbidity and mortality. Further research is needed to establish and validate glucose management protocols to improve glycemic control and patient outcomes.

Table 1: Studies describing glucocorticoid-induced hyperglycemia in pulmonary disease.

Study	Country	Pulmonary Disease	Objective/ Primary end point	Number of subjects/ Study design	Definition of hyperglycemia	Prevalence data	Steroid doses	Outcomes
Leuppi et al. (2013) [33] (REDUCE trial)	Switzerland	COPD	To determine whether 5-days of GC is noninferior to 14-days of GC treatment GC-related adverse events, including hyperglycemia were secondary end points	314 Randomized controlled trial	Fasting glucose ≥100 mg/dL (5.6 mmol/L), random glucose ≥140 mg/dL (7.8 mmol/L), ≥20% increase in insulin dosing, or addition of oral hypoglycemic agents	New or worsening hyperglycemia in 56.9% of 5-day group vs. 57.4% of 14-day group (p>0.99)	IV methylprednisolone 40 mg (day 1) followed by oral prednisone 40 mg for remaining course	Hyperglycemia occurrence was similar in both the 5-day and 14-day GC groups.
Koskela et al. (2013)[36]	Finland	COPD Asthma	To assess hyperglycemia prevalence	153 total: 109 with asthma vs. 44 with COPD exacerbations Prospective, cross-sectional study	Fasting BG > 124 mg/dL (6.9 mmol/L) or postprandial BG > 200 mg/dL (11.1 mmol/L)	82% had hyperglycemia No history of DM in 130 patients; 79% had hyperglycemia History of DM in 23 patients (15%); 96% of DM group had hyperglycemia	Mean daily prednisolone dose: Asthma: 0.61 ± 0.33 mg/kg COPD: 0.55 ± 0.16 mg/kg (p=0.29)	Prevalence of hyperglycemia did not differ between asthma and COPD patients: 79% vs. 80% (p=0.81)
Baker et al. (2016)[37]	United States	COPD	Compare incidence of GC-induced hyperglycemia in high- vs. low-dose steroids (methylprednisolone) *Low dose:* <125 mg *Moderate dose:* 126-187.5 mg *High dose:* 188-500 mg	245 total: 91 in low dose group; 73 in moderate dose group; 81 in high dose group Retrospective review	Random BG >180 mg/dL (10 mmol/L)	Hyperglycemia in: *Low dose:* 42% *Moderate dose:* 49% *High dose*: 54% History of DM in 12% in low dose group, 7% in moderate dose group, 6% in high dose group	Mean daily methylprednisolone dose per group: *Low dose:* 84 ± 34 mg *Moderate dose:* 121 ± 30 mg *High dose:* 170 ± 51 mg	Possible relationship between GC dose and incidence of GC-induced hyperglycemia: Comparing incidence of hyperglycemia in low to moderate dose groups: 42% vs. 49 % (p=0.33) Comparing incidence of hyperglycemia in low to high dose groups: 42% vs. 54% (p=0.10) With DM patients removed, the difference in hyperglycemic events between low dose and high dose groups trended towards significance (p=0.056)

Chakrabarti et al. (2009)[40]	United Kingdom	COPD	To determine if admission hyperglycemia affects NIV outcomes	88 with COPD exacerbations needing NIV within 24-hours of admission Prospective observational study	Random BG ≥126 mg/dL (7 mmol/L)	Hyperglycemia prior to NIV in 50% History of DM in 18%	Not described in the study	Admission hyperglycemia was noted in 41% of NIV successes (n=29/71) vs. 100% of NIV failures (n=11/11) (p<0.001) Comparing NIV failure in hyperglycemic group to euglycemic group: 34% vs. 2% (p=0.003) Pre-existing DM was not associated with NIV failure.
Baker, et al. (2006)[41]	United Kingdom	COPD	To determine relationship between BG and COPD outcomes Length of stay, in-hospital mortality, composite adverse outcomes (death or length of stay greater than 9 days)	433 admissions with acute COPD but only 284 participants had BG data Retrospective review	Hyperglycemia was not defined. Analyzed subjects according to BG quartiles: Group 1 (108 mg/dL or <6 mmol/L), Group 2 (108-124 mg/dL or 6-6.9 mmol/L), Group 3 (126-160 mg/dL or 7-8.9 mmol/L), Group 4 (>162 mg/dL or 9 mmol/L)	BG > 110 mg/dL (6.1 mmol/L) in 72% BG > 200 mg/dL (11.1 mmol/L) in 11% Median BG was 126 mg/dL (7 mmol/L) DM history in 5.3%	Not described in the study	Relative risk of death or composite adverse outcomes was highest in the most hyperglycemic group.
Burt et al. (2013)[42]	Australia	COPD	To detemine if hyperglycemia is related to length of stay using CGM	47 Post-hoc analysis	Hyperglycemia was not defined.	Mean BG: 136.8 ± 34.2 mg/dL (7.6 ± 1.9 mmol/L) Peak BG: 217.8 ± 61.2 mg/dL (12.1 ± 3.4 mmol/L) DM history in 7 subjects; new diagnosis ofm DM in 3 subjects	Mean prednisolone dose was 30 ± 7 mg/day	Positive association between mean BG and length of stay. Length of stay increased by 10% (21 hours) for every 18 mg/dL (1 mmol/L) increase in mean BG (p=0.01).
Wytrychowski et al. (2016)[54]	Poland	Asthma	To determine effect of hyperglycemia on hospitalization	24 with admission BG level >151.2 mg/dL (8.4 mmol/L) Prospective, randomized controlled trial	Hyperglycemia was not defined. 3 groups: Group A, n=11 (IV insulin to maintain BG 81-130 mg/dl or 4.5-7.2 mmol/L). Group B, n=13 (subcutaneous short acting insulin to maintain BG 130-180 mg/dL or 7.2-10 mmol/L). Group C, n=64, was the control group (no BG disturbances)	Mean admission BG: 183.6 ± 32.4 mg/dL (10.2 ± 1.8 mmol/L) in group A; 196.2 ± 54 mg/dL (10.9 ± 3 mmol/L) in group B. DM history in 4 subjects in group A and 5 subjects in group B.	All subjects received IV methylpred-nisolone 2 mg/kg four times daily	Mean duration of hospitalizations varied by treatment: Group A: 8.2 ± 2.4 days Group B: 10.2 ± 5.2 days Group C: 5.8 ± 1.9 days (p<0.001).

Abbreviations: COPD (chronic obstructive pulmonary disease), BG (blood glucose), GC (glucocorticoid), NIV (non-invasive ventilation), CI (confidence interval), CGM (continuous glucose monitor), IV (intravenous)

Table 2: Studies describing outcomes of diabetes and hyperglycemia in COVID-19.

Study	Country	Primary end point/Objective	Number of subjects/ Study design	Definition of hyperglycemia	Diabetes prevalence	Steroid doses	Outcomes
Guan et al. (2020)[71]	China	Admission to ICU, use of mechanical ventilation, or death (composite outcome)	1099 patients with COVID-19. 173 patients identified as having severe disease and 67 patients reached the primary endpoint. Retrospective review	Hyperglycemia was not defined.	History of DM in 7.4% of all patients	Steroid doses were not described. GC were given to 18.6% of all patients, and 44.5% of patients with severe disease.	DM present in 27% of patients reaching primary endpoint. DM present in 16.2% of patients with severe disease.
Zhou et al. (2020)[72]	China	To determine risk factors for increased COVID-19 mortality	191 patients with COVID-19, where 54 were non-survivors and 137 were survivors. Retrospective cohort study	Hyperglycemia was not defined.	History of DM in 19% of all patients	Steroid doses were not described. GC were given to 30% of all patients.	DM present in 31% of non-survivors vs. 14% in survivors (p=0.0051). DM is a risk factor for in-hospital death in COVID-19 (OR 2.85, 95% CI 1.35-6.05, p=0.0062).
Yang et al. (2021)[74]	United States, China, Italy	To assess the relationship between admission hyperglycemia and COVID-19 outcomes	16 studies with 6386 COVID-19 patients Meta-analysis	Varied according to individual study	N/A	Steroid doses were not described	Compared to controls: Admission hyperglycemia is associated with increased risk of mortality in COVID-19 (OR 3.45, 95% CI, 2.26–5.26, I^2 = 56.3%, p=0.015). Admission hyperglycemia is associated with increased risk of severe disease in COVID-19 (OR 2.08, 95% CI, 1.45–2.99, I^2 = 77.9%, p<0.001).
Klonoff et al. (2021)[75]	United States	To determine relationship between glucose levels and hospital mortality in COVID-19. Main outcome: time to mortality Primary exposure: BG control days 2-3 in non-ICU vs. day 2 of ICU	1544 patients with COVID-19 (1184 non-ICU patients; 360 ICU patients) Retrospective review	Mean BG > 180 mg/dL (10 mmol/L) Severe hyperglycemia: BG >250 mg/dL (13.88 mmol/L) Control group: <140 mg/dL (7.77 mmol/L)	History of DM in 40% of non-ICU group. History of DM in 40% of ICU group.	Steroid doses were not described.	*In non-ICU group:* Highest mortality risk was in patients with mean BG >250 mg/dL (13.88 mmol/L) at 21%, compared to lower BG groups (p=0.73 comparing all glucose level groups) at days 2-3 (HR of 7.60, 95% CI 1.95–29.60). *In ICU group:* Highest mortality risk was in patients with mean BG >250 mg/dL (13.88 mmol/L) at 45%, compared to lower BG groups (p=0.52 comparing all glucose level groups). In ICU patients, severe hyperglycemia at admission was associated with increased mortality (HR 3.14, 95% CI 1.44–6.88). This association was not significant for day 2 in ICU.

Bode et al. (2020)[28]	United States	Glycemic control, clinical outcomes, length of stay, in-hospital mortality	1122 patients with COVID-19 (n=451 for DM and/or hyperglycemia group vs. n=671 for euglycemic group). Separate analysis of 570 patients who were discharged or died (n=184 for DM and/or uncontrolled hyperglycemia group vs. n=386 for euglycemic group). Retrospective observational study	≥2 BG >180 mg/dL (10 mmol/L) within 24-hour period	Hyperglycemia in 23% of all patients. History of DM in 17.3% of all patients.	Steroid doses were not described.	In-hospital mortality was higher in the DM and/or uncontrolled hyperglycemia group compared to euglycemic group: 28.8% vs. 6.2% (p<0.001). Mean length of stay was higher in the DM and/or uncontrolled hyperglycemia group compared to euglycemic group: 6.2 ± 3.7 vs. 5 ± 3.3 days (p<0.001). Of the 96 patients who had uncontrolled hyperglycemia without preexisting DM, inpatient mortality was 41.7% vs. 14.8% in the 88 patients who had preexisting DM (p<0.001).
Wu et al. (2020)[76]	China	Development of ARDS, death	201 patients with COVID-19 Retrospective cohort study	Hyperglycemia was not defined.	History of DM in 10.9% of all patients.	30.8% of patients received methylprednisolone, however the dose is not reported.	Diabetes was present in 19% of patients who developed ARDS compared to 5.1% in patients who did not develop ARDS (p=0.002). Diabetes was significantly associated with increased risk of ARDS (HR 2.34, 95% CI 1.35-4.05, p=0.002), but was not significantly associated with increased risk of death (HR 1.58, 95% CI 0.80-3.13, p=0.19).
Shi et al. (2020)[73]	China	In-hospital mortality of COVID-19 patients with DM, risk factors for death of patients with DM	1561 COVID-19 patients Each DM patient was age- and sex-matched to a patient without DM. Retrospective review	Hyperglycemia was not defined.	History of DM in 9.8% (153 patients).	Steroid doses were not reported.	Patients with DM had higher ICU admission rates compared to the control group (17.6% vs. 7.8%, p<0.05). Patients with DM had an increased risk of: ARDS: 24.8% vs. 11.1% (p<0.05) Acute cardiac injury: 30.7% vs. 17% (p<0.05) Infection: 24.2% vs 11.1% (p<0.05) Shock: 20.9% vs. 10.5% (p<0.05) AKI: 12.4% vs. 3.3% (p<0.05) Patients with DM had higher mortality compared to controls (20.3% vs. 10.5%, p<0.05).
Zhu et al. (2020)[77]	China	To assess the association between BG and COVID-19 patient outcomes in T2D	7337 patients with COVID-19 Retrospective review	Hyperglycemia was not defined.	History of T2D in 13%	23.7% of all patients vs. 29.4% in T2D group vs. 22.8% in control group (p<0.001) received systemic GC, however doses are not reported.	In-hospital mortality was higher in T2D group compared to patients without DM (7.8% vs. 2.7%, p<0.001). Risk of all-cause mortality was higher in T2D group compared to patients without DM (adjusted HR 1.70, 95% CI 1.29-2.24, p<0.001). All-cause mortality was lower in patients with well-controlled BG (70 to 180 mg/dL or 3.9-10 mmol/L) compared to poorly controlled BG (>180 mg/dL or 10 mmol/L) (1.1% vs. 11%, p<0.001).

Abbreviations: COVID-19 (coronavirus disease 2019), ICU (intensive care unit), DM (diabetes mellitus), GC (glucocorticoid), OR (odds ratio), CI (confidence interval), BG (blood glucose), HR (hazard ratio), ARDS (acute respiratory distress syndrome), AKI (acute kidney injury), T2D (type 2 diabetes mellitus)

Table 3: Treatment of glucocorticoid-induced hyperglycemia in pulmonary disease.

Study	Country	Pulmonary disease	Primary End point/ objective	Number of subjects/ study design	Definition of hyperglycemia	Steroid Doses	Hyperglycemia intervention	Outcomes/ treatment recommendations
Hitchings et al. (2016)[43]	United Kingdom	COPD	Mean in-hospital BG	52 (34 metformin, 18 placebo); excluded patients with DM Randomized controlled trial	Hyperglycemia was not defined	Prednisolone 30 mg/day for ≥7 days	Metformin 2 grams daily vs. placebo for one month	Mean BG were similar between the groups: 127.8 ± 16.2 mg/dL (7.1±0.9 mmol/L) in the metformin group vs. 144 ± 59.4 mg/dL (8±3.3 mmol/L) in the placebo group (p=0.273). Gastrointestinal side effects were more common in the metformin-treated group.
Gerards et al. (2018)[44]	Netherlands	COPD	Difference in glycemic control (target BG range 70-180 mg/dL or 3.9-10 mmol/L), hypoglycemia incidence	46 with type 2 DM or admission BG > 180 mg/dL (10 mmol/L) Randomized controlled trial	> 180 mg/dL (10 mmol/L) Capillary BG and CGM used	Prednisone ≥ 30 mg daily for 5-14 days	Dapagliflozin 10 mg vs. placebo (add-on treatment to DM regimen)	Glycemic control was similar between the groups: time in target range was 54±27.7% for dapagliflozin group vs. 53.6±23.4% for placebo group (p=0.96). There also was no significant difference in hypoglycemia events between the groups.
Ruiz de Adana et al. (2015)[45]	Spain	COPD Pneumonia Asthma	Mean BG	53 with type 2 DM 49.1% COPD, 26.4% pneumonia, 15.1% asthma, 9.4% other. Randomized controlled trial	>180 mg/dL (10 mmol/L) Capillary BG and CGM used	Methylpred-nisolone>40 mg/ day or deflazacort >60 mg/day	Glargine vs. NPH insulin (weight-based dose of 0.3-0.5 units/kg according to admission BG level) Insulin glulisine was used for all subjects.	There were no statistical differences in mean glucose, % time in range (80-180 mg/dL or 4.44-10 mmol/L), glycemic variability, or hypoglycemia between the groups.
Bellido & Perez (2021)[88]	Spain	COVID-19	To provide advice on management of COVID-19 and hyperglycemia	N/A Review and guidance document Target BG: 140-180 mg/ dL (7.8-10 mmol/L) in critically ill; 110-180 mg/ dL (6.1-10 mmol/L) in non-critically ill	> 180 mg/dL (10 mmol/L)	Steroid doses are not specified.	N/A	Insulin is the preferred treatment for COVID-19-related hyperglycemia. Critically ill patients: IV insulin Noncritically ill patients: basal-correction insulin, basal-bolus-correction insulin regimens. Doses and titration are not specified. Consider patients receiving GC to be in critically ill group.
Pasquel & Umpierrez (2020)[90]	United States	COVID-19	To provide advice on management of COVID-19 and hyperglycemia	N/A Guidance document Target BG: BG 100-180 mg/dL (5.6-10 mmol/L)	Mild hyperglycemia: BG <200 mg/dL (11.1 mmol/L); Moderate hyperglycemia: BG 201-300 mg/ dL (11.2-16.7 mmol/L); Severe hyperglycemia: BG >300 mg/dl (16.7 mmol/L)	N/A	N/A	Insulin: 0.1-0.5 units/kg/ day with dose based on DM history/meds, renal function, glycemic status. Add on sitagliptin or linagliptin for mild and moderate hyperglycemia. Basal-bolus insulin for severe hyperglycemia: 50% basal, 50% prandial; adjust as needed.

Korytkowski,et al. (2020)[91]	United States	COVID-19	To provide advice on management of COVID-19 and diabetes	Case report; review	BG > 180 mg/dL (10 mmol/L)	The authors cite IV hydrocortisone 50 mg every 6 hours	N/A	Consider NPH insulin +/- basal-bolus regimen; intensify home insulin regimens. Specific doses are not mentioned. Consider IV insulin for persistent GC-induced hyperglycemia.
Rayman, et al. (2020)[93,94]	United Kingdom	COVID-19	To provide guidance for managing inpatient hyperglycemia in COVID-19	N/A Guidance document Target BG: 108- 180 mg/dL (6 – 10 mmol/L)	BG >180 mg/dL (10 mmol/L), with up to 216 mg/dL (12 mmol/L) being acceptable	N/A	N/A	Start home basal insulin or new start at 0.15-0.25 units/kg if ≥ two glucoses >216 mg/dL (12 mmol/L). Lower dose for older patients or renal insufficiency. Insulin adjustments and correction doses are recommended based on glucose level. Reduce insulin if GC is stopped. Specific dose is not mentioned.
Gianchandani, et al. (2020)[95]	United States	COVID-19	To review the University of Michigan's treatment algorithms for hyperglycemia in COVID-19	N/A Guidance document Target BG: 150-180 mg/dL (8.3-10 mmol/L)	BG >180 mg/dL (10 mmol/L); >200 mg/dL (11.1 mmol/L) in certain patients (severe disease, tube feeds) Severe hyperglycemia: >450 mg/dL (25 mmol/L)	N/A	N/A	*For BG 200-250 mg/dL (11.1-13.9 mmol/L):* start sliding scale regular insulin; add regular insulin every 6 hours if uncontrolled BG. Start insulin glargine at 0.1-0.3 units/kg if still uncontrolled. Add basal insulin at reduced dose for patients already on home insulin. *For BG 250-350 mg/dL (13.9-19.4 mmol/L):* start basal-bolus regimen at 0.1-0.3 units/kg insulin glargine and 0.1-0.3 units/kg regular insulin every 6 hours with correction scale *For BG >350 mg/dL (19.4 mmol/L):* start 0.2-0.3 units/kg regular insulin; start basal insulin as above. Titration based on glucose level. IV insulin is recommended for severe hyperglycemia. Authors reduced insulin doses when inflammatory biomarkers decreased. Outcomes have not been published yet.

Abbreviations: COPD (chronic obstructive pulmonary disease), BG (blood glucose), DM (diabetes mellitus), CGM (continuous glucose monitor), COVID-19 (coronavirus disease 2019), IV (intravenous)

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