Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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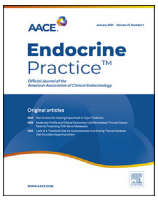

Review Article

Glucocorticoid-Induced Hyperglycemia Including Dexamethasone-Associated Hyperglycemia in COVID-19 Infection: A Systematic Review

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ABSTRACT

Objective: Optimal glucocorticoid-induced hyperglycemia (GCIH) management is unclear. The COVID-19 pandemic has made this issue more prominent because dexamethasone became the standard of care in patients needing respiratory support. This systematic review aimed to describe the management of GCIH and summarize available management strategies for dexamethasone-associated hyperglycemia in patients with COVID-19.

Methods: A systematic review was conducted using the PubMed/MEDLINE, Cochrane Library, Embase, and Web of Science databases with results from 2011 through January 2022. Keywords included synonyms for "steroid-induced diabetes" or "steroid-induced hyperglycemia." Randomized controlled trials (RCTs) were included for review of GCIH management. All studies focusing on dexamethasone-associated hyperglycemia in COVID-19 were included regardless of study quality.

Results: Initial search for non-COVID GCIH identified 1230 references. After screening and review, 33 articles were included in the non-COVID section of this systematic review. Initial search for COVID-19–related management of dexamethasone-associated hyperglycemia in COVID-19 identified 63 references, whereas 7 of these were included in the COVID-19 section. RCTs of management strategies were scarce, did not use standard definitions for hyperglycemia, evaluated a variety of treatment strategies with varying primary end points, and were generally not found to be effective except for Neutral Protamine Hagedorn insulin added to basal-bolus regimens.

Conclusion: Few RCTs are available evaluating GCIH management. Further studies are needed to support the formulation of clinical guidelines for GCIH especially given the widespread use of dexamethasone during the COVID-19 pandemic.

Introduction

The medical literature contains a wealth of writing about glucocorticoid (GC)-induced hyperglycemia (GCIH), which demonstrates the pronounced interest and need for practical information. Several challenges remain, including the lack of uniform terminology, standardized screening recommendations, or randomized controlled trials (RCTs) regarding management. This manuscript consists of a systematic review of literature published since 2011 on GCIH management and extends to publications regarding dexamethasone-associated hyperglycemia in patients with respiratory dysfunction from SARS-CoV-2 infection (COVID-19). For the former, higher-quality studies were included. For the latter, given the paucity of publications, relevant studies involving dexamethasone-associated hyperglycemia management in COVID-19 infection were included regardless of quality.

Abbreviations: BBI, basal-bolus insulin; CGM, continuous glucose monitoring; CI, confidence interval; DKA, diabetic ketoacidosis; DM, diabetes mellitus; FSG, finger-stick glucose; GC, glucocorticoid; GCIH, glucocorticoid-induced hyperglycemia; IMI, intermediate-acting insulin; NPH, Neutral Protamine Hagedorn; RCT, randomized controlled trial; TDD, total daily insulin dose.

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This review aimed to provide practical management strategies in patients who develop GCIH and summarize the available studies of dexamethasone-associated hyperglycemia management in patients with COVID-19.

Epidemiology and Impact

The incidence of GCIH varies depending on the population, GC dose, and duration, ranging from 15% to 70% in those without pre-existing diabetes mellitus (DM).[1-4] The risk of developing DM in individuals with GCIH has been studied in various populations. A nested case-control study involving almost 8000 subjects demonstrated that the adjusted odds ratio for DM with ≥3 prescriptions for oral GC was 1.36 (95% confidence interval [CI], 1.10-1.69).[5] A cohort study of patients with rheumatoid arthritis revealed hazard ratios of 1.30 (95% CI, 1.17-1.45) and 1.61 (95% CI, 1.37-1.89) for incident DM in GC users versus nonusers, respectively, within the previous 6 months.[6] The risk of incident DM with chronic GC use is significant.

Pathophysiology

GCs are nuclear hormones that affect glucose metabolism by influencing β-cell function[7] and inducing insulin resistance at the levels of the skeletal muscle, liver, and adipose tissue through postreceptor defects in insulin signaling, including impaired phosphorylation of insulin signaling proteins.[8,9] GCs decrease insulin-stimulated insulin receptor substrate 1-associated phosphoinositide 3-kinase activity, phosphorylation of protein kinase B/Akt and glycogen synthase kinase-3, insulin-stimulated glucose uptake, and glucose transporter type 4 translocation and inhibit insulin-stimulated glycogen synthase activation.[8,9] Glucose production is increased in the presence of GC,[8] and hyperglycemia results in predisposed individuals.

Methods

A systematic review was performed using the PubMed/MEDLINE, Cochrane Library, Embase, and Web of Science databases from 2011 to January 2022. Initial search identified 1230 studies representing 818 unique studies. Thirty-seven studies were assessed for eligibility between 2011 and 2022; 4 were excluded: 2 were duplicates; and 2 were ineligible by study design. A total of 33 studies were included in the non–COVID-19 section with an emphasis on RCT (Fig. 1 *A*). For the COVID-19 section, 63 studies were identified between 2020 and 2022, 8 duplicates were removed, and 55 studies were screened. Of these, 48 references were removed based on ineligible article type or irrelevant topic. A total of 7 studies were included in the COVID-19 section (Fig. 1 *B*). All article types involving dexamethasone-associated hyperglycemia management, including case reports of ≥2 patients, were included. Additional articles were obtained via manual review of included references. We limited the search to peer-reviewed, English language articles and human studies of adults aged ≥18 years, all of which focused on management. Preprint articles, epidemiology studies, and quality improvement studies were excluded in both sections.

Keywords included synonyms for "steroid-induced diabetes" or "steroid-induced hyperglycemia." Our review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[10] The details of search strategies are shown in the Supplementary Material.

Highlights

- Various antihyperglycemic regimens have been studied for glucocorticoid-induced hyperglycemia (GCIH).
- No standardized treatment guidelines exist for GCIH.
- Effective insulin protocols for dexamethasone-associated COVID-19 hyperglycemia are needed.

Clinical Relevance

Glucocorticoid-induced hyperglycemia (GCIH) is commonly encountered; however, most evidence is from trials conducted in hospitalized patients, and little information exists for dexamethasone-associated hyperglycemia in COVID-19 infection. This is a systematic review of recent controlled trials plus a summary of published literature on GCIH in COVID-19 infection, with practical management recommendations.

Terminology

The estimates of the prevalence and incidence of GCIH vary depending on the population studied and because there are no universal definitions. "Steroid- or glucocorticoid-induced hyperglycemia" is used to describe exacerbation of hyperglycemia resulting from GC use in individuals with or without pre-existing DM, whereas "steroid- or glucocorticoid-associated diabetes" is used to describe hyperglycemia resulting from GC use in individuals without known DM. The term "induced" suggests that the etiology is known, whereas "associated" indicates the timing of onset after GC initiation but acknowledges that the etiology may be uncertain. GCIH is anticipated to resolve after GC are discontinued, whereas GC-associated diabetes describes hyperglycemia that persists while on chronic GC therapy or after GC discontinuation.[7]

There are no standard diagnostic criteria for GCIH, with clinicians using various thresholds, such as fasting glucose levels of ≥126 or ≥140 mg/dL and random glucose levels of ≥180 or ≥200 mg/dL. The majority of studies included in this review were in an inpatient setting.

Results

Management Strategies: GCIH

There are no standardized treatment protocols for GCIH. Although practice guidelines highlight the importance of achieving euglycemia during GC treatment, guidance on optimal therapy is limited.[11,12] Studies have incorporated different GC pharmacokinetics, treatment indications, and dosing schedules to determine adequate management strategies for GCIH. In this review, all GC types were included (Table 1).

Neutral Protamine Hagedorn Insulin With Steroid Administration Added to Basal-Bolus Insulin

Three RCTs have investigated Neutral Protamine Hagedorn (NPH) insulin added to basal-bolus insulin (BBI) in the treatment of GCIH (Table 1). Khowaja et al[13] evaluated a supplementary NPH-based regimen compared with BBI in hospitalized patients with DM (N = 60) receiving steroids where the primary outcome was the mean premeal and bedtime glucose for days 1 to 5 after GC initiation. NPH was added to the home insulin regimen and

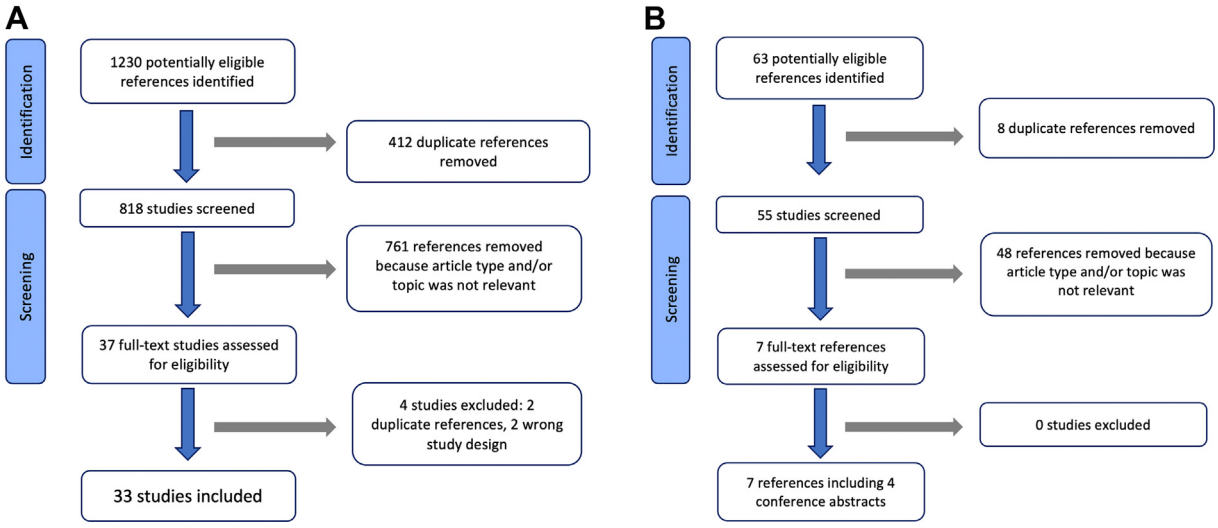

Fig. 1. *A*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study assessment and exclusion for the non-COVID section of systematic review. Literature searches in the PubMed, Embase, Web of Science, and Cochrane databases from 2011 to January 2022 for steroid-induced hyperglycemia or diabetes (non-COVID) resulted in 1230 articles. After screening and review, 33 articles were included. *B*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study assessment and exclusion for the COVID-related section of systematic review. Literature searches in the PubMed, Embase, Web of Science, and Cochrane databases for - dexamethasone-associated hyperglycemia or diabetes in patients with COVID-19 infection resulted in 55 articles. After screening and review, 7 articles were included.

administered concurrently with steroids (1-3 times daily). The mean overall, fasting, and prelunch glucose levels were lower, more glucose levels were within the target range (70-180 mg/dL), and hyperglycemia of ≥300 mg/dL occurred less often in the NPH group over 5 days (Table 2). The NPH group used a higher mean insulin dose added to the usual daily regimen than BBI (46.6 vs 17.4 units/d, P <.0001). After randomization, 3 hypoglycemic episodes (<70 mg/dL) occurred in the NPH group, whereas none occurred in the control group.[13]

Grommesh et al[14] compared BBI versus NPH added to BBI in hospitalized patients with and without DM (N = 61) who received GC within 1 day prior to randomization with hyperglycemia of >180 mg/dL (Table 1). The primary outcome was the mean glucose level. NPH dosing (5-20 units) was determined using DM history and steroid dose; it was administered at the same time as the steroid except for methylprednisolone or hydrocortisone (every 4-6 hours) or dexamethasone where it was dosed 3 times daily. The glycemic control and rates of hypoglycemia were similar between the groups over the study period's 5 days, with day 3 time in range (70-180 mg/dL) trending toward significance in the NPH group (Table 2).[14] Seggelke et al[15] reported significantly lower premeal glucose levels over 3 days in posttransplant patients with cystic fibrosis-related diabetes (N = 20) receiving BBI with NPH given once daily with methylprednisolone than those in patients receiving BBI (Table 2). The latter 2 studies demonstrated a trend toward improved glycemic control with the addition of NPH to BBI despite similar total daily insulin doses (TDDs) between the control and experimental groups.

NPH Insulin 3 Times Daily With Bolus Insulin

Ruiz de Adana et al[16] investigated NPH compared with glargine in hospitalized patients with type 2 DM (N = 53) receiving GC for pulmonary disease (Table 1). Continuous glucose monitoring (CGM) was used, and the primary end point was the mean blood glucose level. Glargine was dosed once each morning, whereas NPH was given in 3 doses with meals. Insulin doses were calculated in the same way for each group. The mean TDD, blood glucose level, time in range (80-180 mg/dL), and glycemic variability were similar over 6 days (Table 2). Three severe hypoglycemic episodes (<40 mg/dL) occurred in the NPH group, whereas none occurred in the glargine group.[16]

NPH Insulin Once Daily With Bolus Insulin

Radhakutty et al[17] compared an NPH-based regimen with BBI in hospitalized patients with and without DM receiving prednisolone (N = 50) with 2 finger-stick glucose (FSG) levels of >180 mg/dL or 1 FSG level of >270 mg/dL in the 24 hours prior to randomization (Table 1). CGM was used, and the primary outcome was the mean glucose on day 1 after steroid initiation. The starting doses of insulin were the same in each group, and both received premeal insulin aspart; however, the NPH group received a higher proportion of aspart with lunch and dinner (Table 2). The glycemic control by CGM, mean glucose, and rates of hypoglycemia were similar between the groups on day 1 after steroid initiation. Day 1 prednisolone doses and TDD were similar. Despite receiving 130% of TDD, patients with prior insulin use experienced more time outside the target range (72-180 mg/dL) and higher mean glucose levels, suggesting the need for higher starting doses (Table 3).[17]

Correctional Insulin According to GC Type

Lakhani et al[18] evaluated BBI compared with BBI combined with a correctional insulin whose pharmacokinetics matched the GC's glycemic profile in hospitalized patients with and without DM (N = 92) who received GC within 24 hours prior to randomization with 2-hour postprandial hyperglycemia of ≥200 mg/dL (Tables 2 and 3). The primary outcome was the mean blood glucose level. BBI was added to correctional insulin for patients with DM history. Patients receiving GC-matched correctional insulin experienced improved glycemic control and had a significantly lower overall mean blood glucose level than patients on BBI, without increasing hypoglycemia (Table 2). Hyperglycemia of >300 mg/dL was also less frequent with correctional insulin.[18]

Add-on Short-Acting Versus Intermediate-Acting Insulin

Gerards et al[19] compared supplemental short-acting versus intermediate-acting insulin (IMI) combined with standard regimens in patients treated with GC-based chemotherapy (N = 26) in a randomized cross-over study of patients with type 2 DM or prior

Table 1
Studies of Glucocorticoid-Induced Hyperglycemia Management

First author (year)	Country	Study population	Mean HbA1c % (mmol/mol) (control vs intervention)[a]	Definition of hyperglycemia (mg/dL)	Target blood glucose (mg/dL)	Glucocorticoid (duration)	n (control vs intervention)	Glycemic management protocol[b]
Randomized pilot study								
Seggelke (2011)[15]	United States	Inpatients with CFRD after bone marrow or solid organ transplant.	7.8 (62) vs 7.5 (58)	n/a	n/a	Methylprednisolone 10-60 mg (3 d)	20 (10/10)	NPH with steroid + BBI vs BBI
Randomized controlled trials: inpatient								
Grommesh (2016)[14]	United States	Inpatients with and without T2DM in non-ICU at a single institution given steroids in the last 24 h with ≥1 capillary BG level of >180 mg/dL. If no history of DM, a second elevated BG level was needed. 58% patients had DM in the control group compared with 40% in the experimental group (P =.16).	6.4 (46) vs 6.5 (48)	≥180 mg/dL	70-180 mg/dL	Prednisone ≥10 mg daily or equivalent (≥5 d)	61 (30/31)	NPH with steroid + BBI vs BBI
Khowaja (2018)[13]	United States	Inpatients with DM on steroids for cancer-related, autoimmune, MSK, or pulmonary disease.	8.85 (73) vs 8.11 (65)	≥180 mg/dL	70-180 mg/dL	Prednisone >10 mg daily or equivalent (≥48 h)	60 (31/29)	NPH with steroid + BBI vs BBI
Ruiz de Adana (2015)[16]	Spain	Inpatients with T2DM in the pulmonology ward at a single center. 49.1% of patients were treated for COPD.	7.5 (58) vs 7.4 (57)	Premeal ≥140.4 mg/dL	Premeal BG target level of 100.8-140.4 mg/dL 80-180 mg/dL	Methylprednisolone >40 mg daily or deflazacort >60 mg daily (6 d or until discharge if earlier)	53 (26/27 with FSG monitoring; 20/11 with CGM)	NPH 3 times daily + premeal bolus insulin vs BBI
		CGM was used.						
Radhakutty (2017)[17]	Australia	Inpatients in a general medical ward on prednisolone at 3 hospitals. Excluded patients with T1DM. 70% of patients had diabetes. 70% of patients were treated for COPD.	7.9 (63) vs 7.2 (55)	Two FSG levels of >180 mg/dL or 1 FSG level of >270 mg/dL in the last 24 h	72-180 mg/dL	Prednisolone ≥20 mg daily (≥3 d)	50 (23/25)	NPH once daily + premeal bolus insulin vs BBI
		CGM was used.						
Lakhani (2017)[18]	India	Inpatients with and without DM who received GC within 24 h at a single center. The included patients had a 2-h postprandial BG level of ≥200 mg/dL.	7.17 (55) vs 6.59 (49)	≥200 mg/dL	n/a	Prednisolone ≥10 mg or equivalent daily (≥2 d)	92 (46/46)	Correctional insulin according to steroid type
Gerards (2018)[22]	Netherlands	Inpatients with T2DM or prior inpatient hyperglycemia of >180 mg/dL. 85% of patients had DM.	7 (53) in both groups	≥180 mg/dL	70.2-180 mg/dL	Prednisolone ≥30 mg daily (5-14 d)	46 (23/23)	Dapagliflozin

Randomized controlled trial: outpatient									
Ochola (2020)[24]	Kenya	Outpatient patients with hematologic cancer without DM on prednisone.	n/a	Fasting BG level of ≥100.8 mg/dL 2-h postprandial BG level of ≥140.4 mg/dL	n/a	Prednisolone ≥30 mg daily (4 wk)	24 (13/11)	Metformin	
Cross-over study: inpatient/outpatient									
Gerards (2016)[19]	Netherlands	Inpatients or outpatients with T2DM or prior GC-induced hyperglycemia (>216 mg/dL) receiving GC-based chemotherapy at 3 hospitals.	Median, 7.5; 6.9%-8.4% (58; 52-68 mmol/mol) with a prior history of DM[a] 6.8; 6.7%-6.8% (51; 50-51 mmol/mol) without DM[a]	≥180 mg/dL	70.2-180 mg/dL	Prednisone ≥12.5 mg or equivalent (3-10 d)	26		Add-on short-acting vs intermediate-acting insulin to routine DM regimens
		CGM was used.							
Prospective, nonrandomized control group study									
Agudo-Tabuenca (2019)[20]	Spain	Inpatients with T2DM admitted to a pulmonary ward. 74% were treated for COPD.	7.5 (58) vs 7.9 (63)	≥200 mg/dL	100-200 mg/dL	Methylprednisolone ≥0.5 mg/kg/day or equivalent for the duration of admission (3-15 d)	131 (60/71)	BBI (twice daily basal vs once daily)	

Abbreviations: BBI, basal-bolus insulin; BG = blood glucose; CFRD = cystic fibrosis-related diabetes; CGM = continuous glucose monitoring; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; FSG = finger-stick glucose; GC = glucocorticoid; HbA1c = hemoglobin A1c; ICU = intensive care unit; MSK = musculoskeletal; NPH = Neutral Protamine Hagedorn insulin; n/a = not available; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Unless otherwise stated. Median HbA1c, 25th-75th interquartile range % (mmol/mol).

[b] Table 3 shows the details of the study protocol.

hyperglycemia of >216 mg/dL (Table 1). Only 4 patients in the study were hospitalized, and the insulin types were not specified. The supplemental short-acting protocol dosed insulin according to the glucose level, whereas the IMI regimen was administered according to the steroid dose and body weight. The IMI protocol involved higher TDD and resulted in a higher proportion of time in range (70-180 mg/dL) (Table 2). CGM-detected asymptomatic hypoglycemia was similar between groups. The mean glucose level was lower with IMI, but glycemic control was not achieved (223.2 ± 52.2 vs 243 ± 50.4 mg/dL, P <.05).[19]

Basal-Bolus Insulin

A prospective nonrandomized study by Agudo-Tabuenca et al[20] evaluated a BBI protocol in hospitalized patients with type 2 DM treated with methylprednisolone for pulmonary disease (Table 1). Both groups were treated with BBI, but the intervention group received higher starting doses. For the experimental group, half of the TDD was given as basal insulin twice daily (glargine or detemir), whereas the remaining insulin was divided prandially (aspart). The overall mean glucose level was lower in the intervention group, which had a higher mean TDD. There was no difference in hypoglycemia (Table 2). Euglycemia was achieved in half the time in the experimental group compared with that in the control (5 vs 10 days).[20]

Noninsulin Antihyperglycemic Therapy and Decision Support Tools

Acarbose and nateglinide may reduce postprandial hyperglycemia in patients treated with prednisolone for connective tissue disorders.[21] In an RCT of patients with type 2 DM with chronic obstructive pulmonary disease exacerbations treated with prednisone, dapagliflozin did not lead to improved glycemic control or reduction in insulin requirements.[22] The EmpAgliflozin compared with NPH Insulin for sTeroId diAbeTEs study is an ongoing non-inferiority trial evaluating the use of empagliflozin versus NPH in the treatment of GCIH.[23]

Metformin has been shown to reduce 2-hour postprandial hyperglycemia in oncology patients without DM receiving prednisone.[24] Metformin significantly reduces postprandial hyperglycemia after 2 weeks of prednisone[24] and has additionally been shown to prevent impaired glucose tolerance and improve insulin resistance in patients without DM receiving supraphysiologic GC.[25] Similar findings have been described with exenatide.[26]

Sitagliptin improves pancreatic islet cell function, but not GC-induced glucose intolerance, in men with metabolic syndrome without DM receiving prednisolone.[27] A study of 5 patients without DM treated with prednisolone for rheumatologic disorders demonstrated that linagliptin did not prevent GCIH; however, it may have reduced the need for insulin. Fasting hypoglycemia occurred during the first 2 weeks of GC administration, which may have been exacerbated by the concomitant use of insulin secretagogues.[28]

Automated decision support tools, such as GlucoTab, a software that recommends BBI dosing (ie, 50% basal and 50% bolus), show promise in GCIH management. Aberer et al[29] demonstrated that GlucoTab use led to a higher mean TDD (38 vs 11 units, P <.001) with lower median, fasting, and bedtime glucose levels and higher time in range (70-180 mg/dL; 67.2% vs 60.2%, P <.001).

COVID-19 and Diabetes

The COVID-19 pandemic presented a new and challenging entity for clinicians beginning in 2020. DM was soon identified as a notable risk factor for severe disease and mortality.[30-32] The bidirectional relationship of COVID-19 and DM has been described; hyperglycemia can occur in patients with and without pre-existing

Table 2
Study Designs, Summary of Results, and Limitations of the Studies of Glucocorticoid-Induced Hyperglycemia Management

First author (year)	Glycemic management protocol/ study design	Primary outcomes	Results	Study limitations
Seggelke (2011)[15]	All patients received basal (glargine) and premeal bolus (lispro) insulin. ***Intervention group****:* additional NPH was dosed at the same time as methylprednisolone once daily where 1 unit was given for every 1 mg of methylprednisolone up to 20 mg; 0.5 units for every 1 mg up to 20-40 mg; 0.25 units for every additional milligram up to >40 mg. ***Control group****:* glargine and premeal lispro, titrated per hospital protocol	Mean fasting capillary and premeal BG levels	The mean TDDs were similar for both groups on day 3 (90 units in the intervention group vs 90 units in control). The mean dose of NPH was 23 ± 5 units. There was no difference in the fasting BG levels between the groups. Day 3 prelunch and predinner glucose levels in the NPH group were lower than BBI (194 ± 25 and 193 ± 22 vs 292 ± 23 and 319 ± 32 mg/dL, respectively; all P <.001).	Small sample size; short follow-up duration
Grommesh (2016)[14]	Patients were randomized to the control group with complete insulin orders ("CIO," glargine, mealtime, and correction lispro) or the experimental group with NPH with CIO ("NPH-CIO"). ***Intervention group:*** starting doses of NPH were based on GC dose and DM history (5-20 units NPH per GC dose). Added to CIO. ***Control (CIO) group:*** starting doses of insulin were based on home DM medications, HbA1c, and prior diet/ exercise plans (correction only or 0.2-0.6 units/kg). TDD was divided into 50% basal and 50% prandial. Insulin titration schedule was provided for both groups.	Mean BG level The secondary outcomes included % in target range and hypoglycemia	The mean BG level was not different between the groups (178.3 in CIO vs 169.2 mg/dL in NPH-CIO [P =.17]). There was no difference in hypoglycemia. Day 3 time in range was slightly better in NPH-CIO (66% vs 48.4% in CIO, P =.07). TDD was similar at day 3 between the groups.	The control group insulin doses did not have to be titrated according to a protocol; however, the experimental group was titrated by the research team. Controlled baseline HbA1c does not reflect real-life practice.[a]
Khowaja (2018)[13]	Both groups received their outpatient insulin regimen to start. If the HbA1c level was >9%, patients in both groups received 0.3 units/kg of insulin glargine. Correction aspart was given in both groups. ***Intervention group:*** High-dose steroids (prednisone ≥40 mg/day or equivalent): NPH 0.3 units/kg dosed between 0600 and 2000 h (or 0.2 units/kg between 2000 and 0600 h if not eating). Low-dose steroids (prednisone 10-40 mg/day or equivalent): NPH 0.15 units/kg dosed between 0600 and 2000 h (or 0.1 units/kg between 2000 and 0600 h if not eating). NPH was administered at the same time as the steroid doses (daily, BID, and TID). ***Control group:*** usual care. BBI with correction aspart as needed.	Mean premeal capillary and bedtime BG levels for days 1-5	The overall mean BG level was lower in the NPH group (226.12 vs 268.57 mg/dL, P <.0001). The mean fasting and prelunch BG levels were lower in the NPH group (fasting BG, 170.96 vs 221.13 mg/dL, P <.0001; prelunch BG, 208 vs 266.48 mg/dL, P <.0001). There was no difference in the mean predinner or bedtime BG levels. The NPH group had more BG levels measured in the range of 70-180 mg/dL (33.1% vs 19.2%, P <.0001). The NPH group experienced less hyperglycemia between 300 and 400 mg/dL (16.9% vs 27%, P <.01).	Starting patients on home insulin regimens that may not be optimized may have impacted BG control at the onset of study as well as hypoglycemia risk.
Ruiz de Adana (2015)[16]	Patients were randomized to receive either glargine (control) or NPH (intervention) as basal insulin. All received insulin glulisine. *DM treated with diet/oral agents:* TDD 0.3-0.5 units/kg based on admission BG. *DM treated with insulin:* home TDD.	Mean capillary BG level	The mean capillary BG level was similar in each group for days 1-6 (205.7 ± 61.9 mg/dL for glargine vs 213.8 ± 52.9 mg/dL for NPH, P =.624). % time in range by CGM for days 1-6 was also similar (42% for glargine vs 38% for NPH, P =.606).	Small sample size, single center. The number of injections required for NPH group daily may not be realistic or preferred by patients.

Table 2 (*continued*)

First author (year)	Glycemic management protocol/ study design	Primary outcomes	Results	Study limitations
	For both groups, the calculated insulin dose was multiplied by 1.5. ***For both groups:*** 50% TDD, basal; 50% TDD, premeal bolus divided equally. Glargine was given daily at 9AM. NPH was divided equally to be given before each meal.		There was no difference in the mean TDD. There was more hypoglycemia in the NPH group (8 vs 4 mild episodes, P =.351; 3 vs 0 severe episodes, P =.13). The mean TDD was similar (56.9+40.6 IU/kg/day for glargine vs 55.4+27.5 IU/kg/day for NPH, P =.430).	
Radhakutty (2017)[17]	Patients were randomized to NPH and aspart (intervention) versus insulin glargine and aspart (control). Patients were stratified according to prior insulin use. Patients received TDD 0.5 units/kg or 130% of current TDD where the higher dose was chosen. ***Intervention group:*** 50% TDD NPH at 7AM; 50% TDD insulin aspart (20% breakfast, 40% lunch, 40% dinner). ***Control group***: 50% TDD glargine at 7AM; 50% TDD aspart given as 3 divided premeal doses. Correctional aspart was given in both groups according to a hospital protocol.	Mean BG; time outside target range on day 1	Day 1 TDD was similar between the groups (P =.57). The time outside target range, mean BG level, and rates of hypoglycemia (<72 mg/dL) on day 1 were similar (P =.28, P =.57, and P =.92, respectively). There was no difference in the time outside target range or mean BG level between the groups at all time blocks examined (7AM-12 PM, 12PM-5PM, 5PM-10PM, and 10PM-7AM). Patients with prior insulin use spent more time outside target range (68.3 ± 7.2% vs 39.5 ± 4.1%, P =.002) with a higher mean BG level (234 ± 19.8 vs 176.4 ± 9 mg/dL, P =.004).	Focusing on day 1 glycemic parameters excludes GC impact on glycemic trends over time. Small sample size.
Lakhani (2017)[18]	Patients were randomized 1:1 to either BBI (control) or correctional insulin ± BBI (intervention). The control group regimen was based on the Endocrine Society guidelines. The experimental group was stratified according to having prior DM (received background glargine and lispro + correctional insulin) vs new GC-associated DM (received only correctional insulin). Correctional insulin type was dosed to match the glycemic profile and dose of the GC, ranging from 0.1 to 0.4 units/kg: • Hydrocortisone was paired with regular human insulin. • Prednisolone and methylprednisolone were paired with NPH. • Dexamethasone was paired with glargine.	Mean BG level	The mean BG level was lower in the experimental group (170.32 vs 221.05 mg/dL, P =.0001). The mean fasting, premeal, and bedtime BG levels were all lower in the experimental group.	A variety of protocols may be difficult to implement in real-life practice.
Gerards (2018)[22]	Patients were randomized to receive dapagliflozin vs placebo as add-on treatment to routine DM medications.	Difference in glycemic control according to time in range and hypoglycemic events.	54% ± 27.7% time in range in the dapagliflozin group vs 53.6% ± 23.4% in the placebo group (P =.96). The mean glucose level was also not different between the groups. The mean TDD was similar in both groups (18.3 units in the dapagliflozin group vs 19.3 units in the placebo group, P =.92).	Routine DM care and regimen adjustments were at discretion of the treating physician rather than standardized to assess the impact of dapagliflozin alone.

(*continued on next page*)

Table 2 (*continued*)

First author (year)	Glycemic management protocol/ study design	Primary outcomes	Results	Study limitations
			% of time >270 and 360 mg/dL was higher in the placebo group but this was not statistically significant.	
Ochola (2020)[24]	Patients were randomized 1:1 to the control group (standard of care) or intervention group (standard of care with metformin 850 mg daily × 2 wk, followed by 850 mg BID × 2 wk).	Presence of GC-induced hyperglycemia	Mean 2-hour postprandial BG were significantly lower in the metformin group at weeks 2-4. There was no difference in fasting BG.	Small sample size
Gerards (2016)[19]	Patients were randomized to either SSI or IMI first as add-on treatment to routine DM medications. SSI was dosed according to the blood glucose level based on a scale. IMI was dosed based on: 0.01 IU/mg prednisone-equivalent GC per kg body weight (capped at 0.5 IU per kg). IMI doses were adjusted by 10% daily if above target. Study team managed insulin.	% time in target range and hypoglycemic events	% time in target range: 34.4% for IMI vs 20.9% for SSI (P <.001). The mean BG level was lower with IMI (223.2+52.2 vs 243+50.4 mg/dL, P <.05). The median TDD was higher for IMI cycle than for SSI (40.3 vs 26.0 IU, P <.01). Two participants in each cycle had asymptomatic hypoglycemia, all of which occurred during days 3-5.	Specific insulin types used were not described.
Agudo-Tabuenca (2019)[20]	***Control group***: basal (glargine or detemir) plus correction insulin (aspart) vs BBI (glargine/detemir and aspart) insulin per hospital protocol. ***Intervention:*** BBI at higher doses. 50% TDD basal in 2 doses, 50% TDD premeal (15%, breakfast; 15%, lunch; 10%, afternoon snack; and 10%, dinner); if a single dose of steroid, prandial aspart was shifted with more emphasis on lunch and snack).	Mean BG level	The mean TDD was lower in the control group than in the intervention group (29.4 ± 21 vs 57.4 ± 24 units, P <.0001). The mean BG level was lower in the intervention group (191.8 vs 205.2 mg/dL, P =.030). The mean lunch and dinner BG levels were lower in the intervention group (lunch, 200.8 ± 43.1 vs 229.5 ± 41.5 mg/dL, P <.0001; dinner, 176.1 ± 37.3 vs 210.6 ± 54.6 mg/dL, P <.0001).	No patient randomization.

Abbreviations: BBI = basal-bolus insulin; BG = blood glucose; BID = twice daily; CGM = continuous glucose monitoring; DM = diabetes mellitus; GC = glucocorticoid; HbA1c = hemoglobin A1c; IMI = intermediate-acting insulin; NPH = Neutral Protamine Hagedorn; SSI = sliding scale insulin; TDD = total daily insulin dose; TID = 3 times daily.
[a] Table 2 shows the details.

DM and is an independent risk factor for worse outcomes in COVID-19.[30,33,34] Potential mechanisms of COVID-19-induced hyperglycemia include stress hyperglycemia from marked inflammation and beta-cell dysfunction.[35-41]

Cases of newly diagnosed DM have been reported with COVID-19 and may reflect varying mechanisms, including stress hyperglycemia, previously unrecognized type 2 DM, or COVID-induced DM.[37,42] Remission has been noted for 40.6% of new DM cases.[43] Worse outcomes have been reported for new versus pre-existing DM with COVID-19.[34] SARS-CoV-2 has been associated with an increased occurrence of diabetic ketoacidosis (DKA) primarily in patients with type 2 DM.[44] Although higher rates of pediatric type 1 DM diagnoses have been reported, a definite causal relationship between COVID-19 and type 1 DM has not been established.[45,46]

Early in the pandemic, optimal treatment was uncertain. This changed with the Randomized Evaluation of COVID-19 Therapy trial, which demonstrated that dexamethasone 6 mg daily for 10 days significantly reduced 28-day mortality in patients requiring oxygen or mechanical ventilation.[47] Dexamethasone became standard of care, and GCIH became more common with a need for evidence and expertise in GCIH management. Although studies report the high prevalence of DM and hyperglycemia in COVID-19, accurate data on the frequency of dexamethasone-induced hyperglycemia are not available. Hyperglycemia of COVID-19 coupled with dexamethasone therapy has been termed a "triple insult" with COVID-19-induced insulin resistance, COVID-19 effects on pancreatic islets to cause impairment of insulin production, and GC-induced metabolic derangements.[39]

Management Strategies: Dexamethasone-Induced Hyperglycemia in COVID-19

Management of severe hyperglycemia is important in COVID-19.[41,48] Few studies have assessed the management of dexamethasone-induced hyperglycemia in COVID-19 although several guidance documents have been published.[39,49-54] The lack of personal protective equipment at the beginning of the pandemic led to a need to minimize direct patient contact while maintaining adequate glycemic control. Recommendations were made to reduce glucose monitoring when feasible and manage insulin infusion pumps from outside the patient's room. Verifying appropriate GC prescribing to minimize hyperglycemia, measuring the hemoglobin A1c level, and point-of-care testing for glucose measurement for patients on dexamethasone were recommended although a reduced frequency of testing in patients without pre-existing DM may be adequate.[55-58]

Table 3
Studies of the Management of Glucocorticoid-Induced Hyperglycemia in COVID-19

First author (year)	Country	Study design	Study population	Glucocorticoid	Primary outcome	Results
Kosiborod (2021)[66] DARE-19	95 hospitals: Argentina, Brazil, Canada, India, Mexico, the United Kingdom, and the United States	Randomized controlled trial	N = 1250 Hospitalized patients with COVID-19 with ≥1 cardiometabolic risk factor. 50.9% had T2DM.	Dexamethasone use reported in 21.3% of dapagliflozin group and 21.8% in the placebo.	Dapagliflozin vs placebo: time to new or worsened organ dysfunction or death and composite outcome of recovery	Dapagliflozin did not reduce the primary composite end point of organ dysfunction or death. Two nonsevere cases of DKA in the dapagliflozin group.
Asiri (2021)[62]	Saudi Arabia	Retrospective study	N = 163	Dexamethasone	BG levels in the target range and mortality	The insulin protocol group had a higher proportion in glucose target range (70-180 mg/dL). In-hospital mortality was lower in the protocol group than in the control group (12.93% vs 29.93%, $P < .01$). **First published study of a GC-induced hyperglycemia insulin protocol in COVID-19 management.**
Cheung (2021)[65] CRITICal	Australia	Cluster randomized controlled trial **(in progress)**	Patients with DM hospitalized with COVID-19, non-ICU on dexamethasone: NPH + BBI vs BBI	Dexamethasone	Mean daily BG level	n/a
Klarskov (2020)[23]	Denmark	Single-center, open-label, randomized controlled, 2-arm parallel group-controlled trial **(in progress)**	Patients with DM with COVID-19	Not yet known[a]	Dexcom G6 vs POCT: BG level, time in range, and percentage of days with time in range	n/a

Abbreviations: BBI = basal-bolus insulin; BG = blood glucose; DARE-19 = Dapagliflozin in Respiratory Failure in Patients With COVID-19; DKA = diabetic ketoacidosis; DM, diabetes mellitus; GC = glucocorticoid; ICU = intensive care unit; NPH = Neutral Protamine Hagedorn; n/a = not available; POCT = point-of-care testing; T2DM = type 2 diabetes mellitus.
[a] This is an ongoing study; thus, the glucocorticoid type in the study is not currently available. Medications used will be collected.

The Food and Drug Administration lifted its restriction on the inpatient use of CGM in April 2020, and CGM has been shown to be feasible in small numbers of patients.[53,59-61] An RCT in Denmark has been initiated to assess glycemic outcomes with CGM compared with point-of-care testing for glucose measurement in patients with COVID-19.[48] Factors such as hypoxia, use of pressors, fluid shifts, edema, and high-dose acetaminophen use can limit the accuracy of CGM in severely ill patients with COVID-19.

Published guidance documents align regarding insulin therapy as the standard of care for GCIH; intravenous insulin infusion is preferred in the intensive care unit, and BBI is recommended for those who are not critically ill. Varying preference exists for the use of NPH twice daily[39] or once daily basal insulins, such as glargine or detemir.[49,50] Although most noninsulin agents should be discontinued, Pasquel et al[50] considered the use of dipeptidyl peptidase-4 inhibitors as an adjunct to insulin to help reduce the frequency of injections. Gianchandani et al[51] suggested trending COVID-19 inflammatory markers, such as procalcitonin, to gauge the need to adjust insulin doses because a correlation was noted.

Asiri et al[62] published the first study to examine the effectiveness of an insulin protocol for the management of dexamethasone-induced hyperglycemia in COVID-19 (Table 3). This study retrospectively assessed non–intensive care unit patients with COVID-19 (N = 163) at a tertiary center in Saudi Arabia managed with an insulin protocol compared with routine treatment. The insulin starting dose included glargine 0.1 units/kg/day (or home basal insulin dose) and rapid-acting insulin 0.1 units/kg/meal. The protocol group had a higher proportion of patients with glucose levels in the target range (70-180 mg/dL) as well as reduced in-hospital mortality (Table 3). The authors comment that their starting dose of glargine may have been too low out of concern for reduced patient contact and to consider using 0.2 units/kg/day.[62] In our experience, weight-based insulin requirements for dexamethasone hyperglycemia in COVID-19 can be considerably higher than traditional dosing formulas and may be positively correlated with hemoglobin A1c.[63] A retrospective study performed in the first pandemic wave found that patients with type 2 DM with DKA and COVID-19 required a significantly larger cumulative insulin dose, longer time, and higher weight-based insulin infusion dose to achieve DKA resolution than patients without COVID-19.[64]

CRITICal, an RCT examining whether NPH combined with BBI compared with BBI alone improves the mean daily glucose levels for dexamethasone-induced hyperglycemia in patients with DM with COVID-19, is in progress in Australia (Table 3).[65] At this time, there are no completed RCT to assess the insulin management of GCIH in COVID-19.

The Dapagliflozin in Respiratory Failure in Patients With COVID-19 trial, a multicenter RCT of non–critically ill patients hospitalized with COVID-19 and at least 1 cardiometabolic risk factor examined the effect of dapagliflozin 10 mg daily versus placebo (N = 1250) on the prevention of severe disease or death (Table 3). The study population included 50.9% of participants with type 2 DM, and 21.5% received dexamethasone. The primary end point was not met; however, dapagliflozin was well tolerated, and only 2 nonsevere cases of DKA were reported in the treatment group.[66] It is important to note that while potentially beneficial in GCIH, sodium-glucose cotransporter inhibitors can be associated with euglycemic DKA, an increased risk of genitourinary infections, and volume depletion.[67]

Observational studies support a correlation between metformin use and reduced mortality from COVID-19; however, inpatient use is not recommended.[68,69] Further studies regarding the potential role of other noninsulin agents in COVID-19 treatment are needed. Research in the area of dexamethasone-induced hyperglycemia in

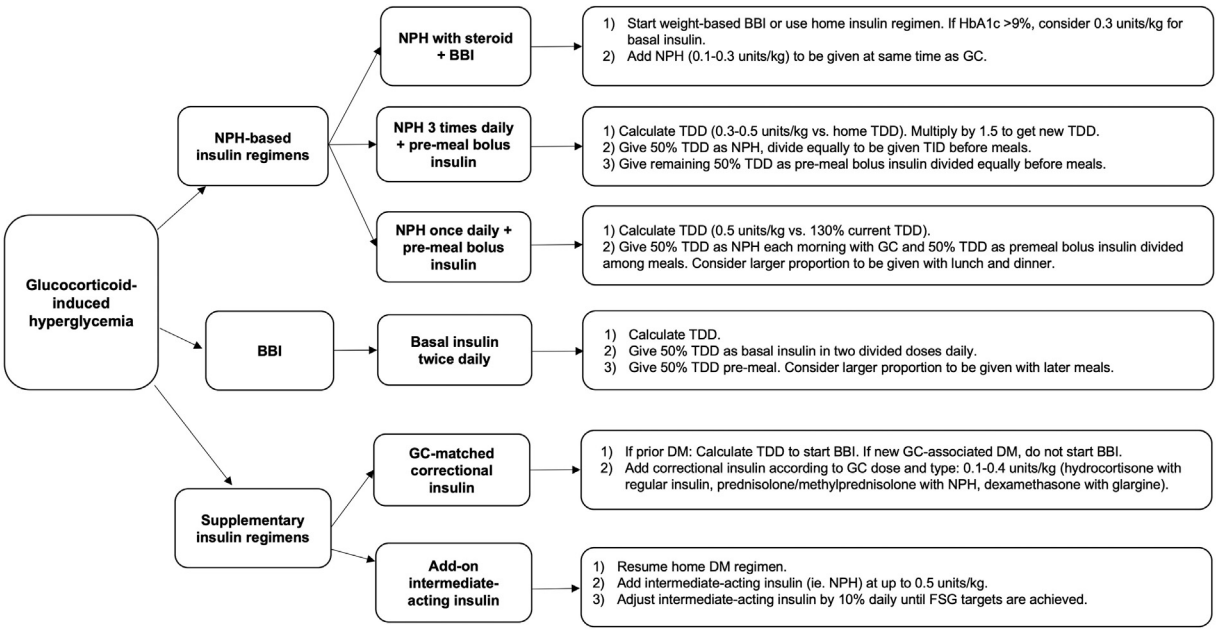

Fig. 2. Summary of insulin management approaches for glucocorticoid (GC)-induced hyperglycemia. *BBI* = basal-bolus insulin; *DM* = diabetes mellitus; *FSG* = finger-stick glucose; *HbA1c* = hemoglobin A1c; *NPH* = Neutral Protamine Hagedorn; *TDD* = total daily insulin dose; *TID* = 3 times daily.

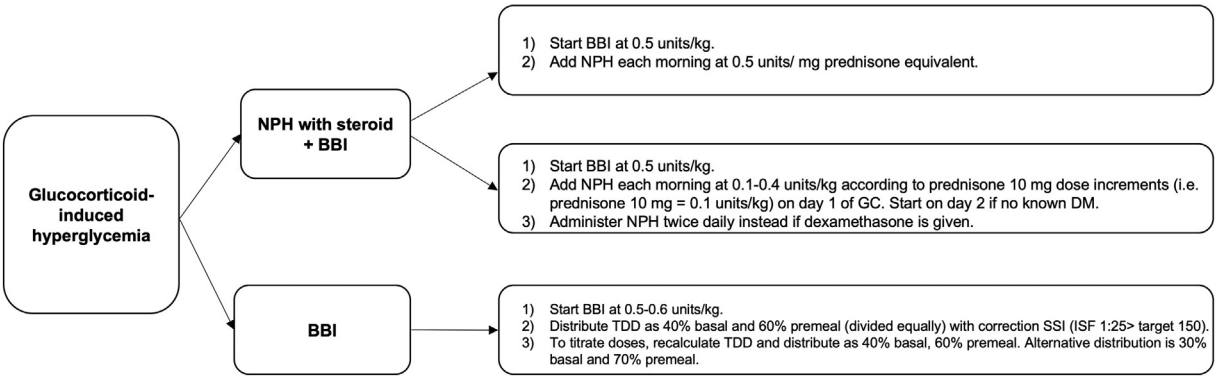

Fig. 3. Practical approaches for glucocorticoid (GC)-induced hyperglycemia according to the authors based on expert opinion. *BBI* = basal-bolus insulin; *DM* = diabetes mellitus; *FSG* = finger-stick glucose; *ISF* = insulin sensitivity factor; *NPH* = Neutral Protamine Hagedorn; *SSI* = sliding scale insulin; *TDD* = total daily insulin dose.

COVID-19 remains limited, and as COVID-19 continues with new variants, clarifying ideal treatment for this challenging population is urgently needed.

Discussion

GCIH management studies have assessed varying combinations of insulin formulations. Few RCTs have been completed, and in the limited group of studies available, the treatment protocols are vastly different. Furthermore, terminology used to define GC-associated hyperglycemia is inconsistent and confusing. Evidence-based guidelines do not exist for GCIH management, and clinical practice varies widely.[11,12]

The insulin regimen with the greatest likelihood of effectiveness was demonstrated in studies using BBI with NPH.[13-15,18] The late peak and prolonged duration of action of NPH more closely matches the insulin resistance and hyperglycemia observed with GC use. However, adequate NPH dosing has not been identified because the insulin regimens assessed thus far have been suboptimal in achieving glycemic control. All of the studies involve small sample sizes, short study duration, and patients with either well-controlled or moderately controlled DM, factors which limit generalizability.

The studies assessed in this review demonstrate a need for higher initial doses of insulin in GCIH management. However, the more physiologic approach using multiple doses of NPH may limit broad applicability due to dosing complexity and administration of multiple insulins. Figure 2 summarizes the treatment protocols assessed in this review. Figure 3 shows 3 practical approaches favored by the authors. We recommend initiating BBI at 0.5 units/kg; NPH can be added using either 0.5 units/mg of prednisone equivalent or 0.1 units/kg per prednisone 10-mg dose increments. NPH may be helpful to use concomitantly with prednisone given their similar pharmacokinetic profiles.[70] An alternative approach without NPH involves starting BBI at 0.5 to 0.6 units/kg with 30% to 40% of TDD as basal insulin and 60% to 70% of TDD as prandial insulin. The authors acknowledge the heterogeneity in GC studied in this review and summarized our preferred approaches for patients receiving supraphysiologic steroids.

Noninsulin agents offer a simpler treatment option for GCIH, particularly for patients without pre-existing DM who require extended GC courses. Unsurprisingly, agents such as dipeptidyl

peptidase-4 inhibitors are not sufficient to manage GCIH in patients with DM[22]; however, metformin and exenatide may have a role in ameliorating hyperglycemia in patients without DM receiving GC.[24-26] Additional research is needed to determine whether non-insulin agents can be used in GCIH prevention or treatment.

The COVID-19 pandemic has dramatically increased the number of patients requiring hyperglycemia treatment, particularly in the setting of dexamethasone use for patients requiring supplemental oxygen or mechanical ventilation.[47] Insulin is the standard of care for dexamethasone-associated hyperglycemia in COVID-19. As with GCIH not associated with COVID-19, practice varies widely with regard to insulin regimens; however, it is clear that insulin requirements exceed standard dosing.

The limitations of this review include variable study designs with multiple GC types for diverse indications, small sample sizes, varying clinical end points, and lack of outpatient data.

Conclusion

With variable study designs, small sample sizes, and differing treatment protocols in GCIH studies, it is not surprising that management guidelines are not well established. Larger studies, pragmatic trials, and real-world data are needed to inform the development of guidelines for effective GCIH treatment because GCs continue to be used extensively, the risk of GCIH is increasing as the prevalence of prediabetes and DM increase steeply, and the prevalence of GCIH increases during the COVID-19 pandemic.

Disclosure

The authors have no multiplicity of interest to disclose.

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