diabetesresearchandclinicalpractice194(2022)110151

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Dexamethasone-induced hyperglycaemia in COVID-19: Glycaemic profile in patients without diabetes and factors associated with hyperglycaemia

Yoon Ji J Rhou [a,b,*], Amanda Hor [a,c], Mawson Wang [a,b], Yu-Fang Wu [a], Suja Jose [a], David R Chipps [a,b], N Wah Cheung [a,b]

[a] Department of Diabetes and Endocrinology, Westmead Hospital, Westmead, Sydney, NSW 2145, Australia
[b] Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2006, Australia
[c] Faculty of Medicine and Health, University of New South Wales, Sydney, NSW 2052, Australia

ARTICLE INFO

Keywords:
COVID-19
Dexamethasone
Glucocorticoid-induced hyperglycaemia
Corticosteroid-induced hyperglycaemia
Glucose profile
Glycaemic profile

ABSTRACT

Aims: To evaluate glycaemic profiles of COVID-19 patients without diabetes receiving dexamethasone and determine factors associated with hyperglycaemia.

Methods: All subjects without pre-existing diabetes receiving dexamethasone 6 mg for COVID-19 in a non-critical care setting were identified. Glucose profiles were obtained from capillary blood glucose (BG). Univariate and multivariate analyses were performed to identify factors associated with dexamethasone-induced hyperglycaemia (BG $\geq$ 10 mmol/L).

Results: Of 254 subjects, 129 (50.8%) were male with age 51.1 $\pm$ 18.2 years and weight 89.7 $\pm$ 26.3 kg. Hyperglycaemia post-dexamethasone occurred in 121 (47.6%). Glucose excursions began within three hours (6.8 $\pm$ 1.4 mmol/L pre-dexamethasone vs 8.7 $\pm$ 2.4 mmol/L at $\leq$ 3 h, $p < 0.001$) and peaked at 7–9 h (10.5 $\pm$ 2.3 mmol/L, $p < 0.001$ vs pre-dexamethasone). BGs post-intravenous were higher than post-oral administration for the initial six hours. Hyperglycaemic subjects were older (57.8 $\pm$ 17.5 years vs 45.0 $\pm$ 16.6 years, $p < 0.001$), had higher initial glucose (6.3 $\pm$ 1.0 vs 5.9 $\pm$ 0.9 mmol/L, $p = 0.004$), higher HbA1c (5.8 $\pm$ 0.3% [40 $\pm$ 3.5 mmol/mol] vs 5.5 $\pm$ 0.4% [37 $\pm$ 4.1 mmol/mol], $p < 0.001$) higher C-reactive protein (CRP) (100 $\pm$ 68 vs 83 $\pm$ 58 mg/L, $p = 0.026$), and lower eGFR (79 $\pm$ 17 vs 84 $\pm$ 16 mL/min/1.73 m^2, $p = 0.045$). Mortality was greater in the hyperglycaemia group (9/121 [7.4%] vs 2/133 [1.5%], $p = 0.02$). Age, HbA1c and CRP were independently associated with hyperglycaemia.

Conclusions: Half of subjects without diabetes experienced hyperglycaemia post-dexamethasone for COVID-19, peak occurring after 7–9 h. Age, HbA1c and CRP were associated with hyperglycaemia.

1. Introduction

Dexamethasone 6 mg daily for up to 10 days is standard of care in the management of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requiring oxygen therapy or ventilation, with reduction in mortality demonstrated in randomised controlled trials [1]. However, dexamethasone increases the risk of hyperglycaemia, which is associated with adverse COVID-19 outcomes [2,3]. There is limited data on glycaemic profiles after commencing dexamethasone for COVID-19.

Although recognised as common, reported rates of glucocorticoid-induced hyperglycaemia (GIH) in the inpatient setting vary widely and are affected by the type of glucocorticoid, dose, baseline population characteristics and the clinical context, occurring in 20–70% of hospitalised patients [4]. Prior to the COVID-19 pandemic, clinical experience and study data were most extensive for prednisolone-induced hyperglycaemia, characterised by a rise from 3-4 h, peak at 5–8 h and duration of 12–16 h [5]. Detailed glycaemic profiling of dexamethasone-induced hyperglycaemia however is lacking. Dexamethasone is a long-acting glucocorticoid with higher potency and longer duration of action than prednisolone. A case report of continuous glucose monitoring (CGM) evaluating the glycaemic profile in a patient with type 2 diabetes receiving single doses of intravenous dexamethasone cyclically suggested a later peak and longer duration of hyperglycaemia following

* Corresponding author at: Department of Diabetes and Endocrinology, Level 2, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, Sydney, NSW 2145, Australia.
E-mail address: jina.rhou@sydney.edu.au (Y.J.J. Rhou).

https://doi.org/10.1016/j.diabres.2022.110151
Received 14 June 2022; Received in revised form 5 October 2022; Accepted 6 November 2022
Available online 11 November 2022

dexamethasone compared to prednisolone [6]. Limited studies evaluating the effect of a single intraoperative dose of dexamethasone in subjects with and without diabetes have reported variable influence on glycaemic profile [7,8].

The impact of dexamethasone on glycaemic profile specifically in the realm of COVID-19 may be more complex, involving daily administration over consecutive days, multiple potential contributors to hyperglycaemia and an important interplay with clinical outcomes. New-onset diabetes, usually defined as elevated glucose and/or HbA1c in patients without prior diagnosis of diabetes, in patients admitted with COVID-19 has been described, with reported rates varying widely from 5% to > 40% [9,10]. Undetected pre-existing diabetes, stress hyperglycaemia, glucocorticoid-induced diabetes and the potential impact of SARS-CoV-2 on beta cell function have been proposed as contributing factors [11]. New onset of hyperglycaemia may be associated with poorer COVID-19 outcomes including higher mortality and intensive care admission rates than pre-existing diabetes [2,3,9,10,12,13]. Detailed evaluation of the risk factors and characterisation of the glucose profile of dexamethasone-induced hyperglycaemia in the setting of COVID-19 may guide early identification of hyperglycaemia and optimal pharmacotherapy for glycaemic control.

We therefore aimed to assess the risk of GIH in patients without prior history of diabetes, admitted to hospital in a non-critical care setting and receiving dexamethasone for COVID-19. We sought to detail the glycaemic profile in these patients, including the magnitude and timing of hyperglycaemia, and identify factors associated with its development.

2. Materials and Methods

A retrospective observational study of subjects without prior history of diabetes admitted with COVID-19 and receiving dexamethasone was performed. Approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee.

2.1. Study population

All patients admitted to a single tertiary hospital at the centre of the 2021 COVID-19 outbreak in Sydney, Australia, with polymerase chain reaction (PCR)-confirmed COVID-19 over a 1-month period in September 2021 were identified. Subjects were included if they did not have previously treated diabetes and they received at least one dose of intravenous (IV) or oral (PO) dexamethasone 6 mg daily during the admission as per the local treatment protocol for COVID-19 pneumonitis. The recommended administration time for dexamethasone was in the morning at 8 am and if the first dose was administered at a different time, subsequent doses were changed to morning administration. Subjects were excluded if they were aged < 16 years, pregnant, were initially admitted to the intensive care unit (ICU) or had an admission HbA1c of ≥ 6.5% (48 mmol/mol). Subjects receiving alternative glucocorticoid regimens and lacking glucose data post-administration of dexamethasone were also excluded.

2.2. Data collection

Demographic and baseline clinical data including history of diabetes and medication history were collected for all subjects from electronic medical records. Socioeconomic status was based on Socio-Economic Indexes for Areas (SEIFA) 2016 from Australian census data, determined from postcodes of residence [14]. Details regarding subjects' COVID-19 including vaccination status, date of symptom onset and COVID-19 confirmation by PCR, treatment regimen for COVID-19, commencement of glucose-lowering therapy during admission and clinical outcomes were also collected. Based on local protocol, pathology collected routinely on admission for all patients with COVID-19 included HbA1c, initial random venous glucose (pre-dexamethasone), renal function and inflammatory markers including C-reactive protein (CRP).

A standardised capillary glucose monitoring and glycaemic management protocol was developed for all inpatients with COVID-19. The protocol recommended that subjects receiving dexamethasone undergo capillary blood glucose (BG) monitoring at fasting and 2-hour postprandial timepoints. If the fasting BG was ≥ 8 mmol/L or 2-hour prandial BG was ≥ 12 mmol/L, antihyperglycaemic therapy was commenced under the management of the COVID-19 inpatient diabetes team. Glucose data were obtained from BGs collected routinely as per the glucose monitoring protocol and any available additional glucose measurements until commencement of glucose-lowering therapy, hospital discharge, ICU admission or death. Times of dexamethasone administration and times of each glucose value were recorded and compared to determine the time of BG monitoring post-dexamethasone.

The primary endpoint was the development of hyperglycaemia exceeding the inpatient glucose target, defined as any BG level ≥ 10 mmol/L in keeping with local and international glucose targets for hospitalised patients [15], after commencement of dexamethasone.

2.3. Glycaemic profile

To determine the glycaemic profile following dexamethasone, glucose levels were examined for the 24 h following each dose of dexamethasone, with each dose and day for each subject being considered an independent episode. Each 24-hour period following administration of dexamethasone was divided into 3-hour time blocks and the BGs were plotted in the corresponding time block after dexamethasone administration. Glucose data were censored at the time of administration of the next dose of dexamethasone if this was within 24 h. Thus, a subject who was treated with five doses of dexamethasone in hospital, approximately 24 h apart, would contribute five episodes of data to the analysis. Data from all subjects were aggregated to form the glucose curve. Glucose curves were generated from all data and from data corresponding to IV and PO dexamethasone administration.

2.4. Statistical analysis

Mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data were calculated. Unpaired t-tests and χ^2 or Fisher exact tests were used for continuous and categorical variables respectively. Binary logistic regression was used to identify factors associated with post-dexamethasone hyperglycaemia. SPSS version 27 (IBM Corporation, NY, USA, 2020) was used for analysis and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population characteristics

700 patients confirmed to be COVID-19 positive over a one-month period in September 2021 were identified through our Inpatient Diabetes Dashboard which monitors glucose levels among all hospitalised patients [16]. Of these, 464 received dexamethasone and 254 met criteria for data analysis (Fig. 1). The median duration of dexamethasone therapy before commencement of glucose-lowering therapy, hospital discharge, ICU admission or death was three [IQR 2, 6] days. A total of 2922 BG measurements in addition to baseline glucose were obtained from the 254 subjects.

The mean age of the cohort was 51.1 ± 18.2 years with weight 89.7 ± 26.3 kg and body mass index (BMI) 31.6 ± 7.7 kg/m^2. Males comprised 129 (50.8%) of subjects. The most common region of birth was Australia (92 subjects, 36.2%), followed by the Middle East (87 subjects, 34.3%) and New Zealand and Pacific Islands (32 subjects, 12.6%). A language other than English was preferred by 88 subjects (34.6%). The majority (162 subjects, 63.8%) were in the most

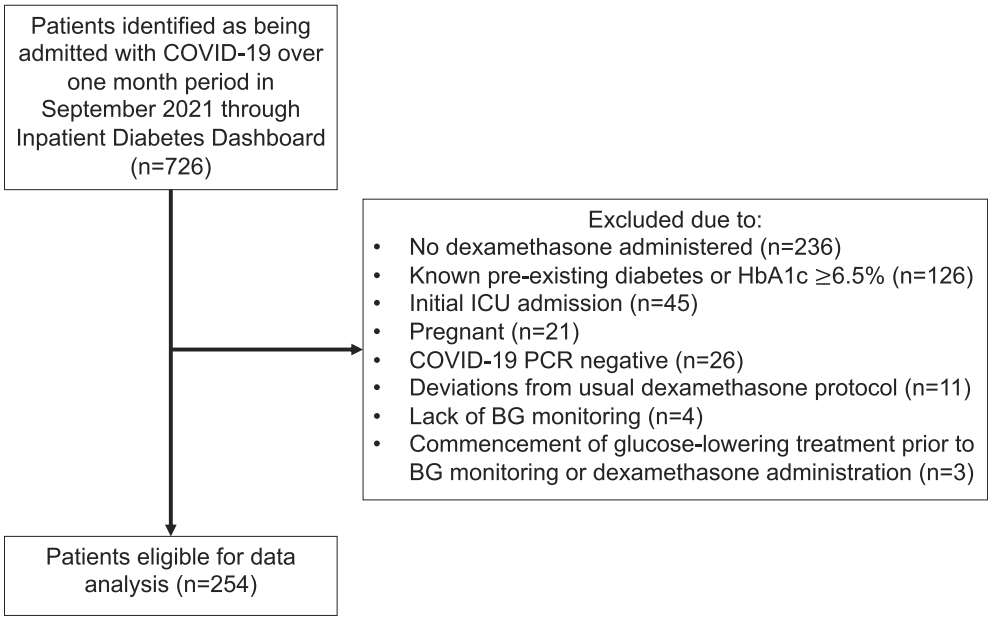

Fig. 1. Overview of subjects identified and included for analysis. ICU = intensive care unit, PCR = polymerase chain reaction, BG = capillary blood glucose.

socioeconomically disadvantaged quintile. Subjects who were not fully vaccinated with two doses comprised 244 (96.1%) of the cohort. Admission HbA1c and initial venous glucose prior to the administration of dexamethasone were 5.6 ± 0.4% (38 ± 4.1 mmol/mol) and 6.1 ± 1.0 mmol/L respectively.

3.2. Hyperglycaemia after dexamethasone

Hyperglycaemia post-dexamethasone, defined as BG ≥ 10 mmol/L, was observed in 121 (47.6%) of subjects. The median first day of hyperglycaemia was on the second day of dexamethasone 6 mg daily. The mean BG after commencement of dexamethasone was 8.4 ± 1.4 mmol/L in the group experiencing hyperglycaemia and 7.0 ± 0.7 mmol/L in the group without hyperglycaemia ($p < 0.001$). The peak BG prior to commencement of any glucose-lowering therapy was 12.2 ± 1.8 mmol/L in the hyperglycaemia group (vs 8.4 ± 1.0 mmol/L in the no hyperglycaemia group, $p < 0.001$). 33 subjects (13.0%) were commenced on antihyperglycaemic therapy, 27 (10.6%) receiving insulin therapy.

3.3. Glycaemic profile after dexamethasone

There were 1412 total episodes of dexamethasone administration. Fig. 2 showcases the glycaemic profile in relation to the timing of dexamethasone for all days with hyperglycaemia. Glucose excursions

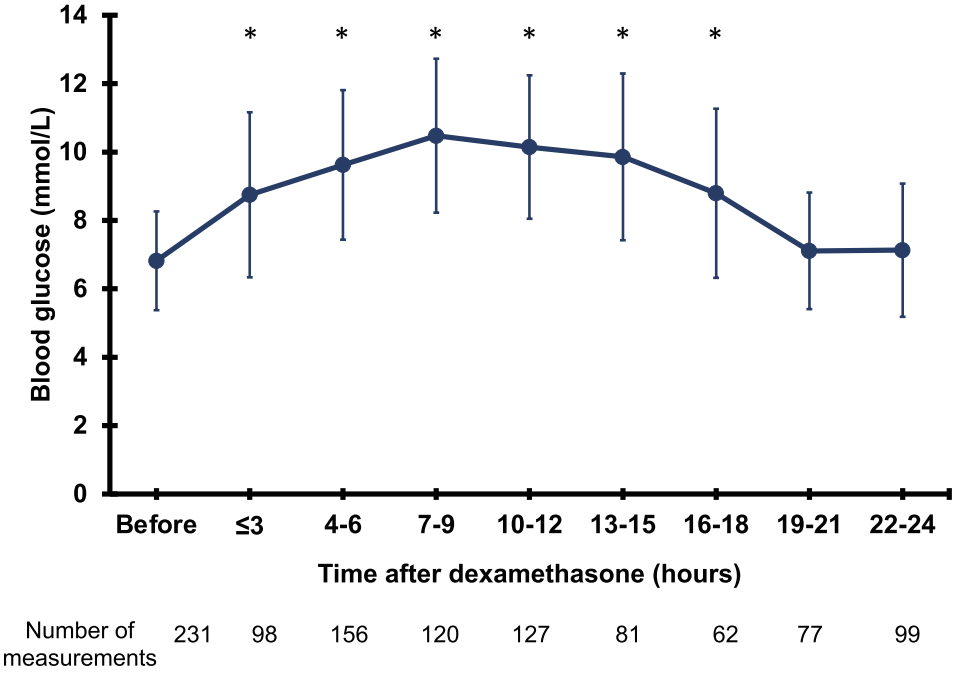

Fig. 2. Mean glucose within 3-hour time blocks after dexamethasone for episodes with any hyperglycaemia. Error bars represent standard deviation. The number of measurements per 3-hour time block is displayed under the figure. * Mean glucose levels post-dexamethasone were significantly greater than glucose pre-dexamethasone from ≤3 h to 16–18 h post-dexamethasone.

began within the first 3-hour time block following dexamethasone administration (6.8 ± 1.4 mmol/L pre-dexamethasone vs 8.7 ± 2.4 mmol/L at ≤ 3 h, p < 0.001; 9.6 ± 2.2 mmol/L at 4–6 h, p < 0.001 compared to pre-dexamethasone). Peak BG was reached at 7–9 h (10.5 ± 2.3 mmol/L, p < 0.001 compared to pre-dexamethasone) and remained significantly more elevated than pre-dexamethasone levels at 10–12 h (10.1 ± 2.1 mmol/L, p < 0.001), 13–15 h (9.9 ± 2.4 mmol/L, p < 0.001) and 16–18 h (8.8 ± 2.5 mmol/L, p < 0.001). BG returned to pre-dexamethasone levels at 19–21 h (7.1 ± 1.7 mmol/L, p = 0.2) and 22–24 h after dexamethasone (7.1 ± 1.9 mmol/L, p = 0.1).

Separate glycaemic profiles were generated using BG data following IV or PO administration of dexamethasone (Fig. 3). Pre-dexamethasone BGs were comparable between the two groups (6.8 ± 1.5 mmol/L pre-IV vs 6.8 ± 1.4 mmol/L pre-PO dexamethasone, p = 0.8). Glucose excursions for both routes of administration occurred within 3 h and reached peak BG at 7–9 h. BGs post-IV were higher than post-PO dexamethasone initially (9.2 ± 2.7 mmol/L post-IV vs 8.0 ± 1.8 mmol/L post-PO at ≤ 3 h, p = 0.047; 9.8 ± 2.1 mmol/L post-IV vs 8.9 ± 2.5 mmol/L post-PO at 4–6 h, p = 0.03). BGs following the different routes of administration were similar at subsequent time blocks with comparable downtrend in BG to pre-dexamethasone levels.

3.4. Factors associated with hyperglycaemia after dexamethasone

There were no significant differences in sex, weight and BMI, socioeconomic status, preferred language and vaccination status between the group that developed hyperglycaemia post-dexamethasone and the group without hyperglycaemia (Table 1). There was a trend towards a higher proportion being born outside Australia in the group that developed hyperglycaemia, not reaching statistical significance. Subjects who developed hyperglycaemia were older (57.8 ± 17.5 vs 45.0 ± 16.6 years, p < 0.001). They also had higher initial venous glucose (6.3 ± 1.0 vs 5.9 ± 0.9 mmol/L, p = 0.004), higher HbA1c (5.8 ± 0.3% [40 ± 3.5 mmol/mol] vs 5.5 ± 0.4% [37 ± 4.1 mmol/mol], p < 0.001), higher initial CRP (100 ± 68 vs 83 ± 58 mg/L, p = 0.026), and lower renal function on admission (eGFR 79 ± 17 vs 84 ± 16 mL/min/1.73 m^2, p = 0.045).

On multivariate analysis, older age, higher HbA1c and higher initial CRP, but not initial venous glucose or renal function, were independent

Table 1
Baseline characteristics of subjects with hyperglycaemia and subjects without hyperglycaemia after dexamethasone.

Characteristic	No hyperglycaemia (n = 133)	Hyperglycaemia (n = 121)	P-value
Male sex (n)	69 (51.9%)	60 (49.6%)	0.7
Age (years)	45.0 ± 16.6	57.8 ± 17.5	< 0.001
Weight (kg)	91.3 ± 27.6	88.0 ± 24.8	0.4
BMI (kg/m^2)	31.6 ± 7.9	31.6 ± 7.5	1.0
Socioeconomic status: SEIFA Decile Score[a] (n)			0.3
1–2 (most disadvantaged)	90 (67.7%)	72 (59.5%)	
3–4	15 (11.3%)	14 (11.6%)	
5–6	6 (4.5%)	12 (9.9%)	
7–8	14 (10.5%)	11 (9.1%)	
9–10 (least disadvantaged)	8 (6.0%)	12 (9.9%)	
Country of birth (n)			0.06
Australia	56 (42.1%)	36 (29.8%)	
Middle East	47 (35.3%)	40 (33.1%)	
Oceania (including NZ)[b]	13 (9.8%)	19 (15.7%)	
Other	17 (12.8%)	26 (21.5%)	
Language other than English spoken at home (n)	45 (33.8%)	43 (35.5%)	0.8
Vaccination status (n)			0.3
Unvaccinated	100 (75.2%)	81 (66.9%)	
One dose	29 (21.8%)	34 (28.1%)	
Two doses	4 (3.0%)	6 (5.0%)	
Initial venous glucose pre-dexamethasone (mmol/L)	5.9 ± 0.9	6.3 ± 1.0	0.004
HbA1c (%)	5.5 ± 0.4	5.8 ± 0.3	< 0.001
HbA1c (mmol/mol)	37 ± 4.1	40 ± 3.5	
Initial eGFR (mL/min/1.73 m^2)	84 ± 16	79 ± 17	0.045
Initial CRP (mg/L)[c]	83 ± 58	100 ± 68	0.026

Data presented as mean ± standard deviation or number of subjects, n (%). Abbreviations: [a]Socio-Economic Indexes for Areas 2016 [14]. [b]New Zealand. [c]C-reactive protein.

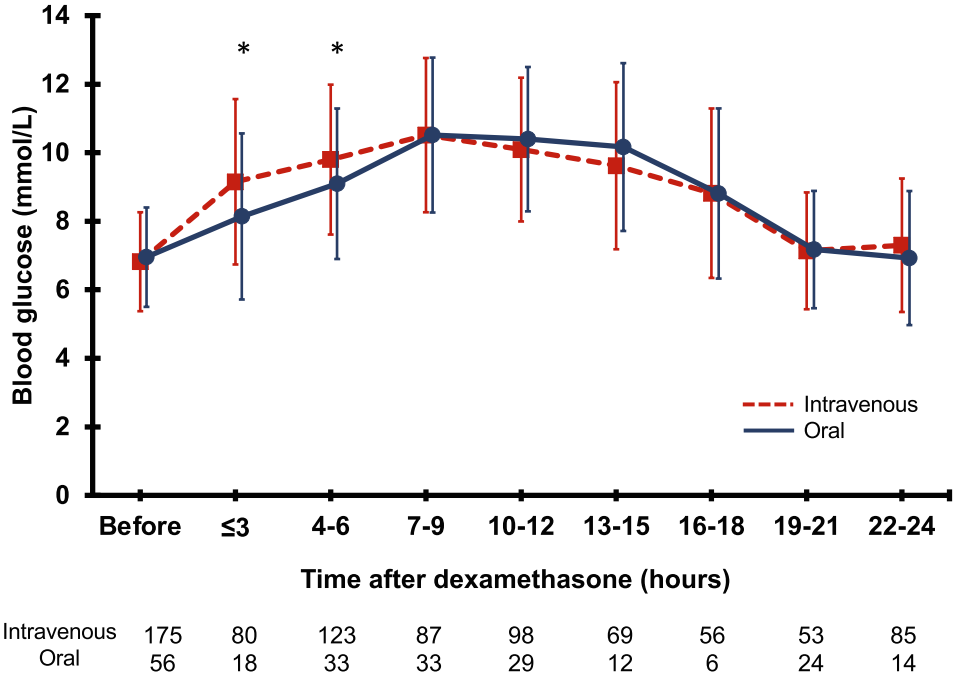

Fig. 3. Mean glucose within 3-hour time blocks after intravenous dexamethasone (dotted line) and after oral dexamethasone (solid line) for episodes with any hyperglycaemia. Error bars represent standard deviation. The number of measurements per 3-hour time block for intravenous and for oral dexamethasone administration is displayed under the figure. * Mean glucose levels at ≤3 h and 4–6 h after intravenous dexamethasone were significantly greater than mean glucose after oral dexamethasone.

predictors of hyperglycaemia after adjusting for BMI and country of birth, with a seven times greater risk per 1% increase in HbA1c, 18% greater risk per 5 year increase in age and 7% increased risk per 10 mg/L higher initial CRP (Table 2).

3.5. Clinical outcomes

Twenty-seven (10.6%) subjects required ICU admission following initial ward care and there were 11 (4.3%) deaths. There was no significant difference in the rate of ICU admission (11/121 [9.1%] vs 16/133 [12.0%], p = 0.4) but higher mortality (9/121 [7.4%] vs 2/133 [1.5%], p = 0.02) was observed in the group developing hyperglycaemia.

4. Discussion

This study represents the first detailed evaluation of the glycaemic profile in subjects without pre-existing diabetes receiving dexamethasone daily for COVID-19. Hyperglycaemia ≥10 mmol/L was common, occurring in almost half of our subjects, and older age, higher HbA1c and higher initial CRP were independently associated with hyperglycaemia. Glucose excursions were demonstrated to occur within 3 h and to peak at 7–9 h post-dexamethasone, but with more rapid excursions following IV compared to PO route of administration.

Glucocorticoids have multiple sites of action leading to potentiation of insulin resistance and inhibition of insulin release. Glucocorticoids directly inhibit insulin signalling in skeletal muscle, resulting in decreased glucose uptake and particularly impacting prandial glycaemic control [17,18]. Hepatic gluconeogenesis is increased, and it is possible that different glucocorticoid types, routes of administration and patient population characteristics may influence this effect [17]. It is speculated that glucocorticoids also interfere with pancreatic beta cell function via inhibition of multiple molecular pathways, the impact on insulin secretion contributing to GIH. This is likely to be influenced by the duration of glucocorticoid treatment, recovery of beta cell function being observed after prolonged exposure in contrast to administration of single or short courses of glucocorticoids [17–19].

GIH is recognised as common in the inpatient setting, with extensive data available for prednisolone-induced hyperglycaemia. Data evaluating the frequency of GIH due to daily dexamethasone in a population without diabetes is limited and thus our findings add insights. Understanding of dexamethasone-induced hyperglycaemia is predominantly from the perioperative setting, usually involving a single dose of IV dexamethasone. A small study assessing a single perioperative dose of 8 mg dexamethasone in women without diabetes noted a significant effect on glucose levels compared to surgical stress alone with 20% measuring glucose levels > 8.5 mmol/L, whereas another reported 30% of subjects without diabetes randomised to receive dexamethasone for elective surgery developed hyperglycaemia > 10 mmol/L [20,21]. Hyperglycaemia ≥ 10 mmol/L was noted in 26% of patients without diabetes receiving glucocorticoids with chemotherapy but interpretation was limited by the heterogeneity in glucocorticoid type and duration and infrequent glucose monitoring, > 30% not having any point-of-care glucose data [22].

We also performed evaluation of the 24-hour glycaemic profile after each dexamethasone administration, which is sparse in literature. In a small cohort of patients with and without diabetes hospitalised with COVID-19, patients receiving dexamethasone had increased BGs at the first and last measurements at 6 am and 10 pm but surprisingly not at the 12 pm and 5 pm time points [23]. Comparison of perioperative 10 mg dexamethasone IV in subjects with and without diabetes demonstrated glucose peaks at two hours in both groups, but this study only evaluated early GIH up to four hours [7]. In contrast, comparison of single versus two perioperative doses of dexamethasone revealed a glucose downtrend from zero to 24 h post-administration but this study included subjects with pre-existing diabetes and receiving insulin and glucose infusion [24].

We censored glucose data when glucose-lowering therapy was commenced to ensure that the generated glycaemic profiles reflected the effect of dexamethasone without the influence of therapy. We found an early effect on glucose levels, excursions occurring within 3 h, peaking at 7–9 h and returning towards pre-dexamethasone levels by 19–21 h. Onset of glucose rise occurred earlier following IV administration, mean glucose after IV exceeding that of glucose after PO dexamethasone initially but without significant differences noted after the initial six hours. This is consistent with the pharmacokinetics of IV and PO routes of dexamethasone. Maximum concentration after PO dexamethasone is reached at two hours, compared to maximum reached within 20 min after the IV route, with no differences in half-life or clearance between the two routes [25].

Dexamethasone is recognised to have a longer duration of action than prednisolone but detailed pharmacodynamic data for dexamethasone is limited. CGM in a subject with diabetes receiving dexamethasone demonstrated a steady state of hyperglycaemia being reached within 3 h and persisting 23–35 h but this may not be applicable to a population without diabetes [6]. Although the glucose profiles in our cohort also suggested a slower waning of effect compared to prednisolone, demonstration of return towards pre-dexamethasone levels at 19–21 h has important implications for therapy. However, as our study included some subjects whose HbA1c was in the prediabetes range, underlying altered glucose metabolism and superimposed insulin resistance due to the inflammatory state of COVID-19 infection would be expected to have impacted the glucose curves generated and these are unlikely to reflect the profile of dexamethasone-induced hyperglycaemia in isolation.

There are well-established associations between hyperglycaemia and adverse COVID-19 outcomes which suggest potential clinical implications of our findings, particularly given that > 10% of our subjects measured BG levels warranting insulin therapy. Elevated glucose in hospitalised COVID-19 patients is associated with increased risk of mortality and ICU admissions in patients with and without glucocorticoid therapy [13]. Interestingly, the risk of mortality and critical illness appears to be higher in COVID-19 patients with new-onset hyperglycaemia than those with pre-existing diabetes, potentially related to those with new hyperglycaemia being more critically ill [2,3,11,26]. Treating new-onset hyperglycaemia with glucose-lowering agents improves COVID-19 outcomes [26]. It is unknown however if failure to identify and optimally manage worsening hyperglycaemia due to glucocorticoids may offset the survival benefits of dexamethasone.

Older age was a traditional risk factor for GIH that we found to be independently associated with dexamethasone-induced hyperglycaemia in the COVID-19 population. Higher HbA1c, likely representing underlying impaired glucose metabolism, and initial CRP, likely reflecting greater disease severity and inflammatory response, were also associated with GIH. This is consistent with previous demonstration of insulin requirements mirroring CRP in COVID-19 patients in the critical care setting, including in those with new diagnosis of diabetes [27]. Surprisingly, weight and BMI were not significantly different between the

Table 2
Multivariate analysis of factors associated with hyperglycaemia after dexamethasone.

Factor	Odds Ratio for Hyperglycaemia [95% CI] [a]	P-value
HbA1c	7.34 [2.44, 22.05] per 1% 1.20 [1.09, 1.33] per 1 mmol/mol	< 0.001
Age	1.18 [1.05, 1.31] per 5 years	0.004
Initial CRP[b]	1.07 [1.01, 1.13] per 10 mg/L	0.02
Initial venous glucose pre-dexamethasone	1.08 [0.74, 1.57] per 1 mmol/L	0.7
Initial eGFR	1.00 [0.98, 1.02] per 1 mL/min/1.73 m^2	0.8

Abbreviations: [a]Confidence interval. [b]C-reactive protein.

group developing GIH and the group that did not, in contrast to previous reports of shared risk factors between GIH and traditional type 2 diabetes such as obesity [7,28]. A lack of association between BMI and GIH has been noted in fewer studies [22,24]. These inconsistent findings suggest that the effect of weight and BMI may be influenced by the underlying characteristics of the study population, such as the specific clinical setting and baseline metabolic profile. Our cohort was predominantly overweight and obese with mean BMI exceeding 30 kg/m^2, and different findings may be observed in a population with fewer overweight and obese subjects.

A limitation of our study was the reliance on capillary glucose testing. Some subjects underwent fewer BG tests than the fasting and 2-hour prandial monitoring prescribed by our protocol due to the operational challenge of our hospital being faced with a sudden large influx of inpatients with COVID-19 for the first time. This may have underestimated the true prevalence of GIH and impacted the completeness of the glycaemic profiles generated. CGM would have enabled more detailed evaluation but was not possible from a practical perspective for the high numbers of patients.

We also assessed glucose levels relative to time after dexamethasone administration rather than in relation to meals. This was to allow aggregation of BGs regardless of the timing of dexamethasone administration and due to the unavailability of dietary data. Given the known effect of glucocorticoids on peripheral insulin resistance and predominant impact on prandial glycaemic control, the BGs are likely to have been affected by whether the levels reflected pre-meal or prandial measurements. Our monitoring protocol recommended fasting and 2-hour prandial measurements but BGs collected may have included pre-meal measurements due to the difficulty following the prescribed protocol strictly for large numbers of COVID-19 patients and variable oral intake in these unwell patients. Interestingly, a case report of CGM in a patient with type 2 diabetes receiving dexamethasone found that the pattern of hyperglycaemia was unrelated to meals [6]. Pairing glucose data with a detailed dietary diary would be valuable in future studies.

However, the large cohort and total number of BGs analysed are strengths of our study and allowed for a valid snapshot of the effect of dexamethasone in this population. It provides the first detailed aggregate 24-hour glycaemic profiling of subjects without diabetes receiving dexamethasone for COVID-19 to our knowledge. The study population was well-characterised with detailed baseline characteristics recorded.

Recommendations specific for the COVID-19 population receiving dexamethasone have been proposed in the United Kingdom, advising insulin-naïve patients with BG $>$ 12 mmol/L to be commenced on insulin therapy using twice daily intermediate-acting insulin (NPH insulin), two thirds of the weight-based total daily dose administered in the morning and one third in the evening [29]. In contrast, another group used a protocol commencing long-acting basal insulin (glargine) and patients managed under the protocol had superior glycaemic control than patients not receiving protocolised management, although analyses included subjects with and without diabetes [30]. There have been no studies comparing the efficacy and safety of different insulin regimens in patients with GIH in the setting of COVID-19. The glucose profiles generated in our study suggest a regimen including intermediate-acting insulin, with or without long-acting basal insulin, more closely reflects the glycaemic effects in this population. Given the downtrend in BGs towards pre-dexamethasone levels from 19-21 h, it may be reasonable to further simplify the initial regimen to once daily intermediate-acting insulin at the time of dexamethasone administration in the morning and to consider addition of rapid-acting insulin with meals. The more rapid glucose rise with IV administration of dexamethasone suggests early introduction of rapid-acting insulin with breakfast or use of mixed intermediate and rapid-acting insulin with breakfast may be considered.

Our findings support routine screening for diabetes and systematic glucose monitoring in patients without prior diagnosis of diabetes receiving dexamethasone for COVID-19. The identified factors associated with hyperglycaemia and the glycaemic profiles generated in our study offer insight into early recognition and therapy for optimal glycaemic control but prospective interventional studies comparing insulin regimens and using CGM are needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the assistance of all diabetes educators of the Department of Diabetes and Endocrinology at Westmead Hospital, Sydney, Australia.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability.

The data that support the findings of this study are available from the authors upon reasonable request.

References

[1] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693–704. https://doi.org/10.1056/NEJMoa2021436.

[2] Klonoff DC, Messler JC, Umpierrez GE, Peng L, Booth R, Crowe J, et al. Association between achieving inpatient glycemic control and clinical outcomes in hospitalized patients with COVID-19: a multicentre, retrospective hospital-based analysis. Diabetes Care 2021;44(2):578–85.

[3] Saand AR, Flores M, Kewan T, Alqaisi S, Alwakeel M, Griffiths L, et al. Does inpatient hyperglycemia predict a worse outcome in COVID-19 intensive care unit patients? J Diabetes 2021;13(3):253–60.

[4] Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract 2013;99(3):277–80. https://doi.org/10.1016/j.diabres.2012.12.023.

[5] Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. J Clin Endocrinol Metab 2011;96(6):1789–96. https://doi.org/10.1210/jc.2010-2729.

[6] Zhang F, Karam JG. Glycemic profile of intravenous dexamethasone-induced hyperglycemia using continuous glucose monitoring. Am J Case Rep 2021;22:e930733-1–930733-7. https://doi.org/10.12659/AJCR.930733.

[7] Hans P, Vanthuyne A, Dewandre PY, Brichant JF, Bonhomme V. Blood glucose concentration profile after 10 mg dexamethasone in non-diabetic and type 2 diabetic patients undergoing abdominal surgery. Br J Anaesth 2006;97(2):164–70. https://doi.org/10.1093/bja/ael111.

[8] Corcoran TB, O'Chan MTV E, Ho KM. Perioperative ADministration of Dexamethasone And blood Glucose concentrations in patients undergoing elective non-cardiac surgery - the randomised controlled PADDAG trial. Eur J Anaesthesiol 2021;38(9):932–42. https://doi.org/10.1097/EJA.0000000000001294.

[9] Fadini GP, Morieri ML, Boscari F, Fioretto P, Maran A, Busetto L, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract 2020;168:108374. https://doi.org/10.1016/j.diabres.2020.108374.

[10] Liu Ye, Lu R, Wang J, Cheng Q, Zhang R, Zhang S, et al. Diabetes, even newly defined by HbA1c testing, is associated with an increased risk of in-hospital death in adults with COVID-19. BMC Endocrine Disorders 2021;21(1). https://doi.org/10.1186/s12902-021-00717-6.

[11] Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, hyperglycemia, and new-onset diabetes. Diabetes Care 2021;44(12):2645–55. https://doi.org/10.2337/dc21-1318.

[12] Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab 2020;22(10):1897–906. https://doi.org/10.1111/dom.14099.

[13] Morieri ML, Fadini GP, Boscari F, Fioretto P, Maran A, Busetto L, et al. Hyperglycemia, glucocorticoid therapy, and outcome of COVID-19. Diabetes Res Clin Pract 2020;168:108449. https://doi.org/10.1016/j.diabres.2020.108449.

[14] Australian Bureau of Statistics. Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA) 2016; Available from https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.0012016?OpenDocument; 2016 [accessed 10 November 2021].

[15] Korytkowski MT, Muniyappa R, Antinori-Lent K, Donihi AC, Drincic AT, Hirsch IB, et al. Management of hyperglycemia in hospitalized adult patients in non-critical

care settings: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2022;107(8):2101–28. https://doi.org/10.1210/clinem/dgac278.
[16] Cheung NW, Hor A, Hng TM. The virtual inpatient diabetes management service: COVID-19 brings the future to inpatient diabetes management. Med J Aust 2022; 216(6):321–2. https://doi.org/10.5694/mja2.51456.
[17] van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest 2009;39(2):81–93. https://doi.org/10.1111/j.1365-2362.2008.02067.x.
[18] Beaupere C, Liboz A, Fève B, Blondeau B, Guillemain G. Molecular mechanisms of glucocorticoid-induced insulin resistance. Int J Mol Sci 2021;22(2):623. https://doi.org/10.3390/ijms22020623.
[19] Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. Diabetes Metab Res Rev 2014;30(2):96–102. https://doi.org/10.1002/dmrr.2486.
[20] Eberhart LHJ, Graf J, Morin AM, Stief T, Kalder M, Lattermann R, et al. Randomised controlled trial of the effect of oral premedication with dexamethasone on hyperglycaemic response to abdominal hysterectomy. Eur J Anaesthesiol 2011;28(3):195–201.
[21] Tien M, Gan TJ, Dhakal I, White WD, Olufolabi AJ, Fink R, et al. The effect of anti-emetic doses of dexamethasone on postoperative blood glucose levels in non-diabetic and diabetic patients: a prospective randomised controlled study. Anaesthesia 2016;71(9):1037–43.
[22] Healy SJ, Nagaraja HN, Alwan D, Dungan KM. Prevalence, predictors, and outcomes of steroid-induced hyperglycemia in hospitalized patients with hematologic malignancies. Endocrine 2017;56(1):90–7. https://doi.org/10.1007/s12020-016-1220-2.
[23] Cardoza-Jiménez KJ, Carranza-Zavala B, Manrique-Franco K, Espinoza-Morales F, Mejia CR. Daily glucose variation influenced by the use of corticosteroids in COVID-19 patients treated in Lima-Peru. Diabetes Metab Syndr 2021;15(4): 102188. https://doi.org/10.1016/j.dsx.2021.102188.
[24] Vogelzang M, Hoekstra M, Drost JT, Janse M, van der Horst ICC, Boonstra PW, et al. The impact of a reduced dose of dexamethasone on glucose control after coronary artery bypass surgery. Cardiovasc Diabetol 2007;6(1):39. https://doi.org/10.1186/1475-2840-6-39.
[25] Spoorenberg SMC, Deneer VHM, Grutters JC, Pulles AE, Voorn GPP, Rijkers GT, et al. Pharmacokinetics of oral vs. intravenous dexamethasone in patients hospitalized with community-acquired pneumonia. Br J Clin Pharmacol 2014;78 (1):78–83.
[26] Lin L, Chen Ze, Ding T, Liu H, Zhou F, Huang X, et al. Newly-diagnosed diabetes and sustained hyperglycemia are associated with poorer outcomes in COVID-19 inpatients without pre-existing diabetes. Diabetes Metab Syndr Obes 2021;14: 4469–82.
[27] Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. Clin Endocrinol 2020;93(4): 390–3. https://doi.org/10.1111/cen.14288.
[28] Darmon P, Dadoun F, Boullu-Ciocca S, Grino M, Alessi MC, Dutour A. Insulin resistance induced by hydrocortisone is increased in patients with abdominal obesity. Am J Physiol Endocrinol Metab 2006;291(5):E995–1002. https://doi.org/10.1152/ajpendo.00654.2005.
[29] Rayman G, Lumb AN, Kennon B, Cottrell C, Nagi D, Page E, et al. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. Diabet Med 2021;38(1): e14378. https://doi.org/10.1111/dme.14378.
[30] Asiri AA, Alguwaihes AM, Jammah AA, Alfadda AA, Al-Sofiani ME. Assessment of the effectiveness of a protocol to manage dexamethasone-induced hyperglycemia among hospitalized patients with COVID-19. Endocr Pract 2021;27(12):1232–41. https://doi.org/10.1016/j.eprac.2021.07.016.