ARTICLE

Incidence and control of steroid-induced hyperglycaemia in hospitalised patients at a tertiary care centre for lung diseases

Matej Dobravc Verbič[1,2] · Jasna Gruban[3] · Mojca Kerec Kos[3]

Abstract

Background The aim of this study was to determine the incidence of steroid-induced hyperglycaemia (SIH) in patients hospitalised at the tertiary centre for lung diseases, to assess glycaemic control during hospitalisation, and to determine the factors associated with the control of SIH.

Methods A 4-month retrospective study was conducted. All patients who received systemic glucocorticoids for ≥ 2 days during hospitalisation, with ≥ 2 elevated blood glucose (BG) readings, were included in the analysis. SIH control was determined by mean BG levels, the number and proportion of elevated and pronouncedly elevated BG readings, and the number of hypoglycaemic events.

Results 60 of 283 patients (21.2%) developed SIH, of which 55 patients were included in further analysis. Mean fasting and daytime BG levels were 7.8 ± 2.9 mmol/l and 10.9 ± 2.2 mmol/l, respectively. 41/55 patients (74.5%) had elevated average BG levels. 45/55 patients (81.8%) had > 5 readings or $> 20\%$ of all readings exceeding hyperglycaemia threshold, and 33/55 patients (60.0%) had pronouncedly elevated BG levels on more than one occasion. 6/55 patients (10.9%) experienced more than one hypoglycaemic event or a severe hypoglycaemia. Only 9/55 patients (16.4%) achieved adequate SIH control according to all defined criteria. Pre-existing diabetes and longer duration of hospital treatment with low glucocorticoid dose were significantly associated with poorer glycaemic control ($p < 0.001$ and $p = 0.003$, respectively).

Conclusions Appropriate SIH management was demonstrated to be challenging. According to the defined criteria, adequate glycaemic control during hospitalisation was not achieved in the large majority of patients with SIH.

Keywords Hyperglycaemia · Glucocorticoids · Blood glucose levels · Antidiabetic therapy · Steroid diabetes

Abbreviations

BG	Blood glucose
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
GC	Glucocorticoids
IQR	Interquartile range
SIH	Steroid-induced hyperglycaemia

✉ Matej Dobravc Verbič
matej.dobravcverbic@kclj.si

1 University Clinic of Respiratory and Allergic Diseases Golnik, Golnik 36, 4204 Golnik, Slovenia

2 Centre for Clinical Toxicology and Pharmacology, University Medical Centre Ljubljana, Zaloška 7, 1000 Ljubljana, Slovenia

3 Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia

Introduction

Systemic glucocorticoids (GC), commonly used in patients with lung disease, are a well-known cause of hyperglycaemia [1]. Cortisol and other GC inhibit insulin secretion from pancreatic β-cells and increase glucagon secretion from α-cells. They stimulate the synthesis of glucose in the liver and reduce insulin sensitivity of fat tissue and skeletal muscles [2–4]. High blood glucose (BG) levels have been associated with increased infection rates, poor wound healing, longer hospital stays, higher treatment costs and higher mortality during hospitalisation [5–9]. In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), hyperglycaemia has been linked to worse outcomes [10, 11]. A meta-analysis showed that intensive glycaemic control was associated with a lower risk of infection in hospitalised patients [12].

The incidence of steroid-induced hyperglycaemia (SIH) is estimated to be around 40–50% [13–16]. Three types of

SIH can be distinguished, namely exacerbation of an existing type 2 diabetes mellitus (DM), newly discovered DM, and transient hyperglycaemia in patients without pre-existing DM [17, 18]. With a morning daily dose of GC, SIH occurs more frequently in the afternoon and evening hours, followed by a gradual decrease in overnight BG levels [4, 16, 19–21]. Its onset is usually within the first week of treatment with GC, but it can also occur 2–4 weeks after starting GC [17, 22].

The risk for SIH increases with higher dose of GC and longer duration of treatment, but does not depend on the type of GC, taking equivalent doses into account [14, 19, 23]. Other factors associated with SIH include pre-existing DM, impaired fasting glycaemia or glucose tolerance, family history of DM, previous gestational diabetes, obesity, polycystic ovarian disease, advanced age, elevated C-reactive protein levels and the Charlson Comorbidity Index [14, 18]. Existing data regarding the influence of these factors on SIH control is very limited [19].

There are no general consensus guidelines for SIH management. Several studies have compared different insulin regimens providing mixed results [13]. Information regarding the use of oral hypoglycaemic agents mainly comes from small clinical trials and case studies [4].

The aim of this study was to determine the incidence of SIH in a tertiary care hospital for lung diseases, to assess SIH control during hospitalisation according to the defined criteria, and to determine the potential influence of age, sex, body mass index (BMI), pre-existing type 2 DM, length of hospital stay, and treatment with systemic GC before admission and during hospitalisation on SIH control.

Materials and methods

Study design and patient population

A 4-month retrospective study included patients with the following characteristics: age $\geq$ 18 years; hospitalisation at the University Clinic Golnik during May–August 2019; systemic treatment with GC for $\geq$ 2 days during hospitalisation; fasting BG levels $\geq$ 7.0 mmol/l or daytime BG levels $\geq$ 10.0 mmol/l on at least 2 readings; signed informed consent form. Patients receiving only topical or inhaled GC were not included. The study was approved by the National Medical Ethics Committee.

Evaluation of steroid-induced hyperglycaemia control

In patients with confirmed SIH, glycaemic control was assessed by monitoring BG levels during hospital treatment with systemic GC. Adequate SIH control was defined with the following criteria:

1. BG levels elevated on < 5 and < 20% of readings (fasting BG $\geq$ 7.0 mmol/l; daytime BG $\geq$ 10.0 mmol/l)
2. BG levels pronouncedly elevated on < 2 readings (fasting BG $\geq$ 10.0 mmol/l; daytime BG $\geq$ 13.0 mmol/l)
3. average BG levels not elevated (average fasting BG < 7.0 mmol/l; average daytime BG < 10.0 mmol/l)
4. < 2 hypoglycaemic events (BG $\leq$ 4.0 mmol/l) and no severe hypoglycaemic events ($\leq$ 2.8 mmol/l)

Data collection

The following data were collected in anonymised form from the medical records and charts of the included patients: patient demographics, level and timing of all BG readings during hospitalisation, treatment with GC and hypoglycaemic agents before and during hospitalisation (type of drugs, dosing regimen, treatment duration, changes in therapy), diagnosis of DM before hospitalisation, and length of hospital stay.

BG readings before breakfast at 7:00 a.m. were considered as fasting levels, while other readings (scheduled before lunch at 11:00 a.m., before dinner at 5:00 p.m., at bedtime at 10:00 p.m., and any other reading) were considered as daytime BG levels.

Statistical analysis

Descriptive statistics were used to determine the incidence of SIH and the proportion of patients who met the criteria for adequate SIH control. The interquartile range (IQR) was reported when median was used. Chi-square test was used to determine the association between SIH control and categorical parameters (sex, pre-existing DM, treatment with systemic GC before admission). Fisher's exact test was applied in cases of expected frequencies less than 5. Mann–Whitney U test was applied to compare the differences in continuous variables (age, BMI, duration of treatment with GC during hospitalisation (GC days), and the length of hospital stay) between patients with adequate and inadequate SIH control. Additionally, the days when patients received high doses (high GC days) and low doses of GC (low GC days) were examined separately. High dose of GC was defined as a daily dose $\geq$ 32 mg methylprednisolone or equivalent. The statistical analyses were performed with the IBM SPSS Statistics 25 software. A p-value < 0.05 was considered significant.

Results

In the 4-month study period, 283 patients were treated with systemic GC for ≥ 2 days during hospitalisation at the University Clinic Golnik (Fig. 1). Of the 168/283 patients who had at least 2 BG readings performed during hospitalisation, 60 patients (21.2%) with SIH were identified, but 5 did not agree to participate in the study; therefore, 55 patients were included in further analyses.

Of the 55 patients with SIH, 20 (36.4%) were female. The median age of the included patients was 70 years

Fig. 1 Patient selection and therapy with glucocorticoids and hypoglycaemic drugs for the included patients
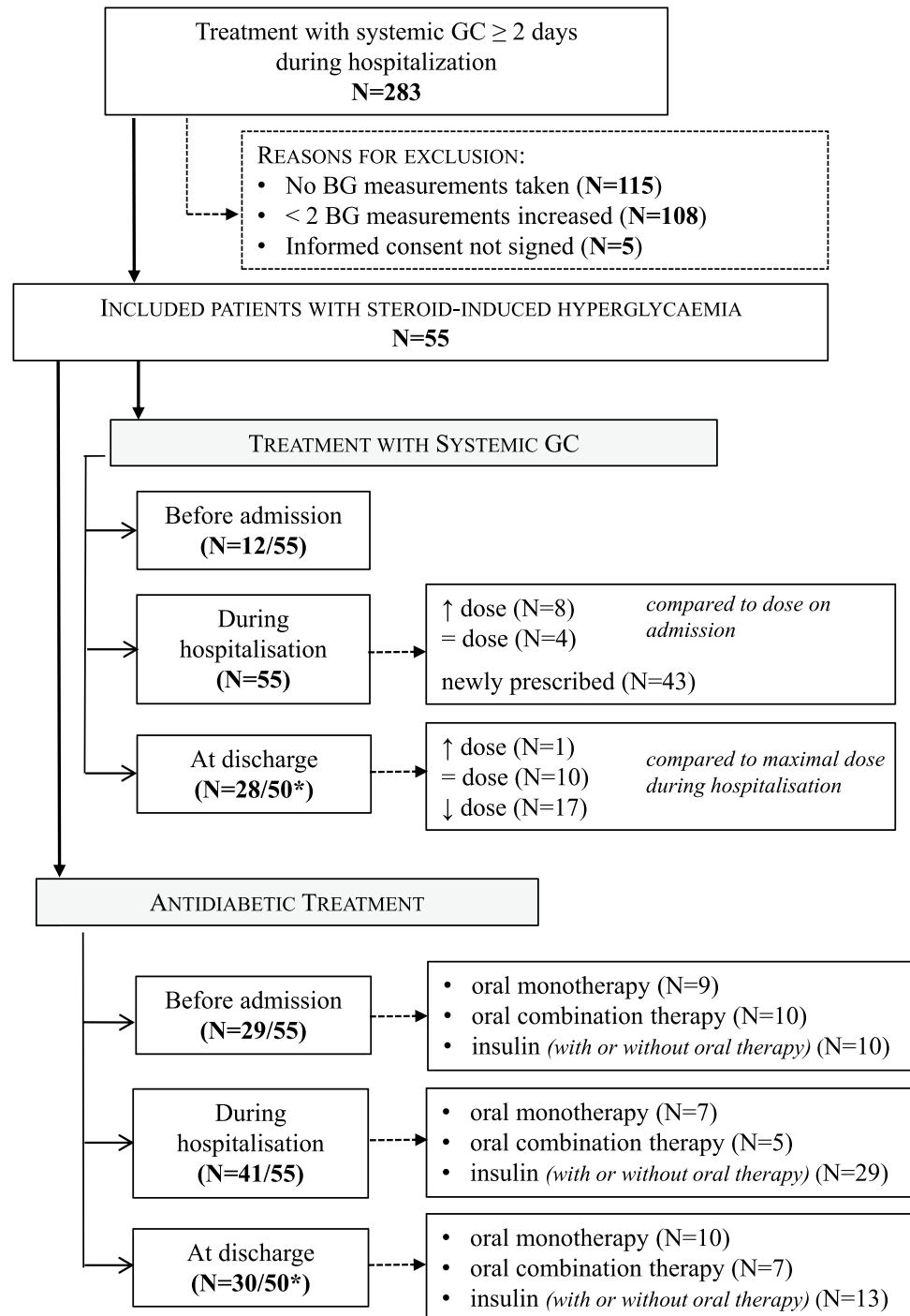
* 5 patients died during hospitalisation

BG – blood glucose; GC – glucocorticoid

(IQR 64–77), and the median BMI was 28.1 kg/m^2 (IQR 24.1–33.7). 30 patients (54.5%) had previously known type 2 DM. The median length of hospital stay of patients with SIH was 12 days (IQR 8–22).

Therapy with glucocorticoids and hypoglycaemic drugs

Information regarding the treatment with GC and hypoglycaemic agents before admission, during hospitalisation, and at discharge is presented in Fig. 1. Methylprednisolone was used for GC treatment in the majority of patients (45/55; 81.8%), whereas 9 patients (16.4%) received dexamethasone. 48 patients (87.3%) received at least one high daily dose of GC ($\geq$ 32 mg methylprednisolone or equivalent). Median daily dose of GC was 32 mg (IQR 20–32), and median cumulative dose during hospitalisation was 208 mg (IQR 160–302) of methylprednisolone or equivalent. The median duration of GC treatment during hospitalisation was 7 days (IQR 5–11).

Metformin was the oral hypoglycaemic agent most commonly used prior to admission (18 out of 21 patients receiving any oral therapy). 11/55 patients received an additional oral hypoglycaemic agent during hospitalisation; 8 of these patients were prescribed repaglinide, and 3 patients were prescribed metformin. 10/55 patients were receiving insulin prior to admission, and additional 19 patients were prescribed insulin during hospitalisation (Fig. 1). Of these, 16 patients received bolus insulin aspart, with only 2 of them receiving concurrent basal insulin. At discharge, compared to admission, 6 additional patients required antidiabetic treatment (30/50 patients vs. 29/55 patients, respectively; 5 patients died during hospitalisation). 4 of them were prescribed new insulin therapy. It is possible that antidiabetic therapy has been discontinued or changed for some patients at a later point (e.g., switching from insulin to oral therapy), as patients were not monitored after discharge.

These results indicate that in the majority of cases, SIH was a transient event that had resolved during hospitalisation. 30 patients experienced an exacerbation of pre-existing

type 2 DM. New onset of diabetes was identified in 3 patients: one patient demonstrated elevated HbA1c, and 2 patients had elevated BG levels several days after discontinuation of GC. 20 patients developed transient SIH, and 2 patients had elevated BG levels requiring antidiabetic therapy at discharge while still receiving GC. These 2 patients most likely developed transient hyperglycaemia, but may have also presented cases of newly discovered DM.

Blood glucose levels

During hospitalisation, patients had a median of 3 BG readings (IQR 2–3) performed daily when receiving systemic GC. Bedtime BG readings represented only 1.6% of all BG readings. As expected, elevated BG levels were more often detected during daytime than in the morning (Table 1).

Figure 2 shows the average BG levels for the scheduled BG readings. BG levels increased continuously during the day and reached the highest levels at bedtime. Similarly, the highest proportion of elevated BG readings was seen at that time (343/497 readings (69.0%) in the afternoon;
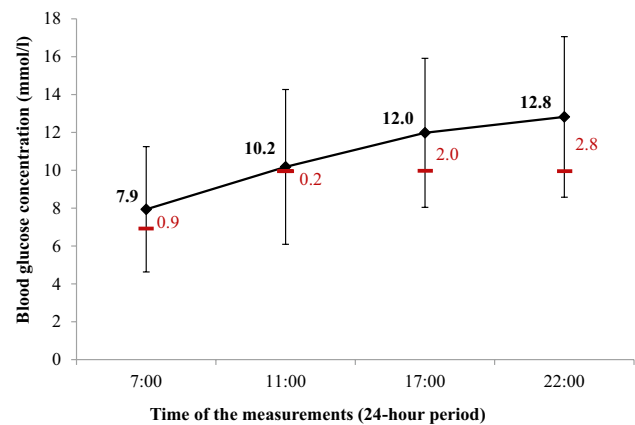
Fig. 2 Blood glucose levels for the scheduled readings (mean ± SD; $n = 1496$). The deviation from the upper limit of reference range at each time point is presented with red numbers (fasting readings 7.0 mmol/l, daytime readings 10.0 mmol/l)

Table 1 Number of blood glucose (BG) readings and number of patients with at least one elevated fasting or daytime BG reading within the particular range ($n = 55$)

BG levels [mmol/l]	Fasting BG levels		Daytime BG levels	
	Number of patients (%)	Number of readings (%)	Number of patients (%)	Number of readings (%)
7.0–9.9	48 (87.3%)	207 (38.5%)	54 (98.2%)	288 (28.9%)
10–12.9	17 (30.9%)	48 (8.9%)	55 (100.0%)	300 (30.1%)
13–14.9	10 (18.2%)	20 (3.7%)	36 (65.5%)	123 (12.3%)
15–19.9	6 (10.9%)	18 (3.3%)	31 (56.4%)	119 (11.9%)
≥20.0	1 (1.8%)	3 (0.6%9	11 (20.0%)	41 (4.1%)

19/25 readings (76.0%) at bedtime). Despite the fact that the majority of patients (45/55; 81.8%) were receiving GC as a once daily morning dose of methylprednisolone, the readings before lunch demonstrated the lowest diagnostic value for SIH. 196/436 BG readings (45.0%) were elevated before lunch, in comparison with 297/538 BG readings (55.2%) before breakfast.

11 patients (20.0%) experienced hypoglycaemia during hospitalisation; 5 of these patients had more than 1 hypoglycaemic event. In total, there were 23 hypoglycaemic events during the study. 4 hypoglycaemic events were severe (≤ 2.8 mmol/l); interestingly, they all occurred during daytime. In 2 patients, BG levels below the hypoglycaemia threshold (≤ 4.0 mmol/l) were found after a reduction of the GC dose, which is a recognised risk factor for hypoglycaemic events in diabetic patients [24].

Criteria for the control of steroid-induced hyperglycaemia

45/55 patients (81.8%) had ≥ 5 or $\geq 20\%$ of BG readings elevated, thus not meeting the 1st criterion for SIH control (Table 2). 33 patients (60.0%) did not fulfil the 2nd criterion, with BG levels pronouncedly elevated on more than one reading (fasting BG ≥ 10.0 mmol/l; daytime BG ≥ 13.0 mmol/l), while 41 patients (74.5%) had elevated average BG levels (the 3rd criterion). With regard to the hypoglycaemic events (the 4th criterion), most of the patients (49/55; 89.1%) received optimal antidiabetic treatment. Altogether, 46/55 patients (83.6%) failed to meet the defined set of criteria for adequate SIH control.

Factors influencing the control of steroid-induced hyperglycaemia

In our study, sex, age and BMI had no significant influence on SIH control, oppositely to pre-existing DM (Table 3; Mann–Whitney U test, $p < 0.005$ for all 4 criteria). In fact, none of the patients with previously known DM had adequate SIH control during hospitalisation with regard to the increased BG levels (1st, 2nd and 3rd criterion). The length

of hospital stay had a significant influence only on the number of hypoglycaemic events (4th criterion) (Mann–Whitney U test, $p = 0.023$). Patients with more than one hypoglycaemic event had longer hospital stay (median 29 days versus 12 days in other patients). This is in accordance with the results of the meta-analysis which demonstrated a longer hospital stay and a greater risk of in-hospital mortality in diabetic patients exposed to hypoglycaemia [24].

Significantly shorter treatment with GC during hospitalisation was observed in patients with adequate SIH control with respect to 3 of the 4 criteria (Table 3; Mann–Whitney U test, $p < 0.05$), but failed short of statistical significance jointly for all 4 criteria (Table 3; Mann–Whitney U test, $p < 0.079$). Unexpectedly, when treatment with high and with low dose of GC (≥ 32 mg and < 32 mg methylprednisolone or equivalent, respectively) were analysed separately, patients with adequate SIH control had significantly shorter treatment with low GC dose compared to the patients with inadequate control (Table 3; Mann–Whitney U test, $p < 0.05$), while the duration of treatment with high GC dose was comparable between the two groups of patients for all criteria. More data regarding statistical analyses can be found in Supplementary Table 1.

Discussion

Low incidence of SIH (60/283 patients; 21.2%) in comparison with similar studies was identified [13–16]. However, only 168/283 patients had ≥ 2 BG readings performed during hospitalisation, and none of the patients had regular 4 times daily BG readings during GC treatment as suggested for patients with SIH [18]. We, therefore, assume that SIH may have been under-recognised in our study.

Moreover, in large majority of patients with SIH included in further analysis (46/55 patients; 83.6%) adequate glycaemic control during hospitalisation was not achieved. Pre-existing DM and longer duration of treatment with low GC were significantly associated with failure to meet our set of criteria for adequate SIH control. Furthermore, hospital stay of the included patients (average 17.4 days; median

Table 2 Number of patients with adequate control of steroid-induced hyperglycaemia (SIH); $n = 55$

	Criteria for adequate SIH control	Patients fulfilling the criteria; n (%)
1	< 5 and $< 20\%$ of BG readings elevated (fasting BG ≥ 7.0 mmol/l; daytime BG ≥ 10.0 mmol/l)	10 (18.2%)
2	< 2 BG readings significantly elevated (fasting BG ≥ 10.0 mmol/l; daytime BG ≥ 13.0 mmol/l)	22 (40.0%)
3	average fasting BG < 7.0 mmol/l and average daytime BG < 10.0 mmol/l	14 (25.5%)
4	< 2 hypoglycaemic events (BG ≤ 4.0 mmol/l) and no severe hypoglycaemic events (≤ 2.8 mmol/l)	49 (89.1%)
ALL 4 CRITERIA		9 (16.4%)

BG blood glucose

Table 3 Factors influencing the control of steroid-induced hyperglycaemia (SIH)

Tested parameter	<5 and <20% of BG levels elevated (n=10/55)	<2 BG readings significantly elevated (n=22/55)	Average fasting BG<7.0 mmol/l and average daytime BG<10.0 mmol/l (n=14/55)	<2 hypoglycaemic events and no severe hypoglycaemic events (n=45/55)	All 4 criteria (n=9/55)
Sex[a]	0.731	0.567	0.953	0.399	0.286
Age[b]	0.400	0.121	0.082	0.948	0.399
BMI[b]	0.813	0.452	0.914	0.510	0.813
Previous DM[a]	**<0.001**	**<0.001**	**0.005**	0.204	**<0.001**
GC therapy before admission[a]	0.624	0.426	0.351	0.110	0.638
GC days (total)[b]	**0.042**	**<0.001**	0.115	**0.002**	0.079
High GC days[b][*]	0.644	0.098	0.925	0.819	0.736
Low GC days[b]	**0.003**	**0.009**	**0.020**	**0.015**	**0.003**
Length of hospital stay[b]	0.412	0.673	0.314	**0.023**	0.182

p- values are reported and value lower than 0.05 was considered significant and is marked in bold

BG blood glucose, *BMI* body mass index, *DM* Diabetes Mellitus, *GC* glucocorticoid, *SIH* Steroid-induced hyperglycaemia

[*] A daily dose ≥ 32 mg methylprednisolone or equivalent was considered as a high dose of GC

[a] Chi-square test or Fisher's exact test

[b] Mann–Whitney *U* test

12 days) was much longer than the average length of hospital stay at the University Clinic Golnik (4.8 days in 2019) [25]. Although the reasons for prolonged hospitalisation were not analysed and may have varied, we might assume SIH having an influence – a relation which has already been established in previous studies [5, 6].

Blood glucose levels

All patients treated with high GC doses should have had regular BG readings, ideally in the afternoon and evening hours for several days to confirm or exclude hyperglycaemia [9, 20]. Given that SIH in most cases develops within 2 days, some authors recommend closer monitoring in the first 48 h, and discontinuation of regular BG readings thereafter in patients without elevated BG levels (≥7.8 mmol/L) [14, 26]. In patients with pre-existing DM and in cases of recognised SIH, the *Joint British Diabetes Societies guidelines* suggest 4 times daily BG readings [18]. To recognise the cases of SIH in non-diabetic patients which may develop after 48 h, we suggest daily BG readings in the afternoon (e.g., before dinner) or evening hours starting on the second or the third day after the initiation of GC treatment, and fasting BG readings every 2–3 days for at least 7 days.

These recommendations were not followed during our study. 115/283 patients treated with systemic GC (40.6%) had no BG readings during hospitalisation, although 60 of these patients received at least one high dose of GC. In the remaining 168 patients, the BG levels were measured more than once during treatment with GC; however, none of the

patients had regular 4 times daily BG readings. We, therefore, assume that SIH might not have been recognised in some patients, and that the actual incidence may have been higher. A less frequent than recommended 4 times daily BG readings may also have had an influence on the assessment of the SIH control.

Average BG levels shown in Fig. 2 confirm that afternoon and bedtime BG readings are the most appropriate for the recognition and assessment of SIH [17, 18]. BG readings scheduled before breakfast (fasting BG levels) and before lunch did not appear to be sufficient. Even though the *Joint British Diabetes Societies guidelines* mention the initial monitoring before lunch to be one of the suitable options, this may not be ideal for every setting [18]. Given the fact that the onset of the hyperglycaemic effects of methylprednisolone or dexamethasone is expected around 4 h after the GC administration, the gap between the morning GC dose and the BG reading before lunch may be too short for SIH to become apparent, which may have been the case in our study [4].

Therapy with glucocorticoids

Methylprednisolone was the most commonly used GC in our study. The study had completed before the emergence of COVID-19 epidemic that has led to increased use of dexamethasone worldwide [9]. Although certain pharmacokinetic and pharmacodynamic differences have been demonstrated among GC (e.g., longer half-life of dexamethasone), the clinical practice recommendations for the management

of SIH are usually given for GC as a group rather than for each specific drug [4, 17, 18]. It is known that the influence of GC on BG levels depends both on the dose and treatment duration [21]. These differed widely in our study, with cumulative GC doses during hospitalisation ranging from 24 to 1496 mg of methylprednisolone or equivalent. GC treatment recommendations for different lung diseases vary substantially, from using short-term high doses of GC, e.g., in acute exacerbation of COPD, to chronic low doses, e.g., in interstitial lung disease [27, 28]. The data regarding indications for GC use was not gathered systematically in our study.

Many previous studies of SIH have included only patients treated with high doses of GC [14, 22] or patients with doses higher than physiological (≥ 10 mg prednisone daily or equivalent) [29, 30]. We included patients regardless of the GC dose, based on the recommendation that patients with previous DM or known risk factors for SIH should have BG levels monitored even if they receive low doses of GC [16]. This may partly, besides the BG readings being performed less often than recommended, explain the lower SIH incidence found in our study (21.2%). In previous studies in hospitalised patients, the incidence commonly ranged from 40 to 50% [13–16]. However, previously reported SIH rates vary between 1 and 70%, depending on the methodology, patient population and defined hyperglycaemia threshold [5, 9, 14, 22, 31–33]. If only patients with a GC dose ≥ 32 mg of methylprednisolone or equivalent had been included, the incidence of SIH in our study would have been 28.7% (58/202 patients).

Therapy with hypoglycaemic drugs

Several authors have argued that transient hyperglycaemia caused by short-term use of GC does not necessarily require treatment [13, 20]. However, even short-term hyperglycaemia can cause acute inflammation and endothelial dysfunction both in patients with and without DM [20, 34]. Long-term fluctuations in fasting BG levels increase cardiovascular mortality in elderly DM patients [20, 35].

There is no clear evidence to support the use of one specific drug or regimen to achieve adequate SIH control [16]. Treatment with oral hypoglycaemic drugs is an option in patients without previously known DM who develop milder forms of SIH. When GC are administered in a morning daily dose, insulin secretagogues are a reasonable choice [17, 18]. In the *Joint British Diabetes Societies guidelines*, gliclazide is recommended [18]. However, sulphonylureas may pose a risk of hypoglycaemia due to long duration of action [4]. On the other hand, repaglinide demonstrates an immediate onset of action, has a low risk of hypoglycaemia and can be titrated in small increments [5, 17]. Metformin and dipeptidyl peptidase 4 inhibitors may also be a safe and effective

option [4, 18]. Radhakuty and Burt recommended metformin for outpatients on chronic low-dose GC [21]. In a study on patients with acute exacerbation of COPD, a sodium-glucose-cotransporter 2 dapagliflozin did not provide a better glycaemic control of prednisone-induced hyperglycaemia compared to placebo [36]. Results from a recent study comparing empagliflozin to insulin isophane in patients with steroid diabetes are awaiting [37]. Evidence for using thiazolidinediones in patients with SIH is weak [4, 18]. In our study, repaglinide was the most commonly prescribed oral agent during hospitalisation. Majority of the patients with pre-existing DM (18) were receiving metformin. Other oral drugs were only prescribed as treatment for SIH when already used for pre-existing DM.

Insulin is the treatment of choice for patients with pre-existing DM receiving any combination therapy, for those with pronounced BG elevations (several consecutive BG readings > 11.1 mmol/l), and for patients not reaching target BG levels with oral hypoglycaemic drugs [5, 18, 21]. Basal-bolus regimens or premixed insulin appear to be suitable and equally effective options [16]. Morning dose of insulin isophane may be the most appropriate to cover BG elevations after a single morning GC dose [4, 18, 21]. The definitive superiority of this regimen has yet to be proven [21]. Adjustments of insulin dose should be performed every 2–3 days if necessary [5, 18]. In our study, most patients that required insulin during hospitalisation, but were not on prior insulin therapy, received only rapid-acting insulin aspart (16), with just 2 patients receiving a basal-bolus regimen. We, therefore, assume that the management of insulin therapy may not have been optimal.

Criteria for the control of steroid-induced hyperglycaemia

Patients who fulfilled the set criteria for adequate SIH control were in minority (9 patients; 16.4%) (Table 2). Taking a look at each criterion separately, apparently more emphasis was given on reducing pronouncedly elevated BG levels, as more patients (22 patients; 40.0%) met the 2nd criterion compared to the 1st (10 patients; 18.2%) or the 3rd criterion (14 patients; 25.5%). We conclude that in the large majority of patients, particularly in the group with pre-existing DM, SIH control could have been optimised, either by adjusting insulin dosing more promptly, or potentially changing anti-diabetic regimen. Undertreatment of SIH has been a recognised issue also in previous studies [19]. A hospital protocol for the treatment of SIH has been developed at the University Clinic Golnik during the study, which may improve SIH control in the future (Supplementary Fig. 1).

In previous studies, average BG levels, and, in some cases, hypoglycaemic events, were used to assess SIH

control [19, 29, 30], which in our opinion do not necessarily demonstrate adequate management of hyperglycaemia. A patient with a mean BG level within the reference range might have had elevated BG levels on some readings and normoglycaemic or even hypoglycaemic levels on others. We have, therefore, defined a broader set of 4 criteria. There was no major difference in the number of patients that had adequate SIH control according to the 1st criterion (< 5 BG readings and < 20% of BG readings elevated) than according to all 4 criteria (10 vs. 9 patients, respectively). Nevertheless, we suggest that at least 3 different criteria should be taken into account when assessing SIH to cover all the aspects of SIH control: first one defining the maximum number or proportion of hyperglycaemic events, second the number or proportion of hypoglycaemic events, and third one the target average BG levels.

Factors influencing the control of steroid-induced hyperglycaemia

Older age, increased BMI and pre-existing DM have already been recognised as risk factors for SIH [14], and similar trends were observed in our study. The existing data regarding factors influencing BG control once SIH has been identified is limited. Even though older age and higher BMI are known risk factors for the development of SIH [5, 23], we should not necessarily assume that the same relations exist for SIH control. Chertok Shacham et al. [19] found an insignificant difference in mean BG levels during hospitalisation in patients treated with GC before hospitalisation in comparison to those who started receiving GC in the hospital. We did not confirm age, sex, or BMI to have an influence on SIH control. We only confirmed pre-existing DM and longer duration of treatment with low GC dose to have a significant influence on SIH control (Table 3 and Suppl. Table 1). We speculate that treatment with low GC dose may have prompted less attention in relation to adjusting antidiabetic therapy to BG levels, which resulted in lower SIH control compared to the treatment with high dose of GC. These results may support the *Joint British Diabetes Societies guidelines* stating that clinical vigilance is recommended, at least initially, in patients taking any GC dose [18].

Study limitations

Patients with different types and severity of lung disease were included, which required different daily and cumulative doses of GC. Due to the small number of patients included, subanalyses based on different indications for GC treatment were not feasible, although these may have influenced both SIH occurrence and control. We did not evaluate patients on long-term and short-term therapy with GC as subgroups. On the other hand, duration of overall GC treatment, high-dose GC treatment, and low-dose GC treatment during hospitalisation, as well as GC treatment prior to admission, were assessed separately as risk factors for inadequate SIH control.

Other potential causes of hyperglycaemia, such as comorbidities and concurrent medications, have not been investigated. Due to the retrospective nature of the study, we had no influence on BG monitoring and hyperglycaemia treatment. If BG readings had been taken more regularly, the incidence of SIH might have been higher and the average BG levels, especially at bedtime, might have been different. Finally, we did not monitor patients after discharge to distinguish the newly discovered DM from transient SIH in confounding cases.

We recognise that for certain groups of patients a strict BG control is not required. The *Joint British Diabetes Societies guidelines* state that BG levels > 12 mmol/l are justified in patients at the end of life and those who may have serious consequences from hypoglycaemic events (patients with dementia; confused; frail elderly patients; people with high risk of falls) [18]. To exclude the critically ill patients, for whom the established criteria for SIH control may be unreasonably strict, our study was not conducted in the intensive care unit and the units for tuberculosis and lung cancer. Nevertheless, patients not necessarily requiring tight glycaemic control may have been treated on other units and were, therefore, included in the study.

Conclusion

The results of this retrospective study demonstrated a lower than anticipated incidence of SIH (21.2%) in hospitalised patients with or without pre-existing DM, which may have partly been due to irregular BG monitoring. Afternoon or evening BG readings should be performed on a regular basis in the first days of treatment with GC to identify SIH. We suggest a set of criteria for the assessment of SIH control during hospitalisation, taking into account the number or proportion of both hyperglycaemic and hypoglycaemic events, as well as mean BG levels. Pre-existing DM and longer duration of treatment with low GC dose were factors significantly associated with poorer glycaemic control. Optimal treatment of SIH remains a challenge. A comprehensive guidance for the management of SIH would be beneficial to reduce risks related to SIH in the future.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

References

1. Lakhani OJ, Kumar S, Tripathi S, Desai M, Seth C. Comparison of Two Protocols in the Management of Glucocorticoid-induced Hyperglycemia among Hospitalized Patients. Indian J Endocrinol Metab. 2017;21(6):836–44.

2. Hall JE. Guyton and hall textbook of medical physiology. 12th ed. Philadelphia: Saunders Elsevier; 2011. p. 921–37.

3. Aldibbiat AM, Al-Sharefi A. Do benefits outweigh risks for corticosteroid therapy in acute exacerbation of chronic obstructive pulmonary disease in people with diabetes mellitus? Int J Chron Obstruct Pulmon Dis. 2020;15:567–74.

4. Wallace MD, Metzger NL. Optimizing the treatment of steroid-induced hyperglycemia. Ann Pharmacother. 2018;52(1):86–90.

5. Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. World J Diabetes. 2015;6(8):1073–81.

6. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocr Pract. 2006;12(4):358–62.

7. Mathioudakis N, Bashura H, Boyér L, Langan S, Padmanaban BS, Fayzullin S, Sokolinsky S, Hill GS. Development, implementation, and evaluation of a physician-targeted inpatient glycemic management curriculum. J Med Educ Curric Dev. 2019;6:2382120519861342.

8. Narwani V, Swafe L, Stavraka C, Dhatariya K. How frequently are bedside glucose levels measured in hospital inpatients on glucocorticoid treatment? Clin Med (Lond). 2014;14(3):327–8.

9. Delfs N, Struja T, Gafner S, Muri T, Baechli C, Schuetz P, et al. Outcomes of hospitalized patients with glucocorticoid-induced hyperglycemia-a retrospective analysis. J Clin Med. 2020;9(12):4079.

10. Gupta KK, Kumar V, Chaudhary SC, Mishra A, Patel ML, Roy B. Effect of hyperglycemia on outcome of acute exacerbation of chronic obstructive pulmonary disease. Int J of Adv Res. 2018;6(2):929–33.

11. Baker EH, Janaway CH, Philips BJ, Brennan AL, Baines DL, Wood DM, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax. 2006;61(4):284–9.

12. Murad MH, Coburn JA, Coto-Yglesias F, Dzyubak S, Hazem A, Lane MA, et al. Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97(1):49–58.

13. Tatalovic M, Lehmann R, Cheetham M, Nowak A, Battegay E, Rampini SK. Management of hyperglycaemia in persons with non-insulin-dependent type 2 diabetes mellitus who are started on systemic glucocorticoid therapy: a systematic review. BMJ Open. 2019;9(5):e028914.

14. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract. 2013;99:277–80.

15. Perez A, Jansen-Chaparro S, Saigi I, Bernal-Lopez MR, Miñambres I, Gomez-Huelgas R. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014;6:9–20.

16. Suh S, Park MK. Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. Endocrinol Metab. 2017;32(2):180–9.

17. Kosnik M. Pljučne bolezni in motnje endokrinega sistema (Pulmonary diseases and endocrine system disorders), Proceedings. Ljubljana, Slovenia: Slovenian Respiratory Society; 2018. p. 18–25.

18. Roberts A, James J, Dhatariya K, on behalf of the Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med. 2018;35:1011–1017.

19. Chertok Shacham E, Kfir H, Schwartz N, Ishay A. Glycemic control with a basal-bolus insulin protocol in hospitalised diabetic patients treated with glucocorticoids: a retrospective cohort study. BMC Endocr Disord. 2018;18(1):75.

20. Clore JN, Thurby-hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15(5):469–74.

21. Radhakutty A, Burt MG. Management of endocrine disease: critical review of the evidence underlying management of glucocorticoid-induced hyperglycaemia. Eur J Endocrinol. 2018;179(4):R207–18.

22. Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, Gomez-Almaguer D, Lavalle-Gonzalez FJ, Tamez-Perez HE, et al. Hyperglycemia related to high-dose glucocorticoid use in noncritically ill patients. Diabetol Metab Syndr. 2013;5:18.

23. 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.

24. Lake A, Arthur A, Byrne C, Davenport K, Yamamoto JM, Murphy HR. The effect of hypoglycaemia during hospital admission on health-related outcomes for people with diabetes: a systematic review and meta-analysis. Diabet Med. 2019;36(11):1349–59.

25. University Clinic Golnik. Letno poročilo Univerzitetne klinike za pljučne bolezni in alergijo Golnik za leto 2019 (Annual report of University Clinic Golnik for 2019). https://www.klinika-golnik.si/o-kliniki/letna-porocila. Accessed 30 April, 2020.

26. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(1):16–38.

27. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309(21):2223–31.

28. Wells AU, Hirani N. Interstitial lung disease guideline. Thorax. 2008;63:v1–58.

29. Grommesh B, Lausch MJ, Vannelli AJ, Mullen DM, Bergenstal RM, Richter SA, et al. Hospital insulin protocol aims for glucose

control in glucocorticoid-induced hyperglycemia. Endocr Pract. 2016;22(2):180–9.

30. Burt MG, Drake SM, Aguilar-Loza NR, Esterman A, Stranks SN, Roberts GW. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. Intern Med J. 2015;45(3):261–6.

31. Braithwaite SS, Barr WG, Rahman A, Quddusi S. Managing diabetes during glucocorticoid therapy. Postgrad Med. 1998;104(5):163–76.

32. Gulliford MC, Charlton J, Latinovic R. Risk of Diabetes Associated With Prescribed Glucocorticoids in a Large Population. Diabetes Care. 2006;29(12):2728–9.

33. Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. Ann Nutr Metab. 2014;65:324–32.

34. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes. 2008;57(5):1349–54.

35. Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R. Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: the Verona Diabetes Study. Circulation. 1997;96(6):1750–4.

36. Gerards, MC, Venema, GE, Patberg, KW, Kross M, Potter van Loon BJ, Hageman IMG, et al. Dapagliflozin for prednisone-induced hyperglycaemia in acute exacerbation of chronic obstructive pulmonary disease. Diabetes Obes Metab. 2018;20(5):1306–1310.

37. Klarskov CK, Holm Schultz H, Persson F, Christensen TM, Almdal TP, Snorgaard O, et al. Study rationale and design of the EANITIATE study (EmpAgliflozin compared to NPH Insulin for sTeroId diAbeTEs): a randomized, controlled, multicenter trial of safety and efficacy of treatment with empagliflozin compared with NPH-insulin in patients with newly onset diabetes following initiation of glucocorticoid treatment. BMC Endocr Disord. 2020;20(1):86.