Continuous Monitoring of Circadian Glycemic Patterns in Patients Receiving Prednisolone for COPD

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Context: Endogenous glucocorticoid excess (Cushing’s syndrome) predominantly increases post-prandial glucose concentration. The pattern of hyperglycemia induced by prednisolone has not been well characterized.

Objective: Our objective was to define the circadian effect of prednisolone on glucose concentration to optimize management of prednisolone-induced hyperglycemia.

Design and Setting: This was a cross-sectional study in a teaching hospital.

Participants: Participants included 60 consecutive consenting subjects with chronic obstructive pulmonary disease admitted to hospital: 13 without known diabetes admitted for other indications and not treated with glucocorticoids (group 1), 40 without known diabetes admitted with an exacerbation of chronic obstructive pulmonary disease and treated with prednisolone (group 2, prednisolone = 30 ± 6 mg/d), and seven with known diabetes treated with prednisolone (group 3, prednisolone = 26 ± 9 mg/d).

Main Outcome Measure: Interstitial glucose concentration was assessed during continuous glucose monitoring.

Results: Significantly more subjects in group 2 [21 of 40 (53%), P = 0.02] and group 3 [seven of seven (100%), P = 0.003] recorded a glucose of at least 200 mg/dl (11.1 mmol/liter) during continuous glucose monitoring than in group 1 [one of 13 (8%)]. The mean glucose concentration between 2400–1200 h for group 3 (142 ± 36 mg/dl) was significantly greater than in the other two groups (P < 0.005), whereas mean glucose concentrations between 2400–1200 h in group 1 (108 ± 16 mg/dl) and group 2 (112 ± 22 mg/dl) were not significantly different. In contrast, the mean glucose concentrations between 1200–2400 h for group 2 (142 ± 25 mg/dl) and group 3 (189 ± 32 mg/dl) were both significantly greater than group 1 (117 ± 14 mg/dl, P < 0.05 for both comparisons).

Conclusions: Prednisolone predominantly causes hyperglycemia in the afternoon and evening. Treatment of prednisolone-induced hyperglycemia should be targeted at this time period. (J Clin Endocrinol Metab 96: 1789–1796, 2011)

Glucocorticoids reduce inflammation and are used to treat a wide range of inflammatory and autoimmune conditions (1). These include exacerbations of chronic obstructive pulmonary disease (COPD), a clinical manifestation of an acute-on-chronic inflammatory process in the airways, often with systemic spillover. A common adverse effect associated with glucocorticoid therapy is the development of hyperglycemia (2). Hyperglycemia is an independent predictor of increased mortality in hospitalized patients with a range of comorbidities, including an
exacerbation of COPD (3–6). Although there is no definitive evidence that treatment of hyperglycemia improves patient outcomes, many hospitalized patients do receive treatment for glucocorticoid-induced hyperglycemia.

Optimal treatment of glucocorticoid-induced hyperglycemia may require a different management approach to that used in other patients. In hospitalized patients outside the intensive care unit, hyperglycemia is often treated using scheduled sc long-acting basal insulin in conjunction with prandial and correctional rapid-acting insulin (7). However, endogenous glucocorticoid excess in Cushing’s syndrome predominantly increases postprandial blood glucose concentration with fasting glucose often in the normal range (8). If exogenous glucocorticoids cause a similar pattern of hyperglycemia, current conventional strategies may inadequately treat postprandial hyperglycemia, and use of long-acting basal insulin may precipitate nocturnal hypoglycemia. Avoidance of hypoglycemia is important because it has been implicated as a potential cause of increased mortality in patients receiving intensive insulin therapy (9). However, no studies have provided a detailed analysis of the effect of glucocorticoids on blood glucose concentration to optimize treatment of glucocorticoid-induced hyperglycemia.

Continuous glucose monitoring systems (CGMS) are increasingly used to optimize management of diabetes in the outpatient setting. CGMS measure interstitial glucose concentration, which closely approximates plasma glucose after a short time lag, every 5 min for up to 72 h (10). CGMS provide detailed information regarding nocturnal and postprandial glycemia, whereas standard finger-prick blood glucose monitoring regimens do not (11). As such, CGMS has the potential to provide great insight into the glycemic effect of glucocorticoids. The aim was to determine the frequency, pattern, and degree of hyperglycemia and factors that influence blood glucose elevation in subjects receiving acute prednisolone to treat an exacerbation of COPD. We hypothesized that prednisolone causes substantial hyperglycemia, predominantly in the postprandial period. A better understanding of the glycemic effect of prednisolone will allow the development of a specific treatment strategy for prednisolone-induced hyperglycemia that targets the time of day during which hyperglycemia predominates.

Subjects and Methods

This open prospective observational study was undertaken in the acute wards of the Repatriation General Hospital, Adelaide, Australia. The first subject was recruited on August 12, 2008, and the last subject on March 8, 2010. The study was approved by the Human Research Ethics Committee, Repatriation General Hospital, and all subjects provided written informed consent.

Subjects

Subjects were eligible for inclusion in the study if they were acutely admitted to Repatriation General Hospital, had been diagnosed with COPD, and were expected to remain in hospital for at least 48 h. Consecutive consenting subjects were enrolled into one of three groups. Group 1 consisted of 16 subjects with known COPD but without known diabetes who were admitted to hospital for other indications and not treated with glucocorticoids. Group 2 included 45 subjects without known diabetes mellitus admitted to hospital with an exacerbation of COPD and treated acutely with at least 20 mg of oral prednisolone per day. Group 3 consisted of nine subjects admitted to hospital with an exacerbation of COPD who were known to have diabetes and administered at least 20 mg of oral prednisolone per day. Subjects were excluded if they had methicillin-resistant Staphylococcus aureus or vancomycin-resistant enterococcus infections or if they were expected to require magnetic resonance imaging.

Because a major aim was to assess the circadian pattern of glucose concentrations in patients receiving prednisolone, subjects were excluded from the analysis if they did not undergo at least a full 24 h of CGMS data collection from 2400 h to 2400 h that contained no technical problem with the CGMS trace. As such, two subjects were excluded from analysis because of a poor quality CGMS trace and seven subjects because of earlier than expected discharge from hospital. One additional subject from group 1 was excluded because they were prescribed prednisolone during CGMS for gout. This left a sample size of 13 in group 1, 40 in group 2, and seven in group 3 that were included in the final analysis (Fig. 1). Thirty-seven subjects had two full days of CGMS data for analysis (six subjects in group 1, 25 subjects in group 2, and six subjects in group 3) and 23 subjects 1 d (seven subjects in group 1, 15 subjects in group 2, and one subject in group 3), resulting in a total of 97 d of CGMS analysis.

Medications and meals

Prednisolone was administered to most subjects at 0800 h. However, on 17 of 78 d of CGMS analysis of prednisolone-treated patients, the dose was administered at midday (n = 15) or before dinner (n = 2). Although it was specified in the study protocol that hyperglycemia could be treated by the admitting medical team, no subject in group 1 or 2 received glucose-low-
ering therapy during CGMS. Subjects in group 3 received treatment of hyperglycemia at the discretion of the medical team under whom they were admitted (oral hypoglycemic medication, \( n = 3 \); basal bolus insulin, \( n = 2 \); oral hypoglycemic medication in combination with intermediate or long-acting insulin, \( n = 2 \)). One of the subjects in group 3 who had previously been diet controlled was started on basal bolus insulin during CGMS, and the other patient on basal bolus insulin had their insulin doses increased. No adjustment of usual therapy was made for the other five subjects during CGMS. Meals are provided at 0730, 1230, and 1730 h in Repatriation General Hospital.

Continuous glucose monitoring

Subjects undergoing monitoring of interstitial glucose using a CGMS (Medtronic Gold; Medtronic/Minimed, Northridge, CA). A sensor was placed into the sc tissue of the abdomen by a trained nurse. Interstitial glucose concentration was recorded every 5 min for up to 72 h using a glucose oxidase-based method. Routine finger-prick blood glucose levels (BGL) were performed before each main meal (0700, 1200, and 1700 h) and at 2100 h and used to calibrate the CGMS.

Laboratory analysis

Glycosylated hemoglobin (HbA1c) was measured using boronate affinity chromatography on a Primus PDQ (Immuno, Sydney, Australia). The between-run coefficient of variation is 2.6% at an HbA1c of 5.4% and 2.9% at an HbA1c of 9.6%. C-reactive protein (CRP) was measured using a Tina-quant immunoturbidimetric assay (Roche Diagnostics GMBH, Mannheim, Germany) on a Roche modular analyzer (Hitachi High-Technologies Corp., Tokyo, Japan). The limit of detection is 0.3 mg/liter. The between-run coefficient of variation is 3.6% at a CRP of 3.9 mg/liter and 2.3% at a CRP of 49.5 mg/liter.

Statistical analysis

Data were analyzed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). \( P < 0.05 \) was considered statistically significant. Unless otherwise stated, values represent mean \( \pm \) SD.

The primary endpoint was the number of patients developing an interstitial glucose of at least 200 mg/dl (11.1 mmol/liter) during CGMS. Differences between groups were first assessed by one-way ANOVA for continuous variables and the \( \chi^2 \) test for nominal variables. If differences were statistically significant, post hoc analysis was undertaken to compare the three groups with a Bonferroni correction to account for multiple comparisons. Interstitial glucose concentrations recorded during each hour of CGMS were averaged and used to create curves demonstrating circadian glucose concentration. For subjects with 2 d of CGMS readings, the hourly CGMS data for the 2 d were averaged before statistical analysis.

A subgroup analysis of the subjects in group 2 was undertaken to determine whether demographic factors could predict which subjects developed hyperglycemia. Unpaired t test or a Mann-Whitney U test were used for normally and nonnormally distributed data, respectively, to compare the characteristics of subjects in group 2 who recorded an interstitial glucose of at least 200 mg/dl (11.1 mmol/liter) during CGMS with those who did not. An analysis was also performed in group 2 to determine whether measuring glucose at the time of mean peak glucose concentration could identify most subjects with hyperglycemia and, in subjects with hyperglycemia, the time after prednisolone administration of the beginning of the first upward excursion of glucose beyond 180 mg/dl (10 mmol/liter). The smaller sample size precluded similar analyses in the other two groups.

Results

Subject characteristics

There were no significant differences in sex, family history of diabetes, age, weight, height, and waist and hip measurements between the three groups (Table 1). The mean body mass index (BMI) and HbA1c of subjects in group 3 was significantly greater than in the other two groups, whereas the BMI and HbA1c in group 1 and 2

### Table 1. Characteristics of subjects with COPD without known diabetes admitted to hospital for other indications and not treated with glucocorticoids (group 1), subjects without known diabetes admitted with an exacerbation of COPD and treated acutely with prednisolone (group 2), and subjects with COPD with known diabetes treated with prednisolone (group 3)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (n)</td>
<td>13</td>
<td>40</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>39</td>
<td>38</td>
<td>29</td>
<td>0.89</td>
</tr>
<tr>
<td>Family history diabetes (%)</td>
<td>23</td>
<td>23</td>
<td>43</td>
<td>0.51</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>74.7 ( \pm ) 12.8</td>
<td>76.8 ( \pm ) 13.5</td>
<td>83.7 ( \pm ) 8.8</td>
<td>0.33</td>
</tr>
<tr>
<td>Prednisolone (mg/d)</td>
<td>0 ( \pm ) 0(^a)</td>
<td>30.3 ( \pm ) 6.4</td>
<td>25.7 ( \pm ) 8.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.0 ( \pm ) 15.1</td>
<td>71.5 ( \pm ) 17.4</td>
<td>87.4 ( \pm ) 22.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 ( \pm ) 0.15</td>
<td>1.67 ( \pm ) 0.09</td>
<td>1.61 ( \pm ) 0.08</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>25.4 ( \pm ) 7.9</td>
<td>25.5 ( \pm ) 5.3</td>
<td>33.5 ( \pm ) 6.8(^b)</td>
<td>0.007</td>
</tr>
<tr>
<td>Waist (m)</td>
<td>1.04 ( \pm ) 0.16</td>
<td>1.02 ( \pm ) 0.17</td>
<td>1.17 ( \pm ) 0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>Hips (m)</td>
<td>1.07 ( \pm ) 0.17</td>
<td>1.03 ( \pm ) 0.15</td>
<td>1.14 ( \pm ) 0.09</td>
<td>0.19</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.97 ( \pm ) 0.03</td>
<td>0.99 ( \pm ) 0.09</td>
<td>1.02 ( \pm ) 0.12</td>
<td>0.44</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 ( \pm ) 0.5</td>
<td>6.0 ( \pm ) 0.5</td>
<td>7.9 ( \pm ) 1.6(^b)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values represent mean \( \pm \) SD unless otherwise stated.

\( a \)\( P < 0.0001 \) vs. group 2 and 3.

\( b \)\( P < 0.05 \) vs. group 1 and 2.
were not significantly different. As per the study design, subjects in group 1 were not receiving prednisolone, whereas mean prednisolone dose was not significantly different in group 2 and 3.

Continuous glucose monitoring (Table 2 and Fig. 2)

Significantly more subjects in group 2 [21 of 40 (53%), P = 0.02] and group 3 [seven of seven (100%), P = 0.003] recorded a glucose of at least 200 mg/dl (11.1 mmol/liter) during CGMS than in group 1 [one of 13 (8%)]. Peak glucose concentration during CGMS in group 3 was 76% higher than in group 1 and 48% higher than group 2 with no significant difference between group 1 and 2. Mean glucose concentration between 2400 and 2400 h in group 3 was 47% higher than in group 1 and 32% higher than group 2, with no significant difference between the other two groups. In accordance, mean glucose concentration between 2400 and 1200 h in group 3 was 31% higher than in group 1 and 27% higher than group 2, with no significant difference between group 1 and group 2. In contrast, the mean glucose concentration between 1200 and 2400 h in group 2 and group 3 were both significantly greater than group 1 by 21 and 62%, respectively. Post hoc analysis was undertaken excluding the 17 d of CGMS data when prednisolone was not administered at 0800 h. Exclusion of these days of CGMS did not significantly affect the above results (see Supplemental Table 1 and Fig. 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).

An analysis of mean glucose concentration in the 2-h period after each meal time was undertaken to quantify postprandial hyperglycemia in greater detail. Mean glucose concentration between 0730 and 0930 h in group 2 was 20% higher than group 1, but the difference did not quite reach statistical significance (P = 0.06). The mean glucose concentration between 1230 and 1430 h in group 2 was 20% higher than group 1, but the difference did not quite reach statistical significance (P = 0.06). The mean glucose concentration between 1730 and 1930 h in group 2 and group 3 were both significantly greater than group 1 by 20 and 76%, respectively.

The percentage of time glucose was at least 180 mg/dl (10 mmol/liter) was also calculated, because a recent con-
sensus statement recommended blood glucose be maintained below this concentration in most patients in general hospital wards (7). The percentage of time glucose was at least 180 mg/dl (10 mmol/liter) was significantly greater in group 3 than in group 1 and 2 but was not significantly different in group 1 and 2.

Subgroup analysis of group 2 (Table 3)

CRP was significantly greater in subjects in group 2 that recorded a glucose of at least 200 mg/dl (11.1 mmol/liter) during CGMS (hyperglycemic subjects) than in subjects in whom all glucose concentrations were less than 200 mg/dl (11.1 mmol/liter, normoglycemic subjects). Sex, family history of diabetes, age, prednisolone dose, weight, height, BMI, waist and hip measurements, HbA1c, and positive sputum cultures were not significantly different in the two subgroups.

In group 2, the beginning of the first upward glucose excursion in subjects with hyperglycemia occurred 3.0 ± 1.1 h after prednisolone administration. Peak glucose concentration in group 2 was recorded 7.5 ± 3.1 h after prednisolone when administered at 0800 h and 5.1 ± 3.2 h after prednisolone when administered later in the day. Because mean peak glucose concentration occurred at approximately 1600 h (Fig. 2), we assessed the potential for measuring glucose at this time point to detect subjects that developed hyperglycemia at some time during CGMS. The area under the receiver operator characteristic curve for 1600 h glucose concentration to detect a glucose of at least 200 mg/dl (11.1 mmol/liter) at 1600 h. A glucose of at least 142 mg/dl (7.9 mmol/liter) at 1600 h in group 2 had a relatively good combined sensitivity (82%) and specificity (81%) to detect subjects that recorded a glucose of at least 200 mg/dl (11.1 mmol/liter) at some point during CGMS.

Finger-prick BGL

Finger-prick BGL monitoring demonstrated a pattern of glycemia that was similar to CGMS with the BGL peak at 1700 h in group 2 and 2100 h in group 3 (Fig. 3). Fourteen of 21 subjects (67%) in group 2 that recorded a glucose of at least 200 mg/dl (11.1 mmol/liter) during CGMS recorded a finger-prick BGL of at least 200 mg/dl (11.1 mmol/liter). Five of seven subjects (71%) in group 3 that recorded a glucose

### Table 3

Characteristics of hyperglycemic (glucose at least 200 mg/dl during CGMS) and normoglycemic (glucose below 200 mg/dl throughout CGMS) subjects without known diabetes admitted to hospital with an exacerbation of COPD and treated acutely with prednisolone (group 2)

<table>
<thead>
<tr>
<th></th>
<th>Hyperglycemic</th>
<th>Normoglycemic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (n)</td>
<td>21</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>38</td>
<td>37</td>
<td>0.94</td>
</tr>
<tr>
<td>Family history diabetes (%)</td>
<td>24</td>
<td>21</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>77.0 ± 15.5</td>
<td>76.5 ± 11.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Prednisolone (mg/d)</td>
<td>31.7 ± 7.0</td>
<td>28.8 ± 5.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.8 ± 17.9</td>
<td>74.5 ± 16.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.66 ± 0.10</td>
<td>1.68 ± 0.07</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 5.5</td>
<td>26.1 ± 5.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Waist (m)</td>
<td>1.00 ± 0.17</td>
<td>1.05 ± 0.18</td>
<td>0.42</td>
</tr>
<tr>
<td>Hips (m)</td>
<td>1.01 ± 0.13</td>
<td>1.05 ± 0.16</td>
<td>0.42</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.99 ± 0.08</td>
<td>1.00 ± 0.10</td>
<td>0.69</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.0 ± 0.3</td>
<td>5.9 ± 0.6</td>
<td>0.61</td>
</tr>
<tr>
<td>CRP (mg/liter)</td>
<td>65 (19–137)</td>
<td>8 (5–27)</td>
<td>0.004</td>
</tr>
<tr>
<td>Respiratory infection (%)</td>
<td>29</td>
<td>16</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean glucose (mg/dl)</td>
<td>139 ± 18</td>
<td>112 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak glucose (mg/dl)</td>
<td>243 ± 29</td>
<td>160 ± 27</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values represent mean ± SD unless otherwise stated. To convert glucose to millimoles per liter, multiply values by 0.05551.

* Median (interquartile range).
at least 200 mg/dl (11.1 mmol/liter) during CGMS recorded a finger-prick BGL of at least 200 mg/dl (11.1 mmol/liter).

Discussion

This study used CGMS to provide a detailed analysis of the frequency and pattern of hyperglycemia induced by prednisolone in patients hospitalized with an exacerbation of COPD. We have demonstrated that patients receiving prednisolone to treat an exacerbation of COPD have significant glucose elevation with afternoon and evening, but not overnight, hyperglycemia. Hyperglycemia is associated with poor outcomes during exacerbations of COPD, but the potential benefits of preventing prednisolone-induced hyperglycemia are still unknown. This study provides information that allows development of a tailored management approach that will enable optimal management of hyperglycemia in prednisolone-treated patients.

Despite recognition that glucocorticoids predominantly increase postprandial blood glucose (12, 13), there is limited evidence for this in the literature. Two small studies have reported that finger-prick BGL were highest after lunch in prednisolone-treated patients with a lesser elevation after dinner (14, 15). Our study extends these findings by demonstrating that glucose concentrations during CGMS in prednisolone-treated subjects and a well-matched control group diverge at midday with glucose approximately 20% higher after lunch and dinner (Fig. 2). When prednisolone was administered in the morning, the peak glucose occurred about 8 h after prednisolone administration, a similar timeframe to that in which the maximal inhibition of lymphocyte proliferation develops (16). If prednisolone was taken later in the day, the mean glucose peak occurred after 5 h, so the time period of glucose elevation was similar to that after morning administration. The effect of prednisolone then wears off overnight with an almost identical mean glucose concentration between 2400 and 1200 h.

Our findings have important implications for clinical practice. First, prednisolone-treated patients should be educated regarding the importance of checking blood capillary glucose concentration after lunch and before and after dinner, because reliance on measurement of morning blood glucose is likely to underestimate prednisolone-induced hyperglycemia. Second, glucose-lowering therapy should be predominantly directed at the time period between midday and midnight. Caution should be exercised with the use of long-acting basal insulin, because it may precipitate nocturnal hypoglycemia when the effect of prednisolone wanes. Because the first glucose excursion begins on average 3 h after prednisolone administration, higher insulin doses at lunch and dinner are likely to be required.

Previous studies have reported that the prevalence of diabetes in patients receiving similar, or higher, glucocorticoid doses to those in our study is 40–50% (2, 14, 15). These studies relied on finger-prick and laboratory glucose concentrations, which were not always systematically recorded (2), and may have underestimated the prevalence of hyperglycemia. However, we recorded a similar prevalence of hyperglycemia in nondiabetic subjects using CGMS. The subjects without known diabetes in our study were elderly, but only 20% were obese and fewer than 25% had a family history of diabetes, factors previously reported to increase risk of glucocorticoid-induced hyperglycemia (17, 18). The prevalence of glucocorticoid-induced hyperglycemia is likely to vary in different patient populations with differing clinical characteristics.

Despite the high prevalence of prednisolone-induced hyperglycemia, the age of hyperglycemia in subjects without known diabetes was relatively modest. The mean glucose concentration in group 2 was 126 mg/dl (7.0 mmol/liter), with no subject recording a mean glucose above 180 mg/dl (10 mmol/liter). Acute or stress hyperglycemia is associated with increased mortality rates in hospitalized patients, and there are a number of physiological mechanisms by which acute hyperglycemia could adversely affect patient outcomes (19, 20). Although a random blood glucose threshold as low as 126 mg/dl (7 mmol/liter) is an independent predictor of poor outcome in patients with an exacerbation of COPD (21), evidence is lacking that lowering glucose improves outcomes. As such, currently, we would not support routine glucose lowering in patients with mild prednisolone-induced hyperglycemia but recommend individualized decision making based on the severity and duration of hyperglycemia, aiming to maintain blood glucose from 72–180 mg/dl (4–10 mmol/liter), in line with general recommendations for most hospitalized patients (7). If a glucose threshold of at least 180 mg/dl (10 mmol/liter) for more than 25% of the day during CGMS was chosen as an indication for initiating glucose-lowering therapy, then only three subjects in group 2 would require treatment.

As expected, prednisolone-treated patients with known diabetes recorded higher glucose concentrations than subjects without known diabetes. Despite receiving a variety of glucose-lowering therapies, the circadian pattern in this patient group also showed predominantly afternoon and evening hyperglycemia. In contrast to group 2, an increase in glucose after breakfast was evident in this group, and the peak glucose occurred later at approximately 2100 h, creating a staircase-like pattern. This may have arisen because of the more severe β-cell defect in subjects with
known diabetes and greater impairment of postprandial insulin release. Caution should be used when interpreting these data because of the small sample size and other hypoglycemic therapies. However, because five of seven subjects in this group recorded a glucose of at least 180 mg/dl (10 mmol/liter) for more than 25% of the day during CGMS, patients with known diabetes are much more likely to benefit from additional treatment to lower blood glucose, with a greater requirement for prandial insulin with each meal.

Previous studies have reported that the risk of glucocorticoid-induced hyperglycemia is greater in subjects with abdominal adiposity or a genetic predisposition to diabetes and in subjects on higher glucocorticoid doses (17, 18, 22). In our study, CRP was significantly higher in subjects in group 2 who recorded a glucose of at least 200 mg/dl (11.1 mmol/liter), suggesting that systemic inflammation contributed to hyperglycemia. However, there were no significant differences in age, prednisolone dose, anthropometric measurements, or HbA1c between subjects in group 2 who recorded a glucose of at least 200 mg/dl (11.1 mmol/liter) and those who did not. Delineation of the effect of these variables on the likelihood of hyperglycemia was not the primary aim of our study, which may have been underpowered to detect a significant difference. Another potential limitation is that this analysis dichotomized subjects based on a single glucose threshold, and two subjects with a similar peak glucose falling either side of the threshold will be categorized differently. However, there was reasonable separation of mean and peak glucose in hyperglycemic and normoglycemic subjects (Table 3). Our data suggest that it is difficult to predict which patients will develop prednisolone-induced hyperglycemia. Although patients with evidence of systemic inflammation may be at greatest risk, we recommend that all hospitalized patients receiving prednisolone be screened for hyperglycemia. Checking blood glucose at approximately 1600 h is likely to provide the greatest information regarding which patients develop prednisolone-induced hyperglycemia, but there is significant interindividual variability in the timing and duration of hyperglycemia, and a single time point will not identify all patients.

A limitation of this study is the cross-sectional design, which results in the possibility that factors other than prednisolone are responsible for differences in glucose concentration. However, subjects in group 1 and 2 were closely matched for variables that predispose to hyperglycemia including age, family history of diabetes, BMI, and waist and hip measurements. Therefore, differences in circadian glucose concentration are likely to relate to prednisolone use. A second potential limitation is that the relationship between blood and interstitial glucose is complex and CGMS may underestimate blood glucose at low glucose concentrations (10). However, modern CGMS are considered reliable and provide clinical information that can be used to guide patient management (23). Other potential limitations of CGMS specific to hospital use include reliance on ward nursing staff to calibrate the CGMS and an inability to use CGMS in patients with methicillin-resistant S. aureus or vancomycin-resistant enterococcus or those requiring magnetic resonance imaging. We included the small number of subjects in whom prednisolone was administered at lunch or dinner because this reflects real-life hospital practice, where not all patients are administered prednisolone in the morning. However, the pattern of hyperglycemia is near identical if these days of CGMS are excluded from the analysis (see Supplemental Table 1 and Fig. 1). This study assessed only prednisolone-treated patients within a relatively narrow dose range, so different glucocorticoids and/or doses may result in a different pattern of glycaemia. Finally, although we elected to study only patients with COPD to reduce heterogeneity in the subject population, these results are likely to be relevant to the large number of patients treated with prednisolone for other medical conditions.

In summary, this study demonstrates that approximately 50% of hospitalized patients with COPD without known diabetes treated with prednisolone record a glucose concentration of at least 200 mg/dl (11.1 mmol/liter). Hyperglycemia predominantly occurs in the afternoon and evening. Screening for prednisolone-induced hyperglycemia should be directed at this time of the day, and any resulting treatment should also be focused on this interval.

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