Cohort Study

Risk Factors of Hyperglycemia After Nerve Blockade with Dexamethasone in Non-Diabetes Mellitus Patients: A Cohort Study

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Background: Glucocorticoids (GCs) are expected to inhibit the synthesis and release of proinflammatory cytokines, which induces local pain. Serious side effects or complications are considered rare with single-dose GC use. However, the amount of systemic absorption and the side effects induced by local GC injections are not well understood.

Objectives: We measured the changes in glucose levels after single-does dexamethasone injection with nerve blockade using a continuous glucose monitoring system (CGMS) in non-diabetes mellitus (DM) patients and investigated the risk factors for hyperglycemia.

Study Design: This is a cohort study.

Setting: This study was conducted at Gifu University Hospital in Japan.

Methods: Forty-six non-DM patients who underwent elective lumbar or sacral nerve root pulsed radiofrequency or lumbar medial branch of the posterior primary rami conventional radiofrequency with dexamethasone (0.1 mg/kg) were analyzed. The patients underwent monitoring of their interstitial glucose using a CGMS. Hyperglycemia was defined as a blood glucose level ≥ 200 mg/dL. The area under the curve (AUC) where the blood glucose level was over 200 mg/dL was calculated and analyzed. The risk factors of hyperglycemia were determined using an applied ordinal regression model analysis with the AUC as the objective variable and 4 factors (age, body mass index, glucose level just before GC injection, and glycosylated hemoglobin) as explanatory variables. The blood glucose levels were predicted by a nonlinear regression model.

Results: The AUC and maximum glucose level were higher on the first day than after the second day. None of the 4 factors were predictors of hyperglycemia. The glucose level before the procedure was associated with the predicted blood glucose level on the first day ($P = 0.042$). However, the 95% upper confidence limit of the maximum predicted blood glucose level was less than the safety margin. The predicted blood glucose levels returned to the usual level after the second day.

Limitations: First, GCs are metabolized by cytochrome p450 3A4, and it is possible that the inhibition of this pathway decreases the clearance of GCs. Some of our patients were taking medications that influence this cytochrome pathway. Second, we cannot eliminate the possibility of stress-induced hyperglycemia. Finally, we were unable to record the exact meal timing and calories the patients had consumed.

Conclusions: The blood glucose levels were higher than usual on the first day following a local dexamethasone injection, but the levels were not critical in most cases. Because we cannot predict which patients will develop hyperglycemia, we must determine whether or not GCs can be safely administered and inform patients about potential complications.

Key words: Glucocorticoids, hyperglycemia, nerve blockade, non-diabetes mellitus patients

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Glucocorticoids (GCs) are essential stress hormones and play a pivotal role in different basic processes, such as metabolic homeostasis, cognition, mental health, cell proliferation, development, reproduction, and inflammation (1). Synthetic GCs, such as dexamethasone and prednisolone, are used to treat various autoimmune, inflammatory, and allergic disorders because of their anti-inflammatory and immune-suppressive effects (1). The long-term use of GCs is known to cause many side effects, such as poor wound healing, osteoporosis, cardiovascular complications, hyperglycemia, and diabetes mellitus (DM) (1). GCs regulate glucose homeostasis through hepatic gluconeogenesis promotion, the uptake of glucose and reduction in the utilization of skeletal muscle and white adipose tissue, as well as the modulation of insulin and glucagon secretion from the pancreas (2).

GCs can exacerbate hyperglycemia in patients with DM (3). Regardless of the route (topical, oral, inhaled, intramuscular, intravenous, and intraarticular), GCs may cause hyperglycemia when administered at supraphysiological doses (3). Patients with DM treated by daily prednisolone reportedly experience postprandial hyperglycemia with a fasting glucose level in the normal range (4). Even transient GC use, which is characterized by a high initial dose and gradual reduction, can lead to initial moderate-severe hyperglycemia with rapid changes in glycemia in response to the GC dose (3). In addition, it has been reported that even a single-dose of epidural betamethasone injection significantly increases the blood glucose levels in DM patients up to 3 days later (5), and that hyperosmolar nonketotic hyperglycemic coma occurs after 80 mg triamcinolone epidural injection to DM patients (6). Therefore we closely monitor the blood glucose levels after GCs administration in DM patients.

GCs can exert both acute and chronic anti-inflammatory effects (1). One of the mechanisms underlying the anti-inflammatory effects of CGs is the inhibition of proinflammatory substance synthesis or release (7). Therefore GCs have been locally injected with or without local anesthetics for pain management, for example, into the epidural space for spine-related pain (7-9), around the nerve root for radiculopathy (8,10,11), around the facet joint for facet joint pain (12), and into the shoulder joint capsule for adhesive capsulitis of the shoulder (13). Serious side effects or complications are considered rare with single-dose GC use, although there are possibilities of pharmacologic complications related to GCs, including the suppression of the hypothalamic-pituitary axis, elevation of blood glucose levels, elevation of blood pressure, and fluid retention (7).

However, the amount of systemic absorption and the side effects induced by local GC injections are poorly understood (14). Recently, several complications were reported after single-dose GC administration, including rhabdomyolysis (15), adrenal suppression (16), persistent hiccup (17), and transient hypokalemic quadriplegia (18). Concerning the blood glucose levels, fasting blood insulin and glucose levels are reportedly increased 24 hours after epidural triamcinolone injection in non-DM patients (6), and postprandial glucose levels are increased after shoulder joint or epidural space GC injection (19). However, information on the glucose metabolism after single-dose GC injection is limited, and the risk factors for hyperglycemia in non-DM patients are still unknown. Furthermore, previous studies have only evaluated the blood glucose levels at several time points, not continuously, after GC administration. Therefore the exact time course of changes in the blood glucose level is still unclear.

In the present study, we measured the changes in the glucose levels after single-dose dexamethasone injection with nerve blockade by a continuous glucose monitoring system (CGMS) in non-DM patients and investigated the risk factors for hyperglycemia among age, body mass index (BMI), glucose level just before GC injection, and glycosylated hemoglobin (HbA1c).

Methods

This study was approved by the ethics committee of Gifu University Graduate School of Medicine (number: 2018-182) and registered in the University Hospital Medical Information Network in Japan (number: UMIN000034249). Written informed consent was obtained from all patients.

Patients

Forty-seven consecutive patients who underwent elective lumbar or sacral nerve root pulsed radiofrequency or lumbar medial branch of the posterior primary rami (facet joint) conventional radiofrequency in Gifu University Hospital (Gifu, Japan) between October 2018 and October 2019 were enrolled. The exclusion criteria were diagnosis of DM (at any time), use of steroids within 3 months, scheduled to receive

steroids or a radiologic examinations within 2 weeks after nerve blockade, considered inappropriate for participation judged by a doctor, and participation refusal.

Continuous Glucose Monitoring and GC Administration

Blood samples were collected to measure glucose level and HbA1c before the nerve blockade, and the patients underwent monitoring of interstitial glucose using the FreeStyle Libre Pro (Abott Japan, Chiba, Japan), which is a blinded professional sensor-based CGMS, to perform retrospective glucose data analyses. After it was confirmed by using contrast medium that the needle tip was not in a blood vessel, pulsed radiofrequency or conventional radiofrequency as nerve blockade was performed. Following nerve blockade, the patients were administered 0.1 mg/kg dexamethasone (maximum 6.6 mg/body) around the nerve. The sensor, worn on the upper arm, requires no patient or health care provider intervention. The proreader is retained by investigators, and the data are not visible to patients or investigators while the sensor is being worn. The sensor automatically captures and stores data every 15 minutes (96 glucose readings/day). After 14 days of wearing the sensor, the glucose data are retrieved wirelessly and transferred to the proreader. Summary glucose reports for review and analyses were generated using the system's software program. Based on previous studies (3,4), hyperglycemia was defined as a blood glucose level ≥ 200 mg/dL.

Sample Size

The sample size was determined as the number that could avoid statistical model overfitting. When using a linear regression model with continuous variables as objective variables and 4 factors (age, BMI, glucose level, and HbA1c) as explanatory variables, 40 cases were deemed to be needed to avoid of model overfitting and to guarantee generalizability (20). To compensate for dropouts, 45 patients were scheduled to be recruited.

Outcomes

The primary study outcome was the area under the curve (AUC) where the blood glucose level exceeded 200 mg/dL. The AUC was calculated according to the trapezoidal rule. The secondary outcome was the predicted blood glucose level after dexamethasone administration.

Statistical Analyses

Descriptive statistics for patient characteristics were calculated as the median and interquartile range (IQR) for continuous variable or the frequency (percentage) for categorical variables. Because the distribution of the AUC was skewed, we employed ordinal logistic regression to assess the independent effect of risk factors on the AUC. Ordinal logistic regression is a popular model for ordinal categorical outcome variables that also works well for skewed continuous outcome variables using ranks of data. The age, BMI, baseline glucose level, and HbA1c were treated as risk factors in the ordinal logistic model. To predict the blood glucose levels over time, a nonlinear regression analysis was performed. The nonlinear association between the glucose level and the measurement time was assessed by including restricted cubic splines in the regression model. Because there were repeated measurements per patient, we used a robust sandwich estimator for estimating the variance of the coefficient obtained from the regression model. A prediction graph of the blood glucose level was drawn based on the predicted value obtained by the nonlinear regression model.

The AUC between the first day and the second day after dexamethasone injection was compared by the Wilcoxon signed-rank test, and the maximum blood glucose levels on the first day and the second day after dexamethasone injection were compared by a paired t-test. $P < 0.05$ was considered statistically significant. All analyses were conducted using R (version 3.6.2, www.r-project.com).

Results

Patients Characteristics

There were 161 patients who underwent elective lumbar or sacral nerve root pulsed radiofrequency or lumbar facet conventional radiofrequency between October 2018 and October 2019. Among them, 43 had been diagnosed with DM, 60 had used steroids within 3 months before or were scheduled to use them within 14 days after, 4 were scheduled to undergo radiologic examinations within 14 days after, 5 were deemed unfit to participate, and 3 refused to participate. After the data collection, one patient withdrew her consent. Therefore the data from 46 patients were analyzed.

The background characteristics of these patients are shown in Table 1. Data were obtained for 14 days from 25 patients, 13 days from 8, 12 days from 3, 11

days from 2, 9 days from 1, 8 days from 3, 7 days from 2, 6 days from 1, and 5 days from 1 patient.

Prognostic Factors of Hyperglycemia

The patients in the present study had not been diagnosed with DM, and we confirmed that their HbA1c value, which is well known to reflect long-term glucose control, was below 6.3% in all cases. According to the diagnosis of DM established by the American Diabetes Association in 2018, HbA1c is one of the defining factors in a DM diagnosis (21). DM is diagnosed when the HbA1c value is ≥ 6.5% according to a laboratory using a method certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes and Complications Trial assay (21).

Table 1. *Patients' characteristics (n = 46).*

Characteristic	Median (IQR)
Age, years	69.0 (54.5-77.8)
Male/female	17/29
Height, cm	158.0 (150.3-166.8)
Weight, kg	54.5 (47.0-61.8)
BMI, kg/m^2	21.5 (20.4-24.7)
HbA1c, %	5.60 (5.50-5.90)
Glucose level, mg/dL	102.0 (95.5-115.0)

Changes in the glucose levels of each patient until the second day are shown in Fig. 1. The patterns of blood glucose levels after 3 days were similar to those on the second day. The maximum glucose level in each patient was observed in 459.8 ± 231.5 (mean ± standard deviation) minutes after the injection (within the first day). The AUC on the first day was significantly higher than that on the next day (Fig. 2A). The maximum glucose level on the first day was significantly higher than that on the second day (Fig. 2B). The median (25%–75% confidence interval [CI]) of the maximum glucose level was 212.0 (185.5–245.0) mg/dL and 163 (140–179.5) mg/dL, on the first and second day, respectively.

No patients reported any symptoms of hyperglycemia. One patient (53-year-old man; BMI: 26.5 kg/m^2; HbA1c: 6.2%; glucose level just before procedure: 135 mg/dL) showed a glucose level ≥ 300 mg/dL on the first day. None of the 4 factors (age, BMI, HbA1c, and glucose level before procedure) were associated with an AUC ≥ 200 mg/dL during the first day or within 2 days (Table 2).

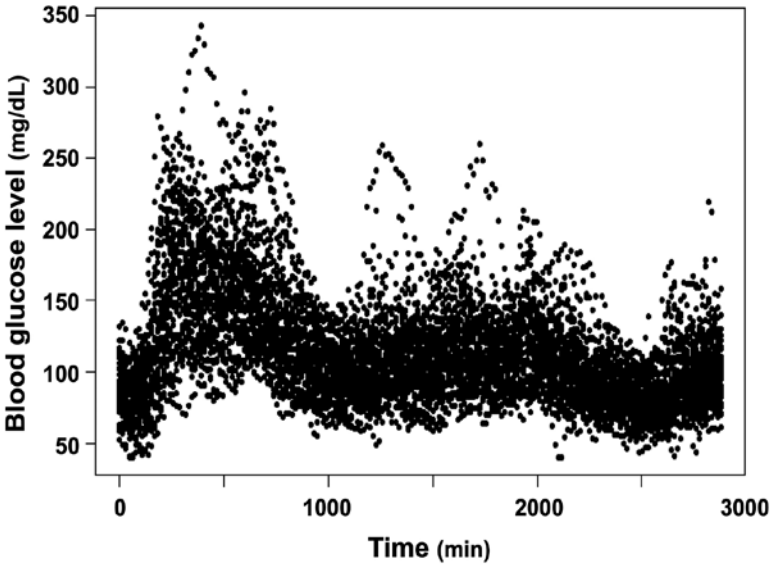

Fig. 1. *Changes in the blood glucose levels in each patient. The patients underwent monitoring of their interstitial glucose using a CGMS. The raw data from the CGMS are presented.*

Prediction of Blood Glucose Levels in the First 2 Days

The changes of blood glucose levels were predicted by a nonlinear regression model. The glucose level just before the procedure was associated with the predicted blood glucose level on the first day (coefficient, 1.063; 95% CI, 1.002–1.128; $P = 0.042$) (Table 3). This result indicates that the increase in glucose level just before procedure from the 25th percentile (95) to the 75th percentile (116) was associated with an approximately 1.06-fold increase in the glucose level after the procedure. However, none of the 4 factors were associated with the predicted blood glucose level within 2 days (Table 3).

The pattern of the predicted glucose level after day 2 was similar to that on the second day after dexamethasone injection. Therefore the changes in the predicted glucose levels within the first 2 days are shown (Fig. 3, adjusted to median values in

Table 1: BMI of 21.51 kg/m^2, HbA1c of 5.60%, age of 69 years, glucose level before procedure of 102 mg/dL). According to the prediction, the 95% upper confidence limit of the blood glucose level was < 170 mg/dL, and the blood glucose level after dexamethasone injection increased twice within 24 hours before returning to the usual levels after the second day. The timing of these 2 peaks on the first day are likely after meals in the day and night, as all patients received dexamethasone in the morning. The blood glucose levels in most patients are suggested to be maintained within a safe margin.

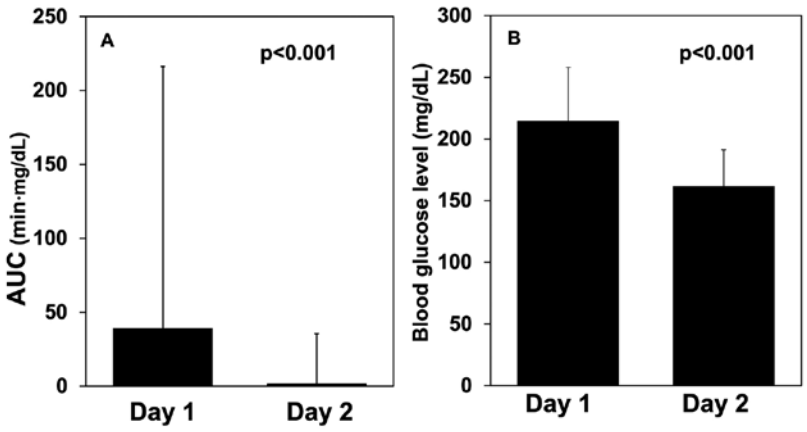

Fig. 2. *The comparison of the AUC (A) and the maximum glucose level (B) between the day of dexamethasone injection and the next day. The patients underwent monitoring of their interstitial glucose using a CGMS. (A) The AUC where the blood glucose level was over 200 mg/dL. (B) The maximum blood glucose level. The AUC between the first day and the second day after dexamethasone injection was compared by the Wilcoxon rank test. The maximum blood glucose level was also compared by a paired t-test. Values are presented as the mean ± standard deviation. P values are indicated in the figure.*

Discussion

The present study provided a detailed analysis of the frequency and pattern of hyperglycemia induced by dexamethasone with nerve blockade in non-DM patients. To our knowledge, this is the first detailed report of the glucose level after local GC injection.

Table 2. *An ordinal regression model analysis of risk factors associated with AUC.*

Factors	Odds Ratio (95% CI)	*P* value
The first day		
Age, years	1.039 (0.993–1.087)	0.1
BMI, kg/m^2	0.928 (0.772–1.115)	0.422
HbA1c, %	1.993 (0.264–15.064)	0.504
Baseline glucose level, mg/dL	1.024 (0.995–1.054)	0.111
Within 2 days		
Age, years	1.039 (0.993–1.087)	0.098
BMI, kg/m^2	0.929 (0.773–1.116)	0.431
HbA1c, %	1.934 (0.257–14.535)	0.521
Baseline glucose level, mg/dL	1.024 (0.995–1.054)	0.108

The patients underwent monitoring of interstitial glucose using a CGMS. The AUC of the blood glucose level and time over 200 mg/dL was calculated. Ordinal logistic regression was used to assess the independent effect of risk factor on the AUC. $P < 0.05$ was considered statistically significant.

Table 3. *Nonlinear regression model analysis of risk factors associated with predicted glucose level.*

Factors (IQR)	Coefficient (95% CI)	*P* value
The first day		
Time, min (360–1080)	0.610 (0.565, 0.659)	< 0.001
Age, years (54–78)	1.058 (0.973, 1.150)	0.185
BMI, kg/m^2 (20.34–24.91)	0.982 (0.938, 1.028)	0.439
HbA1c, % (5.5–5.9)	1.031 (0.960, 1.108)	0.397
Baseline glucose, mg/dL (95–116)	1.063 (1.002, 1.128)	0.042*
Within 2 days		
Time, min (720–2160)	0.719 (0.671, 0.771)	< 0.001
Age, years (54–78)	1.027 (0.949, 1.112)	0.503
BMI, kg/m^2 (20.34–24.91)	0.999 (0.951, 1.050)	0.982
HbA1c, % (5.5–5.9)	1.025 (0.956, 1.098)	0.491
Baseline glucose, mg/dL (95–116)	1.053 (0.992, 1.119)	0.090

The patients underwent monitoring of interstitial glucose using a CGMS. Glucose was natural log-transformed to provide normality in the regression residuals. To predict the blood glucose levels over time, a nonlinear regression analysis was performed. The nonlinear association between glucose and measurement time was assessed by including restricted cubic splines in the regression model. Because there were repeated measurements per patient, we used a robust sandwich estimator for estimating the variance of the coefficient obtained from the regression model. Coefficients were back-transformed, indicating the percent increase of glucose level when factors increase from 25th percentile to 75th percentile.

*$P < 0.05$ was considered statistically significant.

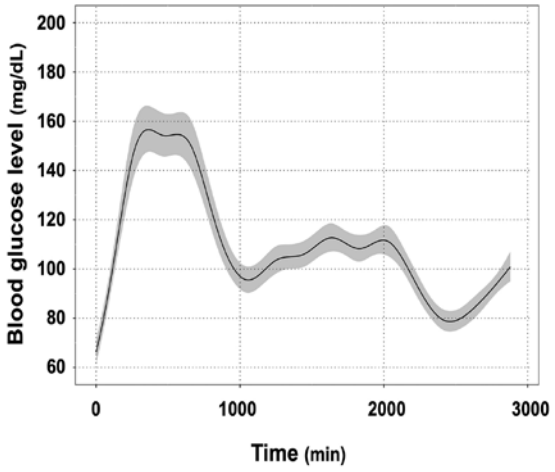

Fig. 3. *Prediction of blood glucose levels after dexamethasone injection. The blood glucose levels were obtained from the data of a CGMS. To predict the blood glucose level over time, a nonlinear regression model was used. The nonlinear association between glucose and measurement time was assessed by including restricted cubic splines in the regression model. Because there were repeated measurements per patient, we used a robust sandwich estimator for estimating the variance of the coefficient obtained from the regression model. Adjusted for a BMI of 21.4 kg/m^2, HbA1c of 5.7%, age of 59 years, and glucose level before the dexamethasone injection of 102 mg/dL. The gray zone indicates the 75% CI.*

We explored the risk factors of hyperglycemia after local dexamethasone injection and found that neither age, BMI, HbA1c, or blood glucose level just before injection was associated with hyperglycemia (AUC > 200 mg/dL). The HbA1c value in our patients ranged from 4.7% to 6.3%. Patients are diagnosed with prediabetes based on an HbA1c of 5.7% to 6.4% (21). According to this definition, some of our patients would have been diagnosed with prediabetes. HbA1c has been used to assess long-term glycemic control, but it does not reflect intra- and interday glycemic variations that may lead to acute events, such as postprandial hyperglycemia (22). Therefore it is suggested that HbA1c is not associated with hyperglycemia after dexamethasone injection.

In the present study, there were patients who showed severe hyperglycemia exceeding 250 mg/dL and even 300 mg/dL during the observation periods. Unfortunately, we were unable to determine the specific risk factors associated with hyperglycemia. Such severe hyperglycemia has not been reported in non-DM patients previously. Because blood glucose levels were not measured continuously in previous studies (6,19), medical providers may simply not have noticed. However, we found that some but not all patients demonstrated unpredictable high blood glucose levels following local single-dose dexamethasone injection with nerve blockade. Patients are not usually hospitalized after the procedures performed in the present study. Therefore we must consider the indication, dose, and interval of GC use and explain potential complications, including hyperglycemia, to patients.

According to the prediction of blood glucose levels, even non-DM patients demonstrate elevated glucose levels than usual on the first day, with the levels decreasing to relatively normal values after the second day. Only the blood glucose level just before injection was associated with the predicted blood glucose levels on the first day. Because the 95% upper confidence limit of the blood glucose level is < 170 mg/dL, which is within the safe margin, it is suggested that the blood glucose levels do not increase to critical values in most cases. On the first day, 2 peaks of blood glucose were noted, probably occurring postprandially. The postprandial blood glucose value is reported to be significantly higher on the day after GCs injection to the shoulder or as an epidural even in non-DM patients despite no marked variations in the fasting blood glucose level (19), and DM patients receiving oral prednisolone for chronic obstructive pulmonary disease are said to demonstrate postprandial hyperglycemia (4). Our results are consistent with those of previous studies. Because the half-life of dexamethasone is 20 to 36 hours (3), it is likely that hyperglycemia was observed only on the first day. We also showed that when patients already have high blood glucose levels before the procedure, the levels are significantly higher after procedures on the first day. These findings suggest that any non-DM patient may demonstrate hyperglycemia after a meal on the day of the procedure, but this is not a critical change. Medical providers should educate patients on avoiding overeating on the day of the procedure.

Patients who suffer from pain, such as those in our study, sometimes require GCs regularly or injections at multiple sites. However, the maximum safe total amount or interval of injection remain unclear (14). Further investigations will be needed to avoid complications, including hyperglycemia, induced by single-dose GC injection.

GCs are expected to inhibit the synthesis and release of proinflammatory cytokines, which induce pain locally (7). However, it has been reported that GC injection for relieving facet joint pain does not ex-

ert significant benefits (23), and there is no evidence supporting the efficacy of GC injection with selective nerve root blockade. The systemic absorption and side effects associated with local injection are often underestimated (14). All side effects known to be induced by systemic GC administration occur with local GC injection (14). We must clarify whether or not the injection of GCs via these procedures are useful for pain management.

Several limitations associated with the present study warrant mention. First, GCs are metabolized by cytochrome p450 3A4 (14), and it is possible that the inhibition of this pathway decreases the clearance of GCs (14). Some of our patients were taking medications that influence this cytochrome pathway. Second, it is well known that surgical stress increases the blood glucose levels. Because no patients received the nerve blockade without dexamethasone, we cannot eliminate the possibility of stress-induced hyperglycemia. Finally, we were unable to record the exact meal timing and calories the patients had consumed.

Conclusions

The blood glucose levels were higher than usual on the first day following a local dexamethasone injection, but the levels were not critical in most cases. Because we cannot predict which patients will develop hyperglycemia, we must determine whether or not GCs can be safely administered and inform patients about potential complications.

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