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ORIGINAL ARTICLE

Glucocorticoid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: an observational cohort study

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ABSTRACT

Background

Patients with cancer are often treated with glucocorticoids (GCs) as part of therapy, which may cause hyperglycemia. We sought to define the prevalence of, and risk factors for, hyperglycemia in this setting.

Methods

Adult patients taking GC as part of therapy protocols for primary brain tumour or metastasis, for lymphoma, or for bone marrow transplant (BMT) were screened with random glucometer measurements taken at least 3 hours after the last dose GCs.

Results

We screened 90 patients [44.4% women, 55.6% men; mean age: 59.6 years (range: 25–82 years); mean body mass index (BMI): 26.4 kg/m^2 (range: 15.8–45.3 kg/m^2)] receiving GC as part of cancer treatment. Mean total daily GC dose in the group was 238.5 mg (range: 30–1067 mg) hydrocortisone equivalents. Hyperglycemia (glucose $\geq$ 8.0 mmol/L) was found in 58.9% (53 of 90), and diabetes mellitus (DM)–range hyperglycemia (glucose $\geq$ 11.1 mmol/L) in 18.9% (17 of 90). The mean time from GC ingestion to glucometer testing was 5.5 hours (range: 3–20 hours). Presence of hyperglycemia did not correlate with traditional DM risk factors such as age, sex, BMI, and personal or family history of DM. A longer interval from GC dose to testing ($p < 0.05$), a higher GC dose ($p = 0.04$), and a shorter interval between the preceding meal and testing ($p = 0.02$) were risk factors for hyperglycemia in some patient groups.

Conclusions

Glucocorticoid-induced hyperglycemia is common in patients undergoing cancer treatment and cannot be predicted by traditional risk factors for DM. We recommend that all cancer patients receiving GC be screened for hyperglycemia at least 4–6 hours after GC administration.

KEY WORDS

Hyperglycemia, glucocorticoids, glucocorticoid-induced diabetes, diabetes mellitus

1. INTRODUCTION

Hyperglycemia is emerging as a potential risk factor for the development of cancer, and it may also be associated with poor cancer treatment outcomes. Diabetes mellitus (DM) and hyperglycemia are associated with an elevated risk of pancreatic [1–4], liver [1–4], colon [5], breast [1,6], and endometrial cancer [1]. Prospective cohort studies that measured insulin response to a glucose load and insulin resistance before the development of cancer have suggested a causative link between impaired glucose metabolism and cancer [7–9]. Those studies also reported a greater risk of cancer mortality in adults with prior impaired glucose tolerance than in those with a normal response. Diabetes is associated with an elevated relative risk of death from colon, pancreatic, and breast cancer [5,10–12]. Hyperglycemia might also be associated with poor cancer treatment outcomes and treatment-related morbidities. In a cohort of 278 adults undergoing induction therapy for acute lymphocytic leukemia (ALL) combined with glucocorticoid (GC) therapy, Weiser *et al.* [13] reported diabetes-range hyperglycemia ($\geq$11.1 mmol/L [14]) in 37% of the patients—a condition that was associated with a lesser duration of complete ALL remission, decreased overall survival, and increased rates of

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infection and sepsis [15]. Another retrospective cohort study of 283 hospitalized patients with acute myeloid leukemia demonstrated increased rates of hospital mortality and sepsis associated with blood glucose levels of 6.1 mmol/L or more [16], and a study of patients with newly diagnosed glioblastoma reported a significantly lesser overall survival duration in the presence of blood glucose levels greater than 7.6 mmol/L regardless of GC dose [17]. Further evidence is needed to demonstrate similar outcomes and morbidities in other types of cancer.

Patients undergoing cancer therapy are frequently treated with GCs, which may cause hyperglycemia. Glucocorticoids are the most common cause of medication-induced hyperglycemia and DM [18,19]. It would be useful to obtain data on the prevalence of GC-induced hyperglycemia and also on the risk factors for that condition so that clinicians can target glycemic interventions to the highest-risk population. The purpose of the present study was to determine the prevalence of, and risk factors for, hyperglycemia in patients with cancer undergoing chemotherapy (CMT) or radiation treatment (RT) involving GCs.

2. METHODS

2.1 Study Design

This prospective observational study was approved by the institutional research review and ethics boards of our institution, and each participant provided written informed consent.

2.2 Study Population

All adult patients seen at the BC Cancer Agency between November 1, 2006, and June 1, 2007, were eligible for inclusion if they were receiving GC and concurrent CMT for lymphoma [continuous GC therapy on days 1–5 of a 21-day CMT cycle with LYCHOP or LYCHOPR (doxorubicin–cyclophosphamide–vincristine–prednisone ± rituximab), or LYCVP or LYCVPR (cyclophosphamide–vincristine–prednisone ± rituximab)] [20]; RT for primary brain tumour or metastasis; or bone marrow transplant (BMT). These cancer treatment groups were chosen because concurrent use of GC is standard. The principal exclusion criterion was the inability to give informed consent. Patients were not excluded based on a prior diagnosis of DM or previously elevated blood glucose.

2.3 Data Collection

Capillary blood glucose (CBG) analysis was performed using the Ascensia Elite XL Diabetes Care System (Bayer HealthCare AG, Leverkusen, Germany) and a capillary sample obtained at least 3 hours after the GC dose. Random rather than fasting glucose was used, because GC classically causes exaggerated postprandial hyperglycemia and has a much lesser effect on fasting glucose [21–23]. One researcher (AB) was responsible for all testing and data collection. At the time of glucose testing, demographic, medical history (including history of personal DM or DM in a first-degree relative), and medications data were collected. Information was also obtained about the type and dose of GC, duration of GC use (in CMT and BMT patients), and the interval between glucometer testing and the most recent administration of GC or consumption of a meal. For purposes of the analysis, all doses were converted to hydrocortisone (HC) equivalents (1 mg prednisone = 4mg HC equivalents or 1.0 mg dexamethasone = 26.7 mg HC equivalents) [24].

2.4 Definitions and Diagnosis of Glucose Metabolism Abnormalities

We defined a random plasma glucose of 8 mmol/L or more as hyperglycemia and a marker of abnormal glucose metabolism. A threshold value of 8 mmol/L was chosen to reflect the lower limit of impaired glucose tolerance [14] because most of the study subjects were sampled several hours after eating. In-hospital, hyperglycemia has similarly been defined as a random plasma glucose of 7.8 mmol/L or more [25]. Our definition of hyperglycemia is also reflective of the range of serum glucose levels shown to be associated with poor cancer treatment outcomes [15–17]. Diabetes-range hyperglycemia was defined as a random blood glucose of 11.1 mmol/L or more, which is diagnostic of DM [14].

2.5 Outcome Measures

The primary outcome measure in this study was the prevalence of hyperglycemia in the three cancer patient cohorts. Secondary outcome measures included the prevalence of DM-range hyperglycemia, interval (in hours) at CBG testing since the most recent GC dose and since the most recent meal, total daily GC dose, and traditional risk factors for hyperglycemia and diabetes [26] [sex, age (years), weight (kilograms), body mass index (BMI: kilograms per metre squared), and personal or family history of DM].

2.6 Statistical Analysis

Sample size was calculated conservatively assuming a prevalence of 40% for GC-induced hyperglycemia (based on published values derived from a cohort of non-Hodgkin lymphoma patients undergoing chemotherapy [27]). Standard deviation was estimated higher (at 50%), given the large deviations in glucose previously reported in similar GC studies [15]. Our target difference was therefore 0.2 ($\mu_1 = 0.4$, $\mu_2 = 0.6$), with a standard deviation of 0.5 [15], type I error α of 0.05, and desired power of 80%, which resulted in a sample size of 99 patients. We finished study

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enrollment with 90 patients because we suspected that our prevalence was underestimated compared with rates seen in other studies [15,27,28].

All data were analyzed using the SPSS software application (version 16.0: SPSS, Chicago, IL, U.S.A.). Chi-square tests were used to determine whether, compared with the euglycemic patients, the patients with hyperglycemia differed in demographic or historical variables. A Bonferroni correction was applied for multiple comparisons within groups. Correlations between the presence of hyperglycemia or DM-range hyperglycemia and secondary outcome measures were calculated using the Kendall tau algorithm (nonparametric rank correlation). Statistical significance was defined as a two-tailed p of less than 0.05. Continuous data (glucose concentration, age, weight, height, interval since the most recent GC dose and meal) were analyzed using logistic regression models. There were no missing data in this study.

3. RESULTS

3.1 Study Group Characteristics

Of the 90 patients enrolled, 50 were receiving CMT; 24, RT; and 16, BMT. The overall mean GC dose was 238.5 ± 142.7 mg (range: 30–1067 mg) HC equivalents. The mean time from GC ingestion to glucometer testing was 5.5 ± 3.0 hours (range: 3–20 hours). Mean time between glucometer testing and the most recent meal was 3.1 ± 1.6 hours (range: 0.15–8 hours). Patients receiving CMT also received prednisone (range: 25–100 mg) for a mean duration of 14.6 days (range: 1–40 total days of GC administration before enrolment) and underwent CBG testing a mean of 5.2 hours (range: 3–8.5 hours) after the most recent GC dose. Patients receiving RT also received dexamethasone (range: 1–4 mg) and underwent CBG testing a mean of 7.0 hours (range: 3–20 hours) after the most recent GC dose. Patients receiving BMT also received prednisone (range: 7.5–107 mg) for a mean duration of 147.6 days (range: 20–309 days) and underwent CBG testing a mean of 4.2 hours (range: 3–8 hours) after the most recent GC dose. The duration of GC therapy was not significantly different between the BMT and CMT groups. Table I summarizes all other group characteristics.

3.2 Prevalence of Hyperglycemia

Hyperglycemia was detected in 58.9% of patients (53 of 90), and 18.9% of patients (17 of 90) had DM-range hyperglycemia. Of the patients experiencing DM-range hyperglycemia, 13.3% (12 of 90) met the criteria for a new diagnosis of DM [14]. The mean CBG for the three treatment groups was 9.4 ± 4.6 mmol/L, with no significant differences between the groups. At baseline, 27.8% of the patients (25 of 90) had already been diagnosed with DM. Of the patients with prior DM, 20% (5 of 25) had DM-range hyperglycemia, 36% (9 of 25) had hyperglycemia, and 44% (11 of 25) were euglycemic. Hyperglycemia was detected in 69.6% (16 of 23) of the patients whose CBG screening occurred 6 or more hours (range: 6–20 hours) after the most recent GC dose.

3.3 Correlations with Hyperglycemia

Table II presents variables that were significantly and positively correlated with hyperglycemia: total GC daily dose ($r = 0.19$, $p = 0.04$) and hours since the most recent meal ($r = 0.27$, $p = 0.02$) in the BMT group, and hours since the most recent GC dose in the BMT and CMT groups (BMT: $r = 0.21$, $p = 0.02$; CMT: $r = 0.49$, $p = 0.04$)). The shorter the interval after the meal, or the longer the interval after the GC dose, the more likely the patient was to have hyperglycemia. Traditional DM risk factors [26], including BMI and a personal history of DM, were not predictive of hyperglycemia in any of the cancer therapy groups. Additionally, we observed no correlations between DM-range hyperglycemia and any secondary measures (data not shown), including a personal history of DM ($r = 0.3948$, $p = 0.072$).

4. DISCUSSION

Glucocorticoids are often used in cancer patients as part of CMT protocols or as an adjunctive agent for nausea and metastasis to the central nervous system. They are the most common cause of medication-induced DM in this clinical setting [29]. Glucocorticoids contribute to the development of hyperglycemia by several mechanisms: inhibiting glucose uptake in muscle, increasing hepatic gluconeogenesis, and exerting multiple effects on the receptor and post-receptor activity of the beta cell in the pancreas [30,31]. However, the major hyperglycemic effect of GC is mediated through increased insulin resistance in skeletal muscle [32].

We are aware of one randomized trial of various treatment options for hyperglycemia in the setting of ALL suggesting that the use of metformin or thiazolidinedione (or both) was associated with improved progression-free survival; however, that benefit may not apply to other treatment strategies [33]. Further data examining the outcomes of glycemic control or management for cancer patients are not yet available, but several such studies are currently underway (see, for example, NCT01236885 and NCT01486043 at http://clinicaltrials.gov). However, hyperglycemia can occasionally cause acute complications such as hyperosmolar hyperglycemia syndrome and diabetic ketoacidosis [34], or increase the risk of infections [15,16,35,36]. Also, hyperglycemia has been associated with reduced overall and disease-free survival in patients with some solid tumours and leukemia [13,37]. Thus, it is relevant to identify

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TABLE I Characteristics of the study groups

Variable	*Patient group*				p *Value*
	Overall	*Chemotherapy*	*Radiation therapy*	*Bone marrow transplantation*	
Patients (*n*)	90	50	24	16	
Mean age (years)	59.6	66.3[a]	60.2	47.8[a]	<0.01
Sex (% women)	44.4	46	50	31	0.48
Mean BMI (kg/m^2)	26.4	26.2	26.9	26.2	0.84
History of DM (%)					
Personal	27.8	12	54.2	37.5	0.6
Family	23.3	32	8	19	0.07
New-onset DM (%)	13.3	16.0	12.5	6.3	0.6
Mean HC dose equivalent (mg)	238.5	320.3[a]	106.7[a]	185.6[a]	<0.01
Mean time since last meal (h)	3.1	2.8	3.4	3.3	0.23
Mean time since GC dose (h)	5.5	5.2	7.0[a]	4.2[a]	<0.05

[a] Statistically significant (defined as $p < 0.05$) compared with overall group mean.
BMI = body mass index; DM = diabetes mellitus; HC = hydrocortisone; GC = glucocorticoid.

TABLE II Correlation between presence of hyperglycemia and study group characteristics

Patient group	*Characteristic*							
	Age	*Sex*	*BMI*	*History of DM*		*GC dose*	*Hours since*	
				Personal	*Family*		*GC dose*	*Meal*
Bone marrow transplantation (*n*=16)								
r	0.11	0.25	0.16	0.16	–0.13	0.19	0.21	0.27
p	0.20	0.81	0.70	0.13	0.23	0.04[a]	0.02[a]	0.02[a]
Chemotherapy (*n*=50)								
r	0.19	–0.14	0.41	0.26	–0.16	0.62	0.49	0.05
p	0.40	0.60	0.07	0.32	0.54	0.79	0.04[a]	0.83
Radiation therapy (*n*=24)								
r	0.04	0.00	0.29	0.13	0.00	0.21	0.04	0.20
p	0.84	1.00	0.13	0.55	1.0	0.32	0.82	0.25

[a] Statistically significant (defined as $p < 0.05$).
BMI = body mass index; DM = diabetes mellitus; GC = glucocorticoid.

hyperglycemia in patients treated with GC to reduce the risk of acute complications while data are being collected on the effects of treatment of hyperglycemia on long-term cancer outcomes.

The high prevalence of hyperglycemia demonstrated in our patient group is consistent with that seen in patients with other chronic medical conditions requiring GC treatment for extended durations (>3 weeks of GC therapy) [18]. Our documented prevalence of hyperglycemia (58.9%) is similar to other published values in cancer patients: for example, 58.1% in pediatric patients with ALL (97 of 167) [15], 43.2% in patients with non-Hodgkin lymphoma (70 of 162), and 49.2% in prostate cancer patients (92 of 187) [27]. Furthermore, a prospective nonrandomized trial of 34 non-DM patients undergoing craniotomy [38] showed that patients given only two perioperative doses of intravenous dexamethasone had a mean postoperative glucose of 11.0 ± 2.0 mmol/L, which was 41% higher than that in patients who did not receive dexamethasone (mean blood glucose: 7.8 ± 2.1 mmol/L).

Currently, the reported information about the time course of the hyperglycemic effect caused by GC use in patients with cancer is limited. Glucocorticoid-induced hyperglycemia typically causes a minimal increase in fasting glucose, but an exaggeration of postprandial glucose. When GCs are administered in the morning, measurement of fasting blood glucose

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(the standard practice for patient blood work before administration of the next dose of CMT) is not sufficient to detect hyperglycemia [22,23,39]. Our data show that, as the interval between GC dose and measurement of blood glucose increases, the prevalence of hyperglycemia also increases. In fact, given that the average interval between glucometer testing and GC dose was only 5.5 hours in our study, our results may be underestimating the true prevalence of hyperglycemia in these patient groups. In the present study, hyperglycemia was detected as late as 20 hours after most recent GC dose. Thus, the risk of hyperglycemia in patients with hematologic and brain malignancies treated with GC is significant.

We recommend that all patients with cancer who are being treated with GCs should undergo routine glucometer testing, with CBG measurements being taken at least 4–6 hours after ingestion of GC. This recommendation would not require prolongation of hospital stay nor time in oncology day care. Nurses in both clinical settings could teach glucometer use at time of GC initiation, providing patients with a glucometer when they are about to start GC therapy and giving instruction about how to check CBG before the noon or the evening meal to screen for hyperglycemia. That recommendation is consistent with current Canadian Diabetes Association clinical practice guidelines, which specify that increased screening for DM should occur for all persons initiating GCs [26]. Glucometers typically cost CA$20–CA$30, and glucose test strips, about CA$40–CA$50 for 50 strips, unless a patient has extended medication coverage.

A significant finding of our study was the inability of traditional risk factors to predict risk of hyperglycemia with GC and cancer therapy. Only an increased GC dose and the interval in hours since the most recent GC dose or meal correlated with hyperglycemia for the BMT and CMT groups. Those positive correlations were expected, because increased doses of GC were previously shown to increase risk of hyperglycemia [18], a longer interval since the administration of GC reflects the longer biologic half-life of synthetic GC (ranging from 8 hours to 72 hours [24]), and a shorter interval since the most recent meal likely reflects the postprandial rise in serum glucose [40]. Although we collected data on the duration of GC exposure for the CMT and BMT groups, the duration of GC therapy was not significantly different in our patient groups, and we therefore cannot draw conclusions about a specific duration of GC therapy that leads to a greater hyperglycemia risk. However, other authors have shown that an extended duration of GC use increases the risk of hyperglycemia [18].

In the present study, common risk factors [26] associated with hyperglycemia and DM, such as age, BMI, sex, and personal or family history of type 2 DM did not predict risk of developing hyperglycemia. Although it is surprising that a personal history of DM did not predict DM risk, it is possible that the physicians administering GC to patients with known DM may have adjusted the DM medications taken by those patients in expectation of an effect of the GC. Also, other authors have shown that the DM risk in patients with non-malignant diseases treated with GC is not consistently predicted by traditional risk factors. Uzu *et al.* [41] previously reported age and BMI, but not sex, as predictors of risk for DM in patients treated with GC for primary renal disease. Studies of patients with systemic lupus erythematosus treated with high-dose GCs showed that age and a positive family history of DM, but not sex, were independent risk factors for DM [42]. Conversely, only increased prednisone dose, and not age, BMI, or family history of DM were correlated with GC-induced DM in a rheumatoid arthritis case–control cohort study [43]. And, in a retrospective study of respiratory diseases in non-DM patients treated with chronic GC therapy, age was the only variable that predicted risk of developing GC-induced DM [44]. Thus, based on our results, we cannot recommend using common risk factors for hyperglycemia [26] or a personal history of DM to target patients in whom screening for hyperglycemia is indicated.

Our study has several limitations. First, it was intended to document the prevalence of, and risk factors for, hyperglycemia; it was not powered to detect an effect of hyperglycemia on patient outcomes, nor was it intended to address blood glucose targets or treatment strategies for hyperglycemia in patients with cancer who are treated with GC. Trials to address those questions are ongoing (such as NCT01236885 and NCT01486043 at http://clinicaltrials.gov). We did not collect data about how DM was managed in patients with a personal history of DM, and so we are unable to confirm our hypothesis that physicians preemptively adjusted DM medications when starting GC, thus explaining our finding that a personal history of DM was not predictive of the risk for hyperglycemia. Our patient population was limited to 3 cancer treatment groups, and the results might therefore not be generalizable to patients receiving GC as part of treatment for other types of cancers. Our study was not powered to determine if the various GCs (prednisone, dexamethasone, HC) have different hyperglycemic potentials in this clinical setting. We did not control for the duration of GC administration before enrolment, and so the groups were not matched for that variable, which might affect the risk of hyperglycemia. Finally, we did not account for the number of people who refused consent for our study, which might have introduced a selection bias.

5. CONCLUSIONS

Hyperglycemia is a common adverse effect of GC therapy for cancer patients undergoing CMT, RT, or BMT. We recommend against the use of traditional risk

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factors to predict which patients should be screened for GC-induced hyperglycemia. Further studies are needed to investigate the link between hyperglycemia and patient or cancer outcomes. We recommend that all cancer patients receiving GC be screened for hyperglycemia with a random glucose test at least 4–6 hours after the most recent GC dose.

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7. CONFLICT OF INTEREST DISCLOSURES

All authors approved the final version of this manuscript and to the best of our knowledge, no conflicts of interest, financial or other, exist.

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