Management of Steroid-Induced Hyperglycemia in Hospitalized Patients With Cancer: A Review

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Glucocorticoids are prescribed for hospitalized patients with cancer for a variety of reasons, including cerebral edema, nausea prevention, and as part of a cancer treatment regimen. Glucocorticoids are known to cause hyperglycemia. Hyperglycemia (steroid-induced or otherwise) among noncritically ill hospitalized patients has been shown to lead to increased length of hospital stay, delayed wound healing, increased infections, and higher mortality rates (Lleva & Inzucchi, 2011), which suggests the need for improved management strategies. The purpose of this review was to integrate the published research on the management and the effects of management of steroid-induced hyperglycemia among hospitalized adult patients with cancer with or without preexisting diabetes.

Background

Inpatient hyperglycemia, which occurs in 32%–38% of hospitalized patients, is defined as having blood glucose values greater than 140 mg/dl during hospitalization (Moghissi et al., 2009; Smiley & Umpierrez, 2010; Umpierrez et al., 2012). This elevated glucose level can occur for various reasons, including omission of antidiabetic agents in patients with known diabetes, stress hyperglycemia as a result of acute illness, and steroid-induced hyperglycemia (American Diabetes Association [ADA], 2013). Regardless of the underlying cause, hyperglycemia in hospitalized patients (with or without diabetes) has been associated with poor outcome (Moghissi et al., 2009). On the basis of the reported incidence of hyperglycemia among hospitalized patients, the ADA's (2011) Clinical Practice Recommendations suggested that all patients with known diabetes and/or those receiving medications associated with hyperglycemia receive glucose monitoring during hospitalization in conjunction with meals or at meal times or every four to six hours if not eating. In 2013, the ADA further recommended that glucose monitoring be conducted in patients without

Problem Identification: Glucocorticoids are prescribed for hospitalized patients with cancer for a variety of reasons, including cerebral edema, treatment and prevention of nausea, and as part of cancer treatment regimens. Glucocorticoids are known to cause hyperglycemia. The purpose of this study was to integrate the published research on the management and the effects of steroid-induced hyperglycemia in hospitalized adult patients with cancer with or without preexisting diabetes.

Literature Search: MEDLINE®, PubMed, EMBASE, CINAHL®, and Scopus electronic databases were used to identify relevant articles. Bibliographies of included studies were reviewed for any pertinent studies that were not obtained through database search.

Data Evaluation: 1,392 studies were identified. A total of 18 studies that met criteria were fully reviewed, 6 of which met all of the inclusion criteria.

Data Analysis: Data were abstracted from the included studies using a systematic code sheet to document characteristics of the studies and findings on management of hyperglycemia. Characteristics of the studies and findings on management of hyperglycemia were organized into three tables: the patients did not have preexisting diabetes, the patients had preexisting diabetes, and patients with or without preexisting diabetes were both included in the study. Management and effects of management of hyperglycemia were then compared and synthesized.

Presentation of Findings: Hyperglycemia occurs in hospitalized patients with cancer irrespective of whether patients have a prior history of diabetes. Hyperglycemia resulting from steroids is treated in a variety of ways, but the resulting glycemic control has not been consistently documented. However, this review suggests that scheduled insulin (basal-bolus) is effective in attainment of glucose targets.

Implications for Practice: Nurses should be aware of the effect that steroids have on glycemic control in patients and should be empowered to request or perform blood glucose monitoring when appropriate. Nurses can identify those patients receiving steroids and assess for signs and symptoms of hyperglycemia. They also can review routine laboratory results and assess for hyperglycemia in patients receiving steroids.

Key Words: hospitalized patients; cancer; steroids

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known diabetes who were receiving therapies with high risk of hyperglycemia, such as parenteral or enteral nutrition, glucocorticoids, immunosuppressive therapy, or octreotide. The Endocrine Society recommended that all patients have blood glucose levels tested on admission, regardless of whether they have a diagnosis of preexisting diabetes. This approach is believed to be warranted by the opportunity to diagnose new diabetes and to assess glycemic control early in the hospital course (Umpierrez et al., 2012).

Hospitalized Patients With Cancer

Inpatients with cancer are treated in a variety of settings, including the general medical, intensive care, and palliative care units. In a study by Rocque et al. (2013) of 149 unscheduled admissions in 119 patients with metastatic cancer, 66% were hospitalized for adverse effects of treatment, including pain (28%), gastrointestinal obstruction (16%), dyspnea (10%), altered mental status (5%), and failure to thrive (4%). Others were hospitalized for cancer treatment, including procedures (magnetic resonance imaging, computed tomography, or ultrasounds), surgery, radiation therapy, or chemotherapy (Rocque et al., 2013). Shah, Cui, Busaidy, Sherman, and Lavis (2008) reported that 20% of patients with cancer who were hospitalized experienced significant hyperglycemia (blood glucose of 200 mg/dl or greater for two days or longer), and Morganstein, Tan, Gore, and Feher (2012) noted that 11% of inpatients had either diabetes or hyperglycemia.

Steroid-Induced Hyperglycemia

Glucocorticoids are known to have a deleterious effect on glycemic control. Prolonged exposure to dexamethasone and prednisone can lead to hyperinsulinemia, inhibitory effects on β-cell function, and diabetes (van Raalte, Ouwens, & Diamant, 2009). This negative effect is believed to be caused by a variety of factors, including increased insulin resistance, increased glucose intolerance, reduced β-cell mass from β-cell dysfunction, and increased hepatic insulin resistance leading to impaired suppression of hepatic glucose production (van Raalte et al., 2009).

Hyperglycemia often is compounded by steroid administration. Steroids are prescribed for patients with cancer as either a component of a chemotherapy regimen or for symptom management. The types and doses of steroids administered vary according to the reasons they are prescribed. The most commonly prescribed steroids for patients hospitalized with cancer include methylprednisolone, prednisone, and dexamethasone. Dexamethasone (8–12 mg) is used in the management of nausea and vomiting (Trigg & Higa, 2010), a common adverse effect of many cancer treatments. Various doses of dexamethasone (4–16 mg per day or more) have been used to control edema associated with brain metastasis (Ryken et al., 2010) Prednisone (100 mg) and dexamethasone (40 mg) have been used in combination with other chemotherapeutic agents as part of chemotherapy protocols (Lee et al., 2014; Romaguera et al., 2005). Methylprednisolone doses as high as 2 mg/kg per day have been used in the treatment of graft-versus-host disease (Holtan, Pasquini, & Weisdorf, 2014; Ruutu et al., 2014). To put these doses in perspective, steroid dose equivalences are as follows: 0.75 mg of dexamethasone equals 5 mg of prednisone equals 4 mg methylprednisolone equals 20 mg of hydrocortisone equals 25 mg of cortisone (National Adrenal Diseases Foundation, 2014). The choice of agent often is based on desired mineral corticoid activity, cost, and physician preference. Regardless of the steroid used, all can induce hyperglycemia in high enough doses. Patients in palliative care have a significantly increased risk of developing steroid-induced diabetes (odds ratio = 1.5–2.5) (Pilkey, Streeter, Beel, Hiebert, & Li, 2012).

Gulliford, Charlton, and Latinovic (2006) reported that, in a primary care population, 2% of incident cases of diabetes were associated with oral glucocorticoids. Among patients with a previous history of diabetes, the prevalence of steroid-induced hyperglycemia has been 20%–50% (Umpierrez et al., 2012). Donihi, Raval, Saul, Korytkowski, and DeVita (2006) stated that, among 617 patients admitted to the general medicine service receiving high-dose steroids (40 mg or higher prednisone or the equivalent) for two or more days, only 66 had blood glucose monitoring performed and, of these, about 50% of patients without known diabetes and 64% of those who were monitored experienced at least one episode of hyperglycemia, with multiple episodes

Table 1. Suggestions for Hyperglycemia Management

Study	Recommendation
American Diabetes Association, 2013	Use a three-pronged approach to treatment: diet, physical activity, and medication.
Clore & Thurby-Hay, 2009	Use sulfonylureas, metformin, thiazolidinediones, and insulin for the management of hyperglycemia.
Oyer et al., 2006[a]	Treat steroid-induced hyperglycemia, steroid-induced diabetes, and drug-induced hyperglycemia similarly.
Umpierrez et al., 2012	Discontinue oral agents and initiate basal-bolus insulin therapy.

[a] Terms all describe the effects of glucocorticoids, mineral corticoids, or corticosteroids on glycemic control.

being associated with more comorbid diseases and longer exposure to steroids. In a study of 25 patients, Iwamoto, Kagawa, Naito, Kuzuhara, and Kojima (2004) reported that steroid-induced diabetes occurred in 13 patients (52%) with no previous history of diabetes who received 30–60 mg per day of prednisone for more than two weeks for the management of neurologic disease.

Various methods for the management of hyperglycemia have been proposed. Suggested modes of management of hyperglycemia are summarized in Tables 1 and 2. The purpose of this review is to evaluate existing methods of managing steroid-induced hyperglycemia among hospitalized patients with cancer and to examine the effects of management on glycemic control, infection rates, hospital length of stay, and adverse outcomes such as diabetic keto acidosis (DKA) and hyperosmolar hyperglycemic state (HHS), as well as to discuss implications for nursing practice.

Methods

The authors conducted a review of the published research to evaluate existing methods of managing steroid-induced hyperglycemia among hospitalized patients with cancer with or without preexisting diabetes and to examine the effects of management on glycemic control. To identify the published research, the authors accessed the following electronic databases: MEDLINE®, PubMed (1946–June 2013), Scopus (1996–June 2013), EMBASE (1947–June 2013), and CINAHL® (1937–June 2013). A search was conducted for all publication types, in English only, using free-text terms, combinations of these terms, and medical subject headings. Studies eligible for inclusion were primary research conducted in an adult population (18 years of age or older) who had cancer, were hospitalized during the study period, were receiving steroids, and, when included, were being treated for hyperglycemia. Reference lists of included studies were reviewed for any pertinent studies not obtained through search of databases, resulting in one additional study being retrieved. If the authors were uncertain from abstracts whether articles met inclusion criteria, full texts were obtained. Eighteen studies were relevant to the topic; six included all required criteria (see Figure 1).

Results

The six included studies are summarized in Table 3. These studies were conducted from January 1996 to August 2013. Two of the studies were experimental prospective studies, one of which was a randomized, controlled trial. The remaining four studies were

Table 2. Management of Hyperglycemia or Diabetes in Hospitalized Patients With Cancer

Intervention	Recommendations
Diet and Physical Activity[a]	
Diet	Low glycemic diet; limited amounts of sweetened foods and beverages (Krone & Ely, 2005); limited intake of concentrated carbohydrates; low-fat, low-calorie, or Mediterranean diets (American Diabetes Association, 2013; Rock et al., 2012)
Exercise	150 minutes of aerobic activity weekly and strength training 2–3 times per week (American Diabetes Association, 2011; Rock et al., 2012)
Oral Antidiabetic Medications	
Biguanides	Not recommended for patients with nausea, vomiting, diarrhea, or evidence of liver disease (Smiley & Umpierrez, 2010)
Secretagogues (meglitinides and sulfonylureas)	Not recommended as first-line therapy for inpatient use because of risk of hypoglycemia (Smiley & Umpierrez, 2010)
Thiazolidinediones	Not recommended for patients with a history of heart disease (Smiley & Umpierrez, 2010)
Insulin	
Long-acting (basal) • Glargine • Detemir Intermediate-acting • NPH • Regular (only one used for IV administration) Short-acting (bolus) • Lispro • Aspart • Glulisine	Drug of choice for management of hyperglycemia (Lleva & Inzucchi, 2011; Moghissi et al., 2009; Smiley & Umpierrez, 2010) Delivery methods for insulin include IV push or bolus, continuous IV infusion, or subcutaneous. Insulin available for subcutaneous delivery includes regular, NPH, glargine, detemir, lispro, aspart, and glulisine. These can either be given on an SS basis, which implies withholding insulin until the blood glucose is at a preset level (usually greater than 180 mg/dl), or basal-bolus. Regular insulin is usually chosen for SS. Basal-bolus therapy requires a long-acting insulin (basal) and a short-acting insulin (bolus), with the basal insulin being administered once or twice daily and the bolus being given with food. However, the type of insulin and the method of delivery depend on the patient and the clinical setting, which remains a topic of discussion.

[a] Dietary modifications and physical activity often are not feasible for hospitalized patients with cancer. Nausea, vomiting, decreased appetite, mucositis, and altered taste frequently impair dietary intake, whereas fatigue and scheduled tests can affect patients' ability to participate in physical activities.

NPH—neutral protamine hagedorn; SS—sliding scale

designed as retrospective chart reviews. Sample sizes ranged from 33–290, with study intervals being 4 months to 10 years. The study by Gogas et al. (1996), which included patients with ovarian cancer, was the only one to include women only; all of the other studies included both men and women. The six studies included in this review represented a heterogeneous population and comprised 583 patients from diverse settings with a variety of cancer diagnoses.

The two studies conducted in patients without preexisting diabetes reported extremes in blood glucose monitoring ranging from every two hours for a total of 12 hours (Lukins & Manninen, 2005) to before supper on Mondays and Thursdays (Pilkey et al., 2012), with similar results (blood glucose, 8.5–11 mmol/L [153–198 mg/dl]).

Blood glucose monitoring also was varied in the studies performed in patients with preexisting diabetes. Gogas et al. (1996) reported monitoring of blood glucose 30 minutes before paclitaxel infusion (n = 18) and during treatment. However, at what times or how often monitoring was done during treatment was not indicated. Gosmanov, Goorha, Stelts, Peng, and Umpierrez (2013) indicated that blood glucose readings were obtained before meals and at bedtime for both groups in the study. In the studies that included patients with or without preexisting diabetes, blood glucose monitoring was reported as being routinely performed four times a day in both populations, except among the control group in Vu et al. (2012), in which regular monitoring was not required. Although timing of blood glucose monitoring varied widely, the majority of the studies indicated the presence of steroid-induced hyperglycemia. Despite the heterogeneous population, small sample size, and wide ranges in dexamethasone dosages, findings suggest that steroid-induced hyperglycemia occurs in hospitalized patients with cancer with the management of hyperglycemia ranging from decreasing steroid doses (Pilkey et al., 2012) to using basal-bolus insulin (Gosmanov et al., 2013; Vu et al., 2012).

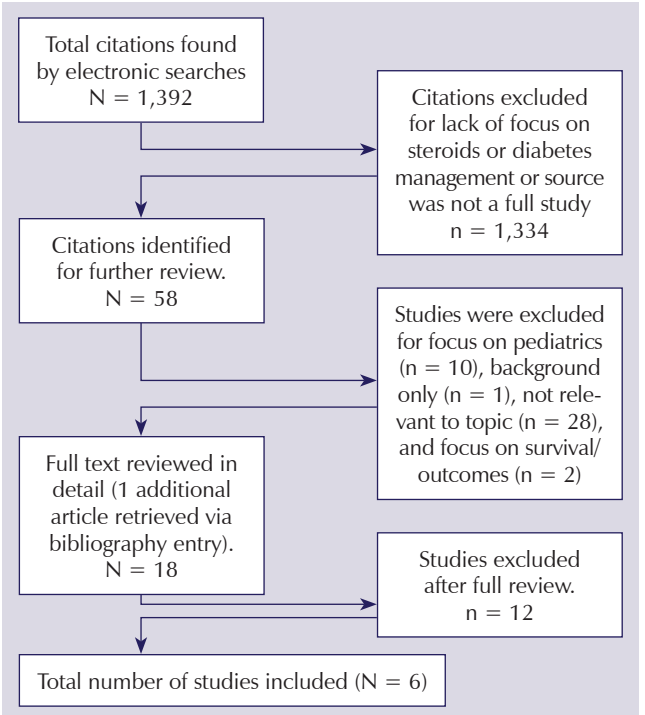

Figure 1. Flow Diagram of Search Strategy

Management of Steroid-Induced Hyperglycemia in Patients Without Diabetes

In one of the studies that did not include patients with preexisting diabetes, the management of steroid-induced hyperglycemia was not discussed (Lukins & Manninen, 2005), although the occurrence was documented. Forty-two of the 134 palliative care patients in Pilkey et al. (2012) were hyperglycemic, 15 of the 134 were diagnosed as having steroid-induced hyperglycemia, and 5 of those 15 patients required treatment with a variety of antidiabetic medications, ranging from oral agents in combination with insulin to multiple-dose insulin. Patients receiving the highest doses of dexamethasone (16 mg) had the most significant rise in blood glucose. These findings suggest that steroid-induced hyperglycemia occurs in patients without a history of diabetes.

Management of Steroid-Induced Hyperglycemia in Patients With Preexisting Diabetes

In the studies of patients with preexisting diabetes, blood glucose values were noted to be above target prior to initiation of steroids despite patients receiving treatment for diabetes with diet, oral agents, or insulin. In Gogas et al.'s (1996) study of 1,254 patients, of which 33 had a history of diabetes, 36% of those with preexisting diabetes were managed with diet, 52% with oral agents, and 12% with insulin. In Gosmanov et al.'s (2013) study (N = 40), 20% of patients were managed with diet, 43% with oral agents, and 37% were on insulin therapy prior to steroid administration.

All of the patients in Gosmanov et al. (2013) were given insulin therapy on the days they received steroids, with the average daily dose starting at 0.66 units/kg in the basal-bolus insulin (BBI) group and beginning with 3 units for blood glucose levels greater than 150 mg/dl in the sliding scale insulin (SSI) group. Gogas et al. (1996) indicated that five patients, whose hyperglycemia had been controlled by diet before initiation of steroids, required a change in therapy (three oral agents, two insulin) to achieve better glycemic control. In Gosmanov et al. (2013), despite having higher blood glucose readings at admission, on each day they

Table 3. Review of Studies on Effects of Modes of Treatment of Steroid-Induced Hyperglycemia in Hospitalized Patients With Cancer

Study	Purpose	Design	Sample	Steroid Type, Dose, and Duration	Definition of Hyperglycemia	Intervention		Outcomes and Effects of Management
						BG Monitoring and Results	Management Before and After	
Patients Without Preexisting Diabetes								
Lukins & Manninen, 2005	To document 12-hour BG concentrations in nondiabetics To identify which patients are at risk for hyperglycemia during craniotomy To compare glucose profiles of patients who received intraoperative dex with or without preoperative dex with patients not receiving any dex	Experimental, prospective, nonrandomized design of three groups: • Preoperative, receiving dex before surgery and continuing • Intraoperative, receiving dex during and continuing • None, not receiving any dex	N = 34 • Preoperative: 9 men and 3 women with a median age of 60 years • Intraoperative: 6 men and 2 women with a median age of 53 years • None: 4 men and 10 women with a median age of 47 years	• Preoperative: 12–24 mg per day of dex for an average of 12 days • Preoperative and intraoperative: 10 mg dex via IV during induction of anesthesia and 4 mg 393 minutes (± 100) later	Target BG of 80–150 mg/dl	BG checked just before anesthesia and every two hours for 12 hours 96% of readings from arterial blood Mean peak BG: • Preoperative: 8.5 mmol/L • Intraoperative: 11 mmol/L • None: 7.8 mmol/L	None	The longer the surgery, the higher the BG. Patients in the intraoperative group had the largest increase in BG (180–249 mg/dl).
Pilkey et al., 2012	To determine prevalence rate of steroid-induced diabetes and whether screening glucose twice per week is appropriate or required To determine whether predictors exist for the development of steroid-induced diabetes	Observational, retrospective, chart review	N = 134 (77 women and 57 men with a median age of 71 years) Participants were in two palliative care units. Types of cancer included lung, colon, prostate, brain, gynecologic, kidney, breast, hematologic of unknown primary, pancreatic, and other.	129 were on dex • 4 mg (n = 81) • 6 mg (n = 18) • 8 mg (n = 72) • 12 mg (n = 15) • 16 mg (n = 37) 5 were on prednisone	Screening BG greater than 11.1 mmol/L (200 mg/dl) without documented symptoms	BG checked at dinner time on Monday and Thursday Mean peak BG: • 4 mg = 8.6 mmol/L • 6 mg = 8.8 mmol/L • 8 mg = 9 mmol/L • 12 mg = 9.5 mmol/L • 16 mg = 10.6 mmol/L 15 patients developed SDM. For five patients, BG was greater than 20 mmol/L. Regimens used included: • 30/70, R and Nl • Met, Novolin • R, NPH • Nl	Decrease steroid dose.	Mean afternoon BG was 8.6–10.6 mmol/L (154–191 mg/dl) Improvement in hyperglycemic symptoms was noted.

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BBI—basal-bolus insulin; BG—blood glucose; dex—dexamethasone; Met—metformin; Nl—novolog; NPH—neutral protamine hagedorn; R—regular; SDM—steroid diabetes mellitus; SSI—sliding scale insulin; TZD—thiazolidinedione

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Study	Purpose	Design	Sample	Steroid Type, Dose, and Duration	Definition of Hyperglycemia	Intervention		Outcomes and Effects of Management
						BG Monitoring and Results	Management Before and After	
Patients With Preexisting Diabetes								
Gogas et al., 1996	To obtain information about neurotoxicity and nephrotoxicity in patients with diabetes To determine the effects of dex on the frequency and severity of hyperglycemia in patients with diabetes	Observational, retrospective, chart review with four treatment groups: • Cisplatin • Paclitaxel • Cisplatin before paclitaxel • Paclitaxel/cisplatin combination	N = 33 women with ovarian cancer, median age of 61 years • Cisplatin (n = 15) • Paclitaxel (n = 10) • Cisplatin before paclitaxel (n = 5) • Paclitaxel/cisplatin combination (n = 3)	18 were given dex 20 mg orally 12 and 6 hours prior to paclitaxel.	Not indicated	BG obtained 30 minutes prior to paclitaxel infusion BG prior to treatment: 5.2–19.2 mmol/L (96–297 mg/dl) On treatment: 6.6–29.5 mmol/L (120–538 mg/dl)	12 = diet • 3 = oral agents • 2 =insulin • 7 = diet 17 = oral agents 4 = insulin	Better control No hospitalizations required for diabetic complications
Gosmanov et al., 2013	To compare BG response of different insulin regimens To compare inpatient outcomes between different insulin regimens	Observational, retrospective, chart review of two groups: BBI and SSI	N = 40 BBI (n = 12; 7 women and 5 men) with a mean age of 57.4 (SD = 9.1) SSI (n = 28; 20 men and 8 women) with a mean age of 55.6 (SD = 7.3)	Dex 8–12 mg per day IV (27) x 3 days Dex 40 mg per day orally (13) x 3 days	Based on targets: Premeal, 100–140 mg/dl Random, more than 180 mg/dl	Before meals and at bedtime Admission BG • BBI = 189.2 (± 51.5) mg/dl • SSI= 136.3 (± 23.8) mg/dl Average BG day 1–3 • BBI = 219 (± 51) mg/dl • SSI = 301 (± 57) mg/dl	BBI • 0 = diet • 5 = oral agents • 7 = insulin Levemir, 0.33 (± 0.13) units/kg per day NI, 0.33 (± 0.12) units/kg per day SSI • 8 = diet • 12 = oral agents • 8 = insulin Novolin R, 3 units BG greater than 150 + 2–3/50	BBI average reduction in BG 52 (± 82) mg/dl SSI average increase in BG 128 (± 77) mg/dl No hypoglycemia in either group For SSI, two patients with insulin-dependent diabetes mellitus were in a hyperosmolar hyperglycemic state; one patient was diabetic keto acidosis

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BBI—basal-bolus insulin; BG—blood glucose; dex—dexamethasone; Met—metformin; Nl—novolog; NPH—neutral protamine hagedorn; R—regular; SDM—steroid diabetes mellitus; SSI—sliding scale insulin; TZD—thiazolidinedione

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						BG Monitoring and Results	Management Before and After	
Patients With and Patients Without Preexisting Diabetes								
Guo et al., 2011	To assess risk of hyperglycemia after neurosurgery To determine optimal care after neurosurgical procedure To assess the influence of hyperglycemia and other variables on rehabilitation and length of stay	Observational, retrospective, chart review	N = 290 Nondiabetes (n = 267; 142 men and 125 women) with a mean age of 48 years (SD = 16) • Glioma (n = 116) • Pituitary (n = 21) • Met (n = 84) • Other (n = 46) Diabetes (n = 23; 15 men and 8 women) with a mean age of 53 years (SD = 10) • Glioma (n = 6) • Pituitary (n = 6) • Met (n = 11)	Hydrocortisone Diabetes: 399 mg (± 284) Non-diabetes: 554 mg (± 256) Note: All dex doses were converted to hydrocortisone by multiplying by 20.	Random BG 200 mg/dl or greater on more than one occasion	BG routinely checked four times per day Postoperative diabetes: • More than 200 mg/dl x 1 = 8 • More than 200 mg/dl ≥ 2 = 8 Postoperative non-diabetes • More than 200 mg/dl x 1 = 15 • More than 200 mg/dl ≥ 2 = 2	SSI in hospital Patients with diabetes received significantly less steroid. • Biguanides (n = 3) • Sulfonylureas (n = 6) • Insulin (n = 13) • Combination (n = 2) • TZD (n = 3) • None (n = 6) For nondiabetes, five discharged on SSI; otherwise, no treatment	–
Vu et al., 2012	To determine whether intensive insulin regimen will improve outcomes compared to conventional treatment To examine the effect of exogenous insulin compared to met and/or TZDs on clinical outcomes	Experimental, prospective, randomized with two groups: control (conventional treatment) and intervention (intensive insulin)	N = 52 patients with acute lymphoblastic leukemia	Dex 40 mg orally every 4 days and methylprednisolone 50 mg every 12 hours for 3 days	BG greater than 180 mg/dl on two or more occasions	Control: regular monitoring not required Intervention: BG checked four times per day Median random baseline BG • Control = 118.5 • Intervention = 104 mg/dl	Control: Met or TZD (n = 5) Treatment at discretion of attending 13 of 25 received schedule insulin or insulin analogs Met or TZD (n = 8) Intervention: Met or TZD (n = 3) Glargine and aspart and dietary intervention Met or TZD (n = 5 Certified diabetes educator and nutritionist	No difference between groups in intensive care unit admissions, infections, or length of stay; mean BG levels significantly lower in the intervention group; intervention mean serum BG was less than 180 mg/dl.

BBI—basal-bolus insulin; BG—blood glucose; dex—dexamethasone; Met—metformin; Nl—novolog; NPH—neutral protamine hagedorn; R—regular; SDM—steroid diabetes mellitus; SSI—sliding scale insulin; TZD—thiazolidinedione

received steroids, those in the BBI group had lower blood glucose readings. Despite receiving insulin, patients in both arms of the study were reported to have blood glucose levels consistently greater than 180 mg/dl.

Findings on Management of Steroid-Induced Hyperglycemia for Patients With or Without Preexisting Diabetes

All patients in the intervention arm (n = 26) of Vu et al. (2012) were treated with BBI, whereas only 52% of those in the conventional treatment group (n = 25) received insulin. Twenty percent of patients in the conventional arm and 12% of those in the intervention arm had received oral agents (thiazolidinediones or metformin) before initiation of steroids. In Guo, Chandran, Palmer, and Bruera (2011), five patients (2%) without preexisting diabetes required treatment with insulin and, although the details about prior management in patients with a previous history of diabetes was not documented, they did note that 17 of the 23 patients (74%) were discharged with oral agents and/or insulin, and those who required insulin were discharged on a sliding scale schedule.

Effects of Management

Three of the 28 patients in the SSI arm of the Gosmanov et al. (2013) study were transferred to the intensive care unit for either DKA or HHS. In Vu et al. (2012), eight patients in the control group and nine from the intervention group were transferred to the intensive care unit, although no significant difference was found between the two arms. In addition, no difference in infections or hospital length of stay was noted between the two arms. Four of the studies (Gogas et al., 1996; Gosmanov et al., 2013; Pilkey et al., 2012; Vu et al., 2012) reported an improvement in glycemic control in patients receiving insulin therapy, with the most significant decrease in blood glucose levels seen in patients receiving BBI. Gogas et al. (1996) reported that no patients required hospitalization for diabetes-related complications, whereas Gosmanov et al. (2013) was the only one to report on the absence of hypoglycemia.

Discussion

The primary aim of this review was to determine how steroid-induced hyperglycemia is managed among hospitalized adult patients with cancer. In studies completed to date, reports of management strategies revealed no consensus. Lowering of steroid doses was documented as the method of management in two of the studies (Guo et al., 2011; Pilkey et al., 2012). However, although some improvement in glycemic control was noted, hyperglycemia persisted. One item of interest from the palliative care study was the proposed use of a guideline or algorithm for glucose monitoring among patients who did not have preexisting diabetes. Pilkey et al. (2012) developed a detailed guideline for monitoring steroid-induced diabetes and presented the benefits of continuing to follow their guidelines. The guideline suggested monitoring of capillary glucose on Mondays and Thursdays before supper, and if glucose was less than 180 mg/dl, monitoring should continue to be done twice weekly; if glucose was 180–360 mg/dl, monitoring should be done twice a day on Monday and Thursday; if glucose was higher than 360 mg/dl and the patient desires treatment, either begin or increase insulin doses and monitor twice a day for two days. Pilkey et al. (2012) suggested that this degree of monitoring is appropriate for the detection of steroid-induced diabetes. Likewise, Guo et al. (2011) suggested that patients without preexisting diabetes may not require glucose monitoring four times a day because of the low risk of developing long-term hyperglycemia.

Although both of these suggestions may have some merit, the idea of a glucose-monitoring algorithm may be the most palatable, in that it would allow for the detection of hyperglycemia that may otherwise go unnoticed if blood glucose monitoring were not performed in this population. In a study of 35 patients with no previous history of diabetes and newly diagnosed acute lymphoblastic leukemia receiving high-dose steroids for two to three months, Gonzalez-Gonzalez et al. (2013) reported that, 50% of the time, steroid diabetes occurred between the second and fourth week. Therefore, continuing blood glucose monitoring may be advisable before meals and at bedtime in patients who exhibit hyperglycemia and definitely among those who require antidiabetic medications.

Another point of interest for all of the studies was the definition of hyperglycemia as blood glucose greater than 180 mg/dl when, according to Moghissi et al. (2009), Smiley and Umpierrez (2010), and Umpierrez et al. (2012), *inpatient hyperglycemia* is defined as any blood glucose greater than 140 mg/dl associated with poor outcomes such as increased length of stay and infections. These discrepancies suggest that

Knowledge Translation

Steroid-induced hyperglycemia occurs in hospitalized patients with cancer regardless of history of diabetes.

Blood glucose monitoring should be performed in patients receiving high-dose glucocorticoids.

Prospective studies are needed to determine how to best manage steroid-induced hyperglycemia in hospitalized patients with cancer.

hyperglycemia may be undertreated in hospitalized patients. Information currently available in the literature suggests that oral agents do not adequately control hyperglycemia in hospitalized patients and that sliding scale regimens have resulted in hypoglycemia (Inzucchi, 2006; Patel et al., 2009). However, studies by Vu et al. (2012), Gosmanov et al. (2013), and Guo et al. (2011) described the use of SSI with only Gosmanov et al. (2013) documenting the absence of hypoglycemia. Clore and Thurby-Hay (2009) suggested that the best way to manage steroid-induced hyperglycemia is with a combination of anticipation of its occurrence and the use of insulin to prevent it. An example of this management strategy is seen in the intervention arm of the Vu et al. (2012) and the BBI arm of Gosmanov et al. (2013). These treatment regimens resulted in significantly lower blood glucose readings. However, in Gosmanov et al. (2013), the BBI regimen was administered by an endocrinologist, and one of the authors of the Vu et al. (2012) study was an endocrinologist. This may suggest that their expertise in diabetes management led to improved glycemic control. Also, four of the studies described the use of oral agents before and after the administration of steroids. However, the effectiveness of the oral agents from these studies was difficult to determine because blood glucose readings were reported as aggregate numbers. In addition, Vu et al. (2012) reported the added benefit of increased progression-free survival with the use of metformin and thiazolidinediones.

Studies of hospitalized patients without a history of cancer have shown rates of steroid-induced diabetes to be 52%–64% (Donihi et al., 2006; Iwamoto et al., 2004) among patients without a history of diabetes receiving steroids for two or more days to more than two weeks. However, in the study by Pilkey et al. (2012), which was designed to determine the prevalence of steroid-induced diabetes in patients receiving palliative care, the rate was 11%, despite the fact that 62% of study participants had been taking steroids before admission.

Strengths and Limitations

This article summarizes the evidence available on the management of steroid-induced hyperglycemia in hospitalized adult patients with cancer. Although the primary outcomes of the studies were not stated as the management of steroid-induced hyperglycemia, some components of management were described in each of those included. Doses of medications used to treat hyperglycemia were included in only one of the studies (Gosmanov et al., 2013). However, for those studies that included patients with a prior history of diabetes, no discussion occurred regarding the duration of disease, current management, glycemic control (i.e., A1C), or comorbidities. The timing and frequency of blood glucose monitoring varied widely between studies. The lack of consistency in timing of glucose monitoring, lack of detail about the doses of antidiabetic medications administered, and scantiness of details of the results of blood glucose monitoring make it difficult to assess the effect of management on glycemic control in a meaningful fashion. The primary deficit that this article exposes is the limitations in the research on the management of steroid-induced hyperglycemia in hospitalized adult patients with cancer. It also suggests that steroid-induced hyperglycemia occurs in patients with or without a history of diabetes. No consensus exists about how to manage this phenomenon.

Implications for Clinical Practice and Future Research

Increased awareness of steroid-induced hyperglycemia in hospitalized adult patients with cancer may lead to earlier interventions, which may have a positive effect on outcomes. The knowledge that hyperglycemia leads to increased hospital length of stay, delayed wound healing, increased infections, and higher mortality rates should encourage healthcare providers to monitor for its occurrence and to manage it appropriately. Nurses at the bedside know which patients are receiving steroids, and they are the first to notice patients who are experiencing adverse effects such as polyuria, polydipsia, polyphagia, or blurred vision. They also can review routine laboratory results and assess for hyperglycemia in patients receiving steroids. As members of the healthcare team, they are in a position to advocate for patients on high-dose steroids to have routine blood glucose monitoring performed and, if hyperglycemia is observed, encourage the healthcare provider to begin appropriate management.

Studies to answer the questions surrounding steroid-induced hyperglycemia, such as who is at risk for steroid-induced hyperglycemia, how often does it occur in patients undergoing cancer treatment with high-dose steroids, the time to glucose increase, the degree of glucose increase, the duration of glucose elevation, and whether glucose profiles differ among patients with and without a history of diabetes, need to be conducted. Also needed are studies of steroid-induced hyperglycemia managed with oral agents compared with treatment with insulin to determine the role of these agents in glucose management and their effect on overall outcome.

Conclusions

This review suggests that as many as 11% of patients without a prior history of diabetes experience hyperglycemia, requiring insulin therapy while receiving

glucocorticoids (Guo et al., 2011; Pilkey et al., 2012). The use of oral insulin sensitizers may provide additional long-term survival benefit and improve glycemic control. Steroids cause hyperglycemia in patients with or without preexisting diabetes, but how to manage this hyperglycemia and the effects of management still need to be determined.

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