How to Manage Steroid Diabetes in the Patient With Cancer

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Glucocorticosteroids (steroids) have profound effects on glucose metabolism, particularly on postprandial hyperglycemia. Patients with cancer often receive steroids as a component of their chemotherapy, as a measure to treat or prevent nausea, or as adjuvant therapy following neurosurgical procedures. The oncology caregiver may not notice steroid-induced hyperglycemia, either because it is not considered or because steroids affect post-meal glucose much more so than morning fasting sugars. A recent study suggests that even a few days of hyperglycemia have deleterious effects on the immune system.[1] The current trend for maintaining near-euglycemia in hospitalized patients is the use of intensive insulin therapy in hyperglycemic patients with or without diabetes. This article will discuss steroid effects on glucose metabolism, recommend levels at which therapy should be considered, and discuss the options available for treating hyperglycemia caused by steroids. At this time, there are no official guidelines for the cancer patient with steroid diabetes, but the guidelines for diabetes care in general will be reviewed.

Pathophysiology

Steroids induce a state of relative insulin resistance. Steroid effects on glucose metabolism include down-regulation of glucose transporter 4 (GLUT-4) in the muscle so that more insulin is needed for the uptake of glucose into cells. Steroids may also promote glucose production in the liver, reduce binding of insulin to the insulin receptor on cells, and decrease insulin secretion from the islet cell. In patients known to have diabetes, steroids will worsen the hyperglycemia, whereas non-diabetic patients, depending on the state of their islet cell reserve, may experience hyperglycemia or even overt diabetes. In rare instances, hyperglycemic nonketotic hyperosmolar coma may even ensue. Increased steroid levels are not the only factor promoting diabetes in cancer patients; infection, inactivity, emotional stress, intravenous glucose, and high carbohydrate diets also increase the tendency toward hyperglycemia.

Multiple reviews have emphasized the importance of intensive insulin therapy in hospitalized patients,[2–5] and several studies reinforce the importance of tight glucose control in this patient population. Furnary et al[1,6,7] showed that aggressive control of postoperative blood glucose levels in diabetic patients who had undergone a coronary artery bypass graft reduced sternal wound infections and also improved morbidity and mortality. The Diabetes Mellitus, Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study[8] showed that, compared with conventional therapy, 48 hours of tight glucose control in patients with acute myocardial infarction reduced mortality.

The Van den Berghe study[9] may be relevant to steroid-induced hyperglycemic patients, since the study population consisted largely of patients in the intensive care unit (ICU) not known to be diabetic who developed hyperglycemia in the hospital. This response may have been related to the infused glucose and the stress-induced endogenous steroid production. Patients who had a glucose reading above 110 mg/dL were randomized to receive intensive insulin therapy or conventional therapy. Patients in the intensive insulin group received insulin infusions set to reduce their glucose level to 80–110 mg/dL, whereas those in the conventional therapy group received insulin treatment only if the glucose level went above 215 mg/dL and maintenance of glucose at a level between 180 and 200 mg/dL. The final glucose averages of the intensive and conventional groups were 103 mg/dL and 153 mg/dL, respectively. The benefits of tight glucose control in the intensive insulin group included a reduction in overall mortality, particularly in patients who remained in the ICU > 5 days, and a reduced risk of sepsis, transfusions, renal failure, and ICU

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Table 1

Preparations of Glucocorticosteroids

PREPARATION	GLUCOCORTICOID POTENCY	MINERALOCORTICOID EFFECT	HALF-LIFE
Cortisone	1.0	++	4–6 h
Prednisone	4.0	+	6–12 h
Methylprednisolone	4.8	+/–	6–12 h
Dexamethasone	20.0	0	1–2 d

neuropathy.

In a more recent study, Van den Berghe et al[10] achieved reduced morbidity, but not reduced mortality, using an intensive insulin therapy protocol in a medical ICU (MICU). Mortality was reduced only in those in the MICU for longer than 3 days. Hyperglycemic patients not known to be diabetic suffered greater morbidity from hyperglycemia than known diabetics with the same degree of hyperglycemia. A 2005 study[11] showed less morbidity postoperatively if the glucose was controlled during surgery to a level < 140 mg/dL by insulin infusions compared with a control group that averaged 180 mg/dL during surgery. In all of these studies, insulin was used for glycemic control, so it is unknown if the benefits result from the lower glucose or possibly from direct effects of the insulin itself.[12,13] In vitro studies have shown that insulin can reduce many of the factors elicited in stress and infection, such as nuclear-factor kappa B,[14] and these factors may be as important in the cancer patient as they are in the ICU patient, which is one reason to prefer insulin therapy over oral therapy. The aforementioned studies were all performed on inpatients, so we can only assume that outpatients might benefit as well. There is no proof that the benefits of intensive glucose control will extrapolate to hyperglycemic cancer patients on steroids, and prospective studies targeting this group are needed.

Preparations of Glucocorticosteroids

Steroid diabetes is related to the dose of steroids used but not the type. Insulin resistance causes primarily postprandial hyperglycemia. This causal relationship is particularly evident with morning doses of prednisone and could be partially related to the steroid effect wearing off overnight, but the improvement in glucose overnight is also seen with the longer-acting dexamethasone. A typical patient will have elevated glucose values after breakfast, lunch, dinner, and at bedtime but will have a significant drop toward normal glucose overnight. Therefore, hyperglycemia is greatest 1–2 hours after a meal, with persistent elevation until the following meal, followed by a return to normal between 4:00 am and 7:00 am. Table 1 shows different preparations of glucocorticosteroids; it is not clear that the hyperglycemic effects will differ despite the different half-lives.

Monitoring Glucose

Ideally, all cancer patients who receive steroids should be monitored with both pre-meal glucose and 2-hour post-meal glucose levels; the most sensitive time to test for hyperglycemia is 2 hours after lunch. The normal range for fasting glucose is below 100 mg/dL, and the normal level for the 2-hour postprandial reading is below 140 mg/dL. Diabetic levels are 127 mg/dL or more for fasting glucose and 200 mg/dL or more for the 2-hour postprandial level. Glucose values between 100 and 126 mg/dL represent impaired fasting glucose, and postprandial glucose levels of 141–199 mg/dL represent impaired glucose tolerance. There is no way to predict whether glucose values will return to normal after cessation of steroids, since steroids may have unmasked a pre-existing tendency toward diabetes. Current glucose monitors for home use are accurate to within ± 10%, and there are few drugs that interfere with the current monitoring strips. Severe anemia may cause false meter readings. A1C testing is not indicated to monitor short-term hyperglycemia, since it represents a 90-day summation of all the glucose variations but should be done at least once whenever hyperglycemia is noted. A high A1C would indicate undetected previous diabetes. It should be noted that the A1C test is only valid if the life of the red cell is normal; in transfused or anemic patients, false low A1C readings may be seen.

When to Treat

For outpatients with only a few days of mild steroid hyperglycemia, therapy may not be needed. Treatment would require patients to learn to test their glucose, take pills, or give insulin, all with no proven benefit. In the hospital, however, this type of management is possible and should be considered for even brief episodes of hyperglycemia. If the patient has only a few days of steroid therapy, and hyperglycemia is not causing symptoms, no therapy is indicated. However, patients in the hospital for 3 days or more with a fasting glucose level over 110 mg/dL or a postprandial glucose level over 140 mg/dL would be candidates for therapy.

Options for Therapy

The first steps in the management of steroid diabetes are diet and exercise. The appropriate diet is low in carbohydrates to minimize postprandial hyperglycemia, but if the cancer patient has anorexia or cachexia, limiting the choices of food is not desirable. In these cases, nutritional consultation is recommended. Avoidance of other medications that may promote hyperglycemia, such as hydrochlorothiazide (> 12.5 mg/d), niacin, and some selective serotonin reuptake inhibitors, might be helpful.

ORAL AGENTS

The role of oral agents in the oncology patient with steroid diabetes is limited because of potential side effects, slow onset of action, and lack of flexibility. Oral secretagogues (Table 2) may be useful in mild cases, although 24-hour secretagogues (sulfonylureas) do not selectively target postprandial hyperglycemia and may increase the risk of hypoglycemia in the morning or if the patient misses a meal. There are two short-acting secretagogues that have unique features. The shortest-acting

Table 2

Uses of Oral Secretagogues

In cases of mild hyperglycemia
During short-term steroid use
For outpatients
For patients unable or unwilling to give injections
To bridge therapy until diabetic education is complete

agent is nateglinide (Starlix), which can be given immediately before meals to control postprandial glucose and has a half-life of about 4–6 hours. The effect of nateglinide typically wears off overnight, an advantage in a patient prone to low glucose levels in the morning. If the patient does not eat, he or she just skips the pill. If the patient takes the pill and then is unable to eat, the risk of hypoglycemia is low. Repaglinide (Prandin) is another pre-meal insulin secretagogue that can be given with meals, but it has a longer half-life than nateglinide and may lead to hypoglycemia in the morning if given with dinner. Both of these secretagogues should be taken before eating, since their effect is blunted if taken during or after a meal.

The other oral antidiabetic agents are even less useful. Metformin has multiple problems in the patient with cancer, with side effects including nausea, diarrhea, or vomiting. It needs to be started at a low dose and increased gradually, and it does not target post-meal glucose. Metformin is contraindicated in renal failure and must be stopped for any iodinated contrast dye studies; it may be resumed 48 hours later, once the creatinine level is documented as normal. Metformin is not indicated in patients with liver disease. The greatest fear with metformin is lactic acidosis, and thus it is not recommended in patients with any medical condition predisposing them to sepsis, dehydration, or hypoxemia.

The thiazolidinediones have appeal because they directly treat the insulin resistance caused by steroids and seldom cause hypoglycemia, but their use is not often practical. They have a long onset of action (1–2 weeks) and prolonged effect after discontinuation (also 1–2 weeks), which does not allow for short-term titration or adjustment. These agents also promote weight gain, fluid retention, and edema, although overt heart failure rarely occurs. The resulting fluid retention may cause a drop in the hemoglobin level of up to 1–2 g/dL. If the patient does not have issues with fluid retention, and the duration of steroid use is prolonged and constant, the thiazolidinediones might play a useful supporting role. The dose would be titrated primarily against the pre-meal morning glucose result.

The incretin mimetics are a new class of drugs for treating type-2 diabetes. Only the glucagon-like peptide 1 mimetic exenatide (Byetta) is currently on the market, but other compounds are likely to follow. Incretin mimetics target postprandial hyperglycemia but have not been studied in steroid diabetes. Worrisome side effects are their tendency to cause nausea and vomiting in about 50% of patients and to decrease appetite with resultant weight loss.

Table 3

Common Insulins

HUMAN INSULIN AND INSULIN ANALOGUES	ONSET	PEAK	DURATION
Basal insulins			
NPH	1–3 h	4–10 h	10–18 h
Glargine	2–4 h	4–12 h	18–24 h
Detemir	2–4 h	4–12 h	12–24 h
Human short-acting insulin			
Regular	30–60 m	2–4 h	4–8 h
Rapid-acting analog insulins			
Lispro	10–15 m	1–2 h	3–6 h
Aspart	10–15 m	1–2 h	3–6 h
Glulisine	10–15 m	1–2 h	3–6 h

Abbreviation: NPH = neutral protamine Hagedorn

Insulin Therapy

For most patients, insulin will be a more appropriate therapy than oral agents. Available insulins are listed in Table 3.

For patients in the ICU or MICU who are not eating, the current standard of care is an infusion of rapid-acting insulin targeting a glucose level of 80–115 mg/dL. Various insulin protocols exist, and examples have been published on the web sites for the American Association of Clinical Endocrinologists[15] and the American Diabetes Association[16] and in the reviews by Clement[3] and Furnary.[1] Although insulin infusions increase the work of nurses, the benefits justify this extra effort. Other long-term trials are in progress to evaluate the advantages of intensive insulin therapy.[17]

Subcutaneous insulin replacement therapy is used for patients who are eating. There are three components to insulin therapy: basal insulin, prandial insulin, and supplemental insulin. Basal insulin is most often a long-acting insulin used to suppress glucose production by the liver; it controls the glucose during fasting and overnight. Prandial insulin is needed to prevent a glucose rise after ingestion of food. Supplemental insulin is used to lower the glucose level when it is high, either with a meal or at other times.

BASAL INSULIN

Three basal insulins are available: neutral protamine Hagedorn (NPH), glargine (Lantus), and detemir (Levemir). In the steroid-induced diabetic, basal insulins should be administered in the morning rather than bedtime. Insulin requirements will be higher during the day and the lowest in the early morning, so the slight peak that the basal insulins have at 4–10 hours post administration should occur during the day and not at night. NPH has a greater tendency to peak than the two analog basal insulins and a shorter duration of action, both of which might be an advantage in steroid diabetes. The newer analog insulins, however, have a flatter and more consistent time course, which is more likely to last 24 hours. A common starting dose of basal insulin is

Table 4

Ten Key Facts About Steroid Diabetes

1.	Primary effect is on postprandial glucose level.
2.	Glucose values tend to normalize overnight.
3.	Glucose levels should be tested before as well as 2 hours after a meal.
4.	Oral agents are usually inappropriate, ineffective, or too inflexible.
5.	Insulin is generally the best therapy.
6.	Prandial insulin is the primary need.
7.	Prandial insulin should be titrated to the glucose 2 hours post prandially (or the next meal).
8.	Basal insulin should be given in the morning and titrated to the glucose level from the following morning.
9.	Target glucose levels are < 115 mg/dL pre-meal and < 140–180 mg/dL 2 hours postprandially.
10.	Steroid diabetes is difficult to control: consults with endocrinologists, certified diabetes educators, and nutritionists are appropriate.

10 U or 0.2 U/kg, whichever is higher. The dose is then adjusted based on the morning glucose result.

PRANDIAL INSULIN

Prandial insulin can be regular or analog insulin. The advantage of the new analog insulins is a more rapid onset of action, a quicker peak, and shorter duration of action. This profile allows them to be given right before a meal, whereas regular insulin ideally should be given 30–45 minutes before a meal. Analog insulin may also be given immediately after a meal, an advantage in nauseated patients unsure of how much they will consume. One disadvantage of the analog insulin for prandial coverage is the shorter duration of action compared with regular insulin, which may allow the glucose level to rise before the next meal or stay high until bedtime. High bedtime readings need to be treated cautiously, if at all, since that is the time of day when glucose starts to decrease naturally. When possible, prandial insulin doses should be evaluated 2 hours after a meal. Doses of short-acting insulin repeated in less than 4 hours need to be reduced to account for the residual effect of the previous dose (about 25% an hour) to avoid hypoglycemia from the overlapping duration of action.

To establish a starting prandial dose, we utilize low-dose, medium-dose, and high-dose protocols based on previous results or intuition. Common starting doses are 5, 10, or 15 U three times daily, with further adjustments as needed. There may be some advantage to teaching patients carbohydrate counting, allowing them to adjust the prandial insulin based on the amount of carbohydrates in a meal. A common starting ratio is 1 U for every 10 g of carbohydrate. Consultation with a dietician or certified diabetes educator will be necessary if carbohydrate counting is required.

SUPPLEMENTAL INSULIN

The third component of insulin therapy is supplemental insulin, a dose of short-acting insulin used to correct a high glucose level. This dose can be given either alone or added to the prandial dose. The insulin sensitivity factor, or correction factor, is often about 40, indicating that 1 U of insulin lowers the glucose level by 40 mg/dL. We have a supplemental insulin scale based on low, medium, and high sensitivity, which correlates with correction factors of 30, 40, and 50 mg/dL per U of insulin. A target glucose level is usually set at 100–120 mg/dL. To calculate the supplemental insulin dose, we use this formula: (current glucose level – target glucose level) / correction factor = units of supplemental insulin required.

TIMING OF THERAPY

Prandial insulin should be started first whenever postprandial hyperglycemia is detected. A standard dose (such as 5 U) can be given and adjusted based on the results, aiming for a postprandial glucose level below 140–180 mg/dL. Some patients may benefit from the more difficult regimen of adjusting the dose based on the carbohydrate content of meals and prevailing glucose levels. A basal insulin given in the morning can help keep glucose levels down during the day but is seldom enough alone to control postprandial hyperglycemia, even with the shorter-acting NPH. The longer-acting basal insulins are used primarily to keep the glucose level down overnight or when the patient is not eating. Inhaled insulin might prove to be useful in patients who need prandial control but cannot be used in anyone with pulmonary disease. For those receiving inhaled insulin, baseline forced expiratory volume in the first second has to be measured and monitored every 3 months. Garg et al[18] provide a good review of insulin therapy. Insulin therapy is complicated and the results are often unsatisfactory; one should never hesitate to ask for help from an endocrinologist.

MONITORING RESULTS

An insulin therapy worksheet and flow sheet are helpful when treating diabetics because the response to previous therapy guides future changes (see an example online at http://www.supportiveoncology.net/journal/0409.html; worksheet adapted courtesy of Marcia Draheim, RN, CDE, of Draheim Dimensional Presentations; flowsheet courtesy of David S. Oyer, MD). If the steroids are stopped, the carbohydrate intolerance may disappear quickly, and when steroids are tapered, the insulin requirements usually recede proportionally to the reduction. Any unexplained hypoglycemia should lead to an automatic reduction in the insulin dose (about 20%). Insulin doses can be lowered in anticipation of reduced steroid doses. When planning repeated cycles of the same steroid doses, historic results can guide therapy. In patients who receive dexamethasone as a one-time dose for prevention of nausea, hyperglycemia may last 2–3 days, and insulin may have to be adjusted with every meal to meet the changing requirements as the dexamethasone wears off. The patient should be aware of the symptoms of hypoglycemia and should have snacks at the bedside in case of a low glucose level. For patients with long-term steroid diabetes, education by a certi-

fied diabetes educator should begin as soon as possible, and difficult cases should be referred to an endocrinologist.

Conclusion

Table 4 lists some of the primary concerns when dealing with steroid diabetes that complicates the therapy of a cancer patient. A goal of pre-meal readings of ≤ 110 mg/dL and 2-hour postprandial readings of ≤ 140–180 mg/dL is ideal but difficult to achieve in steroid diabetes. Since proof of the benefits of tight control in steroid diabetes does not exist, safety and avoidance of hypoglycemia remain equally important goals. The system of basal bolus insulin therapy is the most flexible option but is complicated to use. For many, a basal insulin in the morning and then a standard dose of short-acting insulin before meals will offer the best result. Further studies are needed to develop future protocols for the treatment of steroid diabetes. In today's clinical setting, it is prudent to devote as much attention to glycemic control in the oncology patient as would be appropriate for patients in the ICU.

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