

# Department of Endocrine Neoplasia and Hormonal Disorders NEWSLETTER

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ENDO PERSPECTIVES<sup>®</sup>

## The Challenge of Hyperglycemia In Inpatients with Cancer

THE UNIVERSITY OF TEXAS  
MD ANDERSON  
CANCER CENTER



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Since 2002, multiple observational studies have shown that hyperglycemic hospital patients experience poor short term outcomes, including infection, prolonged stay, incomplete recovery and death in hospital. These observations have been made on cardiovascular and other surgical units, coronary care units, surgical and medical intensive care units (ICUs), and the non-ICU floors of general hospitals.<sup>1-3</sup> To determine if these associations held for patients in a cancer hospital, investigators from the Department of Endocrine Neoplasia and Hormonal Disorders analyzed 5489 consecutive admissions to M.D. Anderson over a 3-month interval in 2006. This team, led by Dr. Pankaj Shah who is now at the Mayo Clinic, showed that sustained significant hyperglycemia (SSH, defined as serum or capillary glucose  $\geq 200$  mg/dL on two different days) was associated with twofold greater length of hospital stay, more frequent discharge to extended-care facilities, greater incidences of infection and worsening renal function, and fivefold greater inpatient mortality when compared with non-hyperglycemia (unpublished data). Further analysis of Dr. Shah's data showed that, among hyperglycemic patients, those with no prior diagnostic coding for diabetes ("new" hyperglycemia) exhibited 42% greater rate of hospital infection, 93% greater rate of doubling of serum creatinine, 77% longer hospital stay and more than double the inpatient mortality, compared with those with known diabetes (unpublished data). These associations were especially striking, given that the patients with diabetes were older and had higher mean blood glucose than those with "new" hyperglycemia. Studies from other hospitals have also shown particularly adverse outcomes associated with "new" hyperglycemia.<sup>2,3</sup> In an attempt to understand this phenomenon, we have tried to characterize the patients with "new" hyperglycemia at MDACC. It turns out that these patients were 48% more likely to have been receiving high-dose glucocorticoids, and 3.5-fold

more likely to have been on parenteral nutrition, than the hyperglycemic patients with known diabetes. Strikingly, patients with "new" hyperglycemia were treated with scheduled therapy for hyperglycemia during only 20% of the admissions.<sup>4</sup> Indeed, when we looked at all admissions with SSH, scheduled therapy was associated with shorter hospital stay, less risk of infection and deterioration of renal function, and 58% less relative risk of inpatient mortality (unpublished data).

These observations raise an obvious question: would aggressive control of blood glucose, particularly for people with "new" hyperglycemia, improve short-term outcomes in the hospital? Certainly there is precedent for this idea. Randomized controlled trials have demonstrated that intensive management of hyperglycemia reduces the development of diabetic complications such as retinopathy and nephropathy over a span of years.<sup>5-8</sup> Data regarding short-term consequences of glycemic control are much more limited. Randomized controlled trials have shown clinical benefits of tight glycemic control for patients in a surgical ICU, and to some degree also for patients in a medical ICU.<sup>9,10</sup> Non-randomized studies using historical controls have favored tight glycemic control in postoperative cardiovascular surgical units.<sup>11,12</sup> For hospital patients outside the ICU, there are no data bearing on the question of whether aggressive glycemic management is beneficial in the short term. (Continued on Page 2)

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From the above, one may infer that inpatient hyperglycemia is an important clinical problem, but its causal relation to poor outcomes has not been determined.

Nonetheless, various expert committees have promulgated recommendations for hospital non ICU glycemic management.<sup>13</sup>

1. Blood glucose should be  $\leq 110$  mg/dL in the fasting state and  $\leq 180$  mg/dL postprandially;

2. Patients should be treated with "basal-bolus" insulin regimens that include basal insulin once or twice daily, and scheduled prandial insulin in addition to correctional doses.

Unfortunately there is essentially no support beyond expert opinion for either of these recommendations. Generation of such support is hampered by at least two problems, which will be discussed further below: (1) the lack of validated strategies for treatment of hyperglycemia and (2) the large sample sizes needed to demonstrate even moderate clinical benefits. Given the poor outcomes of hyperglycemic patients, there is a clear need for more work in this area.

#### Issues in the field

The only safe and useful medicine for acute treatment of inpatient hyperglycemia is insulin. Other medicines may be very helpful for long-term diabetes management, but for various reasons they are not suitable for use in the hospital:

- Metformin is probably the first choice drug for treatment of type 2 diabetes, but it is contraindicated in patients with significant renal insufficiency, a problem that may arise unexpectedly in the hospital. Also, metformin should be discontinued in patients who will undergo imaging procedures with intravenous radiocontrast, which includes just about everyone in MDACC. Finally, the most common side effect of the drug is gastrointestinal distress, particularly problematic for patients who are already struggling with side effects of chemotherapy.

- Sulfonylureas carry the risk of prolonged severe hypoglycemia if renal function deteriorates or if the patient does not eat regularly. Accordingly these drugs are not suitable for use in a cancer hospital.

- Thiazolidinediones (TZDs) may be very effective for people with insulin resistance, but they require 1 to 3 months to act, so they are not helpful for controlling acute hyperglycemia. However, if a patient is being chronically treated successfully with a TZD and can eat or has enteral access, the TZD may be continued.

- Sitagliptin is not a very powerful agent, and doesn't act rapidly enough to be useful for inpatients.

Insulin is the only medicine that acts rapidly enough to control spikes of hyperglycemia after meals or tube feeding, and the only one power-

ful enough to control the massive hyperglycemia often seen with high dose glucocorticoids. Also, insulin can be given parenterally. Clearly insulin is very much the gold standard treatment for hyperglycemia in the hospital.

Published algorithms for administration of insulin by intravenous infusion provide excellent control of glucose level with minimal risk of hypoglycemia.<sup>14</sup> However, safe and effective management of an insulin drip requires hourly determination of capillary glucose and careful attention to the protocol. As a result, insulin drips are quite demanding of nursing time and effort. At MDACC as in many other hospitals, insulin drips are feasible only in the ICU. Outside the ICU, insulin must be given subcutaneously. Despite the facts that subcutaneous insulin was introduced into medical practice about 86 years ago, and that there are now insulin analogs that reasonably simulate physiological insulin secretion after subcutaneous administration, there has been no experimental validation of the best strategy for subcutaneous administration of insulin in the hospital.

For many years the standard strategy for subcutaneous insulin was periodic administration of short-acting insulin in proportion to the degree of hyperglycemia ("sliding scale"). Intense and often emotional criticism by endocrinologists has pointed out several important shortcomings of the "sliding scale" strategy:

- It does not provide basal insulin, despite the fact that about 50% of physiological insulin secretion is basal;

- It does not provide scheduled insulin to cover meals or tube feedings, despite the fact that some patients, especially those on glucocorticoids, exhibit large postprandial glycaemic spikes;

- It does not account for physiological variations of insulin sensitivity during the day, thereby increasing the risk of nocturnal hypoglycemia;

- It provides insulin only when the blood glucose is above target, thus failing to correct persistent hyperglycemia – the equivalent of prn analgesics for a patient with pain due to metastatic cancer.

In view of the above-mentioned deficiencies of "sliding scale" insulin, endocrinologists today usually recommend a "basal-bolus" strategy<sup>13</sup>. This strategy attempts to mimic the sophisticated multiple-dose insulin or insulin pump regimens that have been demonstrated to prevent long-term complications in patients with type 1 diabetes. In the hospital setting, the "basal-bolus" strategy entails

- Intermediate- or long-acting insulin given once or twice daily, by the clock, in a dose estimated to meet the patient's basal needs, independent of nutrition;

- Nutritional insulin - Short- or rapid-acting insulin given in conjunction with meals, or a combination of short- and intermediate-acting insulin given to cover tube feedings; and

(Continued: Lavis, Page 3)

## Upcoming Events

ATA 79th Annual Meeting, Oct 1-5, 2008. Chicago, Ill. [http://www.thyroid.org/ann\\_mtg/2007\\_78th/index.html](http://www.thyroid.org/ann_mtg/2007_78th/index.html)

11th European Congress of Endocrinology, April 25-29, 2009. Istanbul, Turkey <http://www.ece2009.com/>

AACE 18th Annual Meeting and Clinical Congress, May 13-17, 2009 [www.aace.com](http://www.aace.com)

The Endocrine Society ENDO 2009, June 10-13, 2009. Washington, DC. ([www.endo-society.org](http://www.endo-society.org))

World Congress on Thyroid Cancer, August 6-10, 2009. Toronto, Canada. <http://www.thyroid2009.ca/>

North American Neuro-Endocrine Tumor Society Annual Conference, Oct 2-3, 2009. Marriott Hotel, Charlotte, NC. (Additional information to be announced later)

Third Annual Thyroid Neoplasms Conference, Oct. 21-24, 2009 El Dorado Hotel, Sante Fe, NM (Additional information to be announced later)



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- Correction doses for hyperglycemia, given as supplements to the nutritional insulin.

However, implementation of this strategy in the hospital can be difficult. Compared to “sliding scale” insulin, a basal-bolus regimen is more complex, more expensive (4 or 5 injections daily) and requires greater coordination among clinicians, nurses, and nutrition and ancillary services. Also, it is logistically demanding, particularly with regard to coordination of the nutritional insulin with meals. Moreover, the basal-bolus strategy requires fairly extensive in-service education of floor nurses.

Treatment with basal-bolus insulin is especially challenging at M.D. Anderson for several reasons:

- For patients who are eating, matching insulin to food intake is problematic because meal times are not scheduled. Meals are often postponed because procedures are done at night and on the weekends. Also, some chemotherapeutic agents may suppress appetite or cause stomatitis or esophagitis that markedly restricts choice of foods. Conversely, glucocorticoids can promote ravenous and uncontrollable hunger.

- Some of the chemotherapeutic schedules include abrupt changes in dosage of drugs that affect glucose metabolism. For example, lymphoid leukemia is commonly treated with dexamethasone, 40 mg daily, for 4 day cycles that are repeated every 10 days. This huge dose of a potent glucocorticoid can increase insulin requirements threefold or more within a few hours after administration.

- After many surgical procedures, patients require prolonged supplemental nutrition with tube feeding or total parenteral nutrition. Tube feeding schedules commonly are changed every few days to permit resumption of oral intake as well as because of problems such as abdominal distention and diarrhea. Additionally, tube feedings are often stopped and resumed unpredictably in order to accommodate imaging and other procedures.

- At MDACC, where diabetes management is adjunctive rather than the main event, most nurses don’t have a “feel” for this rather sophisticated strategy.

Two recent randomized controlled trials have directly compared glycemic management strategies on the medical floors of general hospitals. One showed better attainment of a glycemic target (<140 mg/dl) with a basal-bolus insulin regimen than with correction-only “sliding scale” insulin.<sup>15</sup> The other, presented so far only in abstract form,<sup>16</sup> showed twice-daily NPH and Regular insulin to be equivalent to a “basal-bolus” strategy with respect to attainment of glycemic targets, but did not examine “sliding scale”. While both of these studies were well done, neither may be applicable to patients at our institution, because they excluded patients with “new” hyperglycemia and those on glucocorticoid therapy – precisely the groups with the worst outcomes at MDACC.

#### What needs to be done?

In light of the above considerations, there’s a pressing need to validate the optimal inpatient glycemic management regimen, with respect to:

1. Attainment of glycemic targets.
2. Patient safety – i.e. avoidance of hypoglycemia, and
3. Improvement of clinical outcomes.

In order to obtain adequate statistical power, a randomized trial will need from 300 to 5000 subjects in each treatment arm in order to discern an impact of glycemic control on clinical outcomes such as length of stay, infection rate and mortality. These numbers suggest that adequate testing of the effect of glycemic control on key clinical outcomes likely will require a multi-center trial. Because of the effort and expense involved in such a trial, it will be important first to validate a management strategy with respect to attainment of targets and avoidance of hypoglycemia.

Therefore the first step should be a feasibility trial of basal-bolus vs. “sliding scale” insulin, with attainment of glycemic target as the measured variable. Patients with “new” hyperglycemia and those on glucocorticoids should be included and their results analyzed as pre-specified subgroups. Based on Dr. Shah’s 2006 study, we estimate that enrollment of about 60 subjects per arm would yield 90% power of detecting a change of 18 mg/dl in mean glucose level at a one-tailed significance level of 0.05. Given the prevalence of hyperglycemia at MDACC, we estimate that it would take about 1 year to complete enrollment in such a trial.

#### What we are doing now

Hyperglycemia is a pervasive problem at MDACC. A recent one-week snapshot by the Department of Clinical Effectiveness showed that 27% of inpatients had at least one glucose level  $\geq 180$  mg/dL during their admissions. In order best to serve a large number of hyperglycemic patients, we are working with our colleagues in General Internal Medicine to develop arrangements for coordination of diabetes care. This process includes working out programs for treatment of inpatient hyperglycemia as well as making recommendations for longer-term diabetes management, including treatment of hypertension and lipid disorders.

Several years of research will likely be required before we will know (a) which management strategies will lead to optimum attainment of glycemic targets with minimum risk of hypoglycemia, and (b) which patients will benefit clinically from intensive basal-bolus regimens as opposed to simpler corrections-only schemes. Meanwhile, our inpatient diabetes consultation service strives to help medical and surgical oncologists by taking care of troublesome hyperglycemia so they can concentrate on dealing with cancer. We also provide valuable follow-up care. This is particularly important for patients recently discovered to have diabetes, many of whom visit Houston for extended periods and do not have access to their primary care physicians. Our diabetes team works closely with Judy Bounds, RN, MSN, CNS, CDE, the M.D. Anderson diabetes educator, who ensures that patients have the skills necessary for self-management of hyperglycemia.

Expert opinion has been presented,<sup>17</sup> but there is no body of evidence pertaining to treatment of inpatient hyperglycemia in people undergoing treatment for cancer. Therefore we are reviewing our experience, and have begun sharing that knowledge.

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In this issue of the newsletter, two of our Advanced Practice Nurses, Veronica Brady, MSN, NPCF, RN, and Kathleen Crawford, MSN, ANP C, review their experiences with the challenges presented by patients receiving changing doses of glucocorticoids and those on tube feedings, respectively. They have presented some of this information at the meeting of the Multinational Association for Supportive Care in Cancer (MASCC) in June, 2008 and will present posters at the national meeting of the American Association of Diabetes Educators (AADE) in August, 2008.

People with type 1 diabetes at MDACC represent a special challenge. Over the 14 months that the inpatient diabetes consultation service has been in operation, we have identified several individuals labeled as type 2 diabetes, but who in fact had adult-onset C peptide negative type 1 diabetes; some with strongly positive GAD antibodies. The distinction is important from the standpoint of patient management, because (1) people with type 1 diabetes are at risk of going into ketoacidosis if not provided with basal insulin every day, even when not receiving nutrition, and (2) at home they derive no benefit from treatment with sulfonylureas and TZDs. Because they can prevent long-term complications by meticulous control of blood glucose, many individuals with type 1 diabetes carefully match their insulin dosage to meals and activity with highly sophisticated regimens that employ multiple injections of different kinds of insulin, or variable dosing with insulin pumps. When being treated for cancer, these patients face the problem of adjusting their insulin programs to account for diagnostic procedures, surgery, chemotherapy and treatment with steroids. We now offer professional support for these patients while they are at M.D. Anderson, so they can maintain excellent control of diabetes while dealing with cancer. A member of our Department, Celia Levesque, MS, RN, is a regional expert on intensive management of type 1 diabetes. In this issue she outlines the pathophysiology

of type 1 diabetes and describes the benefits and requirements of insulin pump therapy.

### Research in progress

Continuous interstitial fluid glucose monitoring with a subcutaneous probe is a technique that has proved useful in outpatient diabetes management, especially for individuals who practice intensive glycemic control. This technique holds promise for improved management of patients being treated with intravenous insulin infusions, with respect both to saving nursing time and effort, and to providing early warning of glycemic fluctuations. However, the reliability of subcutaneous glucose monitoring has not been demonstrated in the intensive care setting. Dr. Naifa Busaidy of our Department is the lead investigator of a multi-center study that will explore the analytical accuracy and clinical utility of continuous glucose monitoring for patients on insulin drips in the ICU.

Dr. Busaidy has shown that diabetes is associated with shortened survival of patients with pancreatic cancer. She is now investigating the effects of intensive glucose management on survival among these patients.

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For a complete list of references, please visit the Diabetes Program webpage at the Department of Endocrine Neoplasia & HD's website at <http://www.mdanderson.org/departments/endocrinology/>

## Diabetes and Cancer Increased Insulin Requirements in Patients with Diabetes Receiving Hyper-CVAD

**Veronica Brady, MSN, NPCF, RN, Dept. of Endocrine Neoplasia and Hormonal Disorders**

Diabetes affects 20.8 million persons in the United States, about 7% of the population. One third of these persons are unaware that they have diabetes. Diabetes is one of the top five killers and more than 200,000 will die this year. There is also an increasing prevalence of diabetes among children and adults.<sup>1</sup>

In 2002 there were 10.1 million Americans living with cancer and there were 1.4 million newly diagnosed cases of cancer in 2006 (Cancer facts). Thus it stands to reason that as the number of persons with cancer increases the number of persons with cancer and diabetes will also increase.

There has been a correlation between diabetes and cancer noted since the 19th century. Over the years researchers have established an epidemiologic link between diabetes and pancreatic, breast, liver, colorectal, endometrial, renal and prostate cancers. Timely diagnosis and treatment of both diseases is necessary for optimal management.

In a side by side comparison there are many similarities between diabetes and cancer. (See Table on Page 5)

These two diseases co-exist in the patient population at MD Anderson Cancer Center, thereby making treatment for hyperglycemia/diabetes the ultimate challenge.

Hyper-CVAD is a chemotherapeutic regimen for lymphoid leukemia consisting of hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone. This regimen includes 40

mg of dexamethasone daily for 4 consecutive days during a treatment cycle. Treatment with these high doses of dexamethasone leads to severe hyperglycemia that can be difficult to control in patients with or without pre-existing diabetes. A study by Weiser et al<sup>2</sup> of patients treated with this regimen at MD Anderson revealed that patients with hyperglycemia had a shorter duration of complete remission, experienced greater overall mortality, and were at increased risk for developing infectious complications. Also recent research by Dr. Pankaj Shah and collaborators at MD Anderson showed that 22% of all patients admitted had hyperglycemia or known diabetes.<sup>3</sup> The patients with hyperglycemia/diabetes had worse short-term outcomes than their euglycemic counterparts. These studies have sparked an interest in determining the amount of insulin required to correct hyperglycemia in patients undergoing treatment with hyper-CVAD.

In an effort to assess the insulin requirements for patients receiving hyper-CVAD at MD Anderson Cancer Center, we reviewed the charts of patients whom we were asked to see for glycemic management. We recorded the doses and types of both basal (long acting) and prandial (rapid acting meal time) insulin for each cycle of steroid administration. We also reviewed blood glucose values prior to and following administration of high dose dexamethasone.

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	Cancer	Diabetes
Definition	A group of diseases characterized by uncontrolled growth and spread of abnormal cells	A group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action or both.
Risks	Increased age. One-third of all cancer deaths are related to nutrition, physical inactivity, overweight/obesity, family history, or race/ethnicity	Older age, obesity, physical inactivity, race/ethnicity, family history
Costs of Care	2005 (in billions) Total (direct/indirect) \$209.9 Direct Medical costs \$74 Indirect costs \$135.9	2002 (in billions) Total (direct/indirect) \$132 Direct Medical costs \$92 Indirect costs \$40

(Brady, continued from page 4)

Near-normoglycemia was difficult to achieve, even with daily adjustment of multiple doses of insulin. For control of hyperglycemia, patients with type 2 diabetes required 2.0 to 2.5 units/kg of insulin daily, compared with typical doses of 0.5 to 1 units/kg daily for patients with type 2 diabetes who are not taking steroids. Patients with type 1 diabetes had a 4-fold increase in their insulin requirements: ~1.0 unit/kg daily. Patients with no previous history of diabetes who developed hyperglycemia on steroids were just as difficult to control as those with diabetes and required more insulin than the usual starting dose for people with type 2 diabetes. We observed that patients required about 40-50% of their insulin as basal (long-acting) insulin and 50-60% as prandial (pre-meal) insulin (Figure 1). All patients needed gradually decreasing doses of insulin over 1 to 2 days after completion of high dose dexamethasone.

**Conclusions/Discussion**

- Patients with diabetes require significant increases of insulin dosage (units/kg/day) when receiving high dose dexamethasone. In our population, it is not unusual for persons with diabetes on high dose dexamethasone to require a doubling of their insulin (Figure 2).
- The hyperglycemic response to high dose dexamethasone persists for 2 or 3 days after the last dose, so patients require tapering of insulin after completion of high dose dexamethasone rather than sudden reduction of dosage.

**Barriers and Future Challenges**

- Larger studies are needed to identify appropriate starting doses of insulin in diabetics receiving steroids and patients who develop hyperglycemia on steroids.
- Larger studies are needed to identify if the insulin needs of patients on steroids undergoing Hyper-CVAD increase with each chemotherapeutic cycle.

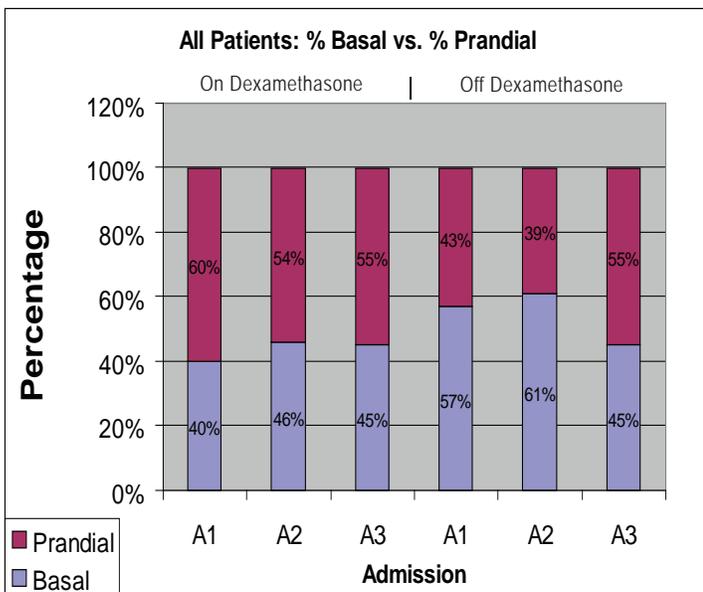


Figure 1. Basal (long-acting) and Prandial (mealtime) insulin needs in patients on and off steroids for each admission cycle. Patients require 40 to 50% of their insulin requirements as basal and 50 to 60% of their insulin as prandial.

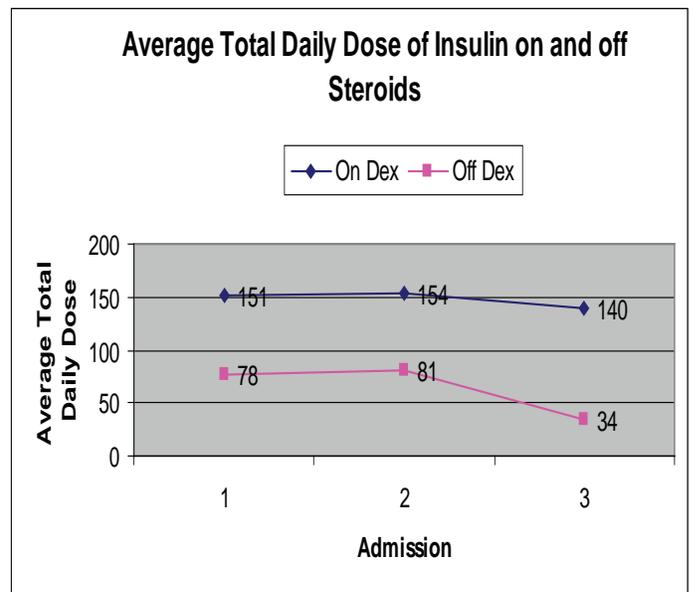


Figure 2. Average total insulin doses required for control of hyperglycemia in diabetes on dexamethasone (shown in blue) compared with average total daily insulin doses required for diabetes off dexamethasone (shown in pink). Patients required a doubling of their insulin doses when given steroids.

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# Type 1 diabetes, Cancer and Insulin Pump Therapy

Celia Levesque, MS, RN, Dept. of Endocrine Neoplasia and Hormonal Disorders

## Normal Glucose Metabolism

The pancreas has approximately 1-2 million islets of Langerhans. The islets are made up of alpha cells that produce glucagon, beta cells that produce insulin and amylin, delta cells that produce somatostatin and PP cells that produce pancreatic polypeptide.

Insulin is secreted in 2 ways: basal and bolus. About half of daily insulin secretion is basal: the insulin produced continuously by the pancreas that maintains euglycemia during the fasting state when the liver is releasing glucose into the bloodstream. Bolus insulin is the surge of insulin produced to maintain euglycemia and permit assimilation of nutrients postprandially.

Type 1 diabetes occurs when the immune system destroys the beta cells of the pancreas leading to insulin deficiency. At diagnosis, immune system markers are present in approximately 85-90% of people with type 1 diabetes and include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2 $\beta$ . The stages of development of type 1 diabetes include a genetic predisposition with an environmental trigger, followed by active autoimmunity, progressive beta cell dysfunction, and finally overt type 1 diabetes. Type 1 diabetes can occur at any age although it is diagnosed more commonly in children. The pathologic and biochemical changes in the pancreas occur as long as 9 years before signs and symptoms develop. Signs and symptoms occur when approximately 85% of the beta cells have been destroyed.<sup>1</sup>

Since people with type 1 diabetes produce little or no insulin, omission of insulin, even for short periods of time, can lead to the development of diabetic ketoacidosis (DKA), which is life threatening. Patients with type 1 diabetes require basal insulin when they are not eating so insulin doses need to be carefully prescribed during states of fasting, and during tests, procedures, and surgery.

## Type 1 diabetes and Cancer

There have been few studies looking at the incidence of cancer in people with type 1 diabetes. Zendejdel et al. conducted a study of 29,187 people hospitalized in Sweden for type 1 diabetes from 1965 to 1999 and found a 20% overall cancer incidence.<sup>2</sup> They found stomach, cervical, and endometrial were the most common types of cancer. Stevens and colleagues from the University of Oxford, UK reviewed findings from nine population-based studies and found the risk of developing pancreatic cancer was twice as high in subjects (n=39) with type 1 diabetes compared to those without type 1 diabetes.<sup>3</sup> In three cohort and six case-control studies, the relative risk for pancreatic cancer in people with type 1 diabetes was 2.00 (95% confidence interval 1.37-3.01).

## Insulin Pump Therapy

The insulin pump is a mechanical device that delivers insulin in a basal and bolus manner. The basal rates are customized to help achieve and maintain euglycemia when the pumper is fasting.

The bolus is used to compensate for food or to treat hyperglycemia. Today, "smart" pumps have built-in calculators that help the patient to determine accurately the amount of bolus needed. The pumper just enters the blood glucose value and the grams of carbohydrate.

There are many advantages of using an insulin pump. The insulin pump only uses short or rapid acting insulin, which results in more predictable onset, peak and duration compared to long acting insulin. One site is used for 3 days, contributing to predictable insulin action. The pump dosages can be customized to the individual patient. The pump can deliver basal rates as small as 0.025 units per hour and bolus rates as small as 0.05 units. When the doses are set correctly, people who use the insulin pump have decreased risk of hypoglycemia and improved HbA1c. The pump allows for a more flexible lifestyle. The patient can delay meals and vary the meal size.

The disadvantages of the pump include the risk of infection at the insertion site, and the development of DKA should insulin flow be interrupted for a prolonged period of time. Since the pump only infuses short/rapid acting insulin, once the insulin depot under the skin wears off, blood glucose levels will increase rapidly and DKA can occur.

The most important consideration in determining if a person should use an insulin pump is proper candidate selection. A pump candidate must desire pump therapy, be willing to check the blood glucose 4 or more times per day, be able to learn how to quantify food, be able to learn how to use the pump and troubleshoot various issues such as hyperglycemia, hypoglycemia, pump alarms, etc., and keep physician appointments. Candidates who particularly benefit from pump therapy are those with elevated HbA1c levels despite their best efforts, a history of severe hypoglycemia, frequent hypoglycemia or hypoglycemia unawareness, gastroparesis, microvascular complications associated with diabetes, or hectic lifestyle.

Patients who have type 1 diabetes and cancer can be difficult to manage. Treatments for cancer can interfere with diabetes control. Fasting for procedures, tests or surgery, anorexia, nausea, vomiting, and weight loss can cause hypoglycemia. Steroids and many other medications, TPN, the lack of activity, mental and physical stress, and the lack of quality sleep can cause hyperglycemia. The insulin pump can be a useful tool in managing blood glucose levels during cancer treatment.

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## Wish to refer a patient to M. D. Anderson?

M. D. Anderson has created a new online referral process, *myMDAnderson*, to help you get your patient into M. D. Anderson as quickly as possible. Once approved, you can use *myMDAnderson* to follow the treatment your patients receive by viewing transcribed reports and accessing your patients' schedules. To qualify for this free service, you must be a licensed, practicing physician.

To get started on the referral through *myMDAnderson* please access this portal: <https://my.mdanderson.org/public/physicians/user/>

To refer a patient to one of the physicians in the Department of Endocrine Neoplasia and Hormonal Disorders, please call 713-563-4400.

# Glycemic Management of Hospitalized Patients Receiving Tube Feeding

**Kathleen Crawford, MSN, ANP-C, Dept. of Endocrine Neoplasia and Hormonal Disorders**

Patients undergoing treatment for cancer pose unique nutritional challenges. Due to surgery, radiation or alteration in appetite, patients frequently require nutritional support to meet their caloric needs. A review of MDACC inpatient dietary records revealed 35 patients received nutritional support on a randomly selected day. Hyperglycemia is a serious problem that often occurs in patients receiving parenteral nutrition, regardless of prior diabetes history. Dr. Pankaj Shah, formerly of MDACC, demonstrated that sustained significant hyperglycemia (defined as serum or capillary glucose  $\geq 200$  mg/dL on two days) was associated with a twofold increase in the length of hospital stay and a fivefold increase in inpatient mortality when compared with non-hyperglycemia.<sup>1</sup> Furthermore, patients without a prior diagnostic code for diabetes ("new" hyperglycemia) required 77% longer hospitalizations and exhibited more than double the inpatient mortality compared to those patients with known diabetes. Of note, patients described as having "new hyperglycemia" were more likely to have received nutritional supplementation than hyperglycemic patients with known diabetes.<sup>2</sup> Although patients receiving tube feeding are at high risk for hyperglycemia and the adverse outcomes associated with it, there are no published treatment guidelines specific to this population.

When consulted to assist with the glycemic management of patients receiving tube feeding, the Endocrinology service often recommends subcutaneous insulin (regular, 70/30 or NPH) every 6-8 hours, starting at ratio of 1 unit of insulin for every 10 grams of carbohydrate supplied via the enteral formula. This approach allows for steady insulin levels while minimizing the risk for hypoglycemia. In an attempt to determine the efficacy of this treatment, we reviewed the charts of 11 hyperglycemic patients with gastrointestinal carcinomas, for whom the Endocrinology Department was consulted to assist with glycemic management. All were receiving continuous tube feedings as

their sole source of nutrition. We reviewed blood glucose values and insulin doses in the 4 days prior to hospital discharge for each patient. The mean dose of insulin prescribed was 0.32 units/kg of body weight daily, amounting to 1 unit for 6.82 grams of carbohydrate. The mean glucose value for all patients was 163 mg/dl. The American Diabetes Association recommends a target of  $<180$  mg/dl for postprandial blood glucose.<sup>1</sup> We noted 76% of the glucose values were  $<180$  mg/dl in the 5 patients without a prior history of diabetes, while 66% of the values were  $<180$  mg/dl in the 6 patients with known diabetes. There was no glucose value  $<70$  mg/dl.

Insulin requirements did not differ significantly with respect to units/kilogram or units/gram of carbohydrate, irrespective of prior diagnosis of diabetes mellitus.

A 2007 study of 44 US hospitals documented 19-38% of patients with blood glucose values  $>200$  mg/dl for 3 days experienced a 5-28% prevalence of hypoglycemia defined as glucose  $<60$  mg/dl.<sup>3</sup> We were able to achieve reasonable glycemic control with no episode of hypoglycemia. We therefore suggest aiming for an ultimate dose of 0.05-0.08 units/kg of regular, 70/30 or NPH insulin every 6 hours (amounting to 0.2-0.3 units/kg daily), while the tube feeding is infusing at goal rate. If the tube feeding is at less than goal rate, the dose of insulin should be reduced proportionately. This should control the blood glucose with minimal risk for hypoglycemia.

We will continue to collect data on this population as this study was limited by the small sample size and variability of insulin preparations used.

#### References:

1. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2007; 30 (Supplement): S27-31.
2. Shah, P. Unpublished work 2008.
3. Wexler D.J., et al. Prevalence of Hyper- and Hypoglycemia Among Inpatients with Diabetes. Diabetes Care 2007; 30 (2): 367-369.

## From the Department Chair



### **Steven I. Sherman, M.D., Chair, Department of Endocrine Neoplasia and Hormonal Disorders**

With this issue of the newsletter, we highlight the emerging importance of diabetes mellitus and hyperglycemia in our care for patients with cancer. Until recently, the potential significance of hyperglycemia and its effect on cancer patient outcomes was underappreciated. As comprehensively reviewed by Dr. Victor Lavis in his cover article,

we have recently recognized the frequency and severity of hyperglycemia among our hospitalized cancer patients, as well as the associations between inpatient hyperglycemia and risk for poor outcomes. This population of patients presents additional challenges for clinical management, including the high rates of glucocorticoid use for oncologic purposes, varied nutritional intake due to chemotherapy and radiation therapy toxicities, and the frequency of exogenous enteral and parenteral nutritional support. Our department has responded to

these challenges by expanding both our clinical and research efforts in diabetes care for cancer patients, recruiting faculty such as Drs. Lavis and Naifa Busaidy and a corps of mid-level providers expert in diabetes management. As a testament to the future importance of this effort, we are creating a Section of Diabetes and Metabolic Disease within the department, effective September 1, 2008, which will be led by Dr. Lavis. Future efforts will focus not only on clinical care paradigms but also on more fundamental research on the role of glucose and metabolic hormones such as insulin on the pathophysiology of cancer itself. For our endocrine staff and their collaborators throughout the institution, this combination of multidisciplinary research and patient care will undoubtedly yield important benefits that enhance our knowledge and improve patient outcomes, contributing further to our mission to Make Cancer History.

## New Addition to the Endocrine Faculty Team



Dr. Mouhammed Amir Habra earned his medical degree from the Faculty of Medicine, Aleppo University, Syria where he also did internal medicine residency at Aleppo University Hospital before moving to the United States. He then completed his internal medicine residency at the University of Missouri-Columbia and his endocrinology fellowship at Baylor College of Medicine and M.D. Anderson Cancer Center. He had additional year of

training focusing on Endocrine neoplasia at M.D. Anderson Cancer Center under the mentorship of Dr. Rena Vassilopoulou-Sellin. His clinical interests include adrenal tumors, novel therapies in thyroid carcinoma, and endocrine paraneoplastic syndromes.

## Clinical Trials

### **A Randomized, Double-blind Study to assess the Safety and Efficacy of Different Dose Levels of Pasireotide (SOM230) s.c. over a 6 month Treatment Period in Patients with De Novo, Persistent or Recurrent Cushing's Disease**

The goal of this clinical research study is to learn if SOM230 (pasireotide) can help to control Cushing's disease. Researchers will compare 2 dose levels of the drug to find out which one may be more effective. The safety of this drug will also be studied.

This study is for adults diagnosed with ACTH-dependent Cushing's disease and for those on medical treatment for Cushing's disease. Patients who received pituitary irradiation within the last 10 years may not be considered for this study.

The trial is a NCI sponsored trial and cannot be administered outside of a NCI designated cancer center.

For more information, please contact Mary Jean Klein, Manager, Clinical Protocol Administration, at 1-713-792-2840 for further information.

For information on other clinical trials conducted at M. D. Anderson Cancer Center, please visit: [http://www.mdanderson.org/Cancer\\_Pro/CS\\_Resources/display.cfm?id=562561A1-751F-11D4-AEBD00508BDCCE3A&method=displayFull](http://www.mdanderson.org/Cancer_Pro/CS_Resources/display.cfm?id=562561A1-751F-11D4-AEBD00508BDCCE3A&method=displayFull). For information on other clinical trials conducted at other institutions, please visit: <http://www.clinicaltrials.gov/>

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