Part One of a Two-Part Series

Collaborative Approach to Managing a 47-Year-Old Male with Stage IIB Rectosigmoid Colon Cancer and New Onset of Diabetes

BETSY DOKKEN, PhD, RN, ANP, and SANDRA E. KURTIN, RN, MS, AOCN®, ANP

From University of Arizona Department of Medicine, Tucson, Arizona

Dr. Dokken has received honoraria from Amylin Pharmaceuticals. Ms. Kurtin has no potential conflicts to disclose.

Correspondence to: Betsy B. Dokken, PhD, RN, ANP, University of Arizona, Medical Research Building, Rm 412, PO Box 245218, Tucson, AZ 85724-5218. E-mail: bdokken@deptofmed.arizona.edu

Abstract

Both cancer and diabetes are significant health-care challenges, and the coexistence of these diseases has been linked with increased mortality. To safely and effectively manage the patient with cancer and diabetes, the advanced practitioner needs a working knowledge of the underlying pathobiology of both diseases, common underlying risk factors, the heterogeneity of each cancer diagnosis, and improvements in treatment approaches for both diseases. Collaboration between advanced practice professionals in oncology, primary care, endocrinology, and nutrition can provide the initial support and continued management needed by the patient with cancer, diabetes, and other comorbidities, as illustrated by the case report included in this review. Familiarity with the diagnostic evaluation of patients at high risk for diabetes, early intervention for sustained hyperglycemia and confirmed diabetes, and support of the patient requiring significant lifestyle changes will promote the best possible outcome.

J Adv Pract Oncol 2010;1:184–194

Diabetes and cancer continue to present challenges to industrialized nations as the incidence of both diseases increases globally. An estimated 1.5 million new cancer cases and 1.6 million new diabetes diagnoses are expected in 2010 in the United States (Jemal, Siegel, Xu, & Ward, 2010; CDC, 2007). Cancer and diabetes, respectively, are the 2nd and 12th leading causes of death in the United States (Giovannucci et al., 2010). Although no registry data specific to patients with both diseases are available, several recent studies have evaluated morbidity and mortality in patients with diabetes and cancer. A group of scientific and clinical experts representing the American Cancer Society and the American Diabetes Association recently published a consensus report emphasizing the link between diabetes and the development of certain cancers, common risk factors for both diseases, and recommendations for proactively screening patients with diabetes for cancer and effectively managing patients with cancer who have diabetes (Giovannucci et al., 2010).

The complexity of the underlying pathobiology of both diseases, common underlying risk factors, the heterogeneity of each cancer diagnosis, and the variability in treatment approaches present a daunting challenge for the advanced practice oncology professional. The robust pace of scientific discovery has provided improved treatment options for both diseases, requiring a working knowledge of these developments to safely and effectively manage the patient with cancer and diabetes.

Adopting a collaborative approach to management with colleagues from endocrinology, oncology, medicine, nursing, nutrition, and pharmacy will provide the best strategy for optimal outcomes. This is the first in a series of two papers to discuss a collaborative approach to management of diabetes in patients with cancer, using a case study to illustrate clinical management strategies as well as to provide an update on current research. The focus of this paper will be the medical and pharmacologic management of diabetes. The second paper in this series will focus on medical nutrition therapy for diabetes.

Diabetes as a Comorbidity: Effect on Outcomes

A population-based analysis of 5,555 newly diagnosed cancer patients found that 9% of this group had diabetes at the time of diagnosis, with the most commonly diabetic subgroups being those with pancreatic cancer (19%) or uterine cancer (14%) and younger males with kidney cancer (8%) (van de Poll-Franse et al., 2007). Patients in this study who had both diabetes and cancer were treated less aggressively. Based on a multivariate Cox regression analysis adjusting for age, gender, stage, treatment, and cardiovascular disease, patients with diabetes and cancer suffered increased mortality (hazard ratio [HR] = 1.44). Preexisting diabetes is associated with later stage at diagnosis for breast, colorectal, and ovarian cancer ($p < .5$; Barone, et al., 2008).

Hemminki and colleagues (Hemminki, Li, Sundquist, & Sundquist, 2010) evaluated 125,126 patients hospitalized for type 2 diabetes in Sweden. The majority of patients (n = 51,468) were over age 69, and 21% (n = 26,641) had a family member with diabetes. A standardized incidence ratio (SIR) of 1.0 is the expected rate in the general population. At a median follow-up of 15 years, 24 different cancer types showed an increased incidence in this diabetic population, the most common being pancreatic (6.08 SIR) and liver cancer (4.25 SIR), with upper aerodigestive tract, esophageal, colon, rectal, lung, cervical, endometrial, ovarian, and kidney cancer also showing increases. Interestingly, the incidence of prostate cancer and melanoma were decreased in this population. The authors suggested shared risk factors and altered insulin-mediated metabolism with secondary physiologic effects as explanations of the increased incidence of these cancers in patients hospitalized for type 2 diabetes. Familial history of diabetes alone was not associated with an increased risk of any cancer in this study.

Case Study

A.F. is a 47-year-old man with a history of Barrett's esophagus, last evaluated in 2005. He is working full time as an electrician. He presented to the emergency department with hematochezia and abdominal pain, hypertension (170/117 mmHg), and nausea with progressive symptoms over a 2-week period. A CT scan showed a lesion in the rectosigmoid area. Colonoscopy was attempted but not completed because of an obstructing lesion in the rectosigmoid area and two tubular adenomas located distally. Biopsies were consistent with adenocarcinoma. The patient underwent a low-anterior resection that confirmed stage II rectal cancer (T3N0) with 22 lymph nodes negative. Antihypertensive therapy was initiated with lisinopril (10 mg) and hydrochlorothiazide (25 mg) daily. Serum glucose levels ranged from 98 to 132 mg/dL (nonfasting) while A.F. was hospitalized. Past medical history is remarkable for Barrett's esophagus, which is followed by gastroenterology and treated with esomeprazole, and knee and elbow surgery due to injury. His father died in a motor vehicle accident, and his mother is alive with a history of hypertension and type 2 diabetes.

A follow-up colonoscopy 2 months after surgery revealed multiple sessile polyps, which were removed with a snare/saline technique, additional sessile polyps that were not removed, a friable anastomotic site, an abnormal cecal fold, and a normal ileum. Biopsies were consistent with hyperplastic polyps and tubular adenomas, with evidence of lymphatic invasion on microscopic review. The patient's carcinoembryonic antigen (CEA) level was 1.8 ng/mL, unchanged from a preoperative measure.

He was seen in follow-up by surgical oncology 2.5 months after his surgery and was referred to medical oncology at that time. Given the high-risk features of his disease, he was started on adjuvant chemotherapy for a planned 12 cycles using the FOLFOX regimen (oxaliplatin at 85 mg/m^2 IV, fluorouracil [5-FU] at 400 mg/m^2 bolus, leucovorin at 400 mg/m^2 bolus, and 5-FU at 2,400 mg/m^2 IV over 46 hours, using an every-2-week schedule).

Following cycle 1, the patient developed significant neutropenia (absolute neutrophil count of 550/mm^3), nausea, and vomiting after requiring a treatment delay of 1 week. Pegfilgrastim (Neulasta) at 6 mg administered subcutaneously after discontinuation of the 5-FU infusion was added to his regimen with cycle 2. The antiemetic regimen was modified to include palonosetron (Aloxi), aprepitant (Emend), lorazepam, and continued corticosteroids, with a 50% dose reduction of his chemotherapy or corticosteroid.

He tolerated cycles 2 and 3 with moderate fatigue and persistent nausea. He experienced a mild hypersensitivity reaction following the third cycle of oxaliplatin, requiring administration of additional corticosteroids and antihistamines to resolve his symptoms and additional premedication for hypersensitivity reactions prior to each treatment. He developed Common Terminology Criteria for Adverse Events (CTCAE) grade 3 diarrhea and fatigue, and CTCAE grade 2 thrombocytopenia (65,000/mm^3) after cycle 4 of therapy, requiring a treatment delay and dose modification for the oxaliplatin (75 mg/m^2) as well as omission of the bolus doses of 5-FU and leucovorin. Prior to cycle 5 of treatment, he reported mild numbness and tingling in his fingers and toes, which resolved within 10 days after cycle 4. He also reported a change from intermittent diarrhea to constipation, with bowel movements every 3 to 4 days.

A.F. required time off from work and was spending an increased amount of time in bed or resting. He began to experience episodes of anger and anxiety, with intermittent panic attacks. He developed progressive and persistent hypertension confirmed by home blood pressure monitoring, requiring a dose adjustment of lisinopril (to 20 mg/d) and hydrochlorothiazide (to 25 mg twice daily). He continued to experience moderate to severe fatigue, muscle cramping, stable chemotherapy-induced peripheral neuropathy (CIPN), and intermittent constipation during cycles 6 through 9. Blood glucose levels remained in the range of 90 to 128 mg/dL (nonfasting) with a single reading of 287 mg/dL (nonfasting) prior to cycle 9.

On presentation for cycle 10 of FOLFOX, A.F. reported a 20-lb weight loss over 6 weeks, profound fatigue with an inability to work for 2 weeks prior to his visit, blurred vision, tremors, a sense of generalized weakness, poor appetite, and extreme thirst. Oral intake consisted primarily of fruit juices and colas. The numbness and tingling in his fingers and particularly in his feet were keeping him up at night due to pain. He had been having more frequent panic attacks. Laboratory measures obtained on arrival to the clinic were remarkable for a serum glucose level of 604 mg/dL, potassium of 2.9 mmol/L, sodium of 125 mmol/L, and CO_2 of 18 mmol/L (Figure 1). An ECG showed normal sinus rhythm and O_2 saturation on room air was 96%. He was noted to be hypotensive and tachycardic (Fig-

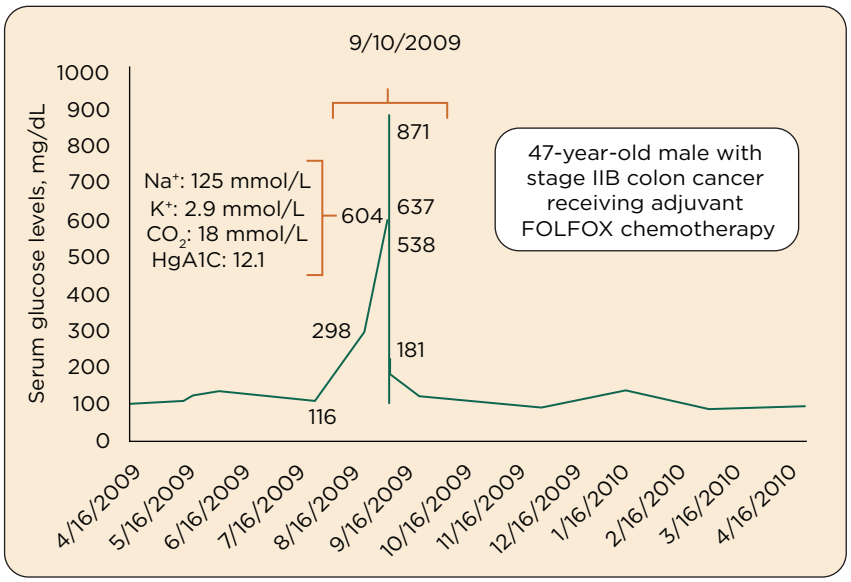

Figure 1. Serum glucose levels in a 47-year-old male with rectosigmoid adenocarcinoma. FOLFOX = leucovorin, fluorouracil, oxaliplatin.

ure 2). The patient was started on aggressive hydration, insulin, diuresis, and bicarbonate with a plan for admission. A repeat blood glucose level after 20 units of regular insulin over 3 hours increased to 871 mg/dL.

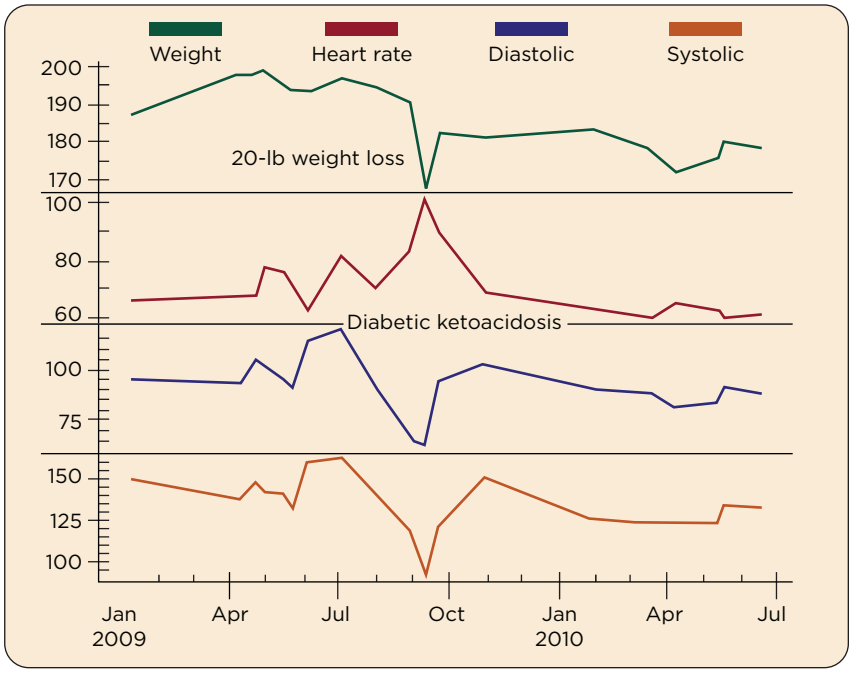

Figure 2. Serial measures for weight, blood pressure, and heart rate in a 47-year-old male with colorectal cancer who developed acute onset of diabetic ketoacidosis.

Update on Diabetes

The clinical characteristics and recommended treatment of diabetes vary depending on the classification of the disease, its duration, and the presence of comorbidities such as obesity, cardiovascular disease, and cancer. The standard of care for patients with type 1 diabetes mellitus is basal/bolus insulin therapy. Basal insulin therapy is defined as exogenous insulin administered to provide a low level of insulin action during the fasting state and between meals. The basal insulin requirement is typically accomplished by a long-acting, peakless insulin. Bolus insulin to correct hyperglycemia and to compensate for meals is provided by a rapid-acting insulin analog (DeWitt & Hirsch, 2003).

Type 2 diabetes mellitus is the most common type, accounting for approximately 95% of all cases (International Diabetes Federation, 2009). It is progressive in nature (Figure 3). The efficacy of noninsulin therapies depends on the ability of the pancreatic beta cells to secrete insulin in both the fasting and postprandial states. In the vast majority of patients with type 2 diabetes, beta cell insulin secretion continuously declines during the course of the disease. Many drugs, such as the sulfonylureas, which stimulate the beta cells to secrete more insulin, are not effective after a certain point in the disease process. The progressive nature of the disease explains the ability to achieve control with one agent early after diagnosis, and also the need to persistently intensify therapy over time. Unless this phenomenon is understood, diabetes management is frustrating for the patient and the provider alike.

Medications for type 2 diabetes are geared toward a number of pathophysiologic features common to patients with the disease (Table 1).

Pathophysiology of Type 2 Diabetes and Targeted Therapies

INSULIN RESISTANCE

Insulin resistance refers to the inability of insulin to affect the target tissue. In skeletal muscle and adipose tissue, this results in a decreased ability of insulin to facilitate glucose transport from the circulation to the intracellular space. In the liver, insulin resistance results in a decreased ability of insulin to inhibit hepatic glucose production. These defects both result in increased blood glucose. The thiazolidinedione class of oral medications (including pioglitazone and rosiglitazone) improves insulin sensitivity in skeletal muscle and adipose tissue, which increases glucose uptake into cells. Recent evidence suggests an increased risk of myocardial infarction in patients using rosiglitazone (Nissen & Wolski, 2007). No such evidence has emerged in association with pioglitazone (Erdmann et al., 2007). The biguanide metformin promotes insulin sensitivity in the liver, which decreases hepatic glucose output.

INSULIN DEFICIENCY

A progressive secretory defect in the pancreatic beta cells is present in patients with type 2 dia-

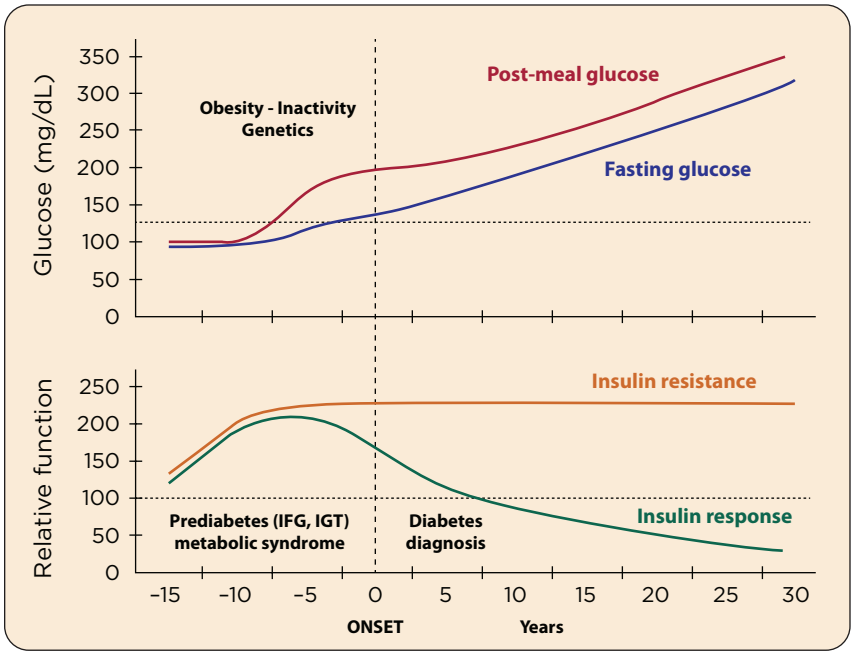

Figure 3. The progressive nature of type 2 diabetes. Before the manifestation of the metabolic defects that lead to type 2 diabetes, fasting and postprandial insulin levels are similar and constant. In the majority of patients in whom type 2 diabetes develops, increasing insulin resistance leads to compensatory increases in circulating insulin, which prevents an increase in glucose levels. As time progresses, the insulin resistance reaches a peak and stabilizes, while the compensatory increase in insulin continues to prevent fasting glucose levels from becoming abnormal. However, at some point, either because of early beta-cell dysfunction or because of a natural limit of beta-cell capacity, challenge of this delicate balance with a glucose load may demonstrate that, although fasting glucose levels remain normal, postprandial glucose levels become abnormal as a limitation in insulin response is reached. Following the onset of beta-cell dysfunction, insulin levels can no longer keep up in overcoming the insulin resistance, and fasting and postprandial glucose levels increase progressively over time (Bergenstal et al., 2001; Goldstein, 2002). Figure adapted with permission from Kendall DM, Bergenstal RM. Copyright © 2005 International Diabetes Center, Minneapolis, MN. All rights reserved.

betes mellitus. Thus, in the early stages of the disease, insulin secretion is normal, or even increased (Figure 1). Long-acting sulfonylureas work to stimulate basal insulin secretion and may also help improve glycemic control while the patient fasts or between meals. Short-acting insulin secretagogues such as the meglitinides stimulate insulin secretion acutely, and may be helpful in controlling postprandial excursions. However, when insulin production from pancreatic beta cells declines, these medications will no longer be efficacious. Insulin deficiency in type 2 diabetes mellitus, particularly after meals, can also be mitigated by the glucagon-like peptide-1 (GLP-1) mimetics, discussed below.

DECREASED INCRETIN EFFECTS

GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones normally released from the intestine during the postprandial state. These incretins have pleiotropic effects that act synergistically to control the plasma glucose concentration. In patients with type 2 diabetes, GLP-1 secretion and GIP action are impaired.

Although GIP replacement therapies are in very early stages of drug development, two GLP-1 mimetics (exenatide [Byetta] and liraglutide [Victoza]) are currently in widespread clinical use for the treatment of type 2 diabetes (Drucker et al., 2008; Piya, Tahrani, & Barnett, 2008). GLP-1 and its analogs contribute to the normalization of blood glucose levels by increasing postprandial insulin secretion, suppressing postprandial glucagon secretion, slowing gastric emptying, and increasing postprandial satiety (Combettes, 2006). In addition, the dipeptidyl peptidase IV (DPPIV) inhibitors increase plasma levels of endogenous GLP-1. Endogenous GLP-1 is rapidly degraded by the enzyme DPPIV. Blocking the action of this enzyme increases the bioavailability of GLP-1.

DECREASED AMYLIN EFFECTS

Amylin is a hormone that is co-secreted from pancreatic beta cells. Patients with type 1 diabetes (who lack functional beta cells) are completely deficient in this hormone. Amylin secretion is variable in patients with type 2 diabetes but declines over the course of the disease in parallel with insulin secretion. Amylin delays gastric emptying, inhibits postprandial glucagon secretion, and acts as a satiety agent (Schmitz, Brock, & Rungby,

Table 1. Summary of (noninsulin) antidiabetic medications currently approved for use in the United States

Drug class/drug	Targeted pathophysiology	Expected decrease in A1C with monotherapy	Advantages	Disadvantages
Biguanides Metformin	Excess hepatic glucose output	1.5%	Low cost, no hypoglycemia, no weight gain, possible weight loss	GI side effects, contraindicated in chronic kidney disease, lactic acidosis (very rare)
Thiazolidinediones (TZDs) Pioglitazone Rosiglitazone	Insulin resistance in skeletal muscle and adipose tissue	0.5%–1.4%	No hypoglycemia, improved lipid profile	Expensive, fluid retention, weight gain, contraindicated in heart failure (NYHA III-IV) Some evidence that rosiglitazone may increase risk of myocardial infarction
Sulfonylureas Glyburide Glipizide Glimepiride	Progressive impairment of insulin secretion from beta cells (insulin deficiency)	1.5%	Low cost	Hypoglycemia (usually mild), weight gain, dose adjustment necessary in chronic kidney disease
Glinides Nateglinide Repaglinide	Progressive impairment of insulin secretion from beta cells (insulin deficiency)	1%–1.5%	Low cost, short duration allows for action only during postprandial period	Expensive, dosing prior to every meal (three times daily)
GLP-1 mimetics Exenatide Liraglutide	Rapid gastric emptying, impaired postprandial insulin secretion, excess postprandial glucagon secretion, decreased satiety	0.5%–1.5%	No hypoglycemia, possible weight loss Liraglutide: once-daily dosing	Expensive, GI side effects, injectable Exenatide: twice-daily dosing (once-weekly dosing in phase III clinical trials)
DPPIV inhibitors Sitagliptin Saxagliptin	Same as GLP-1 receptor agonists; DPPIV inhibitors decrease rate of endogenous GLP-1 degradation	0.5%–1.5%	Oral, once-daily dosing, few side effects, weight neutral	Expensive, dose adjustment necessary in chronic kidney disease
Alpha-glucosidase inhibitors Acarbose Miglitol	These agents decrease rate of carbohydrate (polysaccharide) digestion in the small intestine, blunting the postprandial glycemic excursion	0.5%–0.8%	No hypoglycemia, weight neutral	Expensive, common and frequently severe GI side effects, three-times-daily dosing
Amylin mimetics Pramlintide	Rapid gastric emptying, excess postprandial glucagon secretion, decreased satiety			

Note: DPPIV = dipeptidyl peptidase IV; GI = gastrointestinal; GLP-1 = glucagon-like peptide type-1; NYHA = New York Heart Association. Sources: Nissen & Wolski (2007), Drucker et al. (2008).

2004), all mechanisms that help curb postprandial hyperglycemia. Unlike GLP-1, amylin does not act as an insulin secretagogue. Pramlintide (Symlin) is an amylin mimetic that is approved for use with mealtime insulin in patients with either type 1 or type 2 diabetes.

DIETARY CARBOHYDRATE INTOLERANCE

Normally, the digestion and absorbance of dietary carbohydrate is met with compensatory insulin secretion, insulin facilitates transport of the carbohydrate (glucose) from the circulation into muscle and fat cells, and blood glucose levels remain in the physiologic range. In patients with diabetes, however, dietary carbohydrate is digested and absorbed into the circulation, but insulin secretion is diminished (type 2 diabetes) or absent (type 1 diabetes and some type 2 dia-

betes), resulting in postprandial hyperglycemia (American Diabetes Association, 2008).

Several strategies have been developed to mitigate postprandial hyperglycemia. One is to restrict dietary carbohydrate, another is to enhance insulin action during the postprandial period, and a third is to decrease the digestion of carbohydrate. The alpha-glucosidase inhibitors block the conversion of polysaccharide to absorbable monosaccharides, thereby decreasing the amount of carbohydrate reaching the intestine to be absorbed into the circulation. This mechanism results in a blunting of the postprandial glycemic excursion.

Case Study (continued)

This case study demonstrates the progressive nature of type 2 diabetes mellitus and association with risk factors, including obesity, family history, diet, and insulin resistance. Several factors contributing to the episode of severe hyperglycemia are noted, including high glucose intake, limited physical activity, a high carbohydrate diet, and administration of corticosteroids and the neurokinin-1 inhibitor aprepitant. Aprepitant is both an inhibitor (CYP3A4) and inducer (CYP29A) of CYP450 pathways. Inhibition of CYP3A4 results in a doubling of plasma glucocorticoid levels (Blower, DeWit, Goodin, Aapro, 2005). Reduction of the dexamethasone dose by 50% is recommended when given in combination with aprepitant (Blower et al., 2005). Early signs of underlying diabetes including constipation (possibly related to gastroparesis), fatigue, muscle weakness, irritability, and progressive neuropathy are often difficult to differentiate from the neurotoxicity and general effects associated with the FOLFOX regimen. Concurrent hypertension increases the risk for secondary heart disease in the presence of newly diagnosed diabetes in this young patient.

A.F. was transferred to the intensive care unit for continued treatment including an insulin drip. The blood glucose levels normalized over a 36-hour period. The patient was discharged home with recombinant insulin glargine (Lantus), 100 U/mL at bedtime and instructions for a carbohydrate-controlled diet and home blood glucose monitoring.

A nutritional evaluation conducted in the hospital revealed the following: height = 165.1 cm; weight = 79.9 kg (ideal body weight = 61.5 kg); body mass index (BMI) = 29.3 kg/m^2 (130% ideal body weight); body surface area = 1.874 m^2; baseline weight = 90 kg, percent weight loss and time frame = 9% loss in 1 to 2 months; capillary blood glucose readings = 283–305 mg/dL; laboratory glucose = 185 mg/dL; hemoglobin A1C = 12.1%. Based on the nutritional evaluation, a carbohydrate-controlled diet with estimated nutrient needs of 1,725 to 2,070 calories, 70 to 85 g protein, and intake of 2 to 3 L/d of fluid was recommended to reach the target BMI and maintain target blood glucose levels.

Initiating and Intensifying Medical Management of Type 2 Diabetes

Frequently, patients with cancer are followed more closely by their oncology team than by their primary care team. In addition, medication additions or changes by the oncology team may alter the patient's glycemic control. It is critical for health-care providers to work together to provide the best care for the patient. A delay in the initiation or intensification of diabetes treatment due to the unavailability of a primary care or diabetes specialty care consult is not recommended. Therefore, it is important for oncology health-care providers to be comfortable initiating and intensifying diabetes therapies.

Whether used alone or in combination with older diabetes therapies, the availability of newer agents has provided more options and thus decreased certainty regarding the most appropriate method(s) to treat this very common disease. In response to this dilemma, the American Diabetes Association and the European Association for the Study of Diabetes published a consensus statement for the management of hyperglycemia in type 2 diabetes (Nathan et al., 2006; Nathan et al., 2009). This publication is an excellent starting point for any provider who may be uncomfortable with the medical management of type 2 diabetes. The evidence-based algorithm provided in the consensus statement (Figure 4) relies heavily on findings from well-designed, randomized, placebo-controlled clinical trials.

Due to the lack of high-quality evidence directly comparing one treatment regimen to another, many newer agents have been omitted from these recommendations. Importantly, the treatment algorithm was designed to provide guidance to clinicians lacking in-depth knowledge and experience with diabetes therapies. The

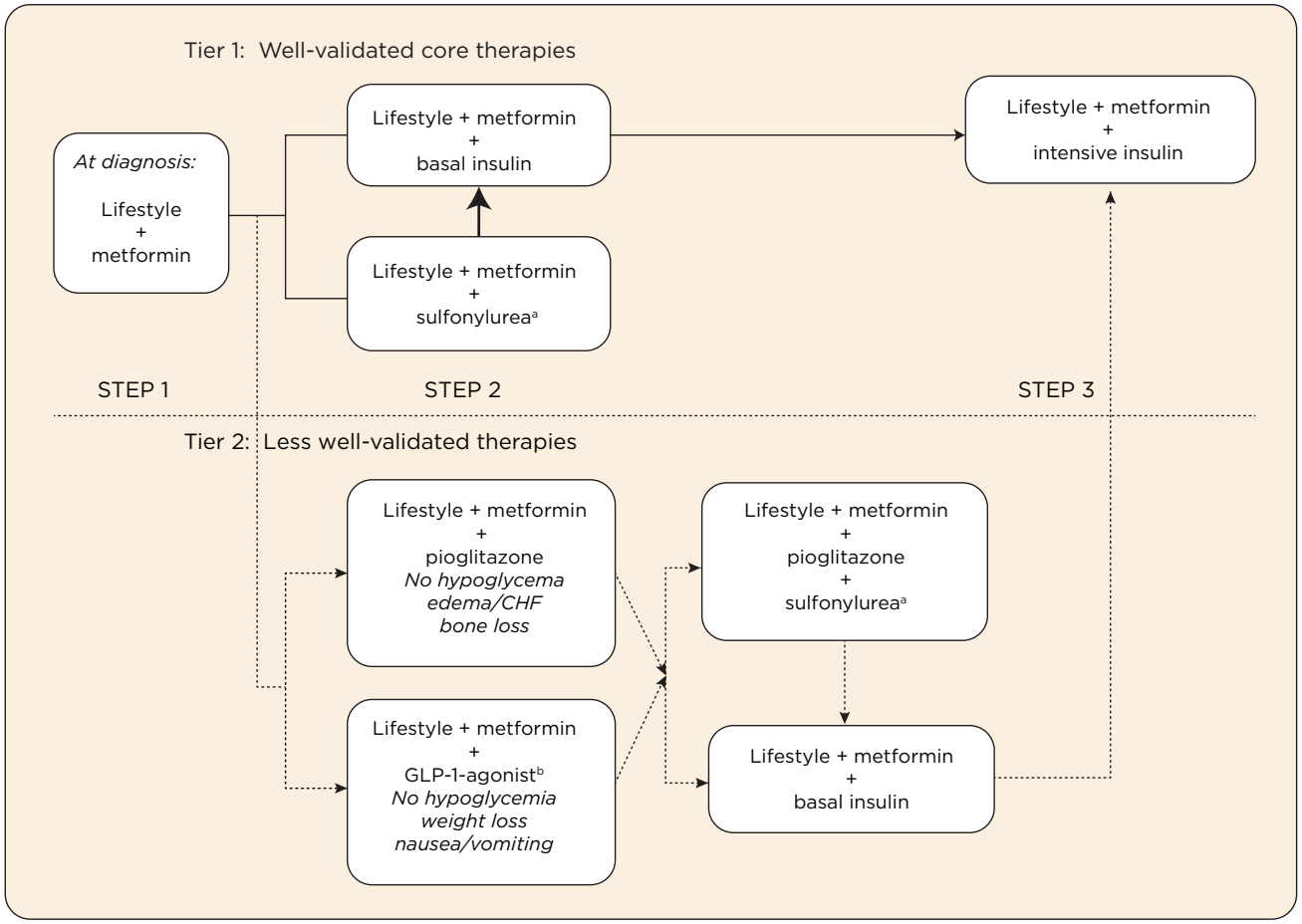

Figure 4. Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7% and then at least every 6 months. The interventions should be changed if A1C is ≥ 7%. [a]Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide. [b]Insufficient clinical use to be confident regarding safety. CHF = congestive heart failure. See Figure 5 for initiation and adjustment of insulin. Source: Nathan, D. M., Buse, J. B., Davidson, M. B., Ferrannini, E., Holman, R. R., Sherwin, R., & Zinman, B. (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care, 32,* 193–203. doi: 10.2337/dc08-9025 Copyright © 2009 by the American Diabetes Association. Reprinted with permission from the American Diabetes Association.

choice of an agent that is not included on the algorithm, but is determined to be the best option for a particular patient, is perfectly acceptable. In fact, a tailored approach to diabetes therapy is most often superior to a standard regimen prescribed to every patient.

Insulin Therapy

TYPE 1 DIABETES

As stated earlier, the standard of diabetes care for patients with type 1 diabetes is basal/bolus insulin therapy. The goal of this therapy is to mimic the pattern of insulin secretion by healthy pancreatic beta cells. Basal insulin provides a low level of insulin action (and a low risk of hypoglycemia) during fasting hours and between meals, and requirements typically do not vary greatly from day to day. Bolus insulin provides rapid insulin action of short duration either to correct hyperglycemia, to compensate for carbohydrate intake during meals, or both. Requirements for bolus insulin vary dramatically from day to day, depending on food (mostly carbohydrate) intake and exercise. The ability to vary bolus insulin administration (timing as well as dose) is the cornerstone of an individually tailored, flexible insulin regimen (DeWitt & Hirsch, 2003).

Basal/bolus insulin therapy can be accomplished through multiple daily insulin injections (usually 3–4/d), or through the use of an insulin pump (DeWitt & Hirsch, 2003). Because nondia-

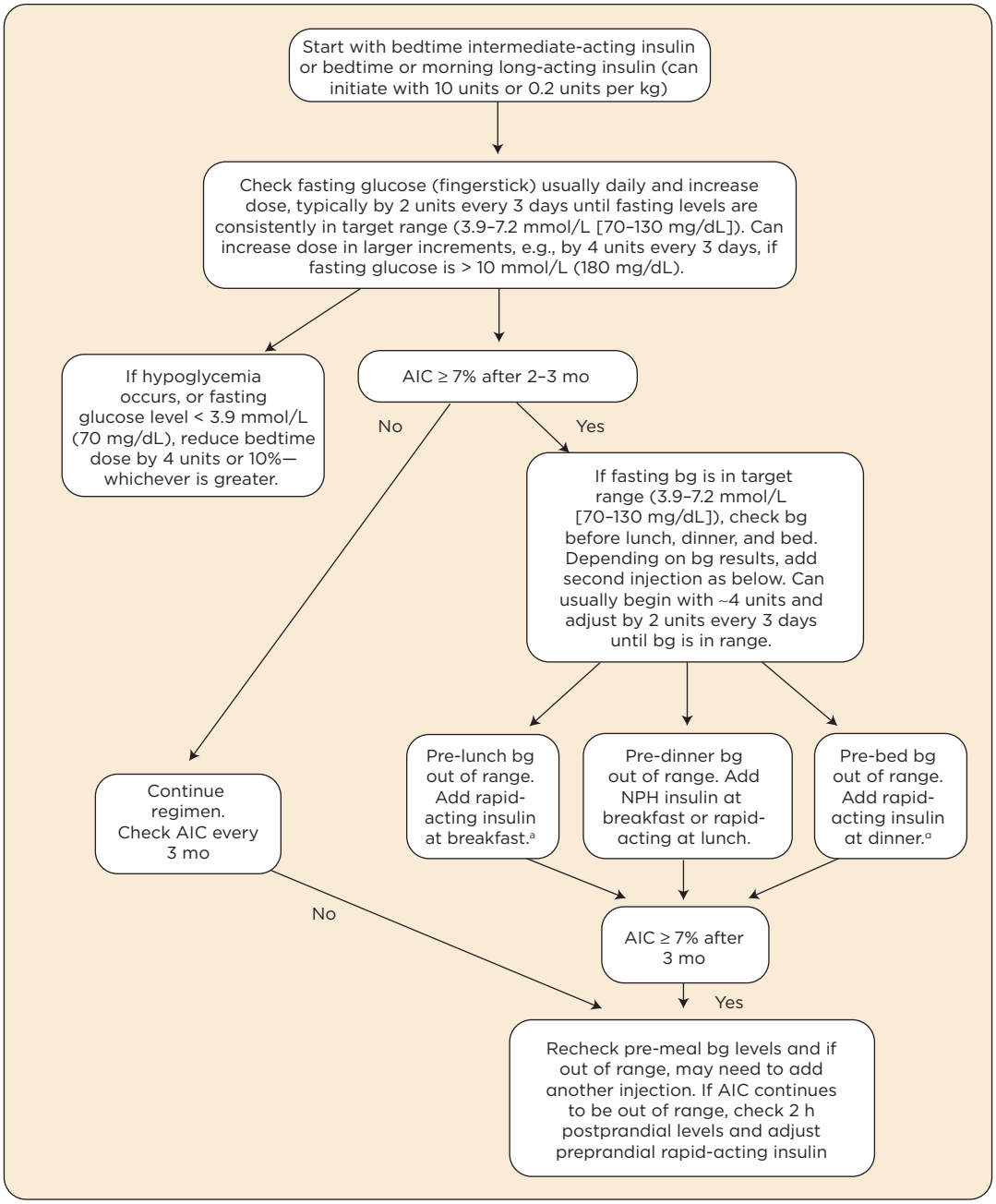

Figure 5. Recommended algorithm for initiating and adjusting insulin therapy (Nathan et al., 2009). bg = blood glucose; NPH = neutral protamine hagedorn. Source: Nathan, D. M., Buse, J. B., Davidson, M. B., Ferrannini, E., Holman, R. R., Sherwin, R., & Zinman, B. (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care, 32,* 193–203. doi: 10.2337/dc08-9025 Copyright © 2009 by the American Diabetes Association. Reprinted with permission from the American Diabetes Association.

betologists lack regular experience with these regimens, consultation with a specialist (diabetologist or diabetes educator) is recommended when prescribing and/or adjusting basal/bolus insulin therapy.

TYPE 2 DIABETES

Because of the progressive nature of this disease, virtually all patients with type 2 diabetes—if they live long enough—will require insulin therapy. The likelihood that a patient will require insulin for glycemic control increases with the metabolic response to stress. Cancer may increase both physical and psychosocial stress, and thus, may accelerate the need for insulin therapy in patients with type 2 diabetes (Psarakis, 2006).

Insulin therapy is recommended when a pa-

tient is on appropriate noninsulin therapies and is not reaching glycemic targets (typically, hemoglobin A1C < 7%). In patients with type 2 diabetes, most experts recommend starting with basal insulin and increasing the dose until fasting blood glucose levels are usually in the recommended range (70–120 mg/dL). At that point, bolus insulin would be required only if blood glucose levels were consistently elevated in response to a meal. Bolus insulin can be added before only one meal of the day (typically the largest), or before two or three meals per day, depending on the individual patient's needs. A full review of insulin therapy is beyond the scope of this paper, but a brief algorithm is provided in Figure 5 (Nathan et al., 2006).

SPECIAL NOTE ABOUT PREDNISONE

Prednisone is a synthetic glucocorticoid commonly used in a variety of ways related to cancer therapy. If administered once daily in the morning, hyperglycemia occurs predictably. Prednisone has little effect on the fasting blood glucose and an exaggerated effect on postprandial glucose (Fowler, 2009). Blood glucose levels in patients taking a daily dose of prednisone in the morning typically peak during mid-late-afternoon, and then tend to decrease in the evening and overnight. Because of the timing of the hyperglycemia, neutral protamine hagedorn (NPH) insulin, administered simultaneously with prednisone, is particularly suited to mitigating hyperglycemia in these patients.

On the Horizon

Drug development for the management of type 2 diabetes is ongoing. Two additional classes of drugs are currently in late-phase clinical trials.

SGLT INHIBITORS

The inhibition of sodium-glucose cotransporters (SGLTs)—proteins responsible for the reabsorption of glucose in the kidney—is under development as a novel strategy for glycemic control in diabetic patients. Increasing glucose excretion in the urine may be a safe and effective way to reduce plasma glucose levels as well as to decrease body weight (Chao & Henry, 2010). In fact, decreasing glucosuria is the major cause of weight gain observed in diabetic patients starting or intensifying insulin therapy.

11b-HSD1 INHIBITORS

11b-Hydroxysteroid dehydrogenase type 1 (11b-HSD1) is an enzyme that catalyzes the conversion of inactive cortisone to cortisol, the active glucocorticoid. Glucocorticoids play a fundamental role in the control of physiologic homeostasis. When present in excess, they can have a deleterious effect on glycemic control, blood pressure, and blood lipids, suggesting that glucocorticoids may have a pathogenic role in the metabolic syndrome and type 2 diabetes (Boyle & Kowalski, 2009; Ge, Huang, Liang, & Li, 2010).

Case Study (conclusion)

A.F. has continued on insulin glargine, 100 units at bedtime, with blood glucose levels between 90 and 120 mg/dL. He is now taking lisinopril, 10 mg daily, for his hypertension. He has continued follow-up of his colon cancer every 3 months. The initial colonoscopy performed 2 months after completion of adjuvant therapy revealed numerous polyps throughout the colon, and biopsies were consistent with tubular adenomas. He presented to clinic for an unscheduled visit with increased abdominal pain, severe constipation, and progressive fatigue 6 months after completing his adjuvant therapy. A repeat CT scan found diverticulosis, constipation, and no evidence of metastatic disease. Repeat colonoscopy showed the development of "carpets of polyps" throughout the colon—new over a 3-month period. A.F. is scheduled for a colectomy with possible rectal preservation to avoid a permanent ileostomy. He has continued follow-up with an endocrinologist and his primary care physician, and is seeing a psychiatrist on a regular basis to assist with the stress and anxiety he experiences due to his illnesses and the lifestyle changes they require. Both cancer and diabetes represent significant health-care challenges. An association between the coexistence of diabetes and cancer with increased mortality has been established. The secondary effects of poorly controlled diabetes may interfere with optimal anticancer therapy and predispose the patient to greater toxicity. Pretreatment evaluation of patients at increased risk for common treatment-related adverse events allows the implementation of prevention strategies including patient education.

In this case study, A.F. did not have hyperglycemia or diabetes at the time of diagnosis. He did, however, have several risk factors for devel-

oping diabetes. Patients with diabetes may be at increased risk for CIPN. A complete neurologic assessment prior to initiation of treatment with chemotherapeutic agents known to cause CIPN (such as oxaliplatin) is critical to effective treatment planning and will provide the basis for continued evaluation of CIPN. Early identification of progressive CIPN will allow dose modifications or treatment delays to reduce the potential for irreversible neuropathy.

Collaboration between advanced practice professionals in oncology, primary care, endocrinology, and nutrition provided the initial support needed by this patient with acute onset of diabetic ketoacidosis as well as continued management of his cancer, hypertension, anxiety, and diabetes. Familiarity with the diagnostic evaluation of patients at high risk for diabetes, early intervention for sustained hyperglycemia and confirmed diabetes, and support of the patient with significant lifestyle changes will promote the best possible outcome.

REFERENCES

American Diabetes Association (2008). Nutrition recommendations and interventions for diabetes. *Diabetes Care, 31(Supplement 1),* S61–S78. doi: 10.2337/dc08-S061

Barone, B. B., Yeh, H. C., Snyder, C. F., Peairs, K. S., Stein, K. B., Derr, R. L., . . . Brancati, F. L. (2008). Long-term all-cause mortality in cancer patients with pre-existing diabetes mellitus: A systematic review and meta-analysis. *Journal of the American Medical Association, 300*, 2754–2764. doi:10.1001/jama.2008.824

Bergenstal, R., et al. (2001). In L. J. DeGroot, J. L. Jameson, H. Burger, et al. (Eds.), *Endocrinology* (4th ed., pp. 821–835). Philadelphia: W. B. Saunders.

Blower, P., DeWit, R., Goodin, S., & Aapro, M. (2005). Drug-drug interactions in oncology: Why are they important and can they be minimized? *Critical Reviews in Oncology/Hematology*, *55*, 117–142.

Boyle, C. D., & Kowalski, T. J. (2009). 11b-hydroxysteroid dehydrogenase type 1 inhibitors: A review of recent patents. *Expert Opinion on Therapeutic Patents, 19*, 801–825. doi:10.1517/13543770902967658

Centers for Disease Control and Prevention (CDC). (2007). National Diabetes Fact Sheet, 2007. Atlanta: CDC. Retrieved from http:/www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf

Chao, E. C., & Henry, R. R. (2010). SGLT2 inhibition—a novel strategy for diabetes treatment. *Nature Reviews: Drug Discovery, 9*, 551–559. doi:10.1038/nrd3180

Combettes, M. M. J. (2006). GLP-1 and type 2 diabetes: Physiology and new clinical advances. *Current Opinion in Pharmacology, 6*, 598–605. doi:10.1016/j.coph.2006.08.003

DeWitt, D. E., & Hirsch, I. B. (2003). Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. *Journal of the American Medical Association, 289*, 2254–2264. doi:10.1001/jama.289.17.2254

Drucker, D. J., Buse, J. B., Taylor, K., Kendall, D. M., Trautmann, M., Zhuang, D., et al. (2008). Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: A randomised, open-label, non-inferiority study. *The Lancet, 372*(9645), 1240–1250.

Erdmann, E., Dormandy, J. A., Charbonnel, B., Massi-Benedetti, M., Moules, I. K., & Skene, A. M. (2007). The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: Results from the PROactive (PROactive 05) Study. *Journal of the American College of Cardiology, 49*, 1772–1780.

Fowler, M. J. (2009). Pitfalls in outpatient diabetes management. *Clinical Diabetes, 27,* 82–85. doi: 10.2337/diaclin.27.2.82

Ge, R., Huang, Y., Liang, G., & Li, X. (2010). 11beta-hydroxysteroid dehydrogenase type 1 inhibitors as promising therapeutic drugs for diabetes: Status and development. *Current Medicinal Chemistry, 17*, 412–422.

Giovannucci, E., Harlan, D., Archer, M., Bergenstal, R., Capstur, S., et al. (2010). Diabetes and cancer: A consensus report. *CA: A Cancer Journal for Clinicians*, *60*, 1–15. doi: 10.3322/caac.20078

Goldstein, B. J. (2002). Insulin resistance as the core defect in type 2 diabetes mellitus. *The American Journal of Cardiology, 90*(5, Suppl. 1), 3–10.

Hemminki, K., Li, X., Sundquist, J., & Sundquist, K. (2010) Risk of cancer following hospitalization for type 2 diabetes. *The Oncologist*. doi:10.1634/theoncologist.2009-0300

International Diabetes Federation. *IDF Diabetes Atlas. 4th ed.* Brussles, Belgium: International Diabetes Federation:2009. Available at www.diabetesatlas.org

Jemal, A., Siegel, R., Xu, J., & Ward, E. (2010). Cancer statistics, 2010. *CA: A Cancer Journal for Clinicians, Jul 7* (Epub ahead of print). doi:10.3322/caac.200.73.

Nathan, D. M., Buse, J. B., Davidson, M. B., Ferrannini, E., Holman, R. R., Sherwin, R., & Zinman, B. (2009). Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care, 32*, 193–203. doi: 10.2337/dc08-9025

Nathan, D. M., Buse, J. B., Davidson, M. B., Heine, R. J., Holman, R. R., Sherwin, R., & Zinman, B. (2006). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care, 29*(8), 1963–1972. doi: 10.2337/dc06-9912

Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine, 356*, 2457–2471. doi: 10.1056/NEJMoa072761

Piya, M. K., Tahrani, A. A., & Barnett, A. H. (2008). Liraglutide: A new option in the management of type 2 diabetes. *Future Prescriber, 9*(2), 6–12. doi: 10.1002/fps.10

Psarakis, H. M. (2006). Clinical challenges in caring for patients with diabetes and cancer. *Diabetes Spectrum, 19,* 157–162. doi: 10.2337/diaspect.19.3.157

Schmitz, O., Brock, B., & Rungby, J. (2004). Amylin agonists: a novel approach in the treatment of diabetes. *Diabetes, 53(suppl 3),* S233–S238. doi: 10.2337/diabetes.53.suppl_3.S233

Van de Poll-Franse, L. V., Houterman, S., Jansses-Heijnen, M. L., et al. (2007). Less aggressive treatment and worse overall survival in cancer patients with diabetes: A large population based analysis. *International Journal of Cancer*, *120*, 1986–1992. doi: 10.1002/ijc.22532