The Complex Dual Diagnosis of Diabetes and Cancer

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Diabetes and cancer are two of the top three killers in the United States. As the number of people surviving cancer increases, more patients will be living with both cancer and diabetes. This integrative review of the literature will provide an overview of diabetes, cancer, and the complex interactions between the two. A literature search was conducted and three main areas were identified that warrant additional discussion: the relationship between glucocorticoids and hyperglycemia, glucose control in the management of diabetes in patients with cancer, and an increased risk of certain cancers with the comorbid condition of diabetes. The hope is that, through additional research, evidence-based practice guidelines can be developed to direct the care of these challenging comorbid conditions. To provide holistic care to patients, diabetes and cancer management must be incorporated into healthcare curricula and should be an essential part of clinical diabetes educator certification.

At a Glance
- The dual diagnoses of diabetes and cancer are complex for patients and providers.
- Cancer treatments can influence control of diabetes.
- Healthcare education curricula must include more information on the relationship between diabetes and cancer.

Diabetes

Diabetes is a complex disease with multiple pathologic components and is an epidemic in the United States. An estimated 8% of the U.S. population (or about 25.8 million people) have diabetes and cancer are among the leading causes of death in the United States (Xu, Kochanek, Murphy, & Tejada-Vera, 2010). To date, one in four deaths in the United States is caused by cancer. New cases of cancer are projected to reach 1,596,670 in 2011, with 569,490 deaths attributed (American Cancer Society [ACS], 2011). Among men, cancers of the prostate, lung, bronchus, colon, and rectum continue to be the most common and fatal cancers. For women, lung, breast, and colorectal cancers are the most common and fatal (Centers for Disease Control and Prevention [CDC], 2011a). As the number of people becoming long-term survivors of cancer increases, a greater number of patients will have to face the challenge of living with both cancer and diabetes. However, very little information is available about the implications of these two serious diseases for patients and practitioners. Understanding the pathophysiology of cancer and diabetes, identifying links between the two, and identifying areas of concern for healthcare providers caring for patients with these comorbidities may improve patient quality of life. This integrative review of the literature will provide an overview of diabetes and cancer and their complex interaction.

A literature search was conducted using CINAHL®, ProQuest, and MEDLINE® and the key terms diabetes, cancer, comorbid, and dual diagnosis. About 75 articles were identified. Articles selected included English-language articles written from 1998–2011 that discussed the relationship between cancer and diabetes. Three main areas warrant additional discussion: the relationship between glucocorticoids and hyperglycemia, glucose control in the management of diabetes in patients with cancer, and an increased risk of certain cancers along with the comorbid condition of diabetes.

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Digital Object Identifier: 10.1188/11.CJON.654-658
Clinical Journal of Oncology Nursing  •  Volume 15, Number 6  •  The Complex Dual Diagnosis of Diabetes and Cancer

diabetes (American Diabetes Association, 2011; CDC, 2011b). The National Health Interview Survey (NHIS) found that people aged 65 years or older accounted for 40% of all diabetes cases, and the prevalence in that age group is more than 10 times that for people younger than age 45. The NHIS found a four-to-eight-fold increase in the number of people who received a diagnosis of diabetes in the last half of the 20th century (Engelgau et al., 2004).

One in three people born in the United States in 2000 are projected to develop diabetes at some point in their lifetime (Ferri, 2008). In 2007, the estimated cost for diabetes and its treatment was $174 billion (American Diabetes Association, 2011; CDC, 2011b). That estimate includes the cost of healthcare providers, hospital and nursing home services, medication, and home health care. The cost of care for diabetes is one of the top three expenditures in total illness and disease in the United States (Eyre, Kahn, & Robertson, 2004).

Two primary types of diabetes are seen, type 1 and type 2. The genes responsible for diabetes type 1 are carried on the DQ band of the short arms of the #6 chromosome. Those genes are responsible for the major histocompatibility system and control of the immune system (Guthrie & Guthrie, 2004; Patti, 2004). When a portion of those genes malfunction, the immune system’s ability to recognize the body’s own cells is impaired. With diabetes type 1, the body recognizes beta cells as foreign, initiates the immune cascade, and causes T lymphocytes to attack the pancreas. That attack results in an inability to produce insulin. The body’s inability to manufacture insulin progresses to death of beta cells, resulting in diabetes type 1 (Guthrie & Guthrie, 2004; Patti, 2004). Environmental factors also are thought to trigger the immune cascade, resulting in beta cell destruction (Guthrie & Guthrie, 2004; Patti, 2004; Ratner, 2003).

Diabetes type 2 is not a single disease, but, instead, a syndrome resulting from insulin resistance and insulin deficiency related to genetics and lifestyle (Guthrie & Guthrie, 2004). Insulin resistance occurs when the normal amount of insulin secreted by the pancreas is unable to enter into the cells. Genetic abnormalities of insulin receptors inhibit the ability of insulin to bind to receptor sites. That alters the movement of glucose into the cells (Guthrie & Guthrie, 2004). In response, cells send a message that they need more glucose, causing increased production of glucose by the liver even when circulating glucose levels are high. To maintain normal blood glucose, the pancreas secretes additional insulin. In some cases, when the body’s cells resist or do not respond to high levels of insulin, glucose builds up in the blood and causes the hyperglycemia seen in diabetes type 2 (Patti, 2004). Insulin deficiency is the second defect seen in diabetes type 2 and may be caused by beta cell exhaustion from increasing insulin secretion or a combination of multiple factors resulting in the body’s inability to use circulating insulin (Vilsboll et al., 2003). The result of this deficiency is the body’s inability to produce enough insulin to meet cellular needs.

The three main complications that arise from elevated blood glucose are macrovascular, microvascular, and neurologic. Macrovascular complications result from injury to the large blood vessels of the heart and brain. The most common manifestations of macrovascular complication occur in the coronary arteries and the large vessels of the legs. Coronary artery disease and atherosclerosis are two of the most common complications seen with diabetic macrovascular disease (Boyle, 2007; Krentz, Clough, & Byrne, 2007; Mazzone, 2007). Increased blood glucose levels may accelerate atherosclerotic plaques, although the causative mechanism remains uncertain (Guthrie & Guthrie, 2004).

Microvascular complications are better understood than macrovascular complications in patients with diabetes. Microvascular complications affect capillaries throughout the body and the extent of the injury can be diffuse. Organs such as the kidneys and eyes often are involved. In fact, diabetic retinopathy is the most common cause of adult blindness in the United States (Guthrie & Guthrie, 2004); 18% of people three to four years after being diagnosed with diabetes have diabetic retinopathy, and as many as 80% of patients 15 years or more since diagnosis of diabetes develop it (Ferri, 2008; Nguyen, Wang, & Wong, 2007). A second microvascular complication is diabetic nephropathy, the leading cause of end-stage renal disease. About 10%–21% of people with diabetes have nephropathy, and about 44% of new cases of end-stage renal disease are attributed to diabetes. In 2008, 48,374 people with diabetes began treatment for end-stage renal disease in the United States, with 202,290 living with chronic dialysis or post-kidney transplantation (American Diabetes Association, 2011; CDC, 2011b).

Diabetic neuropathy is one of the most common complications of diabetes. An estimated 10%–65% of patients with diabetes have some form of neuropathy (Ferri, 2008). In about 8% of patients, neuropathy already is present at the time of diabetes diagnosis, and 40% of patients 10 years after diagnosis develop neuropathy (Bloogarden, 2007; Ferri, 2008). Data from the National Diabetes Facts Sheet estimated that 60%–70% of people with diabetes have mild to severe forms of nervous system damage (CDC, 2011b). Neurologic complications of diabetes are related to injury of sensory, motor, and autonomic nerves. The most common presentation is the loss of sensation seen in peripheral neuropathy (Kilpatrick, Rigby, & Atkins, 2006).

Cancer

In 2010, the total cost of cancer was $263.8 billion; that amount includes direct and indirect medical costs from loss of productivity caused by illness and death (ACS, 2011). Research has shown that cancer currently has the most devastating economic impact of any cause of death in the world (ACS, 2010).

The general process of cancer development can be understood by thinking of cancer as a disease of growth, division, and cell differentiation (Appleman, Tzachanis, Grader-Beck, Van Puijenbroek, & Boussiotis, 2001; Huether & McCance, 2003). Cell proliferation and differentiation are altered in cancer, and cancer is caused by the malfunction or mutation of protein growth factors that regulate cell division and proliferation. Two mutational routes result in uncontrolled cell proliferation in cancer: stimulation of a gene causing hyperactivity and inhibition of a gene causing inactivity (Huether & McCance, 2003; Yoder, 2006). The stimulation mutation route has a dominant

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effect because only one set of genes within the cell has to mutate. The resulting hyperactivity causes overexpression of a growth-related gene product, resulting in tumor formation. The inhibition gene has a recessive effect where both copies of the cell’s particular differentiation gene are inactivated, freeing the cell of controlled growth inhibition. The result of those two processes is freedom for the cell, allowing proliferation without control from protein growth factors (Huether & McCance, 2003; Yoder, 2006). Complications of cancer vary with the type, stage, treatment implemented, and comorbid conditions. For example, hyperglycemia and diabetes may negatively impact a patient’s risk for cancer, the development of certain types of cancer, and outcomes of cancer treatment (Coughlin, Calle, Teras, Petrelli, & Thun, 2004; Extermann, 2007; Goodwin et al., 2002; Schwab & Porter, 2007; Singer, 2007).

Hyperglycemia and Cancer Treatment

One of the leading treatment options available for cancer is chemotherapy. The agents used to treat different forms of cancer have individualized effects on patients. Although not all chemotherapies alter glucose metabolism, one in particular does: Androgen suppression therapy, used in patients with prostate cancer, is known to affect insulin resistance and increase diabetes or hyperglycemia (Redig & Munshi, 2010). In addition, supportive medications given in conjunction with chemotherapy treatments, such as high-dose steroid injections, also elevate blood glucose levels. At times, the induction of chemotherapy treatment is preceded with steroid therapy that can cause a patient predisposed to diabetes to progress to diabetes type 2. Because little research has been conducted on steroid-induced diabetes, treatment often is conducted intuitively. Management of diabetes in patients with cancer who are undergoing treatment can be challenging because steroid action is not fully understood. Some researchers believe that steroids induce a hypermetabolic state by decreasing glucose uptake, increasing hepatic glucose production, and directly inhibiting insulin release (Oyer, Shah, & Bettenhausen, 2006). Glucocorticoids not only increase postprandial hyperglycemia, but also may increase fasting hyperglycemia (Umpierrez et al., 2002). Schwab and Porter (2007) demonstrated that glucocorticoids directly inhibited insulin release and identified the pancreatic beta cells as an important target of the diabetogenic action of glucocorticoids.

Hyperglycemia has been associated with increased hospital mortality in critically ill patients. Umpierrez et al. (2002) reviewed medical records of 2,030 adult patients with recorded hyperglycemia admitted to general hospital wards at Georgia Baptist Medical Center in Atlanta from July 1, 1998 to October 20, 1998. Records were then divided into three study groups. A normal glycemic group included those patients with normal plasma glucose and no history of diabetes. The remaining patients with hyperglycemia were subdivided into two groups, those with a history of diabetes and those without. Results indicated that new, in-hospital hyperglycemia was significantly related to increased in-house mortality, decreased functional outcome, increased hospital stay, and transfer to a transitional care or nursing home facility at discharge. Although the authors did not specifically address the relationships between hyperglycemia, steroids, and cancer, they provided evidence that new hyperglycemia in any seriously ill patient may result in poor clinical outcomes.

Cancer Survival

Blood glucose control is an important piece of cancer treatment in patients with diabetes and in patients with insulin resistance. Several studies have shown a link between blood glucose control and patient outcomes in the hospital and during cancer treatment (Schwab & Porter, 2007; Singer, 2007; Weiser et al., 2004). For example, research has shown a link between hyperglycemia and increased infections and higher rates of cancer recurrence and mortality (Schwab & Porter, 2007). Elevated postprandial insulin and C-peptide levels also have been shown to increase colorectal cancer risk (Meyerhardt et al., 2003). Will, Galuska, Vinicor, and Calle (1998) found that patients with diabetes tended to have a healthier lifestyle than those without diabetes. They were more likely to smoke fewer cigarettes, consume less alcohol, and eat more fruits, vegetables, and cereal daily than non-diabetics. Even with those factors taken into account, patients with diabetes were at greater risk for colorectal cancer than non-diabetics.

Breast cancer research has shown an interesting correlation between insulin levels and breast cancer outcomes. Women with the highest fasting insulin levels had a two-fold increased risk of distant cancer recurrence and a three-fold increased risk of death from cancer compared to those with lower insulin levels (Coughlin et al., 2004; Goodwin et al., 2002). Goodwin et al. (2002) conducted a study of 512 women with early-stage breast cancer and no known diabetes. The women included in the study were younger than age 75, had a complete resection (lumpectomy with margins clear of invasive cancer or mastectomy), and had axillary node dissection. The women underwent baseline measurements from weeks 4 and 12 postoperatively, prior to any adjuvant therapy. The baseline measurements included demographics, risk factors, physical activity, weight after a 12-hour fast, fasting blood glucose, and a series of psychosocial and eating behavior questions. The results yielded a correlation between fasting insulin levels with distance recurrence and death. In a study by Weiser et al. (2004), the complete remission duration, survival, and treatment-related complications were determined for patients with and without hyperglycemia. The results were quite impressive. When compared to patients without hyperglycemia, patients with hyperglycemia had a shorter complete remission duration (24 months versus 52 months), a shorter median survival (29 months versus 88 months), and were more likely to develop a complicated infection (39% versus 25%).

Researchers examining colon cancer have had similar findings when focusing on diabetes and cancer outcomes. Several studies demonstrated that people with the comorbid conditions of diabetes and stage II and III colon cancer experienced significantly higher rates of overall mortality than those without diabetes (Coughlin et al., 2004; Extermann, 2007; Meyerhardt et al., 2003; Singer, 2007). Those rates continued to be higher for patients with diabetes, even when adjusted for other known or suspected predictors of colon cancer survival. Patients with diabetes often have delayed stool transit and other gastrointestinal abnormalities, which are known to be associated with colorectal cancer (Will et al., 1998).
Diabetes and Cancer Risk

The question has been raised if developing diabetes increases a person’s risk of cancer. The association between diabetes and cancer has received the most attention in the context of colorectal cancer, where patients with diabetes have an increased incidence of colorectal cancer (Brauer, McKeown-Eyssen, & Jazmaj, 2002; Coughlin et al., 2004; Extermann, 2007; Meyerhardt et al., 2003; Will et al., 1998). Cancers of the breast and pancreas also have been correlated with diabetes, but little research is available. In a comprehensive review of the literature, Extermann (2007) discussed how conflicting results exist among investigations reviewing the relationship between diabetes and cancer. A higher death rate is seen in men and women with cancer of the pancreas who develop diabetes compared to patients with pancreatic cancer who do not develop diabetes. Pancreatic cancer has a twofold increase in incidence in patients with diabetes compared to patients without diabetes. Diabetes is both a risk factor for pancreatic cancer and can be a consequence of pancreatic cancer. In addition, elevated insulin levels have been shown to promote growth in human pancreatic cell lines. Peripheral insulin resistance is correlated with increased cell turnover of pancreatic islet cells, and that stimulation of islet cell proliferation may enhance the development of pancreatic cancer (Coughlin et al., 2004).

The relationship between breast cancer, diabetes, and obesity is more confounding. The hypothesized association focuses on a biologic relationship of cancer cell proliferation in response to sex hormones and growth factors (Extermann, 2007). Hyperinsulinemia, along with insulin resistance, has been reported as an independent risk factor for breast cancer (Coughlin et al., 2004). Circulating insulin levels have been found to be higher in women with breast cancer than in women of the same age with benign breast disease. Additional investigation is suggested to examine the effects of age, hormone status, and cancer treatment on the relationship of diabetes and cancer (Extermann, 2007).

Liver cancer is another disease that has been linked to diabetes. Although the mechanism is inadequately understood, alcohol consumption is a risk factor for both diabetes and liver cancer. In addition, when researchers controlled for alcohol consumption, diabetes still appeared to play a role in the development of liver cancer (Coughlin et al., 2004; Extermann, 2007).

Implications for Research, Practice, and Education

Based on the available literature, areas for future research and implications for practice and education can be formulated. Potential research on the comorbid conditions of cancer and diabetes are vast; however, they may specifically focus on the implications of glucocorticoids in the treatment of cancer. As previously stated, the mechanism of action of glucocorticoids is not fully understood and reviewed studies showed poorer patient outcomes in the presence of hyperglycemia, warranting additional research related to glucocorticoids (which are a necessary part of cancer treatment) (Schwab & Porter, 2007; Singer, 2007; Umpierrez et al., 2002). Research also has demonstrated that adequate blood glucose management improves patient outcomes in the inpatient setting (Umpierrez et al., 2002). Lastly, additional research on the relationship between diabetes and the increased risk of certain cancers is necessary. Although most information reviewed discussed the relationship between colon cancer and diabetes (Brauer et al., 2002; Coughlin et al., 2004; Extermann, 2007; Meyerhardt et al., 2003; Will et al., 1998), other cancers were briefly discussed in the literature and warrant additional investigation.

The development of evidence-based practice guidelines for patients with comorbid conditions may be facilitated through additional research; therefore, providing healthcare teams and patients with a deeper understanding of the relationship between diabetes and cancer is critical. Providers have the responsibility to medically manage diabetes and to coach patients and families on how to develop and maintain healthy lifestyle behaviors. An educational tool for patients with diabetes and cancer would be one way of providing the necessary information to patients and their families. Time constraints can be an issue, but time for discussion and planning of care is essential to ensure that the focus remains on the patient and that the most appropriate member of the collaborative team directs the patient care (Buttaro, Trybulski, Bailey, & Sandberg-Cook, 2003). To provide the increased amount of time needed to properly manage patients, a case management approach may be of benefit to the patient and the healthcare team.

Expert healthcare practice begins with expert education. Information related to care of patients with the comorbid conditions of diabetes and cancer should be given to students at all levels of healthcare provider education. However, little information exists in available textbooks on the standards of care for patients with diabetes and cancer. Integrating that knowledge into healthcare curricula is essential and must be a part of the diabetes nurse education certificate.

Conclusion

The epidemics of cancer and diabetes are critical issues for healthcare providers and patients alike. The combined economic cost of cancer and diabetes is about $321.5 billion (Eyre et al., 2004). Because people with cancer are surviving for longer periods of time and diabetes is of epidemic proportions in the United States, more patients will be faced with the challenge of living with both cancer and diabetes. A need exists for continued research on these comorbid conditions so that evidence-based practice guidelines can be developed. Because each of these conditions alone can be devastating, challenges in providing care exponentially increases when both conditions are present in the same patient. Providers must be prepared to meet these challenges.

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