

Importance of Glycemic Control in Cancer Patients with Diabetes: Treatment through End of Life

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ABSTRACT

Cancer patients with diabetes are at increased risk for developing infections, being hospitalized, and requiring chemotherapy reductions or stoppages. While it has been hypothesized that glycemic control increases the risk for these adverse events, few studies have explored this hypothesis. The purpose of this paper is to discuss the importance of glycemic control in patients with diabetes and cancer during treatment through end of life. Glycemic control was found to play a role; the overall level of health-related quality of life experienced by patients with cancer and diabetes, level of symptom severity experienced and can impact the overall survival of the individual. Evidence-based

policies and practice guidelines also need to be developed to help clinicians manage these patients during all phases of care. Using diabetes educators and advance practice, nurses to provide management and care coordination services need to be considered. Survivorship care plans should address both cancer and diabetes management. Finally, glycemic control should continue through end of life, with the main goal of avoiding hypoglycemic events.

Key words: Cancer, chemotherapy, diabetes, end of life, glycemic control, survivorship

Introduction

Cancer and diabetes are two of the leading causes of death in the world today,^[1] and their incidence continues to increase. Individuals with diabetes are at higher risk for developing cancer, specifically cancers of the breast, colon, lung, prostate, and pancreas.^[2] At the time of their

cancer diagnosis, approximately 18% of all patients have preexisting diabetes.^[3,4] Some studies have identified a diabetes prevalence up to 30% in cancer patients depending on cancer type.^[5-9] The incidence of diabetes has been noted to be six times greater in cancer patients than in the general

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population.^[10] For clinicians working with cancer patients, the probability of encountering a patient with diabetes is high. Therefore, health-care providers need to know how diabetes affects cancer-related treatment regimens and outcomes including the role of glycemic control.

Treating Cancer and Diabetes: A Growing Issue

Over the past decade, the number of studies exploring the relationship between cancer and diabetes has steadily increased indicating that researchers and health-care providers are becoming more aware of the issues associated with the simultaneous management of these two complex, chronic conditions. In 2010, the American Diabetes Association and the American Cancer Society released a joint report on the relationship between diabetes and cancer.^[2] This report discussed the links between diabetes and cancer, common risk factors, and the influence of diabetes treatments on the risk of developing cancer and cancer prognosis. Liu *et al.* found that cancer patients with type 2 diabetes (T2D) had a significant risk for cause-specific mortality, and those with pancreatic, lung, prostate, and endometrial cancer had the highest mortality rates.^[11] In addition, cancer patients with the diabetes complications of ketoacidosis, circulatory problems, or coma had poorer prognoses.^[11] Cancer patients with diabetes also are at increased risk for developing infections and being hospitalized while undergoing treatment.^[8,9,12-14]

Diabetes can affect the overall health-related quality of life (HrQOL) of cancer patients. A systematic review conducted by Vissers *et al.*^[15] found that cancer patients with diabetes were more likely to report worse health-related outcomes than those without diabetes. In addition to overall HrQol, cancer patients with diabetes reported lower physical functioning and vitality than did those without diabetes.^[15] The results of another study found that cancer patients with diabetes had significantly lower levels of physical function ($P < 0.001$) and mental health over time ($P > 0.05$) compared to those without diabetes.^[16]

Glycemic Control

One hypothesis for the cause of the outcome differences between cancer patients with and without diabetes is glycemic control. However, few researchers have investigated glycemic control's role in the outcomes of cancer patients with diabetes. Several chemotherapy agents and corticosteroids commonly administered to cancer patients to control side effects have been associated with a risk of hyperglycemia in patients without diabetes.^[17] Research results have noted that diabetes patients undergoing chemotherapy are likely to prioritize their cancer

treatment over managing their diabetes, thus increasing their risk for poor glycemic control during this critical period.^[18] In addition, oncologists and patients' primary care providers may not focus on diabetes management while chemotherapy is being administered.^[18,19] Despite this lack of attention, glycemic control levels can play an important role in improving outcomes for cancer patients with diabetes.

Purpose

The objective of this paper was to review and analyze current literature to determine what is known about the role of glycemic control in cancer treatment, survivorship, and end of life for cancer patients (with a solid tumor or lymphoma) who also have diabetes.

Glycemic Control during Treatment

Few studies have explored the relationship between glycemic control and outcomes in cancer patients with or without diabetes. The four studies found used different methods and designs: two were retrospective,^[20,21] one was cross-sectional,^[22] and one was longitudinal.^[14] In addition, there was little consistency in how glycemic control was measured across studies. While three studies used glycated hemoglobin (HbA1c), the timing of HbA1c measurements varied. Two studies found no association between with glycemic control level and outcomes in cancer patients.^[20,22] Boursi *et al.* used previously obtained HbA1c levels, but patients' glycemic control level at the time of their cancer diagnosis and while they were undergoing treatment were unknown.^[20] Hammer *et al.* obtained an HbA1c level to explore the relationship between patients' diabetic state and specific outcomes at one point in time.^[22] The authors of a longitudinal study explored the relationship between baseline HbA1c and specific outcomes over a 12-week period.^[14] These results showed that individuals with a baseline HbA1c ≥ 7.0 were more likely to incur an infection, hospitalization, or a chemotherapy dose reduction or stoppage.^[14] Unlike the other studies included patients with and without diabetes, this small pilot study was designed to help understand the relationship between glycemic status and outcomes only in cancer patients with diabetes.^[14]

Based on the research to date, it is difficult to determine the role of glycemic status in patients undergoing treatment. Studies consistently have found that patients with diabetes are more likely to develop an infection and are hospitalized while receiving treatment.^[3,8,9,12,23] Poor glycemic control can increase the risk for infections and hospitalizations in patients with diabetes.^[24,25] For cancer patients with diabetes, maintaining glycemic control during treatment may be an important factor for improving survivorship.

Glycemic Control and Survivorship

Cancer is now considered a chronic condition. With this change in perspective, along with treatment advances, the number of cancer survivors has increased. A cancer survivor is anyone who is living with and managing the challenges of a cancer diagnosis.^[26] Currently, 33 million individuals worldwide are living with a cancer history.^[27] To lengthen and improve the lives of cancer survivors with diabetes, the role of glycemic control must be further explicated. Prior research has shown that cancer patients with diabetes will prioritize their cancer treatment over their diabetes care, a choice that reduces their level of engagement in diabetes self-management activities.^[18] This lack of attention to their diabetes can affect their glycemic status and increase their risk for hospitalizations and increased symptom severity and may shorten their lives.^[11,28-31] Adults with cancer and diabetes have a higher prevalence of nonadherence to their oral antidiabetic agents than adults with diabetes who do not have cancer, and this nonadherence increases the risk for poor glycemic control. Adherence to oral agents is associated with 24% fewer hospitalizations in cancer patients with diabetes.^[30]

Poor glycemic control during the survivorship period also has been associated with an increased risk for recurrent cancer events, particularly in women with breast cancer.^[28] Women with an HbA1c ≥ 7.0 had a 26% higher rate of breast cancer-related events compared with women who had better glycemic control (HbA1c $\leq 6.5\%$).^[28] Cancer patients with uncontrolled glycemic levels are at risk for a shorter overall survival than are cancer patients with well-controlled diabetes.^[29]

In addition to the increased risk of mortality and recurrence, cancer patients with diabetes who have poor glycemic control are at risk for lower quality of life due to the increase in symptom severity. Diabetes and cancer share similar symptom profiles: fatigue, pain, numbness, tingling, etc. Glycemic control plays a role in the development and severity of these symptoms in diabetes patients.^[32] Vissers *et al.* found that cancer patients with diabetes experienced more neuropathic symptoms and a higher burden from these symptoms regardless of the type of cancer treatment they received.^[31] Poor glycemic control is associated with higher levels of pain severity in patients with diabetes.^[33] Therefore, it can be hypothesized that cancer patients with diabetes who have poor glycemic control are likely to experience higher levels of pain severity. Individuals with diabetes also experience fatigue that is related to their glycemic control level including hyperglycemia, hypoglycemia, and swings between the two.^[34,35] Fatigue is one of the most common symptoms experienced by cancer patients, both during and after treatment.^[36] In cancer patients with diabetes, fatigue

levels can be exacerbated by hyper- or hypoglycemia, making it important for patients to maintain normoglycemia as much as possible.

Few studies have explored the relationship between glycemic control and outcomes in cancer patients with diabetes during the survivorship period. Results of these few studies consistently indicate that cancer patients with diabetes have increased risk for cancer recurrence, mortality, and symptom severity. For cancer patients with diabetes, diabetes management should be coordinated with the primary care provider and included in the survivorship care plan.

Glycemic Control at End of Life

While the issue of diabetes management and glycemic control at end of life has generated increased interest, few researchers have examined the best way to care for individuals with cancer and diabetes during this critical period. The consensus among researchers is that glycemic control plays a role during this period, mainly in symptom management.^[10,37-41] Quinn *et al.* noted that infrequent blood glucose monitoring might result in confusion about whether symptoms are associated with the dying process or caused by diabetes, leading to inadequate symptom management.^[10] Controlling glucose can lead to a longer end-of-life period with fewer troubling symptoms.^[40]

Discussions during the end-of-life period should include glucose management issues such as the recommended frequency of blood glucose checks. While some providers feel continued blood glucose monitoring with finger pricks is painful and unnecessary,^[10,37,39,41] family members often are reluctant to discontinue these practices during this period.^[39] Although some experts have offered recommendations for managing diabetes and desired glycemic control levels based on a patient's stage in the end-of-life period, there is a lack of prospective studies investigating the glycemic control level most beneficial during end of life. Experts agree that treatment for diabetes patients at end of life should focus on preventing hypoglycemic and hyperosmolar hyperglycemic events (polyuria and polydipsia).^[37-39]

For patients with weeks or months to live, researchers recommend maintaining blood glucose levels between 180 and 360 mg/dl.^[37-39,41] The target level should be tailored to patients' needs, preferences, and risk for hyperosmolar hyperglycemic events. During this time, finger sticks for blood glucose monitoring can be reduced from daily to every 3 days for T2D patients, while patients with type 1 diabetes (T1D) should continue their usual blood glucose monitoring regimen.^[37,39] Monitoring glucose control using HbA1c is no longer recommended during this period.^[37] T1D patients should continue using insulin during this

time, but exercise caution when using long-acting insulin. T2D patients on insulin also may need to continue insulin if they are prone to hyperosmolar hyperglycemic events. Oral agent and insulin dosing for T2D patients may need to be adjusted.^[37-39] Educating patients about the warning signs of hypoglycemia is essential during this period.

For patients with only days to live who are advancing to organ failure, preventing hypoglycemia becomes the main focus of care.^[37] Medications can be stopped for T2D patients, and insulin dosing and administration frequency can be decreased for T1D patients.^[37,38] Glucose monitoring is no longer recommended during this period unless, based on the patient symptoms, it is needed to assess for possible hypo- or hyperglycemia.^[37-39] Short-acting insulin can be used for conscious patients with hyperglycemia symptoms.^[41]

During the end-of-life period, glycemic management goals need to shift from maintaining normoglycemia to preventing hypoglycemia. Health-care providers must communicate with the patient and their family members to develop goals for diabetes monitoring, medication administration, and target glycemic levels. Patients with diabetes and their families need to be educated about what to expect during the end-of-life period as well as the signs and symptoms of hypoglycemia and hyperosmolar hyperglycemic states, so they can help prevent diabetes ketoacidosis.^[38,41]

Nursing Implications

Research

Glycemic control can affect an individual's ability to complete treatment as well as their survival and end-of-life quality. The limited research addressing the relationship between glycemic control in diabetes patients and cancer-related outcomes has been retrospective. Rigorous longitudinal studies need to be conducted to understand the relationship between these two factors. In addition, establishing consistency in how glycemic control is measured in such studies needs to be a priority. While HbA1c generally is considered the gold standard for evaluating glycemic control levels, making the timing and interpretation of HbA1c tests consistent across studies would be helpful for analyzing results. In cancer patients, HbA1c levels can be affected by treatment-related complications such as anemia. Therefore, researchers could consider using a fructosamine test, which determines glycemic status by measuring glycated serum proteins found in the albumin.^[42,43] Fructosamine has two key benefits for cancer patients: it gives a picture of glycemic status over the past 4 weeks (vs. 12 weeks with HbA1c) and is unaffected by red blood cell counts.

In addition to conducting prospective studies and attaining consistency in glycemic control measurement, interventions for cancer patients with diabetes need to be developed and tested. Nursing interventions for cancer patients with diabetes that focus on patient education, symptom management, and improved care coordination need to be designed and tested. Irizarry *et al.* used a retrospective diabetes chart audit to compare diabetes education program utilization by patients with cancer and diabetes compared to those with only diabetes.^[44] The results showed that cancer patients with diabetes who received diabetes education were more likely to have regular outpatient follow-up, HbA1c testing, as well as fewer hospitalizations and emergency department visits.^[44] The researchers did not indicate when the diabetes education was delivered in relation to the patient's cancer diagnosis.^[44] It is recommended that future research explores how well using diabetes educators and Advanced Practice Registered Nurses Clinical Nurse Specialist Nurse Practitioner as care coordinators improve glycemic status management in cancer patients with diabetes during the treatment and survivorship periods.

There is a need for evidence-based policies addressing the management and care of cancer patients with diabetes. Currently, there are no established standards or guidelines for the optimal glycemic levels for patients with diabetes who are undergoing cancer treatment. Often, primary care providers, oncology nurses, and patients are unaware of glycemic status.^[18,19] To achieve the best patient outcomes, glycemic status should be addressed by an interdisciplinary team that includes the patient and his or her oncologist, endocrinologist, primary care provider, and nurses.

Evidence-based practice guidelines or policies that recommend an assessment of diabetes patients' glycemic status at the time of cancer diagnosis should be developed. This assessment can be done with either an HbA1c or a fructosamine test. Patients' glycemic control level at the beginning of treatment may affect the symptoms they experience and their ability to complete treatment.^[9,13,14,32] As the health-care industry moves to more precise and personalized medicine, care plans need to be tailored to each patient's unique needs. Care plans for cancer patients with diabetes must consider the pertinent factors of both chronic conditions.

Survivorship care plans should incorporate recommendations for the continued management, assessment, and treatment of both diabetes and cancer. Such plans need to address all the patient's health-care needs to ensure the highest level of quality of life during this period. As the patient moves from survivorship to end of life, discussions with the patient and family about diabetes

management should include when and how to decrease the frequency of glucose monitoring and diabetes medications.

Conclusion

Managing patients with diabetes and cancer can be challenging for health-care providers. Cancer treatments, such as chemotherapy and corticosteroids, can influence patients' glycemic control level. This effect can be compounded by patients' tendency to focus on treating their cancer to the detriment of their diabetes management. Taken together, these phenomena increase the risk that cancer patients with diabetes will experience poorer outcomes.^[13,17,18] Awareness and management of the glycemic status of cancer patients with diabetes should be part of the patients' care plan from diagnosis through end of life.

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Conflicts of interest

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References

- World Health Organization. Secondary World Health Organization; 2017. Available from: <http://www.who.int/mediacentre/en/>. [Last accessed on 2017 Apr 06].
- Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, *et al*. Diabetes and cancer: A consensus report. *Diabetes Care* 2010;33:1674-85.
- Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, *et al*. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: A systematic review and meta-analysis. *JAMA* 2008;300:2754-64.
- Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, *et al*. Postoperative mortality in cancer patients with preexisting diabetes: Systematic review and meta-analysis. *Diabetes Care* 2010;33:931-9.
- Chia VM, O'Malley CD, Danese MD, Lindquist KJ, Gleeson ML, Kelsh MA, *et al*. Prevalence and incidence of comorbidities in elderly women with ovarian cancer. *Gynecol Oncol* 2013;129:346-52.
- Joung KH, Jeong JW, Ku BJ. The association between type 2 diabetes mellitus and women cancer: The epidemiological evidences and putative mechanisms. *Biomed Res Int* 2015;2015:920618.
- Lees B, Leath CA 3rd. The impact of diabetes on gynecologic cancer: Current status and future directions. *Curr Obstet Gynecol Rep* 2015;4:234-9.
- Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, *et al*. Diabetes mellitus and breast cancer outcomes: A systematic review and meta-analysis. *J Clin Oncol* 2011;29:40-6.
- Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J Clin Oncol* 2009;27:2170-6.
- Quinn K, Hudson P, Dunning T. Diabetes management in patients receiving palliative care. *J Pain Symptom Manage* 2006;32:275-86.
- Liu X, Ji J, Sundquist K, Sundquist J, Hemminki K. The impact of type 2 diabetes mellitus on cancer-specific survival: A follow-up study in Sweden. *Cancer* 2012;118:1353-61.
- Park JH, Kim HY, Lee H, Yun EK. A retrospective analysis to identify the factors affecting infection in patients undergoing chemotherapy. *Eur J Oncol Nurs* 2015;19:597-603.
- Psarakis H. Clinical challenges in caring for patients with diabetes and cancer. *Diabetes Spectr* 2006;19:157-62.
- Hesssion S. Chemotherapy and glycemic control in patients with a type 2 diabetes and cancer: A comparative case analysis. *Asia Pac J Oncol Nurs* 2017;4:224-232.
- Vissers PA, Falzon L, van de Poll-Franse LV, Pouwer F, Thong MS. The impact of having both cancer and diabetes on patient-reported outcomes: A systematic review and directions for future research. *J Cancer Surviv* 2016;10:406-15.
- Hershey DS, Given B, Given C, Von Eye A, You M. Diabetes and cancer: Impact on health-related quality of life. *Oncol Nurs Forum* 2012;39:449-57.
- Hershey DS, Bryant AL, Olausson J, Davis ED, Brady VJ, Hammer M. Hyperglycemic-inducing neoadjuvant agents used in treatment of solid tumors: A review of the literature. *Oncol Nurs Forum* 2014;41:E343-54.
- Hershey DS, Tipton J, Given B, Davis E. Perceived impact of cancer treatment on diabetes self-management. *Diabetes Educ* 2012;38:779-90.
- Goebel J, Valinski S. Identifying issues regarding care of patients with diabetes and cancer from multiple perspectives. *Clin J Oncol Nurs* 2016;20:645-51.
- Boursi B, Giantonio BJ, Lewis JD, Haynes K, Mamtani R, Yang YX. Serum glucose and hemoglobin A1C levels at cancer diagnosis and disease outcome. *Eur J Cancer* 2016;59:90-8.
- Brunello A, Kapoor R, Extermann M. Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity. *Am J Clin Oncol* 2011;34:292-6.
- Hammer MJ, Aouizerat BE, Schmidt BL, Cartwright F, Wright F, Miaskowski C. Glycosylated hemoglobin A1c and lack of association with symptom severity in patients undergoing chemotherapy for solid tumors. *Oncol Nurs Forum* 2015;42:581-90.
- Hope C, Robertshaw A, Cheung KL, Idris I, English E. Relationship between HbA1c and cancer in people with or without diabetes: A systematic review. *Diabet Med* 2016;33:1013-25.
- Honish A, Westerfield W, Ashby A, Momin S, Phillippi R. Health-related quality of life and treatment compliance with diabetes care. *Dis Manag* 2006;9:195-200.
- Lee PH, Franks AS, Barlow PB, Farland MZ. Hospital readmission and emergency department use based on prescribing patterns in patients with severely uncontrolled type 2 diabetes mellitus. *Diabetes Technol Ther* 2014;16:150-5.
- Hebdon M, Foli K, McComb S. Survivor in the cancer context: A concept analysis. *J Adv Nurs* 2015;71:1774-86.
- Gordon BE, Chen RC. Patient-reported outcomes in cancer survivorship. *Acta Oncol* 2017;56:166-73.
- Erickson K, Patterson RE, Flatt SW, Natarajan L, Parker BA, Heath DD, *et al*. Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. *J Clin Oncol* 2011;29:54-60.
- Lee SJ, Kim JH, Park SJ, Ock SY, Kwon SK, Choi YS, *et al*.

- Optimal glycemic target level for colon cancer patients with diabetes. *Diabetes Res Clin Pract* 2017;124:66-71.
30. Tan X, Feng X, Chang J, Higa G, Wang L, Leslie D. Oral antidiabetic drug use and associated health outcomes in cancer patients. *J Clin Pharm Ther* 2016;41:524-31.
 31. Vissers PA, Mols F, Thong MS, Pouwer F, Vreugdenhil G, van de Poll-Franse LV. The impact of diabetes on neuropathic symptoms and receipt of chemotherapy among colorectal cancer patients: Results from the PROFILES registry. *J Cancer Surviv* 2015;9:523-31.
 32. Hershey DS, Pierce SJ. Examining patterns of multivariate, longitudinal symptom experiences among older adults with type 2 diabetes and cancer via cluster analysis. *Eur J Oncol Nurs* 2015;19:716-23.
 33. Bair MJ, Brizendine EJ, Ackermann RT, Shen C, Kroenke K, Marrero DG. Prevalence of pain and association with quality of life, depression and glycaemic control in patients with diabetes. *Diabet Med* 2010;27:578-84.
 34. Park H, Park C, Quinn L, Fritschi C. Glucose control and fatigue in type 2 diabetes: The mediating roles of diabetes symptoms and distress. *J Adv Nurs* 2015;71:1650-60.
 35. Singh R, Kluding PM. Fatigue and related factors in people with type 2 diabetes. *Diabetes Educ* 2013;39:320-6.
 36. Barsevick AM, Irwin MR, Hinds P, Miller A, Berger A, Jacobsen P, *et al*. Recommendations for high-priority research on cancer-related fatigue in children and adults. *J Natl Cancer Inst* 2013;105:1432-40.
 37. Angelo M, Ruchalski C, Sproge BJ. An approach to diabetes mellitus in hospice and palliative medicine. *J Palliat Med* 2011;14:83-7.
 38. Jeffreys E, Rosielle DA. Diabetes management at the end of life #258. *J Palliat Med* 2012;15:1152-4.
 39. King EJ, Haboubi H, Evans D, Baker I, Bain SC, Stephens JW. The management of diabetes in terminal illness related to cancer. *QJM* 2012;105:3-9.
 40. Kondo S, Kondo M, Kondo A. Glycemia control using A1C level in terminal cancer patients with preexisting type 2 diabetes. *J Palliat Med* 2013;16:790-3.
 41. McCoubrie R, Jeffrey D, Paton C, Dawes L. Managing diabetes mellitus in patients with advanced cancer: A case note audit and guidelines. *Eur J Cancer Care (Engl)* 2005;14:244-8.
 42. Kim KJ, Lee BW. The roles of glycated albumin as intermediate glycation index and pathogenic protein. *Diabetes Metab J* 2012;36:98-107.
 43. Macdonald DR, Hanson AM, Holland MR, Singh BM. Clinical impact of variability in HbA1c as assessed by simultaneously measuring fructosamine and use of error grid analysis. *Ann Clin Biochem* 2008;45(Pt 4):421-5.
 44. Irizarry L, Li QE, Duncan I, Thurston AL, Fitzner KA, Edwards BJ, *et al*. Effects of cancer comorbidity on disease management: Making the case for diabetes education (a report from the SOAR program). *Popul Health Manag* 2013;16:53-7.