The Impact of Hyperglycemia on Hematopoietic Cell Transplantation Outcomes: An Integrative Review

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Since Van den Berghe et al. (2001) published the results of their groundbreaking study showing that tight glycemic control in the critical care setting significantly improved patient outcomes, researchers have attempted to understand the relationship between hyperglycemia and patient outcomes in a variety of clinical settings. Hyperglycemia, defined by the American Diabetes Association ([ADA], 2013) as a fasting blood glucose (BG) level of 126 mg/dl or greater or a random glucose of 200 mg/dl or greater, is experienced by a large majority of patients during the acute treatment phase of hematopoietic cell transplantation (HCT) (Hammer et al., 2009; Rentschler, 2010), and has, therefore, been studied in this patient population. This review synthesizes the results of these studies.

Hematopoietic Cell Transplantation and Hyperglycemia

HCT is a potentially curative treatment for a variety of malignant and nonmalignant hematologic disorders not resolved through first-line therapies. Although HCT has a high rate of success, it also is associated with a high rate of morbidity and mortality during the acute post-transplantation phase related to infection, organ toxicity, and other complications such as acute and chronic graft-versus-host disease (GVHD) (Appelbaum, Forman, Negrin, & Blume, 2009). Many of the contributors to these adverse outcomes are nonmodifiable. Research is showing, however, that one modifiable factor may be hyperglycemia. Therefore, understanding the scope of the influence of hyperglycemia is essential for optimizing outcomes.

Research completed in a variety of patient populations has shown that hyperglycemia is associated with adverse outcomes in the hospitalized patient and is described in a consensus report by the American Association of Clinical Endocrinologists and the ADA (Moghissi et al., 2009). Hyperglycemia can increase

Problem Identification: Many patients undergoing hematopoietic cell transplantation (HCT) for hematologic malignancies experience hyperglycemic events during treatment, leading to adverse outcomes. Understanding how hyperglycemia during the acute HCT treatment phase impacts outcomes is vital for preventing and mitigating adverse events. This integrative review evaluates the impact of hyperglycemia on adult patients undergoing HCT.

Literature Search: PubMed, MEDLINE®, and CINAHL® electronic databases were used to identify relevant articles.

Data Evaluation: The final sample for this integrative review included 12 empirical quantitative reports of clinical patient outcomes. Of the 12, 10 are retrospective, 1 is case-control, and 1 is prospective.

Data Analysis: Content analysis was used to synthesize and summarize findings.

Presentation of Findings: A review of published literature found associations between hyperglycemia and infection, time to engraftment, development of acute graft-versus-host disease, length of stay, and overall survival. Patient-related risk factors for hyperglycemia included older age, preexisting diabetes, and insulin resistance (i.e., prediabetes). Patients of normal weight experiencing hyperglycemia had worse outcomes than patients who were overweight or obese. Treatment-related risk factors for hyperglycemia include dose and duration of immunosuppressants, specifically corticosteroids, treatment with antihyperglycemic medications, and use of total parenteral nutrition.

Implications for Nursing Practice: HCT is one of the most complex treatments for hematologic disorders. The transplantation nurse, as part of an interdisciplinary team, plays an essential role in glycemic control during the acute phase of HCT. Understanding the effects of hyperglycemia, as well as factors that place the patient at risk for hyperglycemia, allows the nurse to make well-informed, proactive interventions aimed at glycemic control.

Key Words: hyperglycemia; hematopoietic cell transplantation; outcomes; integrative review

oxidative stress, leading to impaired immune function, decreased healing time, prolonged blood coagulation time, and cause endothelial dysfunction (Hammer &

Voss, 2012). Hypoglycemia (Vanhorebeek, Langouche, & Van den Berghe, 2007) and glycemic variability (Egi, Bellomo, Stachowski, French, & Hart, 2006) also have been shown to negatively impact outcomes of acute illness. Hyperglycemia is a frequent occurrence in HCT and, therefore, the focus of this review.

The prevalence of hyperglycemia in recipients of HCT is reported to range from 71% (Rentschler, 2010) to 93% (Hammer et al., 2009). That can be related to the stress of acute illness common in hospitalized patients (Butler, Btaiche, & Alaniz, 2005; Godbout & Glaser, 2006; Inzucchi, 2006) or as a side effect of adjunct HCT treatments such as corticosteroids (Butler et al., 2005; Donihi, Raval, Saul, Korytkowski, & DeVita, 2006; Fernandez-Miranda et al., 1998), calcineurin inhibitors (Butler et al., 2005; Fernandez-Miranda et al., 1998; Ramos-Cebrian, Torregrosa, Gutierrez-Dalmau, Oppenheimer, & Campistol, 2007), and peripheral nutrition (Klein, Stanek, & Wiles, 1998). Hyperglycemia manifests as a worsening of control of preexisting diabetes or as a new symptom in patients without a known history of glucose intolerance. In many patients, hyperglycemia is transient and resolves when treatment concludes, but in about 17%–30% of HCT recipients, frank diabetes develops (Griffith, Jagasia, & Jagasia, 2010; Karnchanasorn, Malamug, Jin, Karanes, & Chiu, 2012). The purpose of the current review is to evaluate existing evidence and discuss implications for nursing practice in the area of hyperglycemia in the context of HCT.

Methods

Following the guidelines for integrative reviews set forth by Whittemore and Knalf (2005) articles were searched for, reviewed, and eliminated until final selection for analyses. Three electronic databases were searched (PubMed, CINAHL®, and MEDLINE®) using key words *hyperglycemia* OR *blood glucose* AND *hematopoietic cell transplantation* OR *bone marrow transplantation*. The inclusion criteria were empirical studies, in English, that examined the impact of hyperglycemia on adult HCT patient outcomes from 2000–2013. Twenty-nine articles were initially found. Three additional articles were added from articles referenced in the initial 29 journals. The abstracts from these 32 articles were reviewed for eligibility by the three authors. Twenty of these articles were eliminated because they did not meet the full inclusion criteria, leaving 12 full-text articles for the review.

Content analysis was performed on the 12 articles to address research questions, synthesize data, and summarize findings. Results were based on the major findings, including associations found between hyperglycemia and patient outcomes and risk factors for hyperglycemia. Table 1 provides a summary of these results.

Results

Hyperglycemia and Infection

Infection is a primary cause of death among HCT recipients due to immunosuppression from both the malignancy and the conditioning regimens (Ninin et al., 2001). Hyperglycemia compounds the risk for infection through further compromising immune function by impairing immune cell signaling (Butler et al., 2005). Infections themselves can cause elevations in BG levels (Turina, Christ-Crain, & Polk, 2006) and further promote proliferation of microorganisms, leading to a vicious cycle of hyperglycemia increasing the risk for infections and infections increasing the risk for hyperglycemia. In the studies reviewed, positive associations were seen between hyperglycemia and infection in four (Derr, Hsiao, & Saudek, 2008; Fuji et al., 2009; Rentschler, 2010; Sheean, Freels, Helton, & Braunschweig, 2006) of the five studies with infection as a primary outcome. An earlier study by Fuji et al. (2007) did not find an association between infection and hyperglycemia.

Hyperglycemia and Time to Engraftment

Until the infused hematopoietic cells migrate to the host's bone marrow, or engraft, the patient remains at high risk for infections. Patients become pancytopenic and, in particular, neutropenic. Neutrophil recovery (absolute neutrophil count greater than $1,000/mm^3$) is the hallmark of engraftment and can take as long as 3–4 weeks depending on the type of transplantation and stem cell source (Cutler & Antin, 2005). Full recovery of hematopoiesis and the immune system can take several months after an autologous transplantation and as long as two years following an allogeneic transplantation (Antin, 2002), leaving the patient susceptible to infections for a prolonged period. The longer the period of pancytopenia, the greater the associated morbidity and mortality; therefore, understanding any impediments to engraftment is critical. Studies related to time-to-engraftment were mixed. Sheean et al. (2006) found hyperglycemia to increase time-to-engraftment, whereas Karnchanasorn, Malamug, Jin, Karanes, and Chiu (2012) did not find this association in the autologous HCT participant sample studied.

Hyperglycemia and Acute Graft-Versus-Host Disease

Acute GVHD is an immunologic-mediated disease that contributes to transplantation-related morbidity and mortality, with a mortality rate as high as 50% for those with the greatest severity (Barton-Burke et al., 2008). Because of histocompatibility antigen differences, T cells from the donor graft attack the host's mucous membranes of the skin, gastrointestinal tract, and liver (Barton-Burke et al., 2008). This occurs in 30%–50% of

Table 1. Literature Review

Study	Design	Patient Population	Measures	Findings	Conclusions
Derr et al., 2008	Retrospective, cohort study. The purpose was to evaluate the association between hyperglycemia and infection in BMT. **Level of evidence:** IV	382 adult patients who received allogeneic or autologous BMT at the Johns Hopkins Sidney Kimmel Cancer Center from November 2002 to November 2006	**Outcome:** Neutropenic infections with statistical adjustments for age, gender, race, type of cancer, BMT type, and cumulative GCs dose; mean glycemia and LOS, critical status, and mortality **BG:** Measured during hospital stay (central laboratory and POC testing); BG was measured between admission and 8 am on date of neutropenia.	**Neutropenic infections:** 22% developed one or more infections, with 13% incurring bloodstream infections. During neutropenia, each 10 mg/dl increase in BG preneutropenia was associated with an OR of 1.08 for any infection (p = 0.14), an OR of 1.15 for bloodstream infection (p = 0.001); without GCs, an OR of 1.21 for any infection (p < 0.0001), and an OR of 1.24 for bloodstream infection (p < 0.0001). **Other outcomes:** No association was found between mean glycemia and LOS, critical status, or mortality.	BMT populations are at risk for antecedent hyperglycemia and later infection, particularly those who receive GCs during neutropenia. Tight glycemic control may reduce infections.
Fuji et al., 2007	Retrospective, cohort study. The purpose was to assess the association between BG and FN, infection during neutropenia, organ dysfunction, acute GVHD, OS, and NRM. **Level of evidence:** IV	112 adult patients who received myeloablative allogeneic HSCT from January 2002 to June 2006 at the National Cancer Center Hospital in Tokyo, Japan	**Outcome:** Occurrence of FN, documented infection during neutropenia, organ dysfunction during neutropenia, acute GVHD, OS, and NRM; OS and NRM were assessed with the clinical factors of age, gender, conditioning regimen, donor match, GVHD prophylaxis, and disease risk. **BG:** Patients were categorized based on mean fasting BG during neutropenic period after conditioning. • Normoglycemia (< 110 mg/dl) • Mild hyperglycemia (110–150 mg/dl) • Moderate to severe (> 150 mg/dl)	**FN and documented infection:** No statistical differences were found with varying levels of BG. **Organ dysfunction:** Hyperglycemia risk for hypercreatinemia (OR = 5.2, p = 0.039), hyperbilirubinemia (OR = 4.9, p = 0.005), and increased inflammatory markers (OR = 6.7, p = 0.001) **Acute GVHD, NRM, OS:** Hyperglycemia risk for acute GVHD (OR = 2.3, p = 0.013), NRM (OR = 2.9, p = 0.013); and OS (OR = 2, p = 0.019)	An association was noted between degree of hyperglycemia during neutropenia and increased risk of post-transplantation complications and NRM.
Fuji et al., 2009	Case-control study. The purpose was to investigate the clinical benefits of comprehensive nutritional support, including IGC and PN management, to decrease adverse outcomes in allogeneic HSCT. **Level of evidence:** III	64 patients who received allogeneic HSCT from June 2006 to May 2007 at the National Cancer Center Hospital in Tokyo, Japan	**Outcome:** Documented infectious complications and organ dysfunction were based on glycemic status comparing patients who received IGC and PN management with those who did not. **BG:** Tested every morning. Target BG was 80–110 mg/dl; if morning BG was above target, testing was increased to 2–4 times per day. Categories of BG were 80–110, 111–140, 141–179, and 180 mg/dl or greater.	The IGC group had lower glucose levels compared to control (least-square mean, 116.4 mg versus 146.8 mg per 100 ml, p < 0.001), as well as lower documented infections (14% versus 46%, p = 0.004) and bacteremia (9% versus 39%, p = 0.002). A trend was noted toward decreased renal dysfunction (19% versus 37%, p = 0.36) and increased CRP (18% versus 38%, p = 0.13) in IGC compared to control.	IGC may have beneficial effects after HSCT.

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ALL—acute lymphoblastic leukemia; AML—acute myeloid leukemia; BG—blood glucose; BMI—body mass index; BMT—bone marrow transplantation; CI—confidence interval; CRP—c-reactive protein; FN— febrile neutropenia; GCs—glucocorticoids; GVHD—graft-versus-host disease; HSCT—hematopoietic stem cell transplantation; HCT—hematopoietic cell transplantation; HR— hazard ratio; IGC—intensive glucose control; LOS—length of (hospital) stay; NRM—nonrelapse mortality; OR—odds ratio; OS—overall survival; PN—parenteral nutrition; POC—point of contact; PTDM—post-transplant diabetes mellitus; TBI—total body irradiation; TPN—total parenteral nutrition; WBC—white blood count

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Table 1. Literature Review *(Continued)*

Study	Design	Patient Population	Measures	Findings	Conclusions
Garg et al., 2007	Retrospective, cohort study. The purpose was to investigate the relationship between hyperglycemia and LOS. **Level of evidence:** IV	118 inpatients in the BMT unit at Brigham and Women's Hospital from January to June 2006	**Outcome:** Mean LOS of normoglycemic versus hyperglycemic groups considering age, gender, presence of infection, diabetes status, renal status, and GC use. **BG:** All BG levels during patient hospitalization were obtained from the central laboratory and did not include bedside monitoring. Categories were less than 91, 91–100, 101–110, 110–120, and greater than 120 mg/dl (Normoglycemia is 100 mg/dl or less and hyperglycemia is greater than 100 mg/dl.).	Mean LOS was significant when comparing the normoglycemic group ($\overline{X}$ = 15.9, SD = 5.7 days) with the hyperglycemic groups ($\overline{X}$ =19.8, SD = 9 days, $p < 0.01$). Significant correlations also were shown between highest BG value and LOS ($r = 0.44$, $p < 0.001$) even when excluding patients with infections ($r = 0.32$, $p < 0.05$). Patients treated with GCs had higher BGs ($\overline{X}$ =111.2, SD = 14.8 mg/dl) and longer LOS ($\overline{X}$ =22.1, SD = 11.54 days) than those who did not receive GCs ($\overline{X}$ =102, SD = 9.9 mg/dl; $\overline{X}$ =17, SD = 6.4 days). Effects persisted when patients receiving GCs were excluded, mean BG and LOS ($r = 0.29$, $p < 0.005$) and highest BG value and LOS ($r = 0.29$, $p < 0.005$). Gender had no effect on LOS. When patients with preexisting diabetes ($\overline{X}$ LOS = 17.5, SD = 7.9 days) were added to analysis, study results did not change. **Other outcomes:** Rates of infection between the groups were not statistically significant. No patients had renal failure.	Inpatient BG levels are associated with increased LOS in patients receiving BMT. GC use is associated with hyperglycemia in the BMT setting.
Gebremedhin et al., 2012	Retrospective, cohort study. The purpose was to investigate whether new-onset hyperglycemia immediately after HCT predicts acute GVHD. **Level of evidence:** IV	328 adults who underwent allogeneic HSCT for AML, ALL, and myelodysplastic syndrome at City of Hope National Medical Center from October 2003 to April 2009	**Outcome:** Hyperglycemia (morning serum glucose) and the development of acute GVHD adjusted for donor/recipient characteristics, prophylactic regimen, and mucositis **BG:** Mean morning serum glucose on days 1–10 was measured daily between midnight and 8 am. Hyperglycemia was categorized as • Mild (6.11–8.33 mmol/L, 110–150 mg/dl) • Moderate (8.34–9.98 mmol/L, 151–179.9 mg/dl) • Severe (> 9.99 mmol/L, > 180 mg/dl).	Among normal to overweight patients, severe hyperglycemia doubled the risk of acute GVHD (HR = 2.71, 95% CI [1.58, 4.65]). In obese patients, severe hyperglycemia did not significantly affect risk of GVHD. Hyperglycemia was associated with male gender, the combination of Hispanic ethnicity with unrelated donor, greater BMI, tacrolimus, GCs, myeloablative conditioning with TBI, and TPN.	Severe hyperglycemia in the first 10 days after allogenic HSCT in nonobese patients was predictive of acute GVHD.

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Table 1. Literature Review *(Continued)*

Study	Design	Patient Population	Measures	Findings	Conclusions
Griffith et al., 2011	Prospective study. The purpose was to investigate the risk factors and incidence for PTDM in the first 100 days after allogenic HCT. **Level of evidence:** III	84 adult patients receiving allogenic HCT without preexisting diabetes at Vanderbilt-Ingram Cancer Center	**Outcome:** Factors associated with PTDM at day +100 and association between PTDM and OS were examined, including c-peptide, insulin level, indication for HCT, weight, peak steroid dose, duration of steroids, and other immunosuppressant therapy. **BG:** Fasting glucose measured weekly until day 100. First fasting glucose ($\geq$ 126 mg/dl) or random glucose ($\geq$ 200 mg/dl) were considered diagnostic of PTDM.	**Independent predictors of PTDM:** Pretransplantation c-peptide level greater than 3.6 ng/ml (OR = 5.9; 95% CI [1.77, 20.22], p = 0.004); unrelated donor allogenic HCT (OR = 4.3; 95% CI [1.34, 14.2], p = 0.014); and peak steroid dose greater than 1 mg/kg per day (OR = 5.09, 95% CI [1.19, 23.2], p = 0.021) **Independent predictor of inferior OS:** PTDM ($\overline{X}$ = 1.7 years versus 2.9 years, p = 0.12), and pretransplantation c-peptide level greater than 3.6 ng/dl (HR = 1.05, 95% CI [1.01, 1.09], p = 0.013)	Higher pretransplantation c-peptide, unrelated donor status, and peak steroid doses in the first 100 days post-transplantation are associated with new-onset PTDM. Patients with PTDM and elevated c-peptide had inferior OS.
Hammer et al., 2009	Retrospective, cohort study. The purpose was to investigate the associations between glycemic status and infection and mortality rates among allogeneic HCT recipients. **Level of evidence:** IV	1,175 patients aged 18 years and older with hematologic malignancies who received allogeneic HCT from 2000–2005 at Fred Hutchinson Cancer Research Center	**Outcome:** Onset of first infection and NRM with statistical adjustments for age at HCT, severity of disease, type of donor, year of HCT, and presence of grades 2–4 acute GVHD **BG:** Measurements within 100 days of HCT (reference, 101–150 mg/dl): 0–70, 71–100, 151–200, 201–300, and greater than 300 mg/dl). Minimum BG is greater than 89 mg/dl (0–89)	**Infection:** HR of 1.29 for a BG level of 151–200 mg/dl compared to 101–150 mg/dl (p = 0.004); variability HR of 1.41 with a standard deviation of greater than 49 mg/dl compared to a SD of 0–18 mg/dl (p < 0.0001) **Mortality:** HR of 1.93 for a BG level greater than 200 mg/dl (p = 0.0009); HR of 2.78 for a BG level greater than 300 mg/dl (p = 0.0004) compared with a BG level of 101–150 mg/dl. BG level of 89 mg/dl or less, HR of 2.17 for day 200 NRM compared with a BG level greater than 89 mg/dl (p < 0.0001) upper quartile of BG variability; HR of 14.57 for day 200 NRM relative to first quartile (p < 0.0001)	Recipients of allogeneic HCT 18 years and older are at risk for infections and NRM with hyperglycemia, hypoglycemia, or increased glycemic variability (collectively termed malglycemia).
Karncha-nasorn et al., 2012	Retrospective, cohort study. The purpose was to examine the impact of BG concentration on the outcomes of autologous HCT. **Level of evidence:** IV	240 adult patients receiving autologous HSCT who were discharged from City of Hope National Medical Center from January to December 2006	**Outcome:** BG average, LOS, time to engraftment, rate of infection; covariates included age, gender, BMI, use of TPN and GCs. Further analysis was conducted to assess the relationship between post-transplantation BG average less than 150 mg/dl and BG average of 150 mg/dl or greater and LOS. **BG:** Measured each morning by laboratory during hospital stay—those done by POC were converted to serum using serum glucose calculation. BG taken from admission to discharge.	Age, BMI, and TPN had a significant positive effects of pre- and post-transplantation average BG. **Correlation:** No correlation between post-transplantation BG and platelet engraftment (p > 0.05). No correlation between post-transplantation BG and neutrophil engraftment (p > 0.05). Post-transplantation BG was correlated with LOS (p = 0.0001). **Infection:** The number of documented infections was not statistically significant between the two groups defined by post-transplantation morning BG less than 150 mg/dl or 150 mg/dl and greater.	Post-transplantation BG was associated with longer LOS but not with platelet or neutrophil engraftment.

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Table 1. Literature Review *(Continued)*

Study	Design	Patient Population	Measures	Findings	Conclusions
Pidala et al., 2011	Retrospective, cohort study. The purpose was to examine the effects of dysglycemia on outcomes of allogenic HCT recipients treated with GCs for GVHD. **Level of evidence:** IV	147 patients with acute GVHD treated with steroids admitted for allogenic HCT from 2004–2008 at Moffitt Cancer Center in Tampa, FL	**Outcome:** The effect of hyperglycemia at 12 weeks post-HCT on OS and NRM, considering the following variables: preexisting diabetes, age, underlying condition, risk category, remission status at time of HCT, donor characteristics, conditioning regimen, and BMI, GVHD characteristics, GC, and antihyperglycemic therapy **BG:** All BG values from date of GCs initiation until death or last follow-up • Max (100–140 mg/dl) • Min (0–150 mg/dl) • Average (85–200 mg/dl or higher)	Baseline diabetes predicted greater maximum, mean, and standard deviation of BG levels. Maximum, average, or standard deviation of glucose values predicted OS, and maximum or average glucose values predicted NRM. Minimum glucose values (0–60 mg/dl) were associated with worsened OS and increased NRM. Patients treated with oral antihyperglycemic agents or insulin had worse OS and increased NRM compared to patients who did not need therapy.	The data suggest an independent adverse effect of dysglycemia in patients treated with GCs for acute GVHD, and argue for stringent glycemic control in this setting.
Rentschler et al., 2010	Retrospective, cohort study. The purpose was to determine the incidence of hospital-related hyperglycemia after HSCT and to assess for association with hyperglycemia and LOS and medical complications. **Level of evidence:** IV	160 patients receiving HSCT without preexisting diabetes in 2004 at the Nebraska Medical Center	**Outcome:** Differences existed between participants with hyperglycemia and those without in regards to treatments (TPN and GCs) and renal, cardiac, and infectious complications, GVHD, LOS, and OS outcomes. LOS was adjusted for gender, age, diagnosis, chemotherapy regimen, cardiac and renal complications, infection, GVHD, immunosuppressive medications, insulin therapy, GC use, and TPN. **BG:** All BG, including POC and venous draws, analyzed the average BG level over the LOS for each patient. BG was categorized by the observed quintiles: Less than 101, 101–108, 109–120, 121–135, and greater than 135 mg/dl. Hyperglycemia was defined as 2 or greater fasting BGs of 126 mg/dl or higher or 1 BG of 200 mg/dl or higher.	**Hyperglycemia:** Seventy-one percent of patients had hospital-related hyperglycemia. Hospital-related hyperglycemia was associated with increased complications (56% versus 39%, p = 0.05), with infection being the most common (38%). Thirteen percent developed a cardiac complication and 6% developed a renal complication. The majority (93%) was treated with steroids and 39% received TPN. **LOS:** LOS was not associated with the development of hyperglycemia after adjusting for confounders.	TPN and increasing age are both risk factors for the development of hospital-related hyperglycemia in HCT recipients. Hyperglycemia was associated with increased risk of complications but was not associated with longer LOS.

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Table 1. Literature Review *(Continued)*

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Sheean et al., 2004	Retrospective, cohort study. The purpose was to determine whether TPN-induced hyperglycemia is associated with adverse outcomes. **Level of evidence:** IV	48 adult patients admitted to Rush-Presbyterian St. Luke's Medical Center or the University of Illinois Medical Center from July to December 2001 for initial autologous or allogeneic HCT	**Outcome:** Hyperglycemia, number and duration of infections, and in-hospital mortality. **BG:** Recorded once a day from morning blood draw. Hyperglycemia was defined as BG greater than 6.1 mmol/L (110 mg/dl).	**Hyperglycemia:** Recipients of TPN experience more hyperglycemia ($p < 0.05$) after TPN initiation. **Infections:** Recipients of TPN experienced 69% of all infections and 100% of all repeat positive blood cultures (not a significant difference between the TPN and non-TPN groups). **Support:** Recipients of TPN had more platelet transfusions than those not receiving TPN ($\bar{X} = 2.2$, SD = 3 versus $\bar{X} = 0.8$, SD = 0.9, $p = 0.08$). **LOS:** Recipients of TPN had greater length of stay and daily charges than those not receiving TPN. **Mortality:** In-hospital differences in mortality were not detected between the TPN groups.	Inpatients receiving HCT and TPN had greater incidence of hyperglycemia when compared to those who did not. The small sample size limited the power of this study.
Sheean et al., 2006	Retrospective, cohort study. The purpose was to assess the incidence of hyperglycemia and its effects on post-HCT outcomes in patients receiving TPN versus those not receiving TPN. **Level of evidence:** IV	357 adult inpatients undergoing autologous and allogeneic HSCT from September 1999 to December 2003 at two urban university hospitals	**Outcome:** A comparison was done of hyperglycemia levels in TPN versus those not receiving TPN with consideration given to GC use and donor type. Number of infections, red cell and platelet transfusions, WBC count, platelet engraftment, and hyperlipidemia were examined in relation to TPN use. **BG:** Recorded once a day from morning blood draw; hyperglycemia was defined as BG of 110 mg/dl or greater. Levels of hyperglycemia were based on percentage of hospital days with BG of 110 mg/dl and greater and 200 mg/dl and greater.	**Hyperglycemia:** All patients developed increases in BG levels the first few days of hospitalization with a return to lower levels on subsequent days. Patients who began TPN had more hyperglycemic days than those without TPN, even when stratified by steroid and donor type (88% versus 8%, $p < 0.001$). **Morbidity:** TPN recipients were two times or more likely to become infected than those not receiving TPN (OR = 2.2; 95% CI [1.4, 3.5]). The association was only slightly attenuated when patients with infections, receiving steroids, and donor type were removed. The association increased in normal and underweight patients with TPN (OR = 4.3; 95% CI [1.7, 10.6]) compared to overweight and obese patients. Allogeneic patients receiving TPN had higher rates of infection ($p = 0.001$), red blood cell ($p = 0.001$), and platelet ($p \geq 0.001$) transfusions. Patients who received TPN compared to those who did not had significant differences in time to WBC engraftment for autologous ($\bar{X} = 11.9$, SD = 2.4 versus $\bar{X} = 11.2$, SD = 1.9 days, $p = 0.01$) and allogeneic ($\bar{X} = 14.8$, SD = 4.8 versus $\bar{X} = 12.3$, SD = 2.5 days, $p = 0.001$).	The broad use of TPN in patients undergoing HSCT was associated with profound hyperglycemia, resultant morbidity (increases in infection rates, greater requirements for transfusions, and time to engraftment), and questionable efficacy in the adult, well-nourished cohort.

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all allogeneic transplantation recipients (Goerner et al., 2002), with increased incidence in mismatched and unrelated transplantations, use of peripheral stem cells, and increased age (Dean & Bishop, 2003). Additional risk factors for GVHD include higher doses of radiation, advanced disease, and viral infections in either the recipient or the donor (Anagnostopoulos & Giralt, 2002).

Fuji et al. (2007) showed a positive correlation between degree of hyperglycemia during neutropenia and the risk for the development of grade II–IV acute GVHD. A subsequent study (Gebremedhin, Behrendt, Nakamura, Parker, & Salehian, 2012) found hyperglycemia during the first 10 days after allogeneic HCT to be positively associated with the development of graft-versus-leukemia (the targeted effect that prevents future malignant cells from forming and proliferating) and acute GVHD (the deleterious point past the graft-versus-leukemic effect that can lead to severe adverse outcomes, including death) to be dependent on the underlying diagnosis and patient characteristics. Patients who were normal or overweight had severe hyperglycemia and double the risk of GVHD, whereas patients who were obese had no increased risk (Gebremedhin et al., 2012).

Hyperglycemia and Length of Stay

HCT requires extensive inpatient time related to a prolonged depleted immune system. One investigation showed the median length of stay (LOS) post-HCT was 20 days for autologous and 28 days for allogeneic patients (Center for Medicare and Medicaid Services, 2010). Increases in LOS can adversely affect patient quality of life (Prieto et al., 2002) and a transplantation center's patient flow and costs (Jones et al., 2008). Four studies addressed length of stay in the HCT patient population. Two studies (Garg, Bhutani, Alyea, & Pendergrass, 2007; Karnchanasorn et al., 2012) found increased overall LOS with patients who experienced elevated mean BG levels throughout the transplantation period. Two studies did not find statistical significance when investigating the association between hyperglycemia and LOS (Derr et al., 2008; Rentschler, 2010). Derr et al. (2008) looked specifically at hyperglycemia in the preneutropenic phase (9.3 days on average from admission), whereas Rentschler (2010) reviewed hyperglycemia during the entire inpatient phase. Neither of these studies evaluated BG pre-HCT through post-HCT, which may have yielded different LOS findings.

Hyperglycemia, Overall Survival, and Nonrelapse Mortality

Studies primarily in the allogeneic HCT patient population have explored the relationship between elevated glucose levels and the primary endpoints of overall survival (OS) and nonrelapsed mortality (NRM). Fuji et al. (2007) found associations between hyperglycemia and decreased OS, and Pidala et al. (2011) found that an increase in glucose levels adversely impacted both OS and NRM. Hammer et al. (2009) found associations between hyperglycemia and NRM in recipients of allogeneic HCT. The study also found that hypoglycemia and increased glycemic variability were associated with NRM in these patients. In addition, the degree of hyperglycemia was inversely associated with OS in several studies (Derr et al., 2008; Fuji et al., 2007; Hammer et al., 2009; Pidala et al., 2011).

Hyperglycemia and Toxicities

Complications of HCT include organ toxicities. Researchers investigated whether hyperglycemia was associated with increased organ dysfunction. In Fuji's earlier retrospective study (2007), an association between hyperglycemia and organ toxicities was noted during the neutropenic stage. In Fuji's subsequent study (2009), intensive glucose control post-HCT was found to reduce the incidence of renal dysfunction. Garg et al. (2007) also looked at the relationship between hyperglycemia and renal function, but none of the 126 participants demonstrated any degree of renal dysfunction and, therefore, relationships between the variables could not be established. Rentschler (2010) did find that patients with hyperglycemia experienced more organ toxicities, including cardiac and renal complications.

Treatment-Related Associations With Hyperglycemia

Corticosteroids are commonly administered during HCT for GVHD prophylaxis and symptom management, in addition to treating other side effects. Corticosteroids cause impairment in insulin secretion and induce peripheral insulin resistance (Donihi et al., 2006). Corticosteroids were highly correlated with hyperglycemic events during the HCT process in numerous studies (Derr et al., 2008; Fuji et al., 2007; Garg et al., 2007; Hammer et al., 2009; Pidala et al., 2011). In addition, the dose and length of treatment with corticosteroids were significantly associated with increased BG levels (Pidala et al., 2011). Because patients undergoing allogeneic HCT receive corticosteroids for immunosuppression, it is not surprising that they were found to experience higher rates of hyperglycemia than their autologous counterparts (Griffith et al., 2011).

Total parenteral nutrition (TPN) often is administered when patients are unable to tolerate oral nutrient intake (often from mucositis). Three studies showed increased rates of hyperglycemia in patients who received TPN (Rentschler, 2010; Sheean, Braunschweig, & Rich, 2004; Sheean et al., 2006).

Knowledge Translation

Management of hyperglycemia during the acute phase of hematopoietic cell transplantation (HCT) is an important role for the transplantation nurse.

An increased awareness of glycemic issues in patients during the acute phase of HCT is vital to nurses when planning care in complex patients receiving HCT.

Early glycemic interventions to mitigate hyperglycemia may decrease adverse events related to poor glycemic control.

Patient-Related Factors Associated With Hyperglycemia

Although all patients undergoing HCT are at increased risk for hyperglycemic events, those with preexisting diabetes are assumed to be at even greater risk for hyperglycemic events during treatment. A few studies confirmed this, showing greater hyperglycemic levels in patients with preexisting diabetes (Derr et al., 2008; Pidala et al., 2011) and insulin resistance (Griffith et al., 2011) compared to those with no known history of diabetes/insulin resistance prior to treatment. An additional finding of interest was two studies that reported that patients with normal body mass and hyperglycemia experienced worse outcomes than those of overweight or obese individuals with hyperglycemia (Gebremedhin et al., 2012; Sheean et al., 2006).

Older adults have higher rates of diabetes compared to younger age groups (Centers for Disease Control and Prevention, 2011); however, independent of diabetic history, older age also can be a risk factor for hyperglycemic events. In the HCT population, older age was confirmed as a risk for hyperglycemia in a number of studies in this review (Fuji et al., 2007; Gebremedhin et al., 2012; Rentschler, 2010,).

Discussion

Although a causal relationship between hyperglycemia and adverse clinical outcomes has not been established, evidence suggesting the deleterious effects of hyperglycemia is mounting. The results of this integrative review showed associations between hyperglycemia and infection, time to engraftment, development of acute GVHD, LOS, toxicities, and OS. Findings regarding patient-related risk factors for hyperglycemia were noted as older age, insulin resistance, and increased body mass index. Patients of normal weight experiencing hyperglycemia had worse outcomes than those who were overweight or obese. Treatment-related risk factors for hyperglycemia included dose and duration of corticosteroids and use of TPN.

A major limitation in the results of this review is the wide variation in the definition of hyperglycemia and the collection of BG data. Of note is the arbitrary assignment of BG levels into categories. For example, Gebremedhin et al. (2012) categorized hyperglycemia by mild (110–150 mg/dl), moderate (151–179.9 mg/dl), and severe hyperglycemia (180 mg/dl and greater), whereas Garg et al. (2007) dichotomized BG values into normoglycemia (less than 100 mg/dl) and hyperglycemia (100 mg/dl or greater). These two studies also provide examples of variations in BG measurements used in the studies. Gebremedhin et al. (2007) used mean morning serum BG levels from daily laboratory draws, whereas Garg et al. (2007) used mean BG values from all available values (central laboratory and point-of-care testing). These discrepancies were found in all studies, making it difficult to synthesize the findings.

Another limitation includes the retrospective design of the majority (10 of 12) of the studies. Therefore, most of the research reports reviewed in this article recommended that prospective studies be conducted to better evaluate the impact of glycemic control on HCT outcomes. Future research ideas were suggested, including testing alternative treatments and supportive care modalities to ascertain whether these mitigate hyperglycemia and subsequent adverse outcomes.

The authors of the current article also noted the benefits of prospective studies as providing the opportunity to determine whether BG data was obtained during the fasting or fed state. The ADA (2013) recommendation for fasting BG levels of between 70–130 mg/dl is based on eight hours of no caloric intake. This provides the rationale for the assumption that morning BG values above this range are hyperglycemic. Because of the wide use of nutritional (parenteral, enternal, and IV) support in the hospital setting, it is difficult to discern if BG values taken during morning blood draws are indeed fasting. Prospective studies would allow for assessment of this variable so better categorization of hyperglycemia could be determined. In addition, prospective studies would allow for greater depth and breadth of the patient experience of having hyperglycemia during the acute HCT phase.

Implications for Nursing

Despite the limitations of these studies, the results have substantial and timely implications for healthcare providers. Population trends, such as the increasing numbers of older adults (Administration on Aging, 2013) concurrent with the ability to offer transplantation as a treatment option to older adults (Karanes et al., 2008), have made the older adult patient population the fastest growing segment of patients receiving HCT (Pasquini, 2013). Because diabetes and

insulin resistance are age-related diseases, healthcare providers will encounter diabetes as a comorbidity of HCT more frequently in the future. Understanding the potential and actual adverse effects of hyperglycemia as well as the patient- and treatment-related risk factors summarized in this article will guide nurses in making informed and appropriate interventions for glycemic control in this complex patient population.

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