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Measurement of Hyperglycemia and Impact on the Health Outcomes in People with Cancer: Challenges and Opportunities

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Hyperglycemia, an elevation in blood glucose, is a major side-effect of cancer and cancer treatment. In patients with cancer, hyperglycemia occurs frequently independent of the diagnosis of diabetes (Farrokhi, Smiley, & Umpierrez, 2011). Researchers have noted the prevalence of hyperglycemia to range from 39% -99% among patients with various types of cancer (Hammer et al., 2009; Sotrey & Von Ah, 2015; Karnchanasorn, Malamug, Jin, Karanes, & Chiu, 2012).

Among both critically and non-critically ill patients, researchers have shown that hyperglycemia has been associated with infection/sepsis, stroke, hemorrhage, ileus, and venous thromboembolism (Zurbier et al., 2016; Jimenez-Ibanez et al., 2012); Mraovic et al., 2010), longer hospital length of stay (Masrur et al., 2015), and increased morbidity and mortality (Egi et al., 2008; Hermanides et al., 2010). Harmful consequences from hyperglycemia have also been noted among patients with cancer (Storey & Von Ah, 2012; Storey & Von Ah, 2015). In pre-clinical and clinical studies, the presence of hyperglycemia has been shown to increase the risk of development and progression of cancer, impact diagnostic imaging studies, attenuate the immune system and increase resistance to chemotherapy (Adham et al., 2014; Biernacka et al., 2013; Germenis & Karanikas, 2007; Harris et al., 2013; Kellenberger et al., 2010; Rabkin, Israel, & Keidar, 2010). However, researchers have found discordant findings as it relates to the impact of hyperglycemia on the health-related outcomes including infection, toxicity, morbidity and/or mortality (Olausson, Hammer, & Brady, 2014; Storey & Von Ah, 2012). The inconsistency in findings from these studies may be attributed to type of cancer and/or treatment, patient characteristics, and/or clinical factors. In addition, variations in the definition and measurement of hyperglycemia may also result in ambiguous findings.

The American Diabetes Association (ADA) has proposed general guidelines for glycemic thresholds and standards for treatment (ADA, 2016). However, people with cancer experience unique challenges to glycemic homeostasis as a consequence of cancer and its treatment (Hammer et al., 2016). Factors contributing to hyperglycemia in people with cancer include: physiologic stress, glycemic status (glucose intolerant, diagnosis of diabetes, pre or unknown diagnosis of diabetes), the administration of glucocorticoids, and changes in nutrition and activity (Dungan, Braithwaite, & Preiser, 2009; Harris et al., 2013; Hershey et al., 2014). An additional challenge is the receipt of frequent blood transfusions to address disease/treatment related anemia which precludes the use of Hemoglobin A_{1c} (HbA_{1c}), the blood test recommended for diagnosing diabetes and monitoring blood glucose (Farrokhi, Smiley & Umpierrez, 2011) (Shrot, Patel, & Foulis, 2007). These challenges present a formidable task for clinicians trying to determine the best treatment plan to manage hyperglycemia in people with cancer. Additionally, the impact of hyperglycemia on subsequent health outcomes may not be fully appreciated due to these variations and ultimately, could result in the inappropriate treatment of hyperglycemia in clinical practice.

The wide variation in the reported prevalence of hyperglycemia, makes it difficult to ascertain the severity of the problem among people with cancer. The ramifications of hyperglycemia on the progression, treatment and response of cancer, and the subsequent inconsistencies reported in health outcomes are important to understand. Identifying glycemic thresholds and measurement processes is imperative to assist clinicians with evidence on which to base treatment decisions, ultimately improving care and outcomes for people with cancer.

The purpose of this review was to explore definitions and measurement issues related to the assessment of hyperglycemia and the subsequent impact on the findings of health-related outcomes in adult people with cancer. Findings will be used to elucidate gaps related to clinically meaningful measurement issues in patients with cancer. Propelling further research to focus on identifying high risk patients and informing the development of standardized criteria to evaluate and treat hyperglycemia in people with cancer.

Methods

Literature Search

Four electronic databases were searched targeting articles focused on hyperglycemia, cancer, and health-related outcomes. The databases included: Ovid®, PubMed®, CINAHL®, and Web of Science™. The search terms used included cancer, hyperglycemia, measurement, adults, and health-related outcomes. To best evaluate the definitions and measurement processes related to hyperglycemia and the subsequent impact, health-related outcomes were included in the search terms. The terms were used as both keywords and MeSH terms to obtain as many publications as possible. Reference lists were also searched for pertinent publications. Inclusion criteria were manuscripts that reported findings from quantitative research that were published in English from 2004 to 2015. See Figure 1 for the diagram of search strategy.

For this review, hyperglycemia was defined as an elevation in blood glucose as defined by each study. The cut points/thresholds used in each study to determine hyperglycemia are reported in Table 1. Health-related outcomes were also defined by study parameters.

Quantitative studies that focused globally on diabetes, hyperglycemia and/or cancer but did not discuss hyperglycemia and its impact on specific health-related outcomes were excluded. In addition, studies that included hyperglycemia in children with cancer were also excluded since the intent of this review was to examine the blood glucose and health-related outcomes of people with cancer.

Data Evaluation

The synthesis of quantitative articles was conducted using the integrative methodology strategies proposed by (Whittemore & Knafl, 2005). These strategies offer a structured format in which at least two researchers conduct an independent review of the articles. If discrepancies occurred, the review was conducted jointly until consensus is reached.

Synthesis

A total of 29 studies met the inclusion criteria. The majority of the studies utilized a retrospective design (25/29, 86%), (3/29, 10%) were prospective, and (1/29, 3%) was a case-control study. The most frequent cancer population (12/29, 41%) in the studies were people receiving stem cell or bone marrow transplant. Other populations included solid tumors, hematologic cancers or multiple diagnoses. Table 1 presents the key characteristics and findings of quantitative studies that examined the parameters used to measure hyperglycemia and the health-related outcomes associated with hyperglycemia in people with cancer.

Prevalence

The occurrence of hyperglycemia among people with cancer was reported (as percent of patients above the established threshold) in seven of the twenty-nine (24%) studies (Ali et al., 2007; Hammer et al., 2009; Luo, Chen, & Chang, 2012; Rentschler et al., 2010; (Matias, Lima, Teixeira, Souto, & Magalhães, 2013; Storey & Von Ah, 2015; Weiser et al., 2004). Only one study reported a calculation of prevalence and provided the formula (Hardy, Nowacki, Bertin, & Weil, 2010).

Glycemic Measurement Issues

Glycemic threshold—Thresholds used to define hyperglycemia varied among the 29 studies. The majority of the studies 17/30 (56%) used thresholds ranging between 99 mg/dL to < 126 mg/dL (Ali et al., 2007; Barba et al., 2012; Derr et al., 2009; Derr, Hsiao, & Sauder, 2008; Garg, Bhutani, Alyea, E. & Pendergrass, M., 2007; Flood et al., 2007; Fuji et al., 2007; Fuji et al., 2009; Gebremedhin, Behrendt, Nakamura, Parker, & Salehian, 2013; Hammer et al., 2016; Ito et al., 2014; Luo, Chen, & Chang, 2012; Matias et al., 2013; Storey & Von Ah, 2015; Storey & Von Ah, 2016; Tieu et al., 2015; Wright et al., 2013).

Two (7%) studies used the threshold for hyperglycemia > 200 mg/dL (Pidala, 2011; Weiser et al., 2004), and two the threshold of 150 mg/dL (Karnchanasorn et al., 2012; Hammer et

al., 2009). One study (3%) used > 130 mg/dL (Villarreal-Garza et al., 2012) and one (3%) used 140 mg/dL (Soysal et al., 2012). Five studies used multiple thresholds to define hyperglycemia (Brunello, Kapoor, & Extermann, 2011; Hardy, Nowacki, Bertin, & Weil, 2010; Sheean, Freels, Helton, & Braunschweig, 2006; Sheean, Kilkus, Liu, Maciejewski, & Braunschweig, 2013; Rentschler et al., 2010). Two authors categorized elevated blood glucose values into either quartiles (beginning at 106mg/dL) (Hong, et al., 2014) or ranges such as mild, moderate and severe beginning at 121 mg/dL (Jackson, Amdur, White, & Macsata, 2012).

The ADA criteria for diagnosing pre-diabetes and diabetes was used in seven (23%) of the studies (ADA, 2016). Two studies used the ADA criteria for diagnosing prediabetes (> 100mg/dL) (Wright et al., 2013; Matias et al., 2013). Three of the studies used the ADA threshold (≥ 126 mg/dL) for diagnosing diabetes (Ito et al., 2014; Luo, Chen, & Chang, 2012; Storey & Von Ah, 2015). One study used the ADA thresholds for the diagnosis of diabetes (fasting blood glucose [FBG] ≥ 126 mg/dL FBG or random blood glucose of ≥ 200 mg/dL) (Rentschler et al., 2010).

Type of glucose measurement—While the majority of the studies (40%) used FBG a variety of testing types were used in the studies (Barba et al., 2012; Flood et al., 2007; Fuji et al., 2007; Gebremedhin et al., 2013; Hammer et al., 2016; J. Luo et al., 2012; Matias et al., 2013; Sheean, Freels, Helton, & Braunschweig, 2006; Sheean et al., 2013; Storey & Von Ah, 2015; Storey & Von Ah, 2016; Villarreal-Garza et al., 2012). Three studies used random blood glucose only (Derr et al., 2009; Soysal et al., 2012; Tieu et al., 2015). Three of the studies specified using morning glucose, however did not specifically identify them as FBG (Fuji et al., 2009; Hardy, Nowacki, Bertin, & Weil, 2010; Wright et al., 2013). Three studies did not disclose the type of blood glucose value measured (Jackson, Amdur, White & Macsata, 2012; Weiser et al., 2004; Wright et al., 2013). Three studies included all available venous blood glucose values (Ali et al., 2007; Garg, Bhutani, Alyea, & Pendergrass, 2007; Hammer et al., 2009). Two of the studies used a combination of venous fasting and blood glucose tests taken at various times throughout the day (Brunello, Kapoor, & Extermann, 2011; Ito et al., 2014; Pidala, 2011; Rentschler et al., 2010). One study used fasting and random blood glucose drawn every 12 hours but did not specify whether the source was venous or capillary via point-of-care (POC) testing (Ito et al., 2014). Two studies used a combination of both fasting taken from venous sampling and random blood glucose capillary values taken from POC monitors (Derr et al., 2009; Karnchanasorn et al., 2012). One study used fasting and post prandial blood glucose (Brunello, Kapoor & Extermann, 2011).

Source of glucose measurement—The majority (26/30, 87%) identified the source of blood glucose measurement as from serum blood drawn from venous sites and analyzed per the hospital laboratory. Five studies did not specify the source of blood glucose sample (Fuji et al., 2009; Ito et al., 2014; Jackson et al., 2012; Weiser et al., 2004 ; Wright et al., 2013). Two studies used both venous and capillary blood glucose values taken from POC monitors (Derr, Hsiao, & Sauder 2008; Karnchanasorn et al., 2012). One study (Hong et al., 2014) reported using all available glucose measurements without defining what those

measurements included. None of the studies in patients with cancer examined whether the source of the blood glucose measurement affected health-related outcomes.

Timing of glucose measurement in the cancer treatment trajectory—Thirteen studies (43%) examined the timing of hyperglycemia at different intervals throughout the trajectory of cancer and cancer treatment (Barba et al., 2012; Brunello et al., 2010; Derr et al., 2008; Flood et al., 2007; Fuji et al., 2007; Hammer et al., 2009; Hammer et al., 2016; Ito et al., 2014; Jackson, Amdur, White, & Macsata, 2012; Matias et al., 2013; Storey & Von Ah, 2015; Storey & Von Ah, 2016; Wright et al., 2013). Two studies examined the impact of hyperglycemia at the time of diagnosis on disease progression and/or recurrence (Barba et al., 2012; Wright et al., 2013). One study assessed the impact of hyperglycemia using FBG, on outcomes at three time points; baseline, 1 year and 4 year post diagnosis in the trajectory of colorectal cancer (Flood et al., 2007).

Five studies examined the impact of hyperglycemia in people with hematologic cancers before, during and/or after the neutropenic period, which is the time in treatment where the white blood cell count is the lowest (Derr, Hsiao & Sauder, 2008; Fuji et al., 2007; Matias et al., 2013; Storey & Von Ah, 2015; Stprey & Von Ah, 2016). One study assessed glycemic status between day 0 (receipt of hematopoietic cells) up to day 100 (Hammer et al., 2009). Another study examined daily morning fasting glycemic status from admission up to discharge or 28 days post-transplant, whichever came first (Hammer et al., 2016).

Two studies examined hyperglycemia on post-operative outcomes. Ito and colleagues (2014) assessed blood glucose every 12 hours for the first 72 hours post-operation for esophageal cancer, followed by every 24 hours thereafter up to the seventh day post-operation. Outcomes of hyperglycemia in patients with colorectal cancer were studied on the operative day and post-operative day 1 (Jackson et al., 2012).

Patterns of hyperglycemia—Only six studies included the number of times an elevation in blood glucose was required to be defined as hyperglycemia (Hammer et al., 2016; Matias et al., 2013; Rentschler et al., 2010; Storey & Von Ah, 2015; Storey & Von Ah, 2016; Weiser et al., 2004). However, these requirements varied among the studies. Four studies stipulated one or more episodes were considered hyperglycemia (Hammer et al., 2009; Matias et al., 2013; Storey & Von Ah, 2015; Storey & Von Ah, 2016). Two studies included two or more episodes were considered hyperglycemia, but did not specify the pattern (random or consecutive) of occurrence (Rentschler et al., 2010; Weiser et al., 2004).

Inconsistent use of guidelines

The majority (19/29) of studies did not identify guidelines on which they based the definition used as the threshold for hyperglycemia. Four authors identified the use of guidelines from empirical research conducted in critical care patients to inform their definition of hyperglycemia (Ali et al., 2007; Hammer et al., 2016; Sheean et al., 2006; Soysal et al., 2012). Five studies stated they used the ADA guidelines to define hyperglycemia (fasting blood glucose ≥ 126 mg/dL and/or random blood glucose > 200 mg/dL) which is in accordance with the ADA criteria for diagnosis of diabetes (ADA, 2016; Ito et al., 2014; Luo, Chen & Chang, 2012; Rentschler et al., 2010; Storey & Von Ah, 2015;

Storey & Von Ah, 2016). One study identified the use of ADA guidelines for categorizing hyperglycemia into groups of > 100 mg/dL impaired glucose and 126 mg/dL as diabetes (Wright et al., 2013). One study defined hyperglycemia as > 100 mg/dL based on the ADA guidelines definition for impaired glucose tolerance (Matias et al., 2013). Gallo, Gentile, Arvat, Bertetto & Gennaro, 2015, suggest the lack of glycemic guidelines for people with cancer, diabetes and/or hyperglycemia result in a “trial and error” approach that culminates in substandard disease management.

Health-related Outcomes

The health related outcomes examined in the studies were reviewed for association with hyperglycemia. The association between hyperglycemia and toxicity was found in each of the six studies that assessed this outcome (Brunello et al., 2010; Fuji et al., 2007; Fuji et al., 2009; Gebremedhin et al., 2012; Sheean et al., 2006; Sheean et al., 2013). Survival was also found to be linked to hyperglycemia in the two studies (Tieu et al., 2015; Villerear-Garza et al., 2012) that examined this outcome. In the two studies that assessed disease progression (Barba et al., 2012) and recurrence (Flood et al., 2007), both noted a significant link to hyperglycemia. However, incongruent findings among the studies were found related to the impact of hyperglycemia on other health-related outcomes of patients with cancer. Mortality was found to be associated with hyperglycemia in the 9/10 studies that examined this outcome (Ali et al., 2007; Derr et al., 2008; Fuj et a; 2007; Hammer et al., 2009; Jackson et al., 2012; Luo et al., 2012; Matias et al., 2013; Pidala et al., 2011; Soysal et al., 2012; Storey & Von Ah, 2016). Equivocal findings were noted among studies that examined infection, with some finding an association (Derr et al., 2008; Hammer et al., 2009, Hammer et al., 2016; Hong et al., 2014; Ito et al., 2014; Jackson et al., 2012; Matias et al., 2013; Rentschler et al., 2010, Sheean et al., 2006; Soysal et al., 2012; Storey & Von Ah 2016; Weiser et al., 2004) and others not (Derr et al., 2009; Fuji et al., 2007; Garg et al., 2007; Hardy et al., 2010; Storey & Von Ah 2015). Inconsistent findings as it related to hyperglycemia and length of stay were found, some showing a relationship (Garg et al., 2007; Karnchanasorn et al., 2012; Sheean et al., 2013) and others not (Rentschler et al., 2010; Storey & Von Ah, 2015; Storey & Von Ah 2016). Some of the studies examined health-related outcomes that were not assessed in the others such as: morbidity, engraftment, number of neutropenic days and complete remission thus not allowing for comparison (Jackson et al., 2012; Karnchanasorn et al., 2012; Storey & Von Ah, 2015; Storey & Von Ah, 2016; Weiser et al., 2014). The disparity in these findings may be due to the measurement issues which have been described as the findings in this review.

Discussion

The purpose of this integrative review was to explore and critically appraise the empirical literature related to the definitions and measurement of hyperglycemia and the subsequent impact on the findings of health-related outcomes in adult people with cancer. Twenty-nine quantitative studies were reviewed. Three key gaps were identified among the studies: 1) variations in the calculation of prevalence, 2) variations in the measurement of hyperglycemia, and 3) inconsistent utilization of standard guidelines.

The majority of studies in this review reported a wide range in the percentage of people with hyperglycemia. Only one of the studies reported prevalence and disclosed the formula used for calculation. The studies reviewed noted ambiguity in regards to the deleterious impact of hyperglycemia on health related outcomes. These discrepancies may be attributed to the various thresholds used and the lack of a standard formula for calculating and the reporting of prevalence. Inconsistency in measurement and reporting may result in under or over treatment of hyperglycemia. In order to better comprehend the magnitude of hyperglycemia in people with cancer, a standard threshold and formula for calculating prevalence is needed.

The type of blood glucose measurement may be important to examine as a predictor of poor outcomes. Epidemiological studies conducted in people without cancer shown that in patients with and without diabetes, elevated FBG is associated with an increased risk of vascular disease (Emerging Risk Factors et al., 2010); whereas elevations in post prandial or random blood glucose is associated with morbidity (Cavalot et al., 2006) and mortality, (Umpierrez et al., 2002) respectively. Twelve studies (40%) in this review used FBG only to determine hyperglycemia, however there were inconsistencies with the type of glucose measurement used in these studies. People with cancer often receive glucocorticoids as part of their treatment regimen which can contribute to exaggerations in blood glucose. Frequent monitoring for glucocorticoid induced hyperglycemia is recommended. FBG may not adequately reflect the influence of glucocorticoids, as post prandial (2 hours post meal) or random blood glucose (4-6 hours after receipt of glucocorticosteroids) best capture their effects on blood glucose (Gallo et al., 2016; Harris et al., 2013). In the studies reviewed, the type of glucose measurement reported may have been influenced by known diabetes status and/or practitioner preference. Further research is needed to identify which people are at high risk and to develop methods to screen for them throughout the cancer trajectory. In addition, it will be important to ascertain when blood glucose should be monitored and establish tolerable thresholds.

The majority of studies in this review used the blood glucose results from venous samples analyzed via the laboratory. Laboratory analyzed venous blood sampling is considered to be the most accurate (Farmer, 2010); however, these results are only a measurement of blood glucose at the time the blood was obtained and may not reflect the real time patient experience. POC testing is most often used and is the standard of care in the hospital setting for frequent monitoring of blood glucose. The advantage to POC testing is that it provides a “real time” analysis of blood glucose. However, POC devices can vary by more than 30% for glucose levels greater than 150mg/dL and by 60% in the hypoglycemic range (Dungan, Chapman, Braithwaite, & Buse, 2007). Certain metabolic factors can also alter POC results in people with cancer such as inadequate tissue perfusion, hypotension, hypoxia and anemia secondary to cancer and/or chemotherapy (Hermayer et al., 2015; Hirsch, 2010). POC testing can also be contraindicated due to the risk of infection with invasive “sticks” to vulnerable immunosuppressed people with cancer.

Most of the studies in this review used FBG as the measure for blood glucose. Unlike studies in other populations, none of the studies reviewed reported the use of HbA_{1c}. It is important to note as the HbA_{1c}, a measure of blood glucose over time is not regularly used in people with cancer due to its dependence on the normal life span of red blood cells. The use of

blood transfusions and/or the diagnosis of anemia alter the result of HbA_{1c} leading to inaccurate results and potentially inappropriate treatment (Oyer, Shah, & Bettenhausen, 2006). Currently, there are no recommendations for the most appropriate source of blood sampling in hospitalized people with cancer. The use of serum and/or POC blood glucose alone or in combination with other measures of hyperglycemia is important to study to facilitate standardization of practice and management. More research is needed to determine if utilization of FBG, post prandial, and/or random blood glucose alone or in combination should be used to detect hyperglycemia in people with cancer. In addition, the utility of POC testing in conjunction with the other types of glucose measurements to identify hyperglycemia and its impact on health-related outcomes needs further exploration.

Recent reports have demonstrated that fructosamine and/or glycated albumin may be an alternative measurement of hyperglycemia, for select people in whom HbA_{1c} may be deemed as unreliable (Danese, Montagnana, Nouvenne & Lippi, 2015; Malmstrom et al., 2014). More research is needed to determine the effectiveness of alternative glucose measures in detecting hyperglycemia in people with cancer. Additionally, non-invasive continuous glucose monitoring devices, currently under development, are a promising option on the horizon that may be beneficial in assessing hyperglycemia in people with immune suppression.

The majority of studies did not utilize or indicate the guidelines upon which their selected threshold was based; as a result various thresholds were used to define hyperglycemia. Of those that used guidelines, the sources varied between those using empirical findings from critical care populations or the ADA guidelines to determine the definition of hyperglycemia. The ADA guidelines are the standard-of-care for treatment of hyperglycemia in hospitalized patients. Many hospitals utilize evidence-based protocols that include the ADA guidelines that provide recommendations to define and guide the treatment of hyperglycemia. However, in the majority of empirical research studies we reviewed, these guidelines were not being utilized to establish thresholds, with no explanation as to the rationale. An additional challenge with the use of the ADA guidelines is that there are different guidelines for hyperglycemia dependent on etiology (diabetes, stress, and steroid induced). This raises the question as to if these guidelines are adequate and/or appropriate for people with cancer or if specific guidelines should be established for this unique population of patients.

Among the studies, the timing and frequency by which blood glucoses were obtained could have varied by degree of illness or diabetic status, with those people having higher acuity and known diabetes being monitored more closely. Some of the studies described the timing of glycemic measurements in the cancer trajectory and its impact on health-related outcomes. Time points studied included: baseline (prior to treatment), post-operative, before and during the neutropenic period and/or at intervals (i. e. baseline, 1 year and 4 years post treatment). These studies found hyperglycemia during these time periods to be associated with poor health outcomes (disease progression, recurrence, survival, graft-versus-host disease, infection and mortality). Although the studies were conducted among heterogeneous patient populations, these studies suggest the onset of hyperglycemia at different time points in the cancer trajectory may influence health outcomes. More research

is warranted to determine if there are critical time periods in which the onset of hyperglycemia is more deleterious, and to inform preventive and screening strategies to identify patients at high risk.

The impact of hyperglycemia on the health outcomes of patients with cancer cannot be fully elucidated until these gaps are addressed. These gaps challenge the appropriateness of current guidelines and suggest that perhaps standard guidelines for glycemic thresholds and measurement processes should be identified and implemented that address the unique needs of people with cancer who experience hyperglycemia. Thereafter, the impact of hyperglycemia on health outcomes can be more thoroughly assessed, while reducing the influence of these confounding issues.

Future Research

There are additional variables such as host, biological and treatment characteristics that contribute to elevation in blood glucose. Host characteristic such as unknown or pre-diabetes status can contribute to hyperglycemia. In the United States, about 8.1 million people with diabetes do not know they have the disease. It is estimated that 37% of adults have pre-diabetes (an elevation in blood glucose that is higher than normal, but not high enough to be considered diabetes) with only 11% aware that they are in this category (Center for Disease Control, 2014). Treatment characteristics such as the disease process and associated stressors may influence hyperglycemia. Additionally, the administration of certain chemotherapies and biological agents and glucocorticosteroids in many treatment regimens may potentiate hyperglycemia in people with cancer, with and without a diagnosis of diabetes. Lastly, behavioral characteristics such as nutritional intake, activity and other lifestyle factors which may be altered due to illness can play a role in hyperglycemia. Among hospitalized people with cancer on call meal services common in many hospitals contribute to challenges in obtaining accurate morning FBG's and subsequent glycemic management. Future research studies should include examining the influence of these factors on hyperglycemia and health-related outcomes in people with cancer.

It is important to address hyperglycemia as it may be indicative of underlying glucose intolerance especially when occurring in the "non-diabetic" people with cancer, and if untreated can result in chronic glucose dysfunction and/or diabetes (Falciglia, 2007; Gallo et al., 2015). Emerging studies have shown that among people with cancer, those who have received hematopoietic cell transplant, are at higher risk for diabetes following treatment (Clark, Savani, Mohty, & Savani, 2016; Fuji et al., 2016). Therefore, it is imperative that hyperglycemia be accurately measured in order to be well managed. The ADA recommends that asymptomatic people should be tested for diabetic status beginning at 45 years of age among people who are overweight, obese or have other risk factors for diabetes (ADA, 2015). Additionally, it is recommended that people who will be receiving glucocorticosteroids as part of their cancer treatment regimen be routinely monitored, for hyperglycemia and/or new onset of diabetes prior to the initiation of therapy as well as throughout the regimen (Rowbottom et al., 2015).

Standard screening of people with cancer prior to the onset of treatment could be beneficial in predicting and managing those patients who may be a higher risk for development of

hyperglycemia. Collaboration with an endocrinologist as part of the healthcare team is appropriate especially in situations where blood glucose is unable to be maintained or adequately managed.

Strengths and Limitations

To our knowledge this is the first review summarizing the empirical research from quantitative studies examining the gaps in measurement thresholds of hyperglycemia in people with cancer. The lack of clear and common thresholds and measurement processes makes comparison across studies difficult. Due to the discrepancies in the reporting of prevalence, thresholds used, variations in timing, frequency and sources used for obtaining blood samples, the ability to assess the nefarious impact of hyperglycemia on health-related outcomes is limited. This review elucidates the need for well-defined thresholds and standards of practice for glycemic management in people with cancer that may influence health-related outcomes.

Implications for Nursing

The development of a standardized definition for and process to measure hyperglycemia, will facilitate its prevention or management; which can ultimately result in improving health-related outcomes in people with cancer. Nurses play a key role in the early identification of people experiencing hyperglycemia. Nurses can engage and communicate the presence of hyperglycemia to oncology advanced practice nurses and physicians to initiate monitoring and treatment practices.

Conclusion

The need for evidence-based guidelines is imperative to abrogate inconsistent and/or inappropriate treatment of hyperglycemia in patients with cancer. Yet to be determined is if the guidelines established by the ADA and/or critical care organizations are beneficial for patients with cancer, or if specific guidelines are needed for treating people with cancer are needed. The deleterious impact of hyperglycemia on the health outcomes of people with cancer cannot be fully appreciated until there is consistency in the definitions, thresholds and measurement practices used to describe the phenomena. Early identification of people with cancer at higher risk for hyperglycemia can promote timely collaboration among the healthcare team to treat and mitigate the untoward effects of hyperglycemia. Future research should focus on defining hyperglycemia, identifying people with cancer at highest risk for hyperglycemia including those with and without a diagnosis of diabetes, development of standards of practice and measurement, and recommendations for the utility of technology in monitoring for hyperglycemia.

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Figure 1.
Diagram of Search Strategy

Table 1

Study Characteristics

Author Year	Design	Population	Threshold (mg/dL)	Type Source	Guidelines	Timing	Pattern	Outcome(s)
Ali et al., (2007)	Retrospective	Acute myeloid leukemia (N = 283)	> 110	All available venous	Critical care	Did not specify	Did not specify	Severe sepsis * Mortality
Barba et al., (2012)	Retrospective	Breast (N = 202) Colorectal (N = 218)	> 99	Fasting venous	Did not specify	At the time of diagnosis	Did not specify	Shorter time to disease progression *
Brunello et al., (2010)	Retrospective	Non-Hodgins Lymphoma (N = 162) Prostate (N = 187)	> 110 fasting > 140 random	Fasting venous Random venous	Did not specify	During neutropenic period of stem cell transplant	Did not specify	Toxicity *
Derr et al., (2008)	Retrospective	Bone marrow transplant (N = 382)	> 100	Fasting venous Random Point-of-care	Did not specify	On admission to first day of neutropenia	Did not specify	Infection *
Derr et al., (2009)	Retrospective	Glioblastoma (N = 191)	> 109	Random venous	Did not specify	Did not specify	Did not specify	Mortality * Infection
Flood et al., (2007)	Prospective	Colorectal (N = 375)	> 99	Fasting venous	Did not specify	Baseline Year 1 Year 4	Did not specify	Recurrence *
Fuji et al., (2007)	Retrospective	Stem cell transplant (N = 112)	> 110	Fasting venous	Did not specify	Did not specify	Did not specify	Toxicity * Mortality * Infection
Fuji et al., (2009)	Case-control	Stem cell transplant (N = 64)	> 110	Did not specify	Did not specify	Did not specify	Did not specify	Toxicity *
Garg et al., (2007)	Retrospective	Bone marrow transplant (N = 126)	> 100	All available venous	Did not specify	Did not specify	Did not specify	Length of stay * Infection
Gebremedhin et al., (2012)	Retrospective	Stem cell transplant (N = 328)	> 110	Fasting venous	Did not specify	Did not specify	Did not specify	Toxicity *
Hammer et al., (2009)	Retrospective	Bone marrow transplant (N = 1175)	> 150	All available glucose venous	Did not specify	0-100 days post-transplant	One or more	Infection * Mortality
Hammer et al., (2016)	Prospective	Bone marrow transplant (N = 53)	110	Fasting venous	Empirical research	Admission through discharge or up to 28 days post-transplant whichever came first	Did not specify	Infection *
Hardy et al., (2010)	Retrospective	Brain craniotomy (N = 114)	> 130 > 150	First measurement of the day did not specify fasting venous	Did not specify	Did not specify	Did not specify	Infection

Author Year	Design	Population	Threshold (mg/dL)	Type Source	Guidelines	Timing	Pattern	Outcome(s)
Hong et al., (2014)	Retrospective	Metastatic colorectal (N = 206)	> 106	All available Source not specified	Did not specify	Did not specify	Did not specify	Infection* Survival
Ito et al., (2014)	Retrospective	Post op esophageal cancer (N = 109)	126	Random and fasting Source not specified	American Diabetes Association	Post-operatively up to 1 week post-operative	Did not specify	Post-operative infection*
Jackson et al., (2012)	Retrospective	Colorectal (post-operative) Day of surgery (n = 7576) Day 1 post op (n = 5773)	121	Did not specify	Did not specify	Operative day and Post-operative day 1	Did not specify	Infection* Morbidity* Mortality
Karnchanasorn et al., (2012)	Retrospective	Stem cell transplant (N = 240)	> 150	Fasting venous Random Point-of-care	Did not specify	Did not specify	Did not specify	Engraftment Length of stay*
Luo et al., (2012)	Retrospective	Non-small cell lung cancer (N = 342)	126	Fasting venous	American Diabetes Association	Did not specify	Did not specify	Mortality*
Matias et al., (2013)	Retrospective	Leukemia Acute myeloid Acute lymphoblastic	> 100	Fasting venous	American Diabetes Association	One week prior to remission induction until 30 days post	1 or more	Infection* Mortality*
Pidala et al., (2011)	Retrospective	Hematopoietic cell transplant (N = 173)	> 200	Fasting venous Random venous	Did not specify	Did not specify	Did not specify	Survival* Mortality*
Rentschler et al., (2010)	Retrospective	Stem cell transplant (N = 160)	126 200	Fasting venous Random venous	American Diabetes Association	Did not specify	2 or more	Infection* Length of stay
Sheean et al., (2006)	Retrospective	Bone marrow transplant (N = 250)	> 110 > 200	Fasting venous	Critical care	Did not specify	Did not specify	Infection* Toxicity*
Sheean et al., (2013)	Retrospective	Bone marrow transplant (N = 122)	> 100 126	Fasting venous	Did not specify	Did not specify	Did not specify	Toxicity* Length of stay*
Soysal et al., (2012)	Retrospective	Lymphomaling, prostate, gastrointestinal (N = 86)	> 140	Random venous	Critical care	Did not specify	Did not specify	Infection* Mortality
Storey & Von Ah (2015)	Retrospective	Leukemia: Acute myeloid Acute lymphocytic Chronic myeloid Chronic lymphocytic (N = 42)	126	Fasting venous	American Diabetes Association	Admission for initial induction to date of date of re-induction, discharge or death	1	Neutropenic days* Infection Length of stay
Storey & Von Ah (2016)	Retrospective	Acute myeloid leukemia (N = 103)	126	Fasting venous	American Diabetes Association	Admission for initial induction to date of date of re-induction, discharge or death	1	Infection* Neutropenic days Hospital length of stay Complete remission

Author Year	Design	Population	Threshold (mg/dL)	Type Source	Guidelines	Timing	Pattern	Outcome(s)
								Mortality
Tieu et al., (2015)	Retrospective	Glioblastoma (N = 196)	> 114	Random venous	Did not specify	Did not specify	Did not specify	Survival *
Villerear-Garza et al., (2012)	Retrospective	Breast (N = 265)	> 130	Fasting venous	Did not specify	Did not specify	Did not specify	Survival *
Weiser et al., (2004)	Prospective	Acute lymphocytic leukemia (N = 278)	> 200	Did not specify	Did not specify	Did not specify	2	Infection * Remission *
Wright et al., (2013)	Retrospective	Prostate cancer (N = 1734)	> 100	Did not specify	American Diabetes Association	At time of diagnosis	Did not specify	Recurrence *

* Denotes statistically significant