Glycosylated Hemoglobin A1c and Lack of Association With Symptom Severity in Patients Undergoing Chemotherapy for Solid Tumors

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The American Cancer Society and American Diabetes Association (ADA) issued a joint statement in 2010 that provided evidence that diabetes was a risk factor for cancer (Giovannucci et al., 2010). Compared to patients without diabetes, patients with diabetes are at greater risk for pancreatic (Huxley, Ansary-Moghaddam, Berrington de Gonzàlez, Barzi, & Woodward, 2005), hepatocellular (El-Serag, Hampel, & Javadi, 2006), breast (Boyle et al., 2012), ovarian (Lee et al., 2013; Shah et al., 2014), endometrial (Zhang, Su, Hao, & Sun, 2013), kidney (Larsson & Wolk, 2011), colorectal (Luo, Cao, Liao, & Gao, 2012), gastric (Yoon, Son, Eom, Durrance, & Park, 2013), thyroid (Schmid, Behrens, Jochem, Keimling, & Leitzmann, 2013), and bladder (Xu et al., 2013) cancers, as well as hematologic malignancies (e.g., non-Hodgkin lymphoma, leukemia, myeloma) (Castillo, Mull, Reagan, Nemr, & Mitri, 2012). About 18% of patients diagnosed with cancer have preexisting diabetes (Barone et al., 2008) compared to only 11% of the general population (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2015).

Hyperglycemia is the hallmark sign of diabetes, and having preexisting diabetes further increases the risk for hyperglycemic events while undergoing treatments for cancer. In addition, hyperglycemia can occur in patients with cancer independent of a diabetic history. Older age (Kezerle, Shalev, & Barski, 2014), higher body mass index (BMI) (Roumen, Blaak, & Corpeleijn, 2009), nutritional imbalances (Butler, Btaiche, & Alaniz, 2005; Jenkins et al., 2002; Martin-Salces, de Paz, Canales, Mesejo, & Hernandez-Navarro, 2008), lower levels of physical activity (Katz, 2007; Moien-Afshari et al., 2008), higher stress levels (Butler et al., 2005; Godbout & Glaser, 2006), administration of glucocorticoids (Butler et al., 2005; Mazali, Lalli, Alves-Filho, & Mazzali, 2008; Willi et al., 2002), some chemotherapy (CTX) regimens (Mazali et al., 2008; Ramos-Cebrián, Torregrosa, Gutiérrez-Dalmau, Oppenheimer, & Campistol, 2007;

Purpose/Objectives: To assess the effects of high blood sugar at the levels of diabetic or prediabetic states during cancer treatment because patients undergoing chemotherapy (CTX) experience multiple symptoms that vary among individuals and may be affected by glucose levels.

Design: Descriptive, cross-sectional.

Setting: Two comprehensive cancer centers, one Veterans Affairs hospital, and four community-based oncology programs.

Sample: 244 outpatients with breast, gastrointestinal, gynecologic, and lung cancers.

Methods: Patients completed demographic and symptom questionnaires. Glycosylated hemoglobin A1c (HbA1c) was evaluated to determine diabetic state. Descriptive statistics and one-way analyses of variance were used in the analyses.

Main Research Variables: HbA1c, symptom severity scores, patient and clinical characteristics (e.g., age, gender, comorbidities, sociodemographic information, body mass index [BMI], lifestyle factors).

Findings: HbA1c results showed 9% of the sample in the diabetic and 26% in the prediabetic state. Patients in the diabetic state reported a higher number of comorbid conditions and were more likely to be African American. Patients in the prediabetic state were older aged. Patients in the diabetic and prediabetic states had a higher BMI compared to nondiabetic patients. No differences in symptom severity or quality-of-life (QOL) scores were found among the three diabetic states.

Conclusions: This study is the first to evaluate for associations between diabetic states and symptom severity and QOL scores in patients receiving CTX. This study confirmed that older age, as well as having higher BMI and having multiple comorbidities, were associated with increased mean glycemic levels.

Implications for Nursing: Clinicians should assess and identify patients with diabetes or prediabetes undergoing treatment for cancer. Patients who are older aged, those with a high BMI, and those with multiple comorbid conditions may be at increased risk for higher glycemic states.

Key Words: glycosylated hemoglobin A1c; chemotherapy; symptom severity; breast cancer; lung cancer; gynecologic cancer; gastrointestinal cancer

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Willi et al., 2002), and infections (Turina, Miller, Tucker, & Polk, 2006) can contribute to hyperglycemic episodes during cancer treatment. In turn, hyperglycemia can increase patients' risk for infection and non–cancer-related mortality (Fuji et al., 2007; Hammer et al., 2009).

Although the association between diabetes and increased risk for cancer is well established, the underlying mechanisms for this association are not well understood. The increased inflammatory responses associated with diabetes may contribute to the development of cancer. For example, hyperglycemia stimulates increased levels of cytosolic calcium, which induce mitochondrial fragmentation and increased levels of reactive oxygen species (ROS) (Yu, Jhun, & Yoon, 2011). These increased levels of ROS result in oxidative stress, which alters the ability of innate immune cells to detect and destroy aberrant cells. This lack of recognition of aberrant cells may lead to the development of cancer (Mantovani, Allavena, Sica, & Balkwill, 2008; Pickup, 2004).

Investigations of the clinical outcomes of hyperglycemic-associated inflammation are lacking. Only 15 studies have investigated the effects of glycemic status during cancer treatment on a variety of patient outcomes (Ali et al., 2007; Bhatnagar et al., 2014; Brunello, Kapoor, & Extermann, 2011; Derr, Hsiao, & Saudek, 2008; Derr et al., 2009; Fuji et al., 2007, 2009; Garg, Bhutani, Alyea, & Pendergrass, 2007; Hammer et al., 2009; Hardy, Nowacki, Bertin, & Weil, 2010; Kondo, Kondo, & Kondo, 2013; Lu et al., 2014; Sheean, Freels, Helton, & Braunschweig, 2006; Srokowski, Fang, Hortobagyi, & Giordano, 2009; Weiser et al., 2004). Glycemic status is categorized as nondiabetic (fasting blood glucose [FBG] of less than 100 mg/dl and glycosylated hemoglobin A1c [HbA1c] of less than 5.7%), prediabetic (FBG of 100–125 mg/dl and HbA1c from 5.7%–6.4%), and diabetic (FBG of 126 mg/dl or greater and HbA1c of 6.5% or greater) (ADA, 2014).

Most of the outcomes studies of hyperglycemic status focused on infection and mortality in patients with cancer. Increased risk for infection with hyperglycemia was found in six studies (Ali et al., 2007; Derr et al., 2008; Fuji et al., 2009; Hammer et al., 2009; Weiser et al., 2004), and increased risk for mortality was found in seven studies (Ali et al., 2007; Bhatnagar et al., 2014; Derr et al., 2008, 2009; Hammer et al., 2009; Kondo et al., 2013; Weiser et al., 2004). In one large epidemiologic study that used the Surveillance, Epidemiology, and End Results–Medicare database, patients with cancer and diabetes (21%) had an increased risk for hospitalization because of CTX toxicity (odds ratio [OR] = 1.38; 95% confidence interval [CI] [1.23, 1.45]) and higher all-cause mortality (hazard ratio [HR] = 1.35; 95% CI [1.31, 1.39]) (Srokowski et al., 2009).

In particular, studies in hematopoietic cell transplantation (HCT) showed an increased risk for mortality with glucose levels of greater than 150 mg/dl (HR = 2, p = 0.013) (Fuji et al., 2007), an increased risk for bloodstream infection with each 10 mg/dl increase in mean preneutropenic glucose (OR = 1.15, p = 0.01) (Derr et al., 2008), and a decrease in the occurrence of infections with tight glucose control compared to standard glucose control (14% versus 46%, respectively; p < 0.001) (Fuji et al., 2009). Similarly, in a study of 1,175 recipients of allogeneic HCT, HRs of 1.93 for glucose of greater than 200 mg/dl (p = 0.0009) and 2.78 for glucose of greater than 300 mg/dl (p = 0.0004) were found for mortality (Hammer et al., 2009). Increasing levels of blood glucose in patients treated for hematologic malignancies significantly increase the occurrence of infections, as well as mortality.

Although the administration of glucocorticoids as part of CTX regimens can result in patients becoming diabetic (Vigneri, Frasca, Sciacca, Pandini, & Vigneri, 2009), only one study has evaluated patients for the prediabetic state during CTX. In the study, patients receiving CTX for breast cancer were evaluated for prediabetic and diabetic states. Compared to the first CTX cycle (51%), fewer patients were classified as prediabetic in the fifth or sixth cycle (28%). However, the percentage of patients with diabetes increased from 25% at the first cycle to 33% at the fifth cycle (Lu et al., 2014).

Among the studies cited previously, only two have included symptoms. In these studies, the association between the single symptom of peripheral neuropathy and glycemic status was evaluated (Bhatnagar et al., 2014; Weiser et al., 2004). In Bhatnagar et al. (2014), 65% of the patients with breast cancer and diabetes who received a taxane required a dose reduction compared to only 35% of patients without diabetes (p = 0.02). In contrast, Weiser et al. (2004) did not find an association between hyperglycemia and peripheral neuropathy in 278 patients with acute lymphocytic leukemia. However, compared to patients without hyperglycemia, patients with hyperglycemia were at increased risk for infection (8% versus 39%, p = 0.03) and decreased survival (52 months versus 24 months, p = 0.001).

Taken together, these findings suggest that prediabetic and diabetic states are relatively common in patients with cancer. However, no studies were identified that evaluated associations between diabetic states and the severity of common symptoms associated with cancer and its treatments. Therefore, the purposes of this study of a sample of outpatients with cancer who were receiving CTX (N = 244) were to evaluate (a) the occurrence of nondiabetic, prediabetic, and diabetic states and (b) for differences in symptom severity and quality of life (QOL) among patients with these diabetic states.

Methods

This study is part of an ongoing, longitudinal study of the symptom experience of outpatients with

cancer receiving CTX. Eligible patients were aged 18 years or older; had a diagnosis of breast, gastrointestinal, gynecologic, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two comprehensive cancer centers, one Veterans Affairs hospital, and four community-based oncology programs in urban and surrounding areas in California and New York.

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. The Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well-established validity and reliability (Karnofsky, Abelmann, Craver, & Burchenal, 1948). Using the KPS scale, patients rated functional status from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms) (Karnofsky, 1977; Karnofsky et al., 1948).

The Self-Administered Comorbidity Questionnaire (SCQ) was developed to measure comorbidity and is short and easily understood (Sangha, Stucki, Liang, Fossel, & Katz, 2003). The 13-item instrument lists 13 common medical conditions that have been simplified so that they can be understood without prior medical knowledge. Patients indicate whether they have the symptom or not using a "yes" or "no" format. If they indicate that they have a condition, they are asked whether they have received treatment for it using a "yes" or "no" format with a proxy for disease severity or whether it limited their daily activities using a "yes" or "no" format with an indication of functional limitations. For each condition, patients can receive as many as three points. SCQ scores range from 0–39, with higher scores indicating more severe comorbidity. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions (Brunner et al., 2008; Cieza et al., 2006).

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy (Lee, Hicks, & Nino-Murcia, 1991). Each item is rated from 0–10, and total fatigue and energy scores are calculated as the mean of the 13 fatigue items plus the 5 energy items, with higher scores indicating greater fatigue severity and higher levels of energy. Patients are asked to rate each item based on how they feel in the moment, within 30 minutes of awakening (i.e., morning fatigue or morning energy), and prior to going to bed (i.e., evening fatigue or evening energy). Cutoff scores of 3.2 or greater and 5.6 or greater indicate high levels of morning and evening fatigue, respectively (Fletcher et al., 2008). Cutoff scores of 6 or less and 3.5 or less indicate low levels of morning and evening energy, respectively. The LFS was chosen for this study because it is relatively short, easy to administer, and has well-established validity and reliability (Gay, Lee, & Lee, 2004; Lee et al., 1991; Lee, Portillo, & Miramontes, 1999; Miaskowski et al., 2006, 2008; Miaskowski & Lee, 1999). In this study, Cronbach alphas for the evening and morning fatigue scales were 0.95 and 0.96, respectively. Cronbach alphas for the evening and morning energy scales were 0.93 and 0.95, respectively.

The 20-item State-Trait Anxiety Inventories (STAI-T and STAI-S) are rated from 1–4. The scores for each scale are summed and can range from 20–80. Cutoff scores of 31.8 or greater and 32.2 or greater indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well-established validity and reliability (Bieling, Antony, & Swinson, 1998; Kennedy, Schwab, Morris, & Beldia, 2001; Spielberger, Gorsuch, Suchene, Vagg, & Jacobs, 1983). In the current study, the Cronbach alphas for the STAI-S and STAI-T were 0.96 and 0.92, respectively.

The 20-item Center for Epidemiological Studies–Depression scale (CES-D) consists of items representing the major symptoms for depression. Scores can range from 0–60, with scores of 16 or greater indicating a need for clinical evaluation for major depression. The CES-D has well-established validity and reliability (Carpenter et al., 1998; Radloff, 1977; Sheehan, Fifield, Reisine, & Tennen, 1995). In the current study, the Cronbach alpha for the CES-D total score was 0.89.

The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess quality of sleep in the past week on a scale of 0 (never) to 7 (every day). The GSDS total score is the sum of the seven subscale scores, ranging from 0 (no disturbance) to 147 (extreme disturbance). A GSDS total score of 43 or greater indicates a significant level of sleep disturbance (Fletcher et al., 2008). The GSDS has well-established validity and reliability (Lee, 1992; Lee & DeJoseph, 1992; Miaskowski & Lee, 1999). In the current study, the Cronbach alpha for the GSDS total score was 0.83.

The 16-item Attentional Function Index (AFI) was designed to measure attentional function (Cimprich, Visovatti, & Ronis, 2011). Scores range from 0–10, and a higher mean score indicates greater capacity to direct attention (Cimprich et al., 2011). Scores of less than 5 indicate low attentional function, scores from 5–7.5 indicate moderate attentional function, and scores of greater than 7.5 indicate high attentional function (Cimprich et al., 2005). The AFI has well-established validity and reliability (Cimprich et al., 2011). In the current study, the Cronbach alpha was 0.93.

Occurrence of pain was evaluated using the Brief Pain Inventory (Daut, Cleeland, & Flanery, 1983). Patients who responded "yes" to the question about having

Table 1. Demographic and Clinical Characteristics by Diabetic State[a] (N = 244)

Characteristic	Nondiabetic (n = 159)		Prediabetic (n = 64)		Diabetic (n = 21)				
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	F	p	PHC
Age (years)	55.2	12	60.3	11.1	60.3	8.8	5.4	0.005	1 < 2
Education (years)	16.2	3.1	15.6	3.1	15.5	3.3	1.39	0.251	–
Body mass index (kg/m^2)	24.7	4.8	27.1	5.9	29.3	8.4	9.66	< 0.0001	1 < 2 and 3
Karnofsky Performance Status scale	79.5	12.6	78.9	12.8	78.8	13.6	0.05	0.948	–
Number of comorbid conditions	2.2	1.4	2.6	1.6	3.4	1.6	7.3	0.001	1 < 3
SCQ	5.3	3.3	5.6	3.2	7.6	4.1	4.67	0.01	1 and 2 < 3
HbA1c level	5	0.4	6	0.3	7.3	1	320.41	< 0.0001	1 < 2 < 3
Number of metastatic sites	1.2	1.2	1.3	1.3	0.7	1	1.84	0.16	–
Number of non-lymph metastatic sites	0.7	1	0.8	1.1	0.3	0.7	2.22	0.111	–
AUDIT score	3.5	3.1	2.4	1.7	1.8	1.5	3.83	0.024	–
Number of MSAS symptoms	14.1	7.1	14.2	7.7	12.6	6.4	0.437	0.647	–
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**χ^2**	**p**	**PHC**
Female gender	125	79	48	75	15	71	0.75	0.688	–
Cancer type							11.44	0.76	–
Breast	71	45	21	33	10	48	–	–	–
Gastrointestinal	50	31	20	31	7	33	–	–	–
Gynecologic	24	15	9	14	–	–	–	–	–
Lung cancer	14	9	14	22	4	19	–	–	–
Ethnicity							17.87	0.007	–
Caucasian	110	69	47	74	9	43	–	–	–
African American	12	8	3	5	7	33	–	–	3 < 1 and 2
Asian or Pacific Islander	18	11	7	11	2	10	–	–	–
Hispanic or other	17	11	7	11	3	14	–	–	–
Missing data	2	1	–	–	–	–	–	–	–
Married or living together	108	69	39	61	9	45	5.2	0.074	–
Living alone	27	17	15	23	5	25	1.62	0.448	–
Currently employed	49	31	23	37	7	33	0.05	0.75	–
Income ($)[b]							–	0.045	–
Less than 30,000	27	17	13	20	5	24	–	–	–
30,000–69,999	20	13	12	19	6	29	–	–	–
70,000–100,000	22	14	13	20	2	10	–	–	–
Greater than 100,000	75	47	19	30	6	29	–	–	–
Missing data	15	9	7	11	2	10	–	–	–
Exercises regularly	121	77	39	63	11	52	7.89	0.019	–
Previous or current smoker	54	34	26	41	10	48	0.93	0.361	–
Has childcare responsibilities	42	27	11	17	5	25	2.43	0.297	–
Has adult care responsibilities	5	3	7	12	3	17	7.79	0.02	–
Comorbidities							–	–	–
Heart disease	8	5	5	8	1	5	0.69	0.707	–
High blood pressure	38	24	25	39	13	62	15.03	0.001	1 < 3
Lung disease	16	10	9	14	3	14	0.9	0.639	–
Diabetes	3	2	10	16	12	57	64.32	< 0.0001	1 < 2 < 3
Ulcer or stomach disease	8	5	3	5	–	–	1.1	0.578	–
Kidney disease	–	–	1	2	–	–	2.82	0.244	–
Liver disease	11	7	2	3	2	10	1.59	0.451	–
Anemia or other blood disease	24	15	8	13	2	10	0.63	0.73	–
Cancer	159	100	61	95	21	100	8.54	0.014	–
Depression	29	18	14	22	4	19	0.39	0.823	–
Osteoarthritis	16	10	10	16	5	24	3.83	0.148	–
Back pain	39	25	17	27	7	33	0.78	0.678	–
Rheumatoid arthritis	2	1	3	5	2	10	5.58	0.061	–

[a] Nondiabetic indicates HbA1c of less than 5.7, prediabetic indicates HbA1c from 5.7–6.4, and diabetic indicates HbA1c of 6.5 or greater.

[b] Kruskal Wallis = 6.18

AUDIT—Alcohol Use Disorders Identification Test; HbA1c—glycosylated hemoglobin A1c; MSAS—Memorial Symptom Assessment Scale; PHC—post-hoc contrasts; SCQ—Self-Administered Comorbidity Questionnaire

Note. Karnofsky Performance Status scores range from 0–100, with higher scores indicating better well-being. SCQ ranges from 1–13, with higher scores indicating more comorbidities. Metastatic sites include scores out of 9. Non-lymph metastatic sites include scores out of 8. AUDIT scores range from 0–4, with higher scores indicating harmful or hazardous alcohol intake. MSAS scores range from 1–38, with higher scores indicating more symptoms.

Note. Because of rounding, percentages may not total 100.

pain were asked to indicate whether their pain was related to cancer treatments. Patients were categorized into one of four groups (no pain, only noncancer pain, only cancer pain, or both cancer and noncancer pain). Patients rated the intensity of the pain (now, average, and worst) using a scale ranging from 0 (none) to 10 (excruciating).

The Memorial Symptom Assessment Scale (MSAS) was used to evaluate the occurrence, severity, and distress of 32 symptoms commonly associated with cancer and its treatment. The MSAS is a self-report questionnaire designed to measure the multidimensional experience of symptoms. Patients were asked to indicate whether or not they had experienced each symptom in the past week (symptom occurrence). If they had experienced the symptom, they were asked to rate its severity and distress. In the current article, the total number of MSAS symptoms is reported. The validity and reliability of the MSAS is well established in studies of inpatients and outpatients with cancer (Portenoy et al., 1994).

The QOL Scale–Patient Version (QOL-PV) is a 41-item instrument that measures four dimensions of QOL (physical, psychological, social, and spiritual well-being) in patients with cancer, as well as a total QOL score. Each item is rated on a 0–10 numeric rating scale, with higher scores indicating better QOL. The QOL-PV has established validity and reliability (Ferrell, 1995; Ferrell, Dow, & Grant, 1995; Padilla, Ferrell, Grant, & Rhiner, 1990; Padilla et al., 1983). In the current study, the Cronbach alpha for the QOL-PV total score was 0.92.

The SF-12® consists of 12 questions about physical and mental health, as well as overall health status. The individual items on the SF-12 are evaluated, and the instrument is scored into two components that measure physical component summary (PCS) and mental component summary (MCS) scores, which can range from 0–100. Higher PCS and MCS scores indicate a better QOL. The SF-12 has well-established validity and reliability (Ware, Kosinski, & Keller, 1996).

Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the institutional review board at each of the study sites. Eligible patients were approached by a research staff member in the infusion unit to discuss participation in the study. Written informed consent was obtained from all patients. Patients completed study questionnaires in their homes for a total of six times during two cycles of CTX (i.e., prior to CTX administration and recovery from previous cycle). The timing per patient varied by their cycle length; about one week after CTX administration related to acute symptoms, and about two weeks after CTX administration related to potential nadir. For the current article, symptom severity scores from the enrollment booklet that asked patients to report on their symptom experience for the week prior to the administration of the next cycle of CTX were analyzed. Medical records were reviewed for disease and treatment information.

Blood glucose was assessed during the same clinical visit when the enrollment booklets were administered. HbA1c provides a 2–3 month assessment of an individual's blood glucose status (Triplitt, 2010; U.S. Department of Health and Human Services, 2006). HbA1c was measured using one droplet of blood that was processed through the Bio-Rad in2it analyzer (Petersen et al., 2010). Samples were processed within minutes of collection. Control samples were run periodically per guidelines to ensure proper calibration of the instrument. For analyses, HbA1c percentages were used. Per the ADA (2014) guidelines, the authors categorized HbA1c levels of 6.5% or greater as diabetic, 5.7%–6.4% as prediabetic, and less than 5.7% as nondiabetic.

Data Analysis

Data were analyzed using SPSS®, version 22.0. Descriptive statistics and frequency distributions were generated on the sample characteristics. One-way analyses of variance (ANOVAs) were used to evaluate for differences in demographic and clinical characteristics, symptom severity scores, and QOL scores among the three diabetic states (i.e., nondiabetic, prediabetic, and diabetic). Post-hoc contrasts were done using the Bonferroni procedure to control the overall family alpha level. Differences among the diabetic states were considered statistically significant at the $p < 0.05$ level.

Findings

Of the 244 patients in the study, 16% self-reported having diabetes on the SCQ. However, based on the HbA1c measurements, 65% (n = 159) of the patients were nondiabetic, 26% (n = 64) were prediabetic, and 9% (n = 21) were diabetic.

As summarized in Table 1, a number of demographic and clinical characteristics differed among the diabetic states. Compared to the nondiabetic and prediabetic states, patients in the diabetic state had a higher SCQ score and were more likely to be African American compared to the other three ethnic groups. Compared to the nondiabetic state, patients in the prediabetic state were significantly older. Patients in the diabetic state reported a higher number of comorbid conditions and high blood pressure than nondiabetic patients. In addition, patients in the prediabetic and diabetic states had a higher BMI than patients in the nondiabetic state. The self-reported occurrence of diabetes was in the expected direction, with the fewest reporting being nondiabetic and the most reporting diabetic.

As shown in Table 2, no differences in any of the symptom severity scores were found among the three diabetic states. All of the patients reported clinically meaningful levels of state and trait anxiety, as well as sleep disturbance, and they reported low levels of morning energy. Patients in the prediabetic and diabetic states reported clinically meaningful levels of morning fatigue. Patients in the diabetic state reported clinically meaningful levels of evening fatigue.

No differences in the SF-12 subscale and PCS and MCS scores were found among the three diabetic state groups. No differences in MQOLS-PV subscale and total scores were found among the three diabetic states.

Discussion

This study is the first to evaluate the occurrence of diabetes and the association between diabetic states and symptom severity and QOL scores in patients receiving CTX. Among the diabetic states, 63% of the patients were nondiabetic, 26% were prediabetic, and 9% were diabetic. These percentages are lower than previous studies, which found that 44% of patients with cancer had prediabetes, and from 19% (Bhatnagar et al., 2014) to 22% (Ji et al., 2013) of patients had diabetes. Reasons for these differences are not readily apparent and warrant additional investigation.

In terms of demographic and clinical characteristics, compared to the nondiabetic state, patients in the diabetic state had a higher BMI, reported a higher number of comorbidities, had a higher SCQ score, were more likely to be African American, and self-reported a higher occurrence of hypertension. However, no differences in symptom severity and QOL scores were found among the three diabetic states. Of note, no differences were found among the diabetic states in terms of cancer diagnoses or number of metastatic sites.

Older age is associated with higher glucose levels (Kezerle et al., 2014). Twenty-seven percent of individuals aged 65 years or older have diabetes (NIDDK, 2015). In older adults, increases in blood sugar may be caused by the normal process of cellular senescence (Campisi & d'Adda di Fagagna, 2007; Campisi & Yaswen, 2009) and related increases in plasma hypertonicity, which result in increased insulin resistance and impaired glucose use (Stookey, Pieper, & Cohen, 2004). Although the current age-related findings are consistent with the general population, other studies of patients with cancer failed to find an association between age and diabetic state (Bhatnagar et al., 2014; Shah et al., 2014).

Higher BMI increases the risk for hyperglycemia (Giovannucci et al., 2010; Makki, Froguel, & Wolowczuk, 2013; Meigs, Hu, Rifai, & Manson, 2004; Roumen et al., 2009). A higher BMI increases insulin resistance (Giovannucci et al., 2010; Makki et al., 2013) and, in obese individuals, induces metabolic inflammation, which leads to impaired glucose metabolism (Makki et al., 2013). Findings from the current study are consistent with previous reports in that the nondiabetic patients had a BMI of 24.7 kg/m^2, which

Table 2. Differences in Symptom Severity by Diabetic State[a] (N = 244)

	Nondiabetic (n = 159)		Prediabetic (n = 64)		Diabetic (n = 21)			
Symptom	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**F**	**p**
AFI	6.4	1.8	6.1	1.8	6.2	1.7	0.43	0.648
STAI								
Trait anxiety	35	11.1	36.4	11.8	36.5	10.6	0.39	0.679
State anxiety	33.5	12	34.5	12.9	34.2	15	0.14	0.868
GSDS	52.6	21.2	56.7	19.8	48.8	21.2	1.35	0.261
CES-D	12.7	9.4	14.1	9.7	15	10.8	0.87	0.419
Lee Fatigue Scale								
Morning fatigue	3.1	2.2	3.5	2.2	3.4	2.8	0.65	0.525
Evening fatigue	5.4	2.1	5.3	2	5.6	2.1	0.12	0.89
Morning energy	4.4	2.1	4.4	2.4	4.6	2.3	0.12	0.885
Evening energy	3.6	2.1	4	2.4	3.5	1.6	0.82	0.441
Brief Pain Inventory	3	1.9	3.2	2	3.7	1.3	0.79	0.455
Symptom	**n**	**%**	**n**	**%**	**n**	**%**	χ^2	**p**
Occurrence of pain							7.28	0.296
None	46	29	11	17	4	19		
Only cancer	42	26	14	22	4	19		
Only noncancer	20	13	12	19	5	24		
Both	46	29	25	39	7	33		
Missing data	5	3	2	3	1	5		

[a] Nondiabetic indicates HbA1c of less than 5.7, prediabetic indicates HbA1c from 5.7–6.4, and diabetic indicates HbA1c of 6.5 or greater.

AFI—Attentional Function Index; CES-D—Center for Epidemiologic Studies–Depression; GSDS—General Sleep Disturbance Scale; HbA1c—glycosylated hemoglobin A1c; STAI—State-Trait Anxiety Inventory

Note. Scores on the AFI range from 0–10, with higher scores indicating greater capacity to direct attention. Scores on the STAI range from 20–80, with higher scores indicating greater levels of anxiety. Scores on the GSDS range from 0–147, with higher scores indicating greater disturbance. Scores on the CES-D range from 0–60, with a score of 16 or greater indicating a need for clinical evaluation for major depression. Scores on the Lee Fatigue Scale range from 0–10, with higher scores indicating greater fatigue severity and energy. Scores on the Brief Pain Inventory ranges from 0–10, with higher scores indicating more pain.

Note. Because of rounding, percentages may not total 100.

borders on being overweight. Patients in the prediabetic range had a mean BMI of 27.1 kg/m^2, which is considered overweight, and those in the diabetic range had a mean BMI of 29.3 kg/m^2, which borders on obesity (ADA, 2014).

In addition, a higher BMI is associated with increased risk for comorbidities. In general, obese individuals have higher rates of cancer, diabetes, and cardiovascular disease (Ligibel et al., 2014). In this study, patients in the diabetic state had a higher number of comorbidities and a higher SCQ score. The most common comorbidities in this group were hypertension (n = 13), self-reported diabetes (n = 12), back pain (n = 7), and osteoarthritis (n = 5).

The primary goal of this study was to evaluate associations between HbA1c levels and symptom severity. Because hyperglycemia induces systemic inflammation (Esposito et al., 2002) and increased inflammatory responses are associated with higher symptom burden (Bower & Lamkin, 2013; Esposito et al., 2002; Irwin, Olmstead, Ganz, & Hague, 2013), the authors hypothesized that patients with higher HbA1c would report higher symptom severity scores. However, the findings do not support this hypothesis. In a previous study (Miaskowski et al., 2014), no associations were found between any disease characteristic (e.g., cancer diagnosis, presence of metastatic disease) and symptom burden.

In hindsight, the most likely reason for this lack of association is that HbA1c was used as a measure of glycemic status. HbA1c was chosen as the measure for this study to avoid the need for patients to have to fast for a blood glucose determination. HbA1c is a reflection of circulating blood glucose that adheres to hemoglobin. Therefore, HbA1c is a mean level of glucose, which is dependent on the lifespan of the red blood cell (RBC). Various conditions, including cancer, can impair normal RBC production and destruction, yielding a potentially altered HbA1c level (Wright & Hirsch, 2012). In addition, in a study of patients with hematologic malignancies who received allogeneic HCT, glucose variability was more likely to be associated with adverse outcomes than hyperglycemia (Hammer et al., 2009). Although this sample of patients with solid tumors was quite different, glucose fluctuations, which were not captured by the HbA1c measurement, may be associated with patients' symptom experiences.

Another limitation was that the associations between HbA1c and symptom severity were done at a single time point. Measurements over time of symptom severity scores and HbA1c levels may have shown significant associations. In addition, exercise is an established regulator of blood glucose (Katz, 2007; Moien-Afshari et al., 2008), and more than 70% of patients in the current study reported exercising regularly. This finding may be indicative of the type of individual who was willing to enroll in the study, which impaired the authors' ability to evaluate patients with cancer who are more sedentary.

Knowledge Translation

Patients with cancer receiving chemotherapy who are older aged, have a body mass index of 25 kg/m^2 or greater, or who have multiple comorbidities may be at increased risk for hyperglycemia.

More than 25% of patients with cancer had glycosylated hemoglobin A1c levels in the prediabetic range, and these patients warrant ongoing assessments and education on healthy behavior.

Additional studies are needed to evaluate changes over time in blood glucose and other inflammatory biomarkers to better evaluate hyperglycemic status in patients receiving chemotherapy.

Conclusion

This study confirmed that older age, higher BMI, and having multiple comorbidities are associated with increased mean glycemic levels. This information has important implications for practice. Patients diagnosed with cancer who are older aged, have a BMI of greater than 25 kg/m^2, or who have multiple comorbidities should be closely monitored for perturbations in glycemic status, whether or not they have preexisting diabetes. In addition, these patients warrant education about diet and exercise. Oncology nurses should consider whether or not these patients with prediabetes should be referred to a dietitian.

Numerous areas for research warrant consideration. Longitudinal studies are needed to describe fluctuations in blood glucose and other inflammatory biomarkers in patients receiving CTX. Studies that determine modifiable risk factors that contribute to interindividual differences in these fluctuations are warranted to identify patients at higher risk for prediabetic and diabetic states. Future longitudinal studies also need to evaluate the associations between changes in blood glucose and symptom severity in patients with solid tumors.

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