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Impact of diabetes and hyperglycemia on health care utilization, infection risk, and survival in patients with cancer receiving glucocorticoids with chemotherapy

Dylan Zylla [a,b,*], Grace Gilmore [a], Justin Eklund [a,b], Sara Richter [c], Anders Carlson [d]

[a] Park Nicollet Oncology Research, Frauenshuh Cancer Center, HealthPartners, Minneapolis, MN, USA
[b] HealthPartners Institute, HealthPartners, Minneapolis, MN, USA
[c] Professional Data Analysts, Inc., Minneapolis, MN, USA
[d] International Diabetes Center, Park Nicollet, Minneapolis, MN, USA

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ABSTRACT

Background: Glucocorticoids are commonly used in chemotherapy regimens and may lead to hyperglycemia and increased infection rates.
Methods: We performed a retrospective analysis on 1781 patients who received intravenous chemotherapy with glucocorticoids between 2010 and 2015. Data was obtained using electronic medical record, billing modules, and tumor registry. We compared new infections and survival between patients with and without diabetes, after adjusting for demographic and cancer-related variables.
Results: In the first 12 months following chemotherapy, patients with diabetes (n = 330) had higher rates of hospital admissions (70.9% vs 57.4%), more infection-related admissions (37.0% vs 29.2%), and increased rates of new infections (61.2% vs 49.2%) when compared to patients without diabetes (n = 1451). One-year survival was worse among patients with diabetes (67.3% vs 78.3%), and in patients with at least one elevated glucose following chemotherapy (60.8% vs 78.5). After adjusting for cancer stage, age, and gender, diabetes history increased the odds of dying within one year after diagnosis by 86% (OR 1.86, 95% CI (1.37–2.52)) and of new infections by 68% (OR 1.68, 95% CI (1.26–2.24)).
Conclusions: Among patients with cancer receiving intravenous chemotherapy with glucocorticoids we demonstrate those with diabetes have more hospital admissions, increased rates of infections, and worse survival.

1. Introduction

Over 30 million adults in the U.S., or about 9.4% of the population, have diabetes, with >95% of those with type 2 diabetes. Unfortunately, approximately 1/4 of people with diabetes are undiagnosed.[4] Specifically within the oncology population, patients with diabetes have been shown to have worse outcomes than those without diabetes; patients with diabetes undergoing cancer treatment have been shown to have increased mortality, higher rates of hospitalization and infection, and shortened survival.[5–9] Glucocorticoid-induced hyperglycemia is a common and potentially serious complication during chemotherapy, where glucocorticoids are often used for their antiemetic effects during use of common chemotherapy regimens.[10] An untoward effect of glucocorticoids can be hyperglycemia, and there are several proposed mechanisms by which hyperglycemia occurs (Fig. 1). It is known that hyperglycemia in the setting of chemotherapy contributes to poor outcomes and in many cases decreased survival.[11–13] This appears true for many types of malignancies, both solid and hematologic.[14–16]

There is a paucity of data regarding the optimal approach to screening and subsequent outpatient management of patients receiving glucocorticoids with chemotherapy. Previous groups have proposed protocols to manage hyperglycemia in oncology patients, but they have been largely inpatient and specific to one type of malignancy.[17–20] Additionally, there are no clear guidelines for monitoring and managing hyperglycemia in patients with advanced cancer, which can be a challenging balance between maintaining a safe blood glucose, and impacting quality of life with excessive monitoring of blood glucose and possibly additional medications.

In a 3-month pilot project at our institution's cancer center in 2016, we found almost 50% of our population on IV chemotherapy regimens had a diagnosis of pre-diabetes or diabetes based on initial hemoglobin

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* Corresponding author at: Park Nicollet Oncology Research, HealthPartners Institute, Frauenshuh Cancer Center, 3800 Park Nicollet Blvd, Minneapolis, MN 55416, USA.
E-mail address: dylan.zylla@parknicollet.com (D. Zylla).

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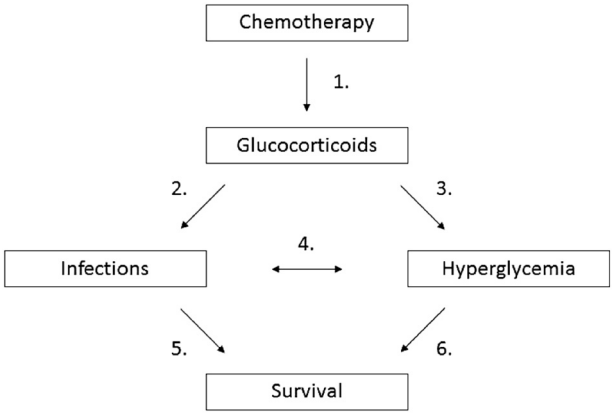

Fig. 1. Potential mechanisms for glucocorticoid-induced increases in morbidity and mortality among patients with diabetes. 1. Glucocorticoids are commonly given with chemotherapy for prevention and treatment of nausea, vomiting, and infusion reactions, and may be a backbone to some chemotherapy regimens. 2. Systemic glucocorticoid therapy is known to be associated with increased infection risk. This is due to the impaired function of phagocytic cells, as well as impaired early recognition of infectious symptoms and fever due to the inhibition of cytokine release. 3. Systemic glucocorticoids are also known to cause an elevation in blood glucose levels due to inhibition of glucose uptake, increase in hepatic gluconeogenesis, and altered receptor functioning[1,2]. 4. Hyperglycemia can impair neutrophil activity, induce lymphocyte killing, and promote growth of bacteria[3]. Conversely, infections can trigger a stress response leading to increased hyperglycemia. 5. Uncontrolled infection is a common cause of death in cancer patients. 6. Hyperglycemia is associated with worse survival in many cancers.

A1c (HbA1c) readings.[21] The aim of this retrospective study is to identify the prevalence of diabetes in our oncology population within a large tertiary care comprehensive cancer center from 2010 through 2015, and also describe the rates of complications (hospitalizations, emergency department or urgent care visits, and infections) in our current oncologic practice. We also aim to investigate any correlation between diabetes and survival.

2. Subjects, materials, and methods

This exhaustive, retrospective study was conducted at a large, urban, community cancer center. The study population included all adult patients who underwent chemotherapy at the study institution from January 1, 2010 to December 31, 2015 and received steroids. Data were extracted from both the Electronic Health Record (EHR) and the Tumor Registry. Based on tumor registry records, nearly 90% of patients were diagnosed with cancer and also received standard care (i.e., primary care, diabetes management) in our organization. All patients who met the above study inclusion criteria were included in the analysis (n = 1781). Participants were separated based on diabetes status.

Demographic, clinical, and health care utilization data were also extracted, including age; gender; cancer type and stage; history of diabetes; medications at baseline; baseline vital signs (weight, height, and BMI); baseline laboratory values (creatinine, HbA1c, glucose, GFR, and hemoglobin); vital status; and emergency room (EC), urgent care (UC), and inpatient (IP) visits. All glucose values obtained during clinic (typically on day 1 of each chemotherapy cycle) or during hospitalizations were analyzed. Participants were placed in the Diabetes group if a Type 1 or Type 2 diabetes ICD-9/ICD-10 code was listed in their medical history list or on any prior inpatient or outpatient billing code. Cancers were grouped based on stage (stage I–III or stage IV). Certain cancers (i.e. lymphoma, leukemia, myeloma) do not have a typical stage I–IV and were placed as unknown/NA.

All EC, UC, and IP visits included dates of encounters and ICD-9/ICD-10 diagnoses. These visits were subset to encounters potentially related to diabetes or infections using keyword searches of ICD-9/ICD-10 codes. Cumulative tallies were generated of all EC/UC/IP visits within the 12 months following initial chemotherapy for all encounters and separately for infection-related visits. Infection-related visits were further separated into new post-chemo infections, defined as a diagnosis of an infection in the 1 year following initial chemo, and no infection in the 30 days prior to initial chemo. Patients presenting to the EC and subsequently admitted to the hospital were only categorized as having an IP visit. Data on total IP stays were obtained from 2010 through the end of study. However, specific diagnoses were not available in 2010 and 2011 (hospital billing module was not added until 2012), so infection- and diabetes-related data were obtained from 2012 through the end of study.

Descriptive summaries were calculated for demographic, clinical, and utilization variables. Total health care utilization between diabetes status groups were compared using Chi-square or Fisher's Exact tests if cell sizes were small (<5). Logistic regression models were used to compare survival rates and new-post chemo infections between the diabetes groups, after adjusting for demographic and cancer-related variables. Overall survival was defined as survival at 1 year following initial cancer diagnosis. Odds ratios (ORs) with 95% confidence intervals are reported. Results did not significantly change when repeating all analyses after removing the 197 patients (11%) who were diagnosed outside of our institution and had only part of their cancer treatment at our institution. Analyses were conducted using SAS v9.4 (SAS Institute, Inc., Cary, NC). Statistical tests were two-sided and the significance level (alpha) was set at 0.05.

3. Results

3.1. Demographics

Of the 1781 patients included in our analysis, 330 (18.5%) had a known history of diabetes (Table 1). When restricted to age to 65 and

Table 1
Demographic and clinical summaries overall and by complication status.

	All patients (n = 1781)	Diabetes status		p-Value[a]
		No diabetes (n = 1451)	Diabetes (n = 330)	
Demographic variables				
Age[b] (years) - Mean (SD)	59.5 (13.4)	58.4 (13.6)	64.6 (11.0)	<0.001
Gender – n (%)				0.527
Female	1060 (59.5%)	858 (59.1%)	202 (61.2%)	
Male	721 (40.5%)	593 (40.9%)	128 (38.8%)	
BMI (kg/m^2) – mean (SD)	28.7 (7.0)	27.9 (6.6)	32.3 (7.9)	<0.001
Cancer type – n (%)				0.455
Solid malignancy	1417 (79.6%)	1149 (79.2%)	268 (81.2%)	
Heme malignancy	364 (20.4%)	302 (20.8%)	62 (18.8%)	
Cancer stage – n (%)				0.705
Stage I–III	981 (55.1%)	796 (54.9%)	185 (56.1%)	
Stage IV	525 (29.5%)	426 (29.4%)	99 (30.0%)	
Unknown/NA	275 (15.4%)	229 (15.8%)	46 (13.9%)	
Diabetes type				
Type 1			33 (10.0%)	
Type 2			297 (90.0%)	
Lab variables				
Creatinine, in mg/dL – Mean (SD)		0.9 (0.5)	1.0 (0.6)	<0.001
GFR, in mL/min/1.73 m^2 – Mean (SD)		58.9 (7.0)	55.9 (10.4)	<0.001
Glucose, in mg/dL – Mean (SD)		105.7 (27.7)	153.7 (61.1)	<0.001
HbA1c, in % – Mean (SD) [c]		5.7 (0.7)	7.1 (1.4)	<0.001
Hemoglobin, in g/dL – Mean (SD)		12.1 (2.1)	11.9 (2.0)	0.067

[a] The p-value compares group differences between diabetes status. 2-Sample *t*-tests were used for continuous variables; chi-square or Fisher's exact for categorical depending on cell size.
[b] Of the 330 patients with diabetes, % breakdown by age: 18–44 (4.1%), 45–64 (16.4%), 65+ (27%).
[c] Only 221 patients with no diabetes history had HbA1c drawn.

above (n = 638), ~27% of our sample has a known diabetes history, consistent with published prevalence data.[22] Patients with diabetes were older (64 vs 58 years, p < 0.001), and had a higher BMI (32.3 vs 27.9, p < 0.001). The majority of patients (80%) had a solid malignancy, with most patients (55.1%) having stage I-III disease at the time of diagnosis. Gender, cancer type, and cancer stage were similar between patients with and without diabetes. When comparing baseline laboratory values, patients with diabetes had higher glucose and HbA1c, however, creatinine, GFR, and hemoglobin values were similar.

3.2. Health care utilization (HCU), infection rates, and survival based on diabetes status

To assess the impact of diabetes and hyperglycemia on HCU, infection rates, and one-year survival, we analyzed rates of hospital admissions and infections based on diabetes status (all patients), hyperglycemia status (for patients with at least one glucose value available in the 12 months following initial chemotherapy), and HbA1c values (for those with diabetes) (Tables 2 and 3).

3.2.1. HCU and infection rates

Patients with diabetes had higher rates of hospitalization in the first 12 months following initial chemotherapy (70.9% vs 57.4%, p < 0.001) (Table 2). When limited to infection-related admissions, patients with diabetes had nearly 8% higher rates of admission (37.0% vs 29.2%, p = 0.007). Rates of new infections diagnosed either inpatient or outpatient were 12% higher in patients with diabetes (61.2% vs 49.2%, p < 0.001).

These trends were similar when looking at all patients, regardless of diabetes status, who had at least 1 documented glucose reading above 300 mg/dL following initial chemotherapy. In the 12 months following chemotherapy, patients with at least one elevated glucose value had higher rates of admissions, infection-related admissions, and new infections (84.4% vs 58.4%, p < 0.001, 44.2% vs 29.7%, p < 0.001, 65.3% vs 50.7%, p < 0.001, respectively). However, no significant differences were seen when analyzing patients with diabetes in different HbA1c categories (Low HbA1c (<6.5), Moderate HbA1c (6.5–8.0), or High HbA1c (>8.0)). There was a trend towards higher rates of ER and UC visits for patients with diabetes, at least one glucose above 300 mg/dL, and higher HbA1c, though this was not statistically significant.

On multivariate analysis, we aimed to determine if the increased rates of infections seen in patients with diabetes were due to other disease and clinical factors. After adjusting for cancer stage, age, and gender, we found diabetes history increased the odds of new infection by 68% (OR 1.68, 95% CI (1.26–2.24), p < 0.001) (Table 3). There was no association between cancer stage, age, or gender on the rate of new post-chemotherapy infections.

3.2.2. One-year survival rates

On univariate analysis, survival was worse among patients with diabetes (67.3% vs 78.3%, p < 0.001), as well as patients with at least one glucose reading above 300 mg/dL in the 12 months following chemotherapy (60.8% vs 78.5, p < 0.001) (Table 2). There was a trend towards improved survival with lower HbA1c values, but this was not statistically significant. A history of diabetes did not impact one-year survival rates in hormonally-driven cancers (e.g., breast, prostate and uterine) or pancreatic cancer, but was worse in all other hematologic/solid cancers.

On multivariate analysis, we aimed to determine if the lower survival rates in patients with diabetes was due to other disease and clinical factors. After adjusting for cancer stage, age, gender, and study year, we found diabetes history increased the odds of death within 1 year of diagnosis by 86% (OR 1.86, 95% CI (1.37–2.52), p < 0.001) (Table 3). Higher cancer stage (stage IV vs stage I-III) was associated with decreased OS (OR 9.177, 95% CI 6.816–12.356, p < 0.001). Additionally, an unknown/NA cancer stage was associated with decreased OS (OR 5.492, 95% CI 3.859–7.815, p < 0.001) when compared to stage I-III cancer. This is likely reflective of the poor prognosis associated with hematologic malignancies that require chemotherapy (i.e. leukemia, lymphoma, myeloma), which comprised a majority of the unknown/NA stage cancers. Older age at the time of initial chemotherapy was associated with decreased OS rates (OR 1.031, 95% CI 1.021–1.042, p < 0.001), but not with post-chemo infection rates. There was a general trend towards better survival as study year increased, likely mirroring the advancements in cancer care and new treatment options available. This was most notable when analyzing patients diagnosed in 2014 and 2015 when compared to 2010.

Table 2
Health care utilization outcomes - Univariate table.

Health care utilization outcome	Diabetes status[a]			Hyperglycemia status in 12 months post-chemotherapy[b]			Baseline HbA1c value[c]			
	No diabetes (n = 1451)	Diabetes (n = 330)	p-Value[d]	All < 300 mg/dL (n = 1539)	At least 1 > 300 mg/dL (n = 199)	p-Value[d]	Low HbA1c (<6.5) (n = 96)	Moderate HbA1c (6.5–8.0) (n = 120)	High HbA1c (>8.0) (n = 47)	p-Value[d]
Admissions (%)			<0.001			<0.001				0.823
No stays	42.6%	29.1%		41.7%	15.6%		30.2%	30.0%	25.5%	
1 or more stays	57.4%	70.9%		58.4%	84.4%		69.8%	70.0%	74.5%	
New infection (%)	49.2%	61.2%	<0.001	50.7%	65.3%	<0.001	61.5%	63.3%	59.6%	0.896
Infection-related admissions (%)			0.007			<0.001				0.798
No stays	70.9%	63.0%		70.3%	55.8%		62.5%	65.0%	59.6%	
1 or more stays	29.2%	37.0%		29.7%	44.2%		37.5%	35.0%	40.4%	
ER visits (%)			0.339			0.532				0.898
No stays	70.4%	67.6%		69.8%	67.3%		69.8%	68.3%	66.0%	
1 or more stays	29.6%	32.4%		30.2%	32.7%		30.2%	31.7%	34.0%	
UC visits (%)			0.580			0.706				0.449
No stays	88.8%	87.6%		88.6%	87.4%		88.5%	86.7%	80.9%	
1 or more stays	11.2%	12.4%		11.4%	12.6%		11.5%	13.3%	19.1%	
Survival (%)	78.3%	67.3%	<0.001	78.5%	60.8%	<0.001	68.8%	64.2%	61.7%	0.657

[a] All patients (n = 1781).
[b] Patients with at least 1 glucose value in the 12 months post-chemotherapy (n = 1738).
[c] Patients with known diabetes history and baseline HbA1c obtained (n = 263).
[d] The p-value compares group differences between diabetes status, glucose status, and baseline HbA1c value. Groups were compared using Chi-square or Fisher's Exact tests if cell sizes were small (<5).

Table 3
Multivariate analysis of the effects of different variables on rates of new post-chemo infection and death 1 year from initial chemo in all patients.

Outcome	Variables	Reference	Odds ratio (95% CI)	p-Value
New post-chemo infection[a] (n = 1346)[c]	Diabetes history	No diabetes	1.680 (1.259–2.242)	<0.001
	Cancer stage			0.266
	Stage IV	Stage I–III	0.811 (0.631–1.044)	0.104
	Unknown/NA	Stage I–III	0.931 (0.678–1.277)	0.657
	Age	N/A[b]	1.005 (0.997–1.013)	0.239
	Gender (female)	Male	1.136 (0.906–1.424)	0.271
Death (n = 1781)[c]	Diabetes history	No diabetes	1.858 (1.368–2.522)	<0.001
	Cancer stage			<0.001
	Stage IV	Stage I–III	9.177 (6.816–12.356)	<0.001
	Unknown/NA	Stage I–III	5.492 (3.859–7.815)	<0.001
	Age	N/A[b]	1.031 (1.021–1.042)	<0.001
	Gender	Male	0.713 (0.554–0.918)	0.009
	Study year			<0.001
	2011	2010	1.633 (1.010–2.639)	0.046
	2012	2010	1.185 (0.739–1.898)	0.481
	2013	2010	0.843 (0.525–1.355)	0.480
	2014	2010	0.585 (0.362–0.944)	0.028
	2015	2010	0.494 (0.307–0.794)	0.004

[a] New-post chemo infection was defined as a diagnosis of infection in 1 year following chemo start date, and no infection in 30 days prior to chemo start date.
[b] No reference required – Age is a continuous variable.
[c] Survival data was obtained from 2010 until end of study (n = 1781). Specific diagnoses were not available in 2010 and 2011 (hospital billing module was not added until 2012), so infection-related data were only obtained from 2012 until end of study (n = 1346).

4. Discussion

Patients with diabetes who undergo chemotherapy for cancer may have increased risk for complications and poor outcomes. We demonstrate that a history of diabetes is associated with increased rates of hospital admissions, infections, and decreased survival among patients receiving IV chemotherapy with glucocorticoids for all types of cancers at our center when adjusted for cancer stage, age, gender and study year.

We found that hyperglycemia, independent of diabetes status, was associated with decreased survival and increased infection/admission rates (Table 2). However, among patients with known diabetes, baseline HbA1c values were not associated with clinical outcomes or HCU. This may suggest that baseline average glucose is not a predictor of outcomes, but rather diabetes itself and/or poorly controlled diabetes during active cancer therapy contributes to poor outcomes.

Recent studies found that hyperglycemia is associated with an increase in cancer-related deaths[23]; increased non-hematologic toxicities among patients with prostate cancer and non-Hodgkin lymphoma[24]; shorter complete remission duration and increased mortality in patients undergoing induction chemotherapy for ALL[25]; and shorter survival in glioblastoma muliforme.[11] When looking specifically at diabetes history, Meyerhardt et al found that patients with colon cancer and diabetes had higher rates of mortality and cancer recurrence.[26] In a small study of patients with advanced breast cancer, Villarreal-Garza et al showed survival may be impacted by both diabetes status and level of glycemic control.[27] Patients with uncontrolled diabetes (mean glucose > 130 mg/dL) had a median survival of 12 months, whereas patients without diabetes (or with well-controlled diabetes having mean glucoses < 130 mg/dL) had median survival of 36 months or longer.

At present, the exact relationship between diabetes, hyperglycemia, and cancer outcomes remains complex and largely unclear (Fig. 1). Most data come from small, retrospective studies that do not always assess infection rates, glucocorticoid use or other potentially confounding clinical variables such as cancer type/treatment, or level of glycemic control. Our study includes a large number of patients in a community setting with a large variety of tumor types all receiving glucocorticoids as part of their chemotherapy regimen. While glucocorticoid dosing in our population is hard to quantify precisely, our standard protocol is dexamethasone 12–20 mg IV (on day of intravenous chemotherapy) with or without dexamethasone 4 mg orally twice daily for 3 days following chemotherapy administration. We carefully assessed factors related to patients (e.g., age, BMI, gender), their cancer treatment (e.g., type/stage of cancer and year diagnosed), and their diabetes (type of diabetes, glucose/HbA1c level). We further strengthen prior publications by demonstrating higher rates of new infections and decreased overall survival in patients with diabetes after adjusting for cancer stage, age, gender, and year of diagnosis. Furthermore, while most patients who developed hyperglycemia likely had pre-existing diabetes, we factored in both diabetes status and hyperglycemia at any point (Table 2) and showed similar outcomes.

There are limitations to our study. First, it is a retrospective study, and a randomized control trial should be undertaken in the future to evaluate these associations further. One could argue that our diabetes population was "sicker" at baseline and more prone to infections given their increased age and higher BMI. However, diabetes status retained its significance in both our new infection and survival models when adjusting for age. Additionally, our assessment of blood glucoses was not well-controlled as we captured any blood glucose values collected regardless of the clinical situation. We are currently enrolling patients with diabetes to a pilot study assessing post-chemotherapy glucose control using continuous glucose monitors to better understand the impact of glucocorticoids and post-chemotherapy hyperglycemia. In addition, patients had myriad types of cancers and chemotherapies, making it difficult to know if our results are generalizable or specific to a few certain cancers/treatments. Finally, like other studies, our data does not establish a specific guideline on what the optimal management of glucose should be.

It is crucial to better understand the complex relationship of glucocorticoids, hyperglycemia, infections and survival for all cancer patients, regardless of their diabetes history. Our results show patients with diabetes and hyperglycemia have more hospital admissions, increased rates of infections, and worse survival. Prospective studies are urgently needed to elucidate what level of glycemic control is needed to potentially improve outcomes for patients with diabetes receiving chemotherapy with glucocorticoids.

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