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Trajectories of Fasting Blood Glucose in Autologous Hematopoietic Cell Transplantation

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Abstract

Background—Patients who receive autologous hematopoietic cell transplantation (HCT) for the treatment of hematologic malignancies are at risk for serious adverse outcomes including infections and death. Hyperglycemia following the HCT is associated with increased risk for these adverse outcomes. However, limited information is available on demographic and clinical characteristics that contribute to changes in blood glucose levels following HCT.

Objective—The objective of this study was to determine the trajectories of fasting blood glucose (FBG) levels as well as the demographic and clinical characteristics that predicted inter-individual differences in these FBG trajectories.

Methods—A sample of adult patients with hematological malignancies who were scheduled to receive autologous HCT (n=53) were enrolled in the study. Patients with pre-existing diabetes were excluded. Demographic and clinical characteristics were abstracted from electronic medical records. Morning fasting laboratory tests (i.e., FBG and absolute neutrophil counts [ANCs]) were obtained. Data were analyzed using hierarchical linear modeling from the day of HCT (day 0) through 14 days post HCT.

Results—Among eight characteristics evaluated, pre-HCT FBG was associated with variability in both the initial levels and the trajectories of FBG. BMI was only associated with initial levels of FBG.

Conclusions—The large amount of inter-individual variability in the trajectories of FBG levels following autologous HCT suggests that glucose control in these patients warrants ongoing assessments and pre-emptive tailoring.

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Implications for Practice—FBG monitoring is warranted. Additional research with larger samples is warranted to identify additional modifiable and non-modifiable characteristics associated with inter-individual variability in FBG levels.

Keywords

autologous hematopoietic cell transplantation; body mass index; fasting blood glucose; hierarchical linear modeling; hyperglycemia

Introduction

Of the one million hematopoietic cell transplantations (HCTs) that were performed since 1957, 58% were autologous.¹ While fewer complications occur than with allogeneic HCTs, patients with multiple myeloma, lymphoma, and other hematological malignancies who have an autologous HCT are at increased risk for serious adverse events including infections and death.^{2–4} These adverse events are associated with severe immunosuppression from the cancer itself and the HCT conditioning regimen.⁵ In addition, hyperglycemia is associated with immune dysfunction and increased risk for infection and poorer outcomes in these patients.^{6–10}

Over 70% of patients undergoing autologous HCT experience one or more hyperglycemic episodes.^{9–12} In prior studies,^{9,10} we found a 1.6-fold increased risk for infections when patients were hyperglycemic. In addition, in a study of patients who received allogeneic HCT, the risk for mortality was 1.9-fold higher for patients with blood glucose (BG) levels of >200 milligrams per deciliter (mg/dL) and 2.8-fold higher for patients with BG levels of >300 mg/dL.⁹ Life-threatening infections are greatest during the first 30 days post HCT.¹³ In our recent study of autologous HCT recipients,¹⁰ we found that almost 45% of patients had infections during the first two weeks post HCT.¹⁰ While associations between hyperglycemia and increased risks for infection and mortality are being reported,^{6,7,9} less is known about modifiable and non-modifiable risk factors for hyperglycemia following HCT. Knowledge of these risk factors may prevent hyperglycemic episodes and decrease the number of life-threatening infections in these patients.

Of note, patients undergoing an autologous HCT can experience hyperglycemia with or without a diagnosis of diabetes.¹⁰ Based on established cutoffs for diabetes,^{10,14} and previous studies in HCT patients,^{6,7,9,10} hyperglycemia-associated with HCT is defined as a fasting BG (FBG) level of ≥ 100 mg/dL.^{10,14} Factors that contribute to the increased risk for hyperglycemic episodes during HCT include: older age,¹⁵ higher body mass index (BMI),^{10,16} receipt of dexamethasone,^{5,9,17} and receipt of certain drugs (e.g., tacrolimus,^{5,18} oxaliplatin,¹⁹ cisplatin²⁰). To date, a direct association between ethnicity/race and risk for hyperglycemia during autologous HCT has not been established. However, because evidence exists that patients who are members of certain racial groups have higher rates of comorbid conditions associated with hyperglycemia (e.g., diabetes, cardiovascular disease among non-Hispanic Blacks),²¹ ethnicity/race may be a risk factor for hyperglycemia following HCT. In addition, recent emphasis is being placed on the evaluation of sex as an important biologic variable in a variety of medical conditions. Finally, pre-HCT absolute neutrophil count

(ANC) may be a modifiable risk factor for hyperglycemia following HCT. The relative contribution of each of these factors, as well as other factors (e.g., nutritional status, levels of physical activity, alcohol consumption, tobacco use) to inter-individual variability in glycemic episodes, immune dysfunction, and adverse events in HCT patients warrants additional research.

In addition to understanding the factors that contribute to hyperglycemia during HCT, increased knowledge of factors that contribute to changes in glycemic status following a HCT and the influence of neutropenia (i.e., ANC $<5.0 \times 10^9/L$ and the timing of ANC reaching a level of $5.0 \times 10^9/L$), particularly during the first two weeks post HCT, will allow for the identification of high risk patients and the implementation of pre-emptive interventions. To our knowledge, no studies have evaluated for inter-individual differences in FBG trajectories following autologous HCT. Therefore, the purposes of this study in a sample of patients with hematological malignancies who underwent autologous HCT (n=53) were to determine the trajectories of FBG from the day of transplant (day 0) through 14 days post HCT as well as the demographic and clinical characteristics that predict inter-individual differences in these glucose trajectories.

Materials and Methods

Study design, sample and setting

The materials and methods for this study were reported elsewhere.²² In brief, this prospective observational cross-sectional study enrolled adult patients who were: 18 years of age, diagnosed with a hematological malignancy, and were scheduled for an autologous HCT on the inpatient bone marrow transplantation (BMT) unit of an urban National Cancer Institute designated Comprehensive Cancer Center between 2010 and 2012. As part of the eligibility criteria for the HCT, patients were assessed for risk of death using a weighted comorbidity scale (0 = low risk, 1–2 = intermediate risk, and 3 = high risk).²³ All of the patients in this study had a score of 0. Other inclusion criteria required that patients be able to read, write, and understand English and give written informed consent. Patients with pre-existing diabetes were excluded.

Measures

Demographic and clinical characteristics that were abstracted from electronic medical records included: age, sex, race/ethnicity, BMI, cancer diagnosis (i.e., multiple myeloma, lymphoma, other), conditioning regimen, total dose of dexamethasone, and laboratory values (i.e., FBG, ANC).

All laboratory values were from morning fasting blood tests that were drawn between 0400 and 0630. Hyperglycemia was defined as a FBG of ≥ 100 mg/dL. This definition of hyperglycemia is based on the American Diabetes Association's guidelines for the level of hyperglycemia that is used as an indicator of increased risk of diabetes.¹⁴

Study procedures

Approval was obtained from the Protocol Review and Monitoring Committee followed by the Institutional Review Board. On admission to the hospital for the HCT, BMT nurses identified eligible patients and introduced them to the study. A member of the research team met with interested patients, confirmed eligibility, discussed the study in detail, and obtained written informed consent before the start of the conditioning regimen.

Data analyses

Data were analyzed using SPSS version 24 (IBM, Armonk, NY). Descriptive statistics and frequency distributions were calculated on the sample characteristics. FBG levels from day 0 to 14 days post HCT (i.e., 15 assessments) were used in the hierarchical linear modeling (HLM) analysis. This time frame was selected because the first phase of immune cell reconstitution, when the absolute neutrophil count (ANC) reaches 500 mm³, occurs within the first two weeks post HCT²⁴

The HLM analysis is described elsewhere.²⁵ In brief, using the software developed by Raudenbush and Bryk,²⁶ HLM was conducted using full maximum likelihood estimation. Changes in FBG levels were analyzed both within persons (level 1) and between persons (level 2). At level 1, FBG levels were a function of person-specific change parameters plus error. For this unconditional model (i.e., no predictors), the best model was determined using likelihood ratio tests (i.e. no time effect, linear time effect, quadratic time effect).

At level 2, FBG levels were modeled using the individual change parameters (i.e. intercept, slope) as a function of the proposed predictors listed in Table 1. To improve estimation efficiency, an exploratory level 2 analysis was done in which each potential predictor was assessed to determine whether it was associated with FBG levels. Only predictors with a *t* value of ≥ 2.0 , indicating a significant association, were selected for subsequent model testing. All of the significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained statistically significant contributions were retained in the final model. Missing data on FBG levels were accommodated with full information maximum likelihood estimation.²⁷ A *p*-value of <0.05 indicates statistical significance.

Results

Patient characteristics

A total of 60 patients were approached, 56 enrolled, and 53 completed the study. Among the three patients who did not complete the study, one died prior to HCT and two did not receive the HCT. As shown in Table 2, the 53 patients in this study were 55.7 (SD=11.3) years of age. In this sample, 52.8% were female and 39.6% were non-White. The mean BMI was 28.8 kg/m² (SD=6.9) and the majority was treated for multiple myeloma (56.6%). The pre-HCT mean FBG was 108.1 mg/dL (SD=20.5). Mean total pre-HCT dexamethasone dose was 64.6 mg (SD=40.0). Mean ANC was 3.3×10^9 /L (SD=1.3). Most of the patients received similar conditioning regimens that included combinations of carmustine, cytarabine,

etoposide, and melphalan. Six patients received bortezomib and melphalan and six patients received melphalan only. Only two patients received hyperalimentation during the HCT.

Individual and mean changes in FBG

The initial HLM analysis examined how FBG levels changed from day 0 to 14 days post HCT (i.e., over 15 days). The final estimate of fixed effects determined that a quadratic model fit the data best (see Table 3; Figure 1A).

The estimates for the quadratic change are reported in Table 3. Because the model has no covariates (i.e., unconditional model), the intercept represents the estimated FBG on day 0 (i.e., 92.013 mg/dL). The estimated linear rate of change in FBG was 1.594 ($p<0.05$) and the estimated quadratic rate of change was -0.140 ($p<0.05$). Figure 1A shows a progressive increase in FBG from day 0 to day 6 post HCT, followed by a decline over the remaining days.

Although the results indicate an increase followed by a decrease in FBG levels, they do not imply that all patients had identical trajectories. The variance parameters (Table 3) indicate substantial inter-individual differences in the intercepts and trajectories for FBG levels. This variability is illustrated in the spaghetti plot of the trajectories for all 53 patients (Figure 1B).

The second stage of the HLM analysis evaluated whether select demographic and clinical characteristics influenced the trajectories of FBG levels. As shown in the final model (Table 3), both BMI and pre-HCT FBG predicted inter-individual differences in the intercept for FBG. Only pre-HCT FBG predicted the slope parameters. To illustrate the effect of BMI and pre-HCT FBG on the intercept and trajectories for FBG levels, Figures 2A and 2B display the adjusted change curves for FBG levels that were estimated based on differences of 1 standard deviation above and below the mean BMI and pre-HCT FBG.

Discussion

To our knowledge, this study is the first to evaluate inter-individual variability in the trajectories of FBG levels following autologous HCT. While the unconditional model demonstrated an increase in FBG levels during the first week post-HCT followed by a decrease during the following week, a substantial amount of variability was identified in this relatively small sample. Among the eight demographic and clinical characteristics evaluated, pre-HCT FBG was associated with variability in both the initial levels and the trajectories of FBG. BMI was only associated with initial levels of FBG.

Body mass index

Increased BMI is a known risk factor for diabetes²⁸ and for hyperglycemic episodes in patients undergoing HCT.^{10,29} Patients in this study had a mean BMI of $28.8 (\pm 6.9)$ kg/m², which is categorized as overweight.¹² Of note, in our previous report, a BMI of 25 kg/m² was associated with increased risk for a higher number of hyperglycemic episodes and post HCT infections.¹⁰

Pre-HCT FBG

Pre-HCT FBG was associated with inter-individual variability in both initial levels of FBG (i.e., on day 0) as well as with the trajectory of the FBG levels over the 14 days post HCT. As illustrated in Figure 2B, a higher pre-HCT FBG was associated with a higher FBG on day 0 that steadily increased over the next six days post HCT, and then decreased over the subsequent week. This association has important clinical implications because in a separate analysis we found that during the first two weeks post HCT, patients with infections had higher daily mean FBG levels compared to patients without infections.¹⁰ In addition, patients with infections had lower ANCs than patients without infections. While ANC was not a predictor of FBG levels in our HLM analysis, future studies with larger samples may demonstrate direct associations as well as interactions between FBG and ANC levels and increased number of infections in HCT patients.

As illustrated in Figure 1B, a large amount of inter-individual variability in FBG levels was observed following HCT. Additional research is warranted with larger samples to determine the demographic, clinical, and lifestyle characteristics that contribute to these glycemic patterns and their impact on other adverse events associated with HCT.

Other characteristics

While age, sex, ethnicity/race, cancer diagnosis, pre-HCT total dose of dexamethasone, and pre-HCT ANC were not associated with either initial levels or the trajectories of FBG, they warrant additional investigation in future studies with larger samples. For example, older age is associated with hyperglycemia as demonstrated by the higher prevalence rate of diabetes in those over 65 years of age (25.2%) compared to the general population (9.4%).^{14,15} These age-related changes may occur as a result of cellular senescence,³⁰ immunosenescence,³¹ and plasma hypertonicity which are associated with insulin resistance, impaired glucose utilization, and hyperglycemia.³² While sex differences in FBG during autologous HCT have not been evaluated, hyperglycemia is associated with obesity¹⁶ and adipose distribution is different between men and women. Similarly, for ethnicity/race, Mexican Americans and African Americans have higher rates of diabetes,²¹ which may place these individuals at higher risk for hyperglycemic episodes during autologous HCT. While the administration of dexamethasone increases BG levels, in our sample, the doses that patients received were relatively consistent. Finally, while we hypothesized that ANC might influence post-HCT FBG trajectories, variability in this risk factor was relatively small. Larger studies are warranted to examine the relationships between these and other risk factors (e.g., diet/nutrition, physical activity, stress, behavioral factors such as smoking and alcohol consumption) and hyperglycemic episodes following HCT.

Limitations and conclusions

Several limitations warrant consideration. First, additional demographic and clinical characteristics associated with variability in FBG may be identified with a larger sample. For example, older age,¹⁵ use of parenteral nutrition,³³ and receipt of steroids^{5,9,17} are associated with episodes of hyperglycemia. In addition, data were not collected on follow-up point-of-care glucose testing following the administration of insulin. However, insulin was

administered only 14 times out of 3,211 patient days. Finally, findings from this analysis are not generalizable to patients who receive an allogeneic HCT.

Clinical implications

Despite these limitations, our findings provide new information on inter-individual variability in FBG levels following HCT. The demonstration of inter-individual variability in the trajectories of FBG levels following autologous HCT suggests that glucose control in these patients warrants pre-emptive and individualized tailoring. In a recent study that used a computer-guided glucose management system to administer insulin to patients with pre-existing diabetes who received allogeneic HCT,²⁶ blood glucose levels ranged from 100–140 mg/dL. However, this level of control required intensive hourly glucose monitoring.³⁴ The implementation of this intense level of monitoring and management may not be clinically feasible. In addition, patients without pre-existing diabetes who experience hyperglycemic episodes during HCT may not require continuous insulin therapy. These patients may benefit from a multi-faceted intervention that includes: dietary modifications and physical activity interventions to maintain FBG levels in the therapeutic range. Additional research with larger samples is warranted to identify modifiable and non-modifiable characteristics associated with inter-individual variability in FBG levels. Once these characteristics are identified, they can be used to design and test interventions to stabilize FBG levels and decrease adverse outcomes (e.g., infections) in patients who undergo autologous HCT.

Based on our findings, closer glucose monitoring and consultation with endocrinology for interventions to prevent hyperglycemic episodes may decrease the risk of infection among patients with higher BMI and higher pre-HCT FBG. Future research may clarify modifiable risk factors that clinicians can use to develop targeted interventions to prevent hyperglycemic episodes following HCT.

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Figure 1.

Figure 1A - A quadratic model of fasting blood glucose levels from the day of autologous hematopoietic cell transplantation (HCT; day 0) to 14 days post HCT.

Figure 1B – Spaghetti plot of the individual fasting blood glucose trajectories for the sample (n=53) from day of hematopoietic cell transplantation (HCT; day 0) to 14 days post HCT.

BG = blood glucose; TXDay = treatment day

Figure 2.

Figure 2A – Influence of higher versus lower body mass index (BMI; plotted as 1 standard deviation above and below the mean enrollment BMI) on initial levels of fasting blood glucose (FBG).

Figure 2B – Influence of higher versus lower pre-hematopoietic cell transplantation fasting blood glucose (pre-HCT FBG; plotted as 1 standard deviation above and below the mean enrollment pre-HCT FBG) on initial levels as well as the trajectories of FBG.

Table 1

Potential Predictors of Morning Fasting Blood Glucose

Variables	Intercept	Linear	Quadratic
Demographic characteristics			
Age			
Sex			
Ethnicity/race			
Clinical characteristics			
Body mass index	■		
Malignancy diagnosis			
Pre-HCT morning fasting blood glucose	■	■	■
Pre-HCT total dexamethasone dose			
Pre-HCT absolute neutrophil count			

Variables identified from exploratory analyses as potential predictors of morning fasting blood glucose values, based on t values of ≥ 2.00 , indicated by a filled in box (■), for patients with hematological malignancies who received autologous hematopoietic cell transplantations.

Abbreviation: Pre-HCT, the last measure prior to the hematopoietic cell transplantation.

Table 2**Demographic and Clinical Characteristics of Patients (n=53)**

Demographic characteristics	
Age (years; mean [SD])	55.7 (11.3)
Sex (% female [n])	52.8 (28)
Ethnicity/race (% non-White [n])	39.6 (21)
Clinical characteristics	
Body mass index (kg/m ² ; mean [SD])	28.8 (6.9)
Cancer diagnosis group (% yes [n])	
Multiple myeloma	56.6 (30)
Lymphoma	26.4 (14)
Other ^a	17.0 (9)
Pre-HCT blood glucose (mg/dL; mean [SD])	108.1 (20.5)
Pre-HCT total dexamethasone dose (mg; mean [SD])	64.6 (40.0)
Pre-HCT absolute neutrophil count (x10 ⁹ /L; mean [SD])	3.3 (1.3)

^a Amyloidosis (n=1), Hodgkin's disease (n=6), other myelomas (n=2)

Abbreviations: Kg/m², kilograms per meter squared; L, liter; mg/dL, milligram per deciliter; n, number of patients; Pre-HCT, the last measure prior to the hematopoietic cell transplantation; SD, standard deviation.

Table 3

Hierarchical Linear Model for Blood Glucose

Blood glucose	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	92.013 (2.133) ^c	92.0277 (1.886) ^c
Linear rate of change	1.594 (0.720) ^b	1.581 (0.708) ^b
Quadratic rate of change	−0.140 (0.055) ^b	−0.139 (.053) ^b
Time invariant covariates		
Intercept		
Body mass index		0.469 (0.206) ^b
PreHCT fasting blood glucose		0.303 (0.094) ^b
Linear rate of change		
PreHCT fasting blood glucose		0.044 (0.035)
Quadratic rate of change		
PreHCT fasting blood glucose		−0.005 (0.003) ^a
Variance components		
In intercept	173.217 ^c	120.535 ^c
In linear slope	19.278 ^c	18.423 ^c
In quadratic slope	0.116 ^c	0.105 ^c
Goodness-of-fit deviance (parameters estimated)	6130.722820 (10) ^c	6108.337527 (14) ^c
Model comparison χ^2 (df)		22.39 (4) ^c

^a
p=.057^b
p<.05^c
p<.0001

Abbreviations: df, degrees of freedom; PreHCT, prior to hematopoietic cell transplant; SE, standard error.