

Association Between Hyperglycemia and Survival in Patients With Newly Diagnosed Glioblastoma

Rachel L. Derr, Xiaobu Ye, Melissa U. Islas, Serena Desideri, Christopher D. Saudek, and Stuart A. Grossman

ABSTRACT

Purpose

Hyperglycemia has been associated with poor outcomes in many disease states. This retrospective study assessed the association between hyperglycemia and survival in patients with newly diagnosed glioblastoma multiforme (GBM).

Patients and Methods

Between 1999 and 2004, before the standard use of temozolomide, 191 patients were accrued onto New Approaches to Brain Tumor Therapy CNS Consortium trials with similar eligibility criteria. Time-weighted mean glucose and mean glucocorticoid dose were calculated for each patient using all values collected regularly in follow-up. The primary outcome was survival.

Results

Mean glucose levels ranged between 65 and 459 mg/dL. These were divided into quartiles: quartile one (< 94 mg/dL), quartile two (94 to 109 mg/dL), quartile three (110 to 137 mg/dL), and quartile four (> 137 mg/dL). Median survival times for patients in quartiles one, two, three, and four were 14.5, 11.6, 11.6, and 9.1 months, respectively. The association between higher mean glucose and shorter survival persisted after adjustment for mean daily glucocorticoid dose, age, and baseline Karnofsky performance score (KPS). Compared with patients in the lowest mean glucose quartile, those in quartile two (adjusted hazard ratio [HR], 1.29; 95% CI, 0.85 to 1.96), quartile three (adjusted HR, 1.35; 95% CI, 0.89 to 2.06), and quartile four (adjusted HR, 1.57; 95% CI, 1.02 to 2.40) were at progressively higher risk of dying ($P = .041$ for trend).

Conclusion

In these patients with newly diagnosed GBM and good baseline KPS, hyperglycemia was associated with shorter survival, after controlling for glucocorticoid dose and other confounders. The effect of intensive management of glucocorticoid-related hyperglycemia on survival deserves additional study in patients with GBM.

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INTRODUCTION

A growing body of evidence in the diabetes literature suggests that short-term, and even relatively mild, hyperglycemia leads to excess morbidity and mortality in acute illness.^{1,2} In the setting of cancer, in particular, large epidemiologic studies have suggested that survival is shorter in patients with comorbid diabetes.³⁻⁷

Patients with glioblastoma multiforme (GBM) are at particular risk for hyperglycemia, because their peritumoral edema is routinely treated with high-dose glucocorticoids, which are known to increase plasma glucose, due to impairing glucose transport.⁸⁻¹⁰ Furthermore, because patients with GBM have a poor prognosis and are thus unlikely to be at risk for long-term diabetes complications, the goal of hyperglycemic management in these patients is, in general, the avoidance of acute hyperglycemic

complications, rather than intensive management. In this study, we tested the hypothesis that hyperglycemia is associated with shorter survival in patients with newly diagnosed GBM.

PATIENTS AND METHODS

This retrospective study, approved by the institutional review board, analyzed the association between hyperglycemia and survival among patients with newly diagnosed GBM accrued onto five New Approaches to Brain Tumor Therapy CNS Consortium phase II trials. These trials were conducted between 1999 and 2004, before the standard use of temozolomide. They assessed the effect on survival of noncytotoxic therapies, including penicillamine, carboxyamido-triazole, suramin, gadolinium-texaphyrin, and celecoxib, which were administered in combination with postoperative external-beam radiation therapy (60 Gy in 30 fractions).¹¹⁻¹⁵ None of the experimental agents

are known to affect glucose homeostasis, and none were associated with improved survival.

Patients

Patients eligible for this review had histologically confirmed supratentorial grade 4 astrocytoma (GBM), which was untreated except for biopsy or surgery, and glucocorticoid administration. Other eligibility criteria for accrual onto the five trials included: age ≥ 18 years, Karnofsky performance score (KPS) ≥ 60, estimated life expectancy ≥ 2 months, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000 μL, hemoglobin ≥ 9.0 g/dL, creatinine ≤ 1.7 mg/dL, bilirubin ≤ 1.2 to 1.5 mg/dL, aminotransferases ≤ 2 to 4 times above the upper limit of normal, and ability to provide informed consent. Exclusion criteria included the presence of an intercurrent illness that could interfere with protocol treatment, and concurrent malignancy unless disease free for ≥ 5 years. Prior diabetes was not an exclusion criterion.

Glycemia and Glucocorticoid Assessment

Each patient had basic chemistries, which included glucose, performed approximately weekly during radiation therapy, and every 1 to 2 months thereafter. The fasting status of the patient at the time of testing was not known. Mean glucose was calculated for each patient using all available glucose results. The primary analysis used a time-weighted approach for calculating mean glucose, in which each glucose value was weighted according to the number of days between it and the next record or the censor date.

Glucocorticoids were prescribed by the patients' oncologists based on clinical need. The doses were recorded during follow-up approximately every 1 to 2 months. Three patients had no recorded glucocorticoid doses, and were excluded from the analysis. A time-weighted mean dexamethasone dose was calculated using the same method used for glucose.

Statistical Analysis

Mean glucose was divided into four groups according to the quartiles of distribution. Patient characteristics—including mean daily dexamethasone dose, age, KPS, sex, race, extent of surgical resection (craniotomy for resection v biopsy), and trial onto which accrued—were compared across quartiles using linear regression for continuous variables, and logistic regression for dichotomous variables.¹⁶⁻¹⁹

The primary end point of this study was survival. Overall survival time was calculated as time from histologic diagnosis to death as a result of any cause. Event times were censored if the patient was alive at the time of last follow-up.

Univariate Cox proportional hazards regression analysis was used to assess the association between individual patient characteristics and overall survival status.²⁰ We used $P \leq .05$ as the criterion for selecting covariates to be included in the multivariate Cox regression model. The unadjusted and adjusted hazard ratios (HRs) with respect to the mean glucose quartiles were reported. Moreover, multivariate Cox proportional hazards regression was also employed to estimate adjusted HRs associated with each increase of 10 mg/dL in mean glucose.

A secondary end point was infection, which was recorded prospectively by medical record review. Multivariate logistic regression was used to evaluate the effect of mean glucose on the development of infection, and Cox proportional hazards regression was used to assess the effect of infection on survival. All analyses were performed using STATA software (STATA Corp, College Station, TX; Computing Resource Center, Santa Monica, CA), and all reported P values are two sided.

RESULTS

Of the 191 patients studied, the mean age was 55.7 years (standard deviation, 11.2 years), the median KPS was 90 (range, 60 to 100), 64% were male, and 93% were white. Mean daily dexamethasone dose ranged between 0 and 48 mg (median, 5 mg). The mean time-weighted glucose varied between 65 and 459 mg/dL, and was divided into quartiles: quartile one (< 94 mg/dL), quartile two (94 to 109

mg/dL), quartile three (110 to 137 mg/dL), and quartile four (> 137 mg/dL).

Comparisons of demographic and clinical characteristics according to quartile of time-weighted mean glucose are listed in Table 1. Consistent with the glucose-elevating effect of glucocorticoids, mean daily dexamethasone dose increased with increasing quartile of mean glucose ($P = .006$ for trend). Additionally, mean age increased and KPS decreased with increasing quartile of mean glucose ($P = .001$ and $.040$ for trend, respectively). There was no difference in the distribution of sex, race, or surgical debulking versus biopsy with regard to quartile of mean time-weighted glucose.

Of the 191 patients accrued onto the studies, 187 (98%) died in the follow-up period, which encompassed 214.3 person-years. The mortality rate was 0.87 deaths per person-year, and the median survival was 11.0 months. The four surviving patients were observed between 35 and 82 months.

Median survival was 14.5 months in quartile one, 11.6 months in quartile two, 11.6 months in quartile three, and 9.1 months in quartile four. In an unadjusted Cox proportional hazards model, relative to quartile one, the estimated HRs were 1.30 for quartile two (95% CI, 0.86 to 1.95), 1.56 for quartile three (95% CI, 1.02 to 2.37), and 2.06 for quartile four (95% CI, 1.35 to 3.14, with a P value of $.001$ for trend; Table 2). For every 10 mg/dL increase in time-weighted mean glucose, the HR was 1.05 (95% CI, 1.02 to 1.07; $P < .0001$). In addition, mean daily dexamethasone dose, age, and KPS were each statistically significantly associated with survival in the univariate analysis (Table 2).

After we controlled for mean daily dexamethasone dose, age, and KPS in a multivariate Cox proportional hazards regression model, the association between hyperglycemia and survival persisted. Figure 1 displays the adjusted survival curves for the four quartiles of time-weighted mean glucose. Compared with patients in the lowest quartile of mean glucose, those in quartile two (adjusted HR, 1.29; 95% CI, 0.85 to 1.96), quartile three (adjusted HR, 1.35; 95% CI, 0.89 to 2.06), and quartile four (adjusted HR, 1.57; 95% CI, 1.02 to 2.40) were at progressively higher risk of dying ($P = .041$ for trend; Table 3). An incremental increase of 10 mg/dL in time-weighted mean

Table 1. Patient Characteristics According to Quartile of Time-Weighted Mean Glucose

Characteristic	Quartile of Mean Glucose				P
	One (n = 46)	Two (n = 50)	Three (n = 48)	Four (n = 47)	
Dexamethasone dose, mg					.006
Median	3	4	6	8	
25%-75% percentiles	0-6	1-10	2-15	4-14	
Age, years					.001
Mean	53	54	55	60	
SD	14	10	9	10	
Sex					.926
Male, %	65	66	54	70	
Race					.459
White, %	96	94	88	94	
KPS					.053
≥ 90, %	74	76	67	54	
Surgery					.257
Debulked, %	96	74	83	83	

Abbreviations: SD, standard deviation; KPS, Karnofsky performance score.

Table 2. Univariate Association Between Patient Characteristics and Survival

Characteristic	HR	95% CI	P
Mean glucose			.001
Quartile one, n = 46	Reference		
Quartile two, n = 50	1.30	0.86 to 1.95	
Quartile three, n = 48	1.56	1.02 to 2.37	
Quartile four, n = 47	2.06	1.35 to 3.14	
Mean daily dexamethasone dose, per 10 mg/d	1.29	1.14 to 1.45	< .0001
Age, per 10 years	1.50	1.30 to 1.73	< .0001
KPS, per 10 points	0.82	0.71 to 0.94	.006
Race, white v other	1.47	0.84 to 2.59	.181
Sex, male v female	1.04	0.77 to 1.41	.794
Biopsy v surgery	1.34	0.91 to 1.98	.133
Trial			.908
Penicillamine	Reference		
Carboxyamido-triazole	0.95	0.63 to 1.44	
Suramin and XRT	1.20	0.79 to 1.81	
Gadolinium-texaphyrin	0.83	0.35 to 1.97	
Cox-2 inhibitor	0.99	0.62 to 1.57	

NOTE. The time-weighted mean glucose values for quartiles one to four are < 94, 94 to 109, 110 to 137, and > 137 mg/dL, respectively. Abbreviations: HR, hazard ratio; KPS, Karnofsky performance score; XRT, radiation therapy.

Table 3. Multivariate Association Between Patient Characteristics and Survival

Characteristic	HR	95% CI	P
Mean glucose			0.041
Quartile one, n = 46	Reference		
Quartile two, n = 50	1.29	0.85 to 1.96	
Quartile three, n = 48	1.35	0.89 to 2.06	
Quartile four, n = 47	1.57	1.02 to 2.40	
Mean daily dexamethasone dose, per 10 mg/d	1.34	1.17 to 1.53	< .001
Age, per 10 years	1.47	1.27 to 1.72	< .001
KPS, per 10 points	0.84	0.72 to 0.97	.021

NOTE. The time-weighted mean glucose values for quartiles one to four are < 94 mg/dL, 94 to 109 mg/dL, 110 to 137 mg/dL, and > 137 mg/dL, respectively. Abbreviations: HR, hazard ratio; KPS, Karnofsky performance score.

glucose was associated with an adjusted HR of 1.03 (95% CI, 1.00 to 1.06; $P = .035$).

The strength of our findings was demonstrated by several sensitivity analyses. Our results were unchanged when we excluded 68 patients with gaps longer than 2 months between glucose or glucocorticoid recordings (adjusted HR associated with a 10 mg/dL increase in time-weighted mean glucose, 1.05; 95% CI, 1.00 to 1.11; $P = .036$), and when we excluded 18 patients with outlying survival times (HR, 1.03; 95% CI, 1.00 to 1.06; $P = .051$). The results were also largely unaffected when average glucose not weighted for time was used as the exposure variable (HR, 1.04; 95% CI, 1.00 to 1.07; $P = .032$), and when

the standard deviation of each patient's mean glucose was adjusted for in the model (HR, 1.03; 95% CI, 1.00 to 1.06; $P = .081$).

The secondary outcome (infection) was experienced in follow-up by 27 patients (14%), 18 of whom had pneumonia. Patients who developed infections had worse survival compared with patients without infections, with an HR of 1.64 (95% CI, 1.08 to 2.48; $P = .02$). In a multivariate logistic regression analysis, there was a trend toward an association between infection and mean glucose, with an odds ratio for infection of 1.06 (95% CI, 0.99 to 1.13; $P = .09$) for every 10 mg/dL increase in time-weighted mean glucose. However, adjusting for infection in the multivariate model did not alter the significant association between mean glucose and survival (adjusted HR associated with a 10 mg/dL increase in time-weighted mean glucose remained 1.03; 95% CI, 1.00 to 1.06; $P = .035$).

DISCUSSION

In this study, we report a shorter survival time associated with hyperglycemia in a group of patients with GBM and good baseline KPS. Even after adjustment for mean daily dexamethasone dose and other prognostic variables, the HR increased with increasing quartile of time-weighted mean glucose.

Recent large population-based studies have suggested that diabetes and impaired glucose tolerance are risk factors for developing certain types of cancer.^{21,22} Furthermore, pre-existing diabetes at the time of cancer diagnosis has also been shown to be associated with increased all-cause mortality and cancer recurrence, most definitively in colon and breast cancers.^{4-7,23} In the specific case of glioma, small studies have not shown that premorbid diabetes increases cancer incidence,²⁴⁻²⁸ but the effect of hyperglycemia on survival after GBM diagnosis has never before been assessed.

One mechanism that has been proposed to explain the association between diabetes and worse survival in colon and breast cancers is that hyperinsulinemia resulting from hyperglycemia stimulates tumor growth. Insulin is a member of a family of growth factors, and similar to its cousins (insulin-like growth factors 1 and 2), may promote tumor proliferation.²⁹ Patients with colorectal cancer have demonstrated higher fasting insulin levels than have control patients,³⁰ and a prospective study has shown that patients with breast cancer with higher fasting insulin concentrations have decreased survival and

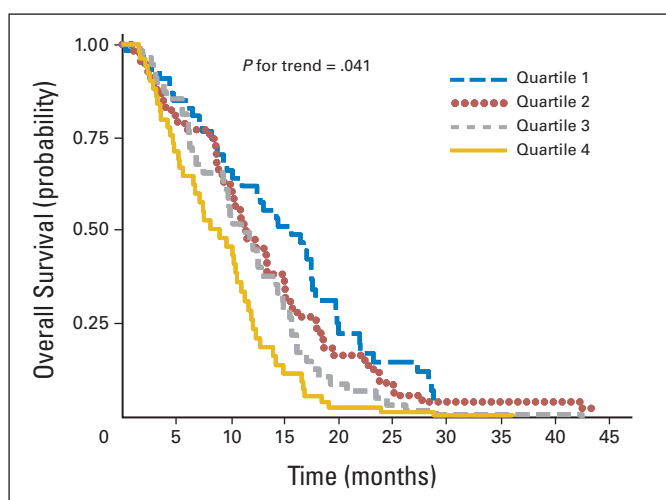


Fig 1. Adjusted survival curves comparing quartiles of mean time-weighted glucose, constructed using multivariate Cox proportional hazards regression, and adjusting for mean daily dexamethasone dose, age, and Karnofsky performance score. The ranges of time-weighted mean glucose for quartiles one, two, three, and four were < 94, 94 to 109, 110 to 137, and > 137 mg/dL, respectively.

higher rates of recurrence.³¹ In vivo studies have shown that high insulin levels enhance colorectal and breast cancer cell proliferation via receptors on the tumors.^{32,33} Furthermore, treatment with metformin, which lowers insulin levels, decreases the incidence and size of mammary adenocarcinomas in tumor-prone transgenic mice.³⁴ Human glial tumors possess insulin receptors with binding activities and characteristics identical to peripheral insulin receptors, and insulin has been shown to stimulate glucose uptake in cultures of human GBM cells.³⁵

Another mechanism may be that hyperglycemia itself promotes tumor growth. Glucose is the major substrate for cerebral metabolism, and high-grade brain tumors have high glucose consumption.³⁶⁻³⁸ The glucose content in the brains of healthy mice increases minimally after an intraperitoneal bolus of glucose, whereas mice with gliomas experience an increase in intratumoral glucose content of 2.5 times after induction of hyperglycemia.³⁹ High glucose levels within GBMs could provide extra substrate for glycolytic metabolism, and support unchecked tumor growth. Unfortunately, we were not able to directly evaluate this proposed biologic mechanism in this study, because radiation therapy for GBM commonly results in pseudoprogression, which would have complicated this assessment.^{40,41}

It is also possible that the association between hyperglycemia and worse survival is mediated not by tumor growth, but rather by other adverse effects of hyperglycemia, such as increased infection rates. Hyperglycemia is known to increase the risk of infection in outpatients and inpatients,⁴²⁻⁴⁴ and this risk is likely magnified when glucocorticoids are received, because glucocorticoids suppress the immune system and predispose patients to infection.^{45,46} Although we did observe a trend toward a relationship between hyperglycemia and infection in our study sample, infection had no impact on the association between hyperglycemia and survival. This finding suggests that the mechanism by which hyperglycemia may shorten survival does not include increasing infection rates.

To our knowledge, this is the first study to evaluate the association between glucose levels during cancer treatment and survival. An important strength of our study was our large study population, which was homogeneous with regard to eligibility criteria and treatment. Data collection was reliable and relatively uniform, because all patients were receiving research protocols. Moreover, patients with GBM, in particular, are at high risk for hyperglycemia, given the routine use of glucocorticoids in their management. Because glucocorticoid dose would also be expected to reflect the extent of residual disease and peritumoral edema, the validity of our results was strengthened by carefully adjusting for glucocorticoid dose in the analysis.

This study had several limitations inherent to its retrospective design. As with any observational study, there remains a possibility that unmeasured confounders influenced our findings. For example, residual tumor burden, which would have shortened survival and

might have increased glucose because of physiologic stress, may have been incompletely controlled for in this analysis, despite our adjustment for glucocorticoid dose. Also, there was heterogeneity in the frequency of glucose and glucocorticoid recordings, although a sensitivity analysis did not suggest that this biased our results. Furthermore, the glucose measurements available were performed at random. Hemoglobin A1c levels would have provided a better index for evaluating long-term glycemia. Other potentially important variables that were not assessed in this retrospective study of patients diagnosed and treated from 1999 to 2004 include O⁶-methylguanine–DNA methyltransferase methylation status, exogenous insulin dose, and serum insulin level. These will be measured in a future prospective study aimed at confirming our results in the post-temozolomide era.

Our findings raise the question of whether intensive management of hyperglycemia would lead to improved survival in patients with newly diagnosed GBM. To answer this question, a randomized trial is being planned to compare survival between hyperglycemic patients with GBM whose hyperglycemia is managed intensively by an endocrinologist, and hyperglycemic patients with GBM whose hyperglycemia is managed by an oncologist according to the standard of care.

In conclusion, we observed significantly shorter survival in patients with GBM who experienced hyperglycemia, compared with patients with GBM who did not experience hyperglycemia, after controlling for several important confounders, including glucocorticoid therapy. Future studies evaluating whether lowering glucose improves cancer survival are warranted, especially considering the relatively benign nature of diabetes interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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