Journal of Clinical Neuroscience 19 (2012) 996–1000

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Hyperglycemia is independently associated with post-operative function loss in patients with primary eloquent glioblastoma

Thomas W. Link [a], Graeme F. Woodworth [a], Kaisorn L. Chaichana [a], Stuart A. Grossman [a,b], Robert S. Mayer [c], Henry Brem [a,b,d,e], Jon D. Weingart [a,b], Alfredo Quinones-Hinojosa [a,b,]*

[a] Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[b] Department of Oncology, Division of Neuro-Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[d] Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[e] Department of Biomedical Engineering, Johns Hopkins School of Medicine, Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 29 May 2011
Accepted 30 September 2011

Keywords:
Function
Glioblastoma
Hyperglycemia
Rehabilitation

ABSTRACT

The poor prognosis for patients with glioblastoma (GB) heightens the importance of maintaining function throughout treatment. Hyperglycemia has been linked to poor neurological outcomes following stroke, traumatic brain and spinal cord injury. We hypothesized this may also be true following the resection of GB. We assessed associations with post-operative function with the goal of identifying modifiable factors in the peri-operative period with a particular focus on blood glucose levels. Independent associations with worse post-operative function included: patient age, pre-operative motor deficit, deep tumor location, post-operative motor deficit, and elevated mean peri-operative glucose. Interestingly, controlling for associated factors including dexamethasone dosing, patients with elevated peri-operative glucose levels were nearly twice as likely to have new post-operative neurological deficits. These results suggest, together with the broad literature supporting a role for hyperglycemia in neurological injury, that this may represent a modifiable factor in the peri-operative care of these patients.

1. Introduction

Glioblastoma (GB) is the most common primary malignant brain tumor in adults. Median survival is generally less than 16 months, which increases the importance of maintaining function following surgery. Improved patient function, measured by quantitative assessment measures such as the Karnofsky performance scale (KPS) score, the Glasgow outcome score (GOS), the modified Rankin Scale score, and the Medical Research Council brain prognostic index, has consistently shown a positive association with survival.[1–4]

Factors associated with post-operative function have included younger age, better pre-operative functional status, and higher degree of resection.[1,5,6] Our group has shown recently that neurological performance (pre-operative KPS score and post-operative motor function) are associated with long-term functional independence.[7] Of particular interest would be to distinguish modifiable factors in the peri-operative period affecting post-operative function in these patients.

Hyperglycemia has been linked to poor neurological outcomes following stroke[8–13] and traumatic brain and spinal cord injury.[14–18] Potential mechanisms for this may include alterations in brain tissue pH, cerebral blood flow, and blood–brain barrier transport.[19,20] We hypothesized that peri-operative hyperglycemia may also have a role in post-operative neurological function following GB resection. In this study, we assess associations with post-operative performance in those patients with GB particularly susceptible to function loss. We sought to identify modifiable factors in the peri-operative period with particular focus on blood glucose levels.

2. Methods

2.1. Patient population

This study was approved by the Johns Hopkins Hospital Institutional Review Board (NA 09171). Medical records of patients undergoing resection or biopsy of GB at this institution between 1996 and 2009 were retrospectively reviewed. Information collected for each patient included: demographics, clinical presentation, co-morbidities, pre-operative and post-operative medications, pre-operative and post-operative neuroimaging, peri-operative laboratory values, intra-operative data, pathological findings, post-operative neurological function, and additional treatments. Neurological and functional assessments, such as the presence and frequency

* Corresponding author. Address: 4940 Eastern Avenue, 301 Mason Lord Drive, Suite 2100, Baltimore, MD 21224, USA. Tel.: +1 410 550-3367; fax: +1 410 550 0748.
E-mail address: aquinon2@jhmi.edu (A. Quinones-Hinojosa).

0967-5868/$ - see front matter
http://dx.doi.org/10.1016/j.jocn.2011.09.031

of seizures, motor deficits, speech and language problems, and cognitive deficits were taken retrospectively from clinical notes. The KPS was also assigned retrospectively based on clinical records and used to classify patients' functional independence before surgery. CT scans, MRI, and radiology reports were reviewed to detail lesion characteristics such as the size (largest diameter based on contrast-enhanced imaging), specific region involved, degree of edema and mass effect, and presence of a hemorrhagic component. Technical improvements during this study included advancements in pre-operative and intra-operative imaging (including functional MRI, diffusion tensor imaging, and tractography), increased use of intra-operative functional mapping (including awake craniotomy and electrocorticography), and improved operative equipment (including microscopes, cautery devices, and tumor resection equipment). Given these changes over time, when possible, this information was collected and included as variables in the analysis.

To limit variables that may affect patient outcomes, such as previous surgical and adjuvant therapies and response to treatments, we included patients with primary, untreated GB only. In addition, patients with tumors in non-eloquent locations were excluded. Although these criteria may limit the generalizability of this study, we aimed to increase the likelihood of identifying factors associated with post-operative function. Eloquent GB locations were defined as having the major component of the tumor in the left parietal, left posterior frontal or left temporal lobe, and/or deep brain (thalamus, basal ganglia, insula, or midbrain) on either side. Due to the often less aggressive surgical management of deep compared to convexity tumors, "deep location" was included as a covariate to distinguish and account for these differences. Data regarding patient handedness was only sporadically available in the clinical records and hence could not be included as a covariate.

2.2. Functional outcome assessment

The goal of this study was to determine factors in the peri-operative period associated with new neurological deficits. An important aim was to minimize the recording bias related to retrospective assignment of patient performance or functional outcome scores from a diverse set of clinical documentation styles and degrees of thoroughness. This was achieved by using the patient's discharge disposition, set by careful evaluations by highly skilled rehabilitation specialists at the time of discharge, as our assessment of post-operative functional status.

Prior to discharge from the neurosurgery service, all patients with brain tumors were evaluated by the physical therapy and occupational therapy services. Based on the type and degree of neurological problems, speech-language pathology and/or physical medicine and rehabilitation physicians are also included in these post-operative evaluations. At the time of patient discharge, a composite summary of the recommendations from this team is recorded in the patient medical record. Included in this summary is the designation for the patient to receive additional home-based, outpatient, or inpatient rehabilitation services. In very few instances, patients came for surgery from an inpatient facility in a severely debilitated state. For the purposes of this study, only patients with a new inpatient rehabilitation designation at the time of hospital discharge following surgery were considered to have new, functionally significant post-operative neurological deficits. This designation was termed "discharge to rehabilitation" (DCR). Some patients chose to not follow the rehabilitation team's suggestion; for this reason, the recommendation rather than the actual patient disposition was used to establish this binary, primary outcome measure. This also served to minimize the contribution of factors such as family support and socioeconomic status in determining this outcome measure.

2.3. Treatment paradigm

Patients undergoing surgery for newly discovered, suspected GB were offered biopsy or resection based on the recommendation of the neurosurgeon. In addition, complex cases were reviewed by the institutional multi-disciplinary Neuro-oncology team. The type of surgical treatment offered to each patient depended on the patient's general health and suitability, lesion location, associated mass effect, and neurological deficits. Because there were nine different neurosurgeons involved in this study, each one was assigned a number and included in the analysis to control for differences in surgical technique and approach.

Degree of tumor resection was retrospectively classified from the MRI obtained within 48 hours of surgery. Near total resection (NTR) was defined as tumor with no residual enhancement, representing a >95% resection. Subtotal resection was defined as tumor with some residual enhancement, representing a <95% resection. Biopsy was defined as either open or stereotactic biopsy without any attempt made to debulk the tumor. Motor and somatosensory-evoked potentials were used in most patients, and surgical navigation (CT scans and/or MRI) was used in all patients after 2001. Speech and motor mapping with electrocorticography (functional mapping) was performed in all relevant patients and was included in the analysis as a covariate.

For all patients, serum glucose concentrations were recorded from the day of surgery (post-operative day 0), through to post-operative day 4. From these data, average and maximum values were generated for each patient for the logistic regression analysis. Patients were assigned to groups according to blood glucose concentration: (i) >8.88 mmol/L (160 mg/ml) or (ii) <8.88 mmol/L glucose. This number was selected to reflect clinically significant hyperglycemia as well as to show the greatest difference among the two groups. In general, worse tumors required higher dexamethasone (Dex) dosage post-operatively. To account for any effect that higher steroid dosage would have on serum glucose levels, an additional covariate was included to control for Dex in the peri-operative period. Patients were assigned to two dosage groups: (i) high dose (Dex $\geqslant$ 40 mg/day) or (ii) intermediate dose (Dex < 40 mg/day).

2.4. Statistical analysis

Summary statistics comparing the two disposition groups (DCR; and discharge to home [DCH]) were calculated and given as mean (standard deviation [SD]), median (interquartile range [IQR]), and number (percentage). Parametric data were compared using the Student's *t*-test; non-parametric data were analyzed using the Mann–Whitney *U*-test, and percentages were compared using Pearson's chi squared (χ^2) or Fisher exact test, where appropriate (JMP 8, SAS Institute, Cary, NC, USA). Statistically significant differences were defined as having a p value $\leqslant$ 0.05.

Function status (related by the intended discharge disposition) was used as the primary dependent variable in univariate and multivariate logistic regression analyses to assess associations following surgery. This included a stepwise multivariate logistic regression model to determine independent associations with worse post-operative function (DCR), where a p value $\leqslant$ 0.10 was required to enter the model and a p value $\geqslant$ 0.05 to exit (JMP 8).

3. Results

3.1. Patient Population

We reviewed the records of 596 patients with primary, untreated GB who initiated their care at our institution. Of these patients, 157 had GB in eloquent regions based on our location criteria (Table 1). The mean age of this final cohort was 54 ± 17 years, the mean KPS score was 80 ± 10, the mean tumor size was 4.0 ± 1.7 cm, and the median survival was 12.9 [interquartile range, 7.6–22.7] months. Of the 157 patients, 123 (78%) were designated for DCH while 34 (22%) were designated for DCR.

3.2. Factors associated with post-operative function

Patients designated to DCR were more often older, had diabetes, suffered from pre-existing language and motor deficits, and had less functional independence (lower KPS score). More patients assigned to DCR also had tumors in deep locations and underwent more limited surgery (more biopsies, fewer NTR). In the post-operative period, more of these patients had new motor deficits, higher average glucose levels and higher glucocorticoid dosages (Table 1).

Univariate associations with post-operative performance were those variables that were significantly different between patients allocated to DCH and DCR. These included patient age ($p = 0.01$), diabetes mellitus ($p = 0.02$), pre-operative language deficit ($p = 0.05$), pre-operative motor deficit ($p < 0.01$), multiple pre-operative deficits ($p < 0.01$), pre-operative KPS ($p < 0.01$), deep brain involvement ($p < 0.01$), biopsy only ($p = 0.02$), NTR ($p = 0.03$), new post-operative motor deficit ($p < 0.01$), new multiple post-operative deficits ($p = 0.02$), and mean serum glucose level during days 0–4 after surgery >160 mg/dL (8.88 mmol/L) ($p = 0.04$).

Entering these variables into a stepwise multivariate logistic regression model, patient age (>50 years) (odds ratio [OR]: 2.63; 95% confidence interval [CI]: 1.37–6.25; $p = 0.01$), pre-operative motor deficit (OR: 2.24; 95% CI: 1.32–3.84; $p < 0.01$), deep location (OR: 3.25; 95% CI: 1.45–8.31; $p = 0.01$), new post-operative motor deficit (OR: 3.66; 95% CI: 1.18–11.94); $p = 0.02$), and elevated mean glucose level (>160 mg/dL [8.88 mmol/L] during post-operative days 0–4) (OR: 1.79; 95% CI: 1.03–3.09; $p = 0.04$) were independently associated with DCR (Fig. 1). Although diabetes mellitus and Dex dose were included in the multivariate model, they were not independently associated with worse post-operative function. Mean serum glucose levels were higher in the DCR group throughout the majority of the post-operative period (Fig. 2), with statistically significant differences at day 0, 1, and 2 after surgery. Individual surgeon associations with discharge disposition were not significant.

4. Discussion

In this study, we assessed associations with post-operative function in patients with primary, untreated GB located in eloquent regions. Older patient age, pre- or post-operative motor deficits, deep tumor location, and peri-operative hyperglycemia were independently associated with worse post-operative functional outcome. Interestingly, after controlling for other related factors (including diabetic status and steroid dose), patients with elevated peri-operative glucose levels were nearly twice as likely to have worse post-operative performance assessments.

Other studies exploring factors associated with post-operative function have shown variables such as younger age, better pre-operative functional status, and higher degree of resection are independently correlated with improved long-term functional status.[1,5,6] Importantly, worse post-operative function has also been shown to correlate with poor survival.[2–4,21–25] Our previous study

Table 1
Pre-operative and post-operative characteristics of 157 patients with primary, untreated glioblastoma (GB) in eloquent locations

Variable	Post-operative group		P value[a]
	Good function (DCH, $n = 123$)	Poor function (DCR, $n = 34$)	
Demographics			
Age	52 ± 17	60 ± 13	*0.01*
Male	73 (59%)	15 (44%)	0.15
African–American/Hispanic	5 (4%)	3 (9%)	0.26
Diabetes mellitus	6 (5%)	6 (18%)	*0.02*
Cardiac disease	6 (5%)	0 (0%)	0.25
Pre-operative symptoms and function			
Seizures	20 (16%)	2 (6%)	0.13
Language deficit	36 (29%)	16 (47%)	*0.05*
Motor deficit	13 (11%)	17 (50%)	*<0.01*
Cognitive impairment	7 (6%)	2 (6%)	0.95
Multiple deficits (⩾2)	13 (11%)	11 (32%)	*<0.01*
KPS	80 ± 8	74 ± 9	*<0.01*
Imaging findings			
Tumor size (cm) largest diameter	4.0 ± 1.7	4.0 ± 1.8	0.95
Hemorrhage	8 (7%)	2 (6%)	0.88
Deep location	4 (3%)	9 (26%)	*<0.01*
Surgical variables			
Functional mapping	7 (6%)	2 (6%)	0.97
Biopsy	5 (4%)	5 (15%)	*0.02*
STR (<95%)	29 (24%)	11 (32%)	0.30
NTR (>95%)	89 (72%)	18 (53%)	*0.03*
Post-operative symptoms and function			
New seizures	12 (10%)	3 (9%)	0.87
New language deficit	6 (5%)	4 (12%)	0.15
New motor deficit	3 (2%)	5 (15%)	*<0.01*
New cognitive decline	3 (2%)	3 (9%)	0.09
New multiple deficits (⩾2)	3 (2%)	4 (12%)	*0.02*
Mean glucose (day 0–4) >160 mg/dL	10 (9%)	6 (19%)	*0.04*
High steroid dose (Dex ⩾ 40 mg/day)	10 (37%)	17 (58%)	*0.11*

DCH = intended discharge to home, DCR = intended discharge to rehabilitation, KPS = Karnofsky performance score, STR = sub-total resection, NTR = near-total resection, Dex = dexamethasone.
[a] p values in italic font are statistically significant.

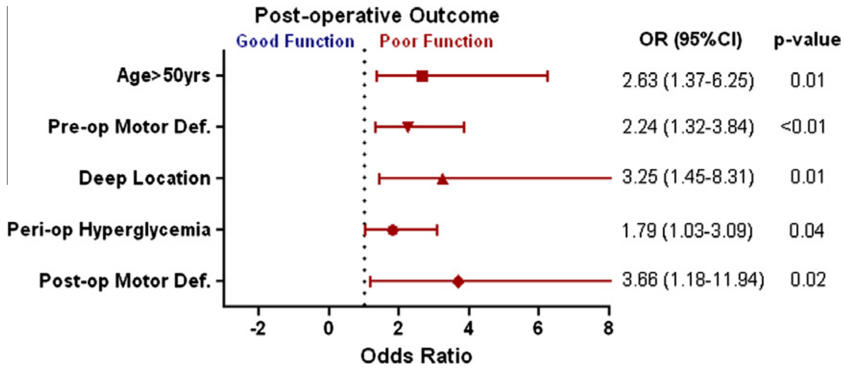

Fig. 1. Forest plot detailing the results from the stepwise multivariate logistic regression model assessing independent associations with intended discharge to rehabilitation (DCR): $p < 0.10$ to enter, $p \leqslant 0.05$ to exit. These included: patient age <50 years, pre-operative (pre-op) motor deficit (def.), deep tumor location, new post-operative (post-op) motor deficit, and mean peri-operative (peri-op) glucose days 0–4 > 160 mg/dL (8.88 mmol/L). Patients with elevated peri-operative glucose levels were nearly twice as likely to be recommended for DCR.

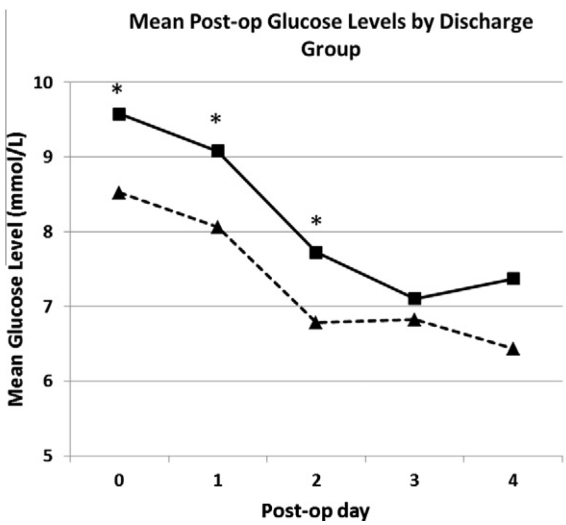

Fig. 2. Mean post-operative (post-op) serum glucose levels (mmol/L) of patients designated for discharge to home (DCH) and for discharge to rehabilitation (DCR). Significant differences were noted on days 0, 1 and 2 after surgery. * = indicates statistical significance ($p \leqslant 0.05$).

examining long-term post-operative function showed that pre-operative KPS score, pre-operative seizures, gross-total resection, and temozolomide chemotherapy were independently associated with prolonged functional independence, while older age, coexistent coronary artery disease, and new post-operative motor deficits were associated with decreased functional independence.[7] In this study, we focus on the perioperative period and explore modifiable factors associated with performance, including degree of resection and blood glucose level. To our knowledge, this is the first study to show that peri-operative hyperglycemia may negatively impact post-operative neurological function in GB.

The effects of hyperglycemia on vascular changes,[26–28] CNS ischemic and traumatic injury,[15,20,29] and outcomes in surgical critical care settings[16,30,31] in both diabetics and non-diabetics have been extensively studied. Following acute stroke, new-onset hyperglycemia has consistently been shown to increase morbidity and mortality, increase length of hospital stay, reduce long-term functional recovery, and diminish ability to return to work, regardless of a patient's prior diabetes status.[8–13] Acute hyperglycemia following ischemic and traumatic brain injury has also been associated with larger infarct volume and worse neurologic outcomes.[14–18] Numerous groups have shown that maintaining blood glucose below 140 mg/dl (7.77 mmol/L) significantly decreases morbidity and mortality among critically ill patients.[30–32] In addition to the broad literature on this topic, we have examined the relationships between hyperglycemia and outcomes in other diseases with potential for associated neurological injury, including carotid endarterectomy, stereotactic brain biopsy, spinal cord tumor resection, and aneurysmal subarachnoid hemorrhage.[33–36] In each of these studies, hyperglycemia was found to be significantly associated with worse neurological outcomes. This current study suggests this also occurs with neurological performance immediately following GB resection.

Numerous basic science studies have reinforced this concept in models of spinal cord injury, traumatic brain injury, and stroke.[19,20,29,35,37] One group studying cerebral ischemia in rats found that hyperglycemia reduced cerebral plasma volume, cerebral blood flow, and blood-brain barrier transport.[20] Another study investigating the effects of glucose levels following traumatic brain injury found that acute but not delayed hyperglycemia increased the contusion area and elevated neutrophil accumulation in the area of the cortical contusion.[19]

Elevated blood glucose levels are also known to be associated with physiologic stress, advanced or more severe disease processes, and undiagnosed diabetes mellitus.[31,32,38,39] Chronic hyperglycemia plays a significant role in vascular disease leading to retinopathy, nephropathy, coronary artery disease, and more.[40–42] Glycosylated hemoglobin A1C (HA1C) is commonly used to measure long-term exposure to elevated blood glucose. In this study, HA1C values were not available for the majority of patients and therefore could not be used to distinguish between the more chronic and acute effects hyperglycemia may play in neurological injury and function loss.

Based on these results, suggestions regarding clinical application and patient selection may be discussed, but further prospective studies are needed to provide more evidence to direct clinical decision-making. We included and aimed to control for each available variable found to show an association with the primary functional outcome measure. We also sought to limit the bias associated with interpreting clinical records by defining this outcome from the decisions made about each patient at the time of discharge by an independent, physician-led team. We feel this simplified primary outcome helps to strengthen the retrospective nature of this study. In addition, patients with more extensive GB may also be subject to elevated blood glucose due to increased stress and disease burden. In addition, these patients are often treated with high dose glucocorticoids, also known to elevate blood glucose, to help control tumor-associated cerebral edema. These findings in combination may mark the sickest, most-debilitated patients with hyperglycemia, thereby relating this as an epiphenomenon rather than a true association. While this may be the case, we attempted to control for these possibilities by including pre-operative diabetic status, pre-operative functional status, and high dose steroids as covariates in the analysis. With this, hyperglycemia remained independently associated with poor functional outcome. This design, in conjunction with the broad literature supporting a role for hyperglycemia in neurological injury, together suggest that this may represent a modifiable factor in the peri-operative care of these patients.

5. Conclusion

Post-operative function loss in patients with untreated eloquent GB is associated with well-studied factors including older age, pre- and post-operative neurological deficits, and deep tumor locations. Controlling for associated factors including Dex dosing, peri-operative hyperglycemia was significantly associated with worse post-operative functional outcome.

References

1. Bussière M, Hopman W, Day A, et al. Indicators of functional status for primary malignant brain tumour patients. *Can J Neurol Sci* 2005;**32**:50–6.
2. Stark AM, Stepper W, Mehdorn HM. Outcome evaluation in glioblastoma patients using different ranking scores: KPS, GOS, mRS and MRC. *Eur J Cancer Care* 2010;**19**:39–44.
3. Taphoorn MJB, Stupp R, Coens C, et al. Health-related quality of life in patients with glioblastoma: A randomised controlled trial. *Lancet Oncol* 2005;**6**:937–44.
4. Brown PD, Ballman KV, Rummans TA, et al. Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. *J Neurooncol* 2006;**76**:283–91.
5. Brown PD, Maurer MJ, Rummans TA, et al. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. *Neurosurgery* 2005;**57**:495–503.
6. Recht L, Glantz M, Chamberlain M, et al. Quantitative measurement of quality outcome in malignant glioma patients using an independent living score (ILS): Assessment of a retrospective cohort. *J Neurooncol* 2003;**61**:127–36.
7. Chaichana KL, Halthore AN, Parker SL, et al. Factors involved in maintaining prolonged functional independence following supratentorial glioblastoma resection. *J Neurosurg* 2010;**114**:604–12.
8. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke* 2003;**34**:2208–14.
9. Barber M, Wright F, Stott DJ, et al. Predictors of early neurological deterioration after ischaemic stroke: a case-control study. *Gerontology* 2004;**50**:102–9.
10. Bhalla A, Sankaralingam S, Tilling K, et al. Effect of acute glycaemic index on clinical outcome after acute stroke. *Cerebrovasc Dis* 2002;**13**:95–101.
11. Christensen H, Boysen G. Blood glucose increases early after stroke onset: a study on serial measurements of blood glucose in acute stroke. *Eur J Neurol* 2002;**9**:297–301.
12. Tracey F, Crawford VL, Lawson JT, et al. Hyperglycaemia and mortality from acute stroke. *Q J Med* 1993;**86**:439–46.
13. Tracey F, Stout RW. Hyperglycemia in the acute phase of stroke and stress response. *Stroke* 1994;**25**:524–5.
14. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg* 1991;**75**:545–51.
15. Matchar DB, Divine GW, Heyman A, et al. The influence of hyperglycemia on outcome of cerebral infarction. *Ann Intern Med* 1992;**117**:449–56.
16. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. *Neurosurgery* 2000;**46**:335–42 [discussion 342–3].
17. Williams LS, Rotich J, Qi R, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 2002;**59**:67–71.
18. Zygun DA, Steiner LA, Johnston AJ, et al. Hyperglycemia and brain tissue pH after traumatic brain injury. *Neurosurgery* 2004;**55**:877–81 [discussion 882].
19. Kinoshita K, Kraydieh S, Alonso O, et al. Effect of posttraumatic hyperglycemia on contusion volume and neutrophil accumulation after moderate fluid-percussion brain injury in rats. *J Neurotrauma* 2002;**19**:681–92.
20. Kawai N, Keep RF, Betz AL, et al. Hyperglycemia induces progressive changes in the cerebral microvasculature and blood-brain barrier transport during focal cerebral ischemia. *Acta Neurochir Suppl* 1998;**71**:219–21.
21. Buckner JC. Factors influencing survival in high-grade gliomas. *Semin Oncol* 2003;**30**(6 Suppl. 19):10–4.
22. Casartelli G, Dorcaratto A, Ravetti JL, et al. Survival of high grade glioma patients depends on their age at diagnosis. *Cancer Biol Ther* 2009;**8**:1719–21.
23. Krex D, Klink B, Hartmann C, et al. Long-term survival with glioblastoma multiforme. *Brain* 2007;**130**:2596–606.
24. Li SW, Qiu XG, Chen BS, et al. Prognostic factors influencing clinical outcomes of glioblastoma multiforme. *Chin Med J* 2009;**122**:1245–9.
25. McGirt MJ, Mukherjee D, Chaichana KL, et al. Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. *Neurosurgery* 2009;**65**:463–9 [discussion 469–70].
26. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;**287**:2570–81.
27. Henry RM, Kostense PJ, Dekker JM, et al. Carotid arterial remodeling: a maladaptive phenomenon in type 2 diabetes but not in impaired glucose metabolism: the Hoorn study. *Stroke* 2004;**35**:671–6.
28. Harik SI, LaManna JC. Vascular perfusion and blood-brain glucose transport in acute and chronic hyperglycemia. *J Neurochem* 1988;**51**:1924–9.
29. Voll CL, Auer RN. The effect of postischemic blood glucose levels on ischemic brain damage in the rat. *Ann Neurol* 1988;**24**:638–46.
30. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy critically ill patients. *N Engl J Med* 2001;**345**:1359–67.
31. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2004;**164**:2005–11.
32. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004;**79**:992–1000.
33. McGirt MJ, Woodworth GF, Brooke BS, et al. Hyperglycemia independently increases the risk of perioperative stroke, myocardial infarction, and death after carotid endarterectomy. *Neurosurgery* 2006;**58**:1066–73 [discussion 1066–73].
34. McGirt MJ, Woodworth GF, Coon AL, et al. Independent predictors of morbidity after image-guided stereotactic brain biopsy: a risk assessment of 270 cases. *J Neurosurg* 2005;**102**:897–901.
35. McGirt MJ, Gok B, Shepherd S, et al. Effect of hyperglycemia on progressive paraparesis in a rat etastatic spinal tumor model. *J Neurosurg Spine* 2009;**10**:9–15.
36. McGirt MJ, Woodworth GF, Ali M, et al. Persistent perioperative hyperglycemia as an independent predictor of poor outcome after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2007;**107**:1080–5.
37. Sala F, Menna G, Bricolo A, et al. Role of glycemia in acute spinal cord injury. Data from a rat experimental model and clinical experience. *Ann N Y Acad Sci* 1999;**890**:133–54.
38. Kernan WN, Inzucchi SE. Type 2 Diabetes Mellitus and Insulin Resistance. Stroke Prevention and Management. *Curr Treat Options Neurol* 2004;**6**:443–50.
39. Khoury W, Klausner JM, Ben-Abraham R, et al. Glucose control by insulin for critically ill surgical patients. *J Trauma* 2004;**57**:1132–8.
40. Clements RS, Bell DS. Complications of diabetes. Prevalence, detection, current treatment, and prognosis. *Am J Med* 1985;**79**:2–7.
41. Krolewski AS, Warram JH, Freire MB. Epidemiology of late diabetic complications. A basis for the development and evaluation of preventive programs. *Endocrinol Metab Clin North Am* 1996;**25**:217–42.
42. Resl M, Clodi M. Diabetes and cardiovascular complications. *Wien Med Wochenschr* 2010;**160**:3–7.