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The effect of diabetes mellitus on in-hospital hyperglycemia, length of stay and survival in patients with brain tumor receiving dexamethasone: A descriptive and comparative analysis

Panteleimon Pantelidis*, Parmenion P. Tsitsopoulos, Eleni Pappa, Elpida Theologou, Nikolaos Karanikolas, Christos Drosos, Christos Tsonidis

Department of Neurosurgery, Hippokration General Hospital, Aristotle University School of Health Sciences, Faculty of Medicine, Thessaloniki, Greece

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ABSTRACT

Objectives: To perform a comparative analysis on the impact of Type 2 Diabetes Mellitus (DM) on in-hospital hyperglycemia, length of stay (LOS) and survival of patients suffering from brain tumor who receive dexamethasone.

Patients and Methods: Patients with brain tumor hospitalized in a Neurosurgery department between 2011 and 2018, were studied. Data referring to medical history, clinical characteristics and in-hospital survival was collected and analyzed. Morning plasma glucose levels (PGL) were obtained for seven consecutive days after the start of dexamethasone.

Results: Fifty-six patients were identified. Of them, 21 (37.5%) were diabetic. During dexamethasone administration, a difference in morning PGL values during different days was noted ($p = 0.003$). No difference in glucose levels among different glucocorticoid doses was seen. DM was associated with higher average PGL (aMPGL), calculated as the mean of morning PGL values for the last six days ($p = 0.001$) and with higher rates of persistent hyperglycemia ($p = 0.002$). The change of aMPGL from the morning PGL value of day one did not differ between the two cohorts ($p = 0.729$). DM neither affected LOS nor in-hospital survival ($p = 0.745$ & $p = 0.438$, respectively).

Conclusion: Although morning glucose values were higher in diabetic, compared to non-diabetic patients, their change from day one was similar between the two cohorts. LOS and in-hospital survival were not affected by DM.

1. Introduction

In 1952, Ingraham introduced the use of steroids for the treatment of vasogenic cerebral edema in patients with brain cancer [1]. Dexamethasone has been the most commonly administered corticosteroid for this purpose [2]. Although dexamethasone has been used for over 50 years, there is no consensus on its indications and dosage [3]. Common clinical practice suggests the use of dexamethasone only in symptomatic patients and at daily doses starting from 4 to 8 mg that may gradually increase usually up to 16 mg, but higher doses have also been reported [4,5]. Although dexamethasone can temporarily control brain edema and lower intracranial pressure, it can induce a series of adverse reactions including hyperglycemia [4]. Furthermore, it has also been shown that dexamethasone can affect survival in patients with glioblastoma multiforme, presumably through elevating plasma glucose levels (PGL) [6–12].

Type 2 Diabetes Mellitus (T2DM), besides disruption of plasma glucose balance, can have an additive hyperglycemic effect on blood glucose levels, especially in patients with other predisposing factors for hyperglycemia such as glucocorticosteroid administration [13]. Up to now, there have been only two relevant studies investigating the effect of prior T2DM on PGL increase, where it was shown that T2DM acts additively to the corticosteroid-induced hyperglycemia [14,15]. However, in one of these studies, various types of corticosteroids were given including dexamethasone, while in both studies, subjects did not suffer exclusively from neurosurgical pathologies [15,16].

In the literature, it has been scarcely reported how diabetes mellitus, the use of dexamethasone, concomitant comorbidities and other factors affect the severity of hyperglycemia and survival of patients with brain tumors. Therefore, we investigated the hypothesis that pre-

* Corresponding author.
E-mail address: pan.g.pantelidis@gmail.com (P. Pantelidis).

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existing T2DM: 1) Exacerbates the dexamethasone-induced hyperglycemia in patients with brain tumor and, 2) Affects length of stay and in-hospital mortality.

2. Materials and methods

2.1. Clinical setting and participants

The medical records of all patients operated for brain tumors and treated with dexamethasone in the Department of Neurosurgery, at Hippokration General Hospital, Thessaloniki, Greece, between May 2011 and July 2018, were retrospectively analyzed. Patients younger than 15 years old, as well as those suffering from conditions other than T2DM and those treated with any medication or intravenous fluids that could affect PGL were excluded. Patients with incomplete measurements of PGL for seven consecutive days (more than three missing values) that would alter the results were also excluded from the analysis. With the application of the eligibility criteria, the sample was divided into subjects previously diagnosed with T2DM (DM cohort) and into those without a prior diagnosis of T2DM or any other condition that would affect glucose balance (non-DM cohort). We evaluated whether the two cohorts differed in terms of glycemic control, length of stay and in-hospital survival.

2.2. Data extraction

Patients' demographics and medical history were recorded. The "Charlson Comorbidity Index" (CCI) was calculated to evaluate the comorbidity burden of each patient [17,18]. Data on hospitalization was also obtained. Brain tumors were divided into primary and metastatic. Length of stay at the hospital (LOS) was calculated as the difference between the dates of admission and discharge/ death and served also as an outcome variable. In-hospital outcome (discharge at home or death) was also documented (OuH).

2.3. PGL measurements

The average daily dose of dexamethasone (aDEX) was calculated as the average of the daily dose given in the first seven days of hospitalization. The values of morning PGL for the first seven days of hospitalization were used. Blood glucose levels were measured with blood tests using venous blood samples with glucose finger prick test obtained early in the morning before food intake and after overnight fast. Testing was done by experienced nurses and care was taken to ensure that the testing device was working properly. This method has been used successfully for decades [19]. Patients did not receive any sugary drinks and intravenous fluids containing sugar steadily administered throughout the day, so that they could affect morning glucose values. The average morning plasma glucose level (aMPGL) was calculated by averaging the morning values of PGL for the days 2 to 7. The value of day 1 was not included, because it served as a baseline number, just before the first dose of dexamethasone. Therefore, the value of day 2 was the first to be included, since dexamethasone exhibits its hyperglycemic effects hours after its administration [15,20]. The difference from baseline morning PGL (dMPGL) was calculated as the change between aMPGL and the morning PGL on the first day.

A dichotomous outcome variable was created to evaluate the occurrence of persistent hyperglycemia according to the following algorithm: Subjects were classified depending on whether or not the days they had PGL higher than 140 mg/dL were equal or more than half of the measured days (days[PGL > 140] ≥ total_days/2) [21]. All aMPGL, dMPGL and PHG were employed as outcome measures for the evaluation of the glycemic state after the onset of dexamethasone. The daily dose of dexamethasone and the aDEX were measured in mg/day. Daily morning PGL, as well as aMPGL and dMPGL, were measured in mg/dL.

If the missing values of morning GPL measurements or dexamethasone daily doses were equal or less than 3 (half or more of the measurements were available), aMPGL and aDEX were calculated by averaging the remaining values. As previously noted, if more than 3 measurements were missing, the subject was excluded from the analysis.

2.4. Statistical analysis

Values were obtained using frequencies and percentages for categorical variables. Normality of data was assessed with the use of Kolmogorov-Smirnov test. Normally distributed data is reported as means and standard deviations (SD), whereas non-normally distributed data is reported as medians and interquartile ranges (IQR). The Student's *t*-test was applied for the analysis of parametric data, the Mann-Whitney U test was employed for the analysis of non-parametric data analysis, while the Fisher exact test was used to explore differences in categorical variables. The daily dose of dexamethasone and morning PGL were tested for differences in their distributions during the 7 days with the use of Related-Samples Friedman's Two-Way ANOVA test.

Possible associations of other characteristics with outcomes were also examined. Mann-Whitney U test was employed to compare groups with non-normally distributed data. Kendall's tau (τ) correlation coefficient was used to explore any correlation between two continuous variables in non-normally distributed data [22]. Simple logistic regression models were used to produce odds ratios (OR) in categorical outcome variables. The effect sizes (r) of the significant associations were calculated and are reported. Generalized linear and logistic regression models were employed, including as possible confounders those factors previously identified to influence outcome. Each regression model compared the differences between DM and non-DM groups in each outcome. P values below 0.05 were considered statistically significant.

Data handling and statistical analysis was conducted with SPSS version 20 (IBM Corp., Armonk, New York, USA) and G*power (version 3.1.9.2, Universität Kiel, Germany). Figures were created with GraphPad Prism 6 (GraphPad Software, La Jolla, California, USA).

2.5. Ethical considerations

The study was approved by the Institutional Board of Hippokration General Hospital (approval number 290/21.05.2018) All personal data was encoded at the level of their retrieval and no sensitive information was used or disclosed in later stages of processing. The anonymity of subjects was protected and data handling was conducted according to the current legislation and the ethical principles of the declaration of Helsinki [23,24].

3. Results

3.1. Baseline characteristics

Of the 106 patients with brain tumor operated in our department during the study period, a total of 56 patients met the criteria for inclusion and were included. The median age was 64.0 years (IQR: 13.25). Thirty-five (62.5%) were male. Primary brain tumor was the leading diagnosis, accounting for 44 (78.6%) of the cases, while metastasis was diagnosed in 12 (21.4%) patients. Most patients were operated shorty after being admitted to the Department of Neurosurgery (< 3 days). Twenty-one patients (37.5%) had a medical history of DM. All DM patients were on antihyperglycemic oral agents, and 3 (14.3%) of them were also on long-acting insulin. Forty-five subjects (80.3%) stayed on mechanical ventilation for some period of time with the median duration of mechanical ventilation being 3 days (IQR: 3). Eleven patients (19.6%) died during hospitalization (Table 1).

Table 1
Baseline Characteristics and clinical data of 56 patients with brain tumor receiving dexamethasone.

	Total (N = 56)	DM cohort (N = 21)	Non-DM cohort (N = 35)	P value**
Sex (%)				0.395
Male	35 (62.5)	15 (71.4)	20 (57.1)	
Female	21 (37.5)	6 (28.6)	15 (42.9)	
Age - median (IQR)	64.0 (58.25 - 71.50)	65.0 (62.0–72.50)	64.0 (55.0–70.0)	0.170
Tumor type (%)				–
Glioma	39 (69.6)	13 (61.9)	26 (74.3)	
Pituitary tumor	1 (1.8)	1 (4.8)	0 (0)	
Neuroendocrine tumor	1 (1.8)	1 (4.8)	0 (0)	
Meningioma	3 (5.4)	3 (14.3)	0 (0)	
Metastasis	12 (21.4)	3 (14.3)	9 (25.7)	
Tumor type (grouped) (%)				0.503
Primary tumor	44 (78.6)	18 (85.7)	26 (74.3)	
Metastasis	12 (21.4)	3 (14.3)	9 (25.7)	
CCI - median (IQR)	5.00 (4.0–6.0)	6.0 (5.0–6.50)	4. 0 (4.0–6.0)	0.003
Surgery type (%)				1
Tumor excision	50 (89.3)	19 (90.5)	31 (88.6)	
Biopsy	6 (10.7)	2 (9.5)	4 (11.4)	
ICU (%)				0.730
Yes	45 (80.4)	16 (76.2)	29 (82.9)	
No	11 (19.6)	5 (23.8)	6 (17.1)	
Duration of mechanical ventilation - median days (IQR)*	3.0 (1.0–4.0)	1.5 (1.0–3.75)	3.0 (1.0–6.50)	0.067

P values show the statistically significant differences between the DM and non-DM cohorts.
* Refers to patients admitted to ICU.
** Differences in sex, admission to ICU, tumor type and surgery type were evaluatedwith Fisher's exact test, while differences in age, CCI and the duration of mechanical ventilation with Mann-Whitney U test. A higher CCI score in DM patients was the only significant difference found (effect size $r = -0.401$, $P = 0.003$); IQR, Interquartile range; Min, Minimum; Max, Maximum; DM, Diabetes Mellitus; CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; PGL.

3.2. Dexamethasone dose and PGL

Dexamethasone was given in all subjects on a daily basis, with starting doses varying from 4 mg/day to 32 mg/day. The daily doses did not differ during the 7 days of measurements ($p = 0.239$) with no-difference between the two cohorts ($p = 0.065$ & $p = 0.937$ for the DM cohort and the non-DM cohort respectively) (Fig. 1). The median daily dose of dexamethasone (aDEX) was 12 (IQR: 7.57) mg/day. CCI was significantly higher in the DM cohort (6 vs. 4, $p = 0.003$).

A difference in morning PGL values during the course of the 7 days of measurements was noted ($p = 0.003$), which was more evident in the non-DM cohort ($p < 0.001$), than in the DM cohort ($p = 0.857$). Post-hoc tests showed that in the non-DM cohort, except for day 3, the values on the 1st day were significantly lower than those of all other days ($p < 0.05$). Overall, there was no other significant change in the morning PGL values after day 2 (Fig. 2). The median aMPGL was 114.92 (IQR: 54.04) mg/dL. The median values (IQR) for dMPGL and LOS were 17.50 (31.17) mg/dL and 16.0 (15.75) days, respectively. During the days of measurement, persistent hyperglycemia was present in 15 (26.8%) of the patients (Table 2).

3.3. Effect of DM

Differences between DM and non-DM cohorts are shown in Table 2. aMPGL was higher in the DM cohort (147.17 vs. 106.0 mg/dL, $p = 0.001$). The percentage of PHG was also higher in the DM cohort (52.4% vs. 11.4%, $p = 0.002$). However, dMPGL did not differ significantly (17.33 vs. 21.25 mg/dL, $p = 0.729$) (Fig. 3). LOS was similar for DM and non-DM cohorts (17.0 vs. 16.0 days, respectively, $p = 0.745$). In-hospital survival (OuH) did not differ between the two groups (85.7% vs. 77.1%, $p = 0.438$) (Fig. 4).

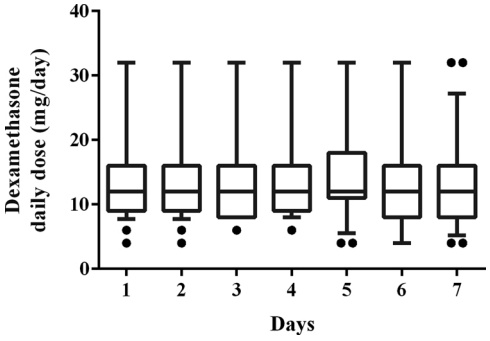

Fig. 1. Dexamethasone daily dose during the seven days of measurement. Description: Values are reported as median and interquartile range. Outliers are marked as dots. Values did not differ across different days ($p = 0.239$).

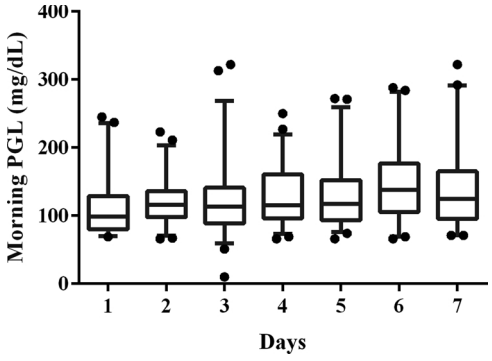

Fig. 2. Morning plasma glucose levels during the seven days of measurement. Description: Values are reported as median and interquartile range. Outliers are marked as dots. PGL: Plasma glucose levels. Values were significantly different across different days ($p = 0.003$), with day 1 displaying the lowest values.

Table 2
Outcomes of 56 patients with brain tumor receiving dexamethasone.

	Total (N = 56)	DM cohort (N = 21)	Non-DM cohort (N = 35)	P value*
Daily morning PGL - median (IQR)				
Day 1	98.50 (80.0–128.75)	129.0 (99.50–160.0)	84.0 (79.0–102.0)	< 0.001**
Day 2	116.0 (97.75–135.75)	136.0 (115.50–179.50)	109.0 (89.0–120.0)	< 0.001**
Day 3	113.0 (88.50–141.0)	143.0 (100.50–200.50)	106.0 (86.0–118.0)	0.004**
Day 4	115.50 (96.0–160.50)	135.0 (101.50–196.50)	109.0 (90.0–135.0)	0.008**
Day 5	117.0 (93.50–152.0)	147.0 (98.25–202.50)	114.0 (92.0–137.0)	0.025**
Day 6	138.0 (105.50–176.50)	149.0 (123.50–218.50)	114.0 (99.0–150.0)	0.040**
Day 7	124.50 (95.50–165.0)	157.0 (121.50–196.0)	109.0 (88.0–130.0)	0.019**
aMPGL - median (IQR)	114.92 (100.50–154.54)	147.17 (114.0–186.92)	106.0 (95.67–132.50)	0.001**
dMPGL - median (IQR)	17.50 (2.67–36.83)	17.33 (−9.50–44.75)	21.25 (5.50–32.83)	0.729
PHG (%)				0.002**
Yes	15 (26.8)	11 (52.4)	4 (11.4)	
No	41 (73.2)	10 (47.6)	31 (88.6)	
LOS*** - median (IQR)	16.0 (12.0–24.0)	17.0 (11.0–27.25)	16.0 (12.0–22.0)	0.745
OuH (%)				0.438
Survived	45 (80.4)	18 (85.7)	27 (77.1)	
In-hospital death	11 (19.6)	3 (14.3)	8 (22.9)	

* P values show the statistically significant differences between the DM and non-DM cohorts. Differences in daily morning PGL, aMPGL, dMPGL and LOS were evaluated with the use of Mann-Whitney U test, while those in PHG and OuH by obtaining odds ratios.

** Denotes statistical significance. Morning PGL values, as well as aMPGL, were higher in the DM group (effect size r, for morning PGL days 1–7 and aMPGL: −0.503, −0.511, −0.386, −0.355, -0.308, −0.325, −0.37 and −0.433, respectively, $p < 0.05$ for all comparisons).

*** Refers to patients that survived; IQR, Interquartile range; Min, Minimum; Max, Maximum; DM, Diabetes Mellitus; PGL, Plasma glucose level; aMPGL, Average morning plasma glucose level; dMPGL, Difference between aMPGL and baseline value; PHG, Persistent hyperglycemia; LOS, Length of staying at the hospital; OuH, Outcome of hospitalization.

3.4. Prognostic factors

No variable was found to have a statistically significant impact on aMPGL and PHG. Admission to the ICU resulted in higher dMPGL compared to non-ICU hospitalization (30.7 vs. 19.7 mg/dL, r = 0.267, p = 0.045). CCI inversely correlated with LOS (tau = -0.281, p = 0.013). Patients with a primary brain tumor stayed longer at the hospital compared to those with a metastatic tumor (26 vs. 12.4 days, r = 0.432, p = 0.003). LOS was longer for those undergoing operation for tumor excision than those who underwent tumor biopsy (24.6 vs. 10.6 days, r = 0.335, p = 0.023). Moreover, ICU admission resulted in longer length of stay (25.73 vs. 13.45 days, r = 0.39, p = 0.008).

The only factor that was found to significantly affect the outcome and reduced in-hospital survival was the prolonged duration of mechanical ventilation (OR = 0.341, 95% CIs = 0.172, 0.674, p = 0.002). (Table 3). According to the associations identified in Table 3, we performed regression analyses to adjust for one confounding factor each time. After adjusting for CCI, tumor type, surgery type and admission to the ICU, DM still did not affect LOS in each regression model. Moreover, DM did not affect dMPGL after adjusting for ICU admission. Adjustment for the days in mechanical ventilation did not alter the effect of DM on in-hospital mortality ($p > 0.05$ for DM as a predictor in all models).

4. Discussion

The current study indicates that a medical history of Diabetes Mellitus affects the glycemic state of neurosurgical patients who receive dexamethasone. In particular, prior diabetes contributes to even higher values of morning plasma glucose levels and increases the risk of persistent hyperglycemia. However, it does not affect LOS and in-hospital survival. The above findings were retained when possible confounders were taken into consideration. Although LOS was not affected by DM, the type of tumor, type of surgery and CCI were found to be associated with it. In-hospital mortality was not affected by prior DM but prolonged mechanical ventilation resulted in higher mortality rates.

In order to eliminate food intake as a confounder, we used the morning daily PGL and not the peak daily PGL. Moreover, none of the included patients received intravenous fluids containing dextrose or had any other condition that could affect glucose values or was under treatment with any glucose-affecting medications (except for the antidiabetic medications of the DM cohort). To avoid confounding, the average morning PGL (aMPGL) was used as an outcome variable, instead of the last day's morning PGL or the maximum of the morning PGL values among different days. Although patients with DM had higher aMPGL values, their change from the baseline did not differ significantly compared to that of non-DM patients, suggesting that prior DM does not affect the magnitude of change from baseline measurements. Subjects with DM exhibited higher glucose levels, but a similar increase in morning PGL from their baseline values was noted in both cohorts. It remains, however, unknown how the glycemic state would be affected if uncontrolled diabetic patients were included.

Corticosteroid-induced hyperglycemia can reach percentages up to 60% [25,26]. In the study by Low et al. [27], higher doses of dexamethasone were associated with higher PGL values. In the current study, the average daily dose of dexamethasone (aDEX) presented an on/off effect on glucose levels, as it neither correlated, with the absolute values of morning PGL (measured with aMPGL and PHG) nor with the change from baseline values (measured with dMPGL). Since we failed to show any difference in the glucose levels among different glucocorticoid doses, it is likely that larger doses of dexamethasone given for a prolonged period of time are needed to result in a significant increase.

It has been shown that prior DM can result in decreased survival through its hyperglycemic effect [7,8,28–31]. A possible explanation is the augmented resistance of tumor cells to radiotherapy caused by hyperglycemia [6,10,11]. However, only two such studies were prospective, with the only one referring to the effect of prior DM on corticosteroid-induced hyperglycemia not including neurosurgical patients [15,32]. Although we found that DM did not significantly affect survival during hospitalization, it could possibly shorten it after discharge, as it is described in other reports [6–12].

With regard to the study limitations o, besides its retrospective nature, a significant drawback is the small study sample and the short follow-up period. Samples were not matched, and thus, selection bias may have occurred. Although the study sample was small, it was associated with sufficient statistical power (> 80%) for most statistical comparisons, but the possibility of type II error cannot be ruled out. Data on tumor volumes and sizes was available for the minority of

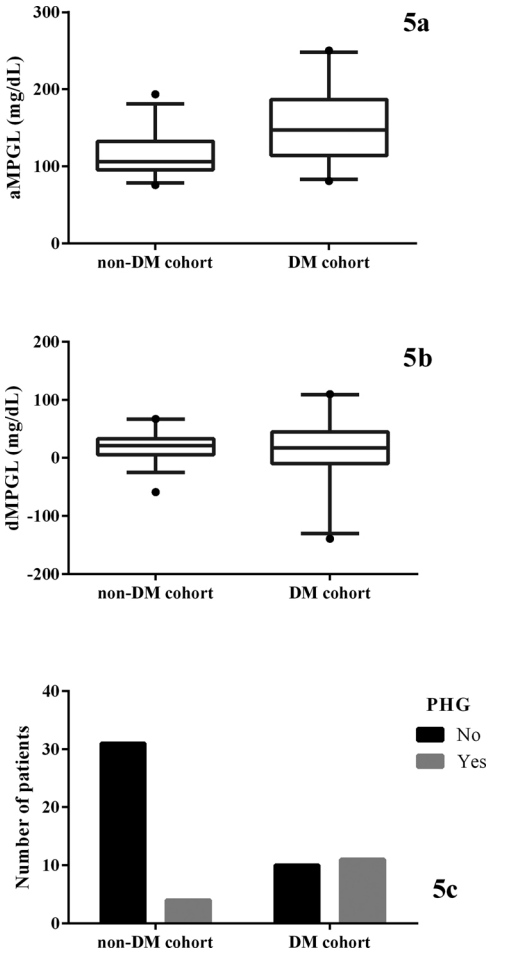

Fig. 3. Glycemic outcomes in non-DM and DM cohorts. Description: 3a: aMPGL; 3b: dMPGL; 3c: PHG. Values are reported as median and interquartile range. Outliers are marked as dots. aMPGL and PHG were significantly higher in the DM cohort (p = 0.001 & p = 0.002, respectively), while dMPGL was not significantly different (p = 0.729). aMPGL, Average morning plasma glucose level; dMPGL, Difference from baseline morning plasma glucose level; PHG, Persistent hyperglycemia; DM, Diabetes Mellitus.

patients because up to recently, there was no digitized imaging system available at the hospital.

On the contrary, a number of strengths exist. Subjects were free of any other factors that could disrupt glucose balance, such as intravenous administration of glucose-containing fluids. Moreover, in our department, patients' diet is tightly supervised and guided by doctors and nurses and when needed, by dieticians. Ward nurses provide all meals and refreshments, including water, to ensure that especially in the morning, patients were at an overnight fasting state. Personnel is even more cautious with food and fluid intake in diabetics and in patients receiving corticosteroids. This tight control contributed to a betterestimation of the effect of DM and other factors on outcome, as possible confounders were ruled out. The PGL values were measured for 7 days and only the last days were taken into consideration for calculating the outcome aMPGL avoiding, thus, possible outliers as an effect measure. In addition to measuring total glucose levels, changes from the baseline were also evaluated. PHG was calculated as described by ADA and could serve as a standard dichotomous outcome, in similar studies [21]. Moreover, to our knowledge, this is the first study assessing the glycemic effect of prior DM in neurosurgical patients treated with dexamethasone, since in previous reports, various types of corticosteroids were given and in patients not suffering exclusively from a brain tumor [14–16].

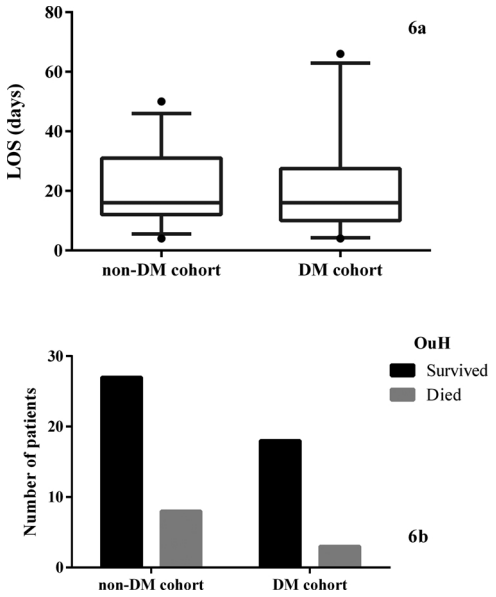

Fig. 4. LOS and OuH in non-DM and DM cohorts. Description: 4a: LOS; 4b: OuH. Values are reported as mean and Standard Deviation or median and interquartile range. LOS and OuH did not differ between the two cohorts (p = 0.745 & p = 0.438, respectively). LOS, Length of stay; OuH, Outcome of hospitalization; DM, Diabetes Mellitus.

Table 3
Association between possible predictors or confounders and outcomes of 56 patients with brain tumor receiving dexamethasone.

	aMPGL	dMPGL	PHG	LOS**	OuH
Sex	0.912	0.339	0.815	0.476	0.055
Age	0.630	0.910	0.202	0.751	0.485
CCI	0.286	0.074	0.070	0.013*	0.706
Tumor type (grouped)	0.920	0.074	0.565	0.003*	0.770
Surgery type	0.398	0.321	0.686	0.023*	0.480
ICU	0.164	0.045*	0.968	0.008*	0.344
Duration of mechanical ventilation***	0.614	0.113	0.991	0.081	0.002*
aDEX	0.349	0.387	0.317	0.707	0.571

Age, CCI, duration of mechanical ventilation and aDEX were correlated with aMPGL, dMPGL and LOS using Kendall's tau coefficient. Mann-Whitney U test was used for the following associations: Sex, tumor type, surgery type and admission to ICU with the outcomes aMPGL, dMPGL and LOS. These categorical possible predictors, along with the continuous age, CCI, duration of mechanical ventilation and aDEX were associated with PHG and OuH using simple logistic regression (obtaining odds ratios).

* Denotes statistical significance. The strength and the direction of each significant association are reported in the text.

** Refers to the 45 patients that survived during hospitalization.

*** Refers to the 45 patients that were admitted to the ICU; CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; aDEX, Average of daily dexamethasone dose; aMPGL, Average morning plasma glucose level; dMPGL, Difference between aMPGL and baseline value; PHG, Persistent hyperglycemia; LOS, Length of staying at the hospital; OuH, Outcome of hospitalization.

5. Conclusion

Although the present results suggest that prior DM is associated with higher plasma glucose levels in neurosurgical patients under treatment with dexamethasone, prospective research is needed with larger samples and longer follow-up periods. Most importantly, a common practice for the evaluation of the glycemic state should be adopted, to lead to utilizable results.

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Declaration of Competing Interest

The authors have no competing interests to declare.

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