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ORIGINAL ARTICLES

CORTISOL LEVELS AND HBA1C-BASED GLYCEMIC VARIABLES FOR THE ASSESSMENT OF STRESS RESPONSE IN ACUTE STROKE

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ABSTRACT

INTRODUCTION: In various acute conditions, including acute ischemic stroke (AIS), a stress response occurs, often leading to elevated blood glucose (BG) levels, the so-called stress hyperglycemia (SH). Its adequate assessment would be particularly useful in clinical practice, both for identifying high-risk patients and for therapeutic behavior.

AIM: The aim of this article is to analyze cortisol levels and glycated hemoglobin (HbA1c)-based glycemic variables as markers for assessment of stress response in AIS and to look for an association with adverse clinical outcome.

MATERIALS AND METHODS: A cross-sectional study including 114 patients with AIS, stratified according to BG at admission (admBG) and the presence of diabetes mellitus (DM)—with normoglycemia, SH, previously and newly diagnosed type 2 DM was conducted. Serum cortisol levels, as well as HbA1c-based glycemic variables were evaluated according to the severity of stroke (assessed by National Institutes of Health Stroke Scale, NIHSS score) and the prevalence of fatal outcome.

RESULTS: The SH group demonstrated the greatest AIS severity at admission, accompanied by the highest serum cortisol levels, with a significant difference in both indicators compared to the NG group (NIHSS 15.33±8.39 vs.10.63±6.12, p=0.016; serum cortisol 1039±668 vs. 701.7±380.8 p=0.046). Furthermore, in patients with a fatal outcome compared to survivors, we observed significantly more severe AIS (NIHSS 15.93±5.31 vs. 9.72±6.31, p<0.0001), as well as higher serum cortisol levels (1060±572.1 vs. 610.5±284.8, p<0.0001). In contrast to admBG, HbA1c-based glycemic variables demonstrated the highest values in the SH group. Both cortisol and glycemic variables, but not admBG, showed positive correlation with AIS severity at admission.

CONCLUSION: Serum cortisol levels could be useful in assessing the severity of AIS and identifying high-risk patients. HbA1c-based glycemic variables are better determinants of stress response than absolute BG values.

Keywords: *cortisol, HbA1c-based glycemic variables, stroke*

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INTRODUCTION

Various acute conditions, including acute ischemic stroke (AIS), place the body in a state of stress. The subsequent stress response aiming to restore homeostasis is mainly mediated by the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system (1). As a result of the acute metBabolic and hormonal changes that occur, an increase in blood glucose (BG) levels is often observed (2), the so-called stress hyperglycemia (SH). Its development is due to the complex interaction of counterregulatory hormones and cytokines (3). Elevated levels of glucagon, epinephrine, cortisol and growth hormone lead to a number of changes in carbohydrate metabolism, such as insulin resistance (IR), increased hepatic glucose production, impaired peripheral glucose uptake, and relative insulin deficiency (2,4). During stress, the secretion of proinflammatory cytokines is also increased, in particular, tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, as well as C-reactive protein (CRP), which also induce peripheral IR by suppressing postreceptor insulin signaling (2,3,5).

Stress hyperglycemia is usually limited to patients without diabetes mellitus (DM). However, some authors take into account that diabetics could also react with hyperglycemia in response to stress (3,5). The difficulty of distinguishing SH from poorly controlled DM, given the possibility of their combination (6, 7), has led to the introduction of the concept of relative hyperglycemia. Using glycated hemoglobin (HbA1c)-based glycemic variables for its measurement avoids the influence of the patient's usual BG levels (the so-called background glycemia). A number of studies have shown that they are better biomarkers for identifying high-risk critically ill patients (6,8,9,10,11).

Serum cortisol has been studied in various acute conditions (12,13,14), but to our knowledge no direct comparison between HbA1c-based glycemic variables and levels of this stress hormone has been made to date.

AIM

The aim of this article is to analyze cortisol levels and HbA1c-based glycemic variables as markers for assessment of stress response in AIS and to look for an association with adverse clinical outcome.

MATERIALS AND METHODS

We conducted a cross-sectional study of patients hospitalized for AIS in the Second Clinic for Nervous Diseases of St. Marina University Hospital in Varna for the period of June 2021 to May 2023. We divided the cohort of 114 patients into four groups, according to BG at admission (admBG) and the presence of DM in view of HbA1c value—with normoglycemia (NG), SH, previously diagnosed type 2 DM (T2DM), and newly diagnosed T2DM (ndT2DM). We determined the severity of stroke at admission (NIHSS1) and at discharge (NIHSS2) according to the National Institutes of Health Stroke Scale (NIHSS) (Table 1), as well as the prevalence of fatal outcome.

Table 1. National Institutes of Health Stroke Scale.

NIHSS Score	Stroke Severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke
21–42	Severe stroke

Within 24 hours of hospitalization, regardless of the time of day, a blood sample was taken for HbA1c and plasma cortisol testing. Levels of HbA1c were measured by immunoturbidimetric assay (Olympus) and serum cortisol levels by chemiluminescent immunoassay (Immulite 2000). According to stroke severity and outcome, we assessed serum cortisol levels as well as HbA1c-based glycemic variables. Some of these variables were calculated using mean BG according to HbA1c level, the so-called ADAG (HbA1c **D**erived **A**verage **G**lucose (mmol/L)) = (1.59 x HbA1c (%)) – 2.59:

- Stress hyperglycemia ratio (SHR) = admBG (mmol/L) / ADAG;
- Modified SHR (mSHR) = admBG (mmol/L) / HbA1c;
- Glycemic gap (GG) = admBG (mmol/L) – ADAG.

Exclusion criteria were type 1 DM, chronic use of glucocorticoids, anemic syndrome (Hb<90 g/L), hemotransfusion performed up to 3 months before the current hospitalization, end-stage renal

failure (eGFR<15 mL/min/1.73m2), pregnancy or breastfeeding.

Data analyses were performed with GraphPad Prism 8.3.0. Continuous variables were expressed as the mean ± standard deviation or median with an interquartile range, depending on the normality of the distribution, and categorical variables were described by number of observations (n) and relative frequency (in percentages). According to the normality of the distribution we used Student's t-test or Mann-Whitney U test (for two groups) and One-Way ANOVA or Kruskal-Wallis test (for more than two groups) to compare the sample characteristics, as well as Pearson's (r) or Spearman's (r_s) correlation analyses. ROC curve analysis was performed to compare the potential of different variables to predict development of moderate to severe and severe AIS (NIHSS1>15). Significance was accepted if p<0.05.

RESULTS

Fig. 1 shows the distribution of patients by group according to glycemic status. Of those examined, 13.16% were with SH.

Patient characteristics in the NG, SH, T2DM and ndT2DM groups are presented in Table 2.

We found a significant difference between the groups regarding AIS severity at admission

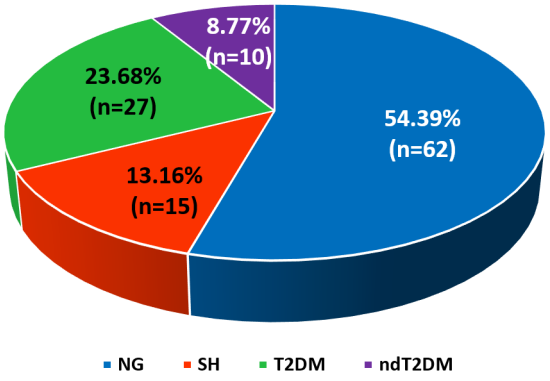


Fig. 1. Distribution of patients by groups.

(p=0.0497; SH/NG p = 0.016; SH/T2DM p=0.304, ns; SH/ndT2DM p=0.036), as well as serum cortisol levels (p=0.013; SH/NG p=0.046; SH/T2DM p=0.025; SH/ndT2DM p=0.097, ns), with the highest values of both indicators in the group with SH. A significant difference was also observed both in terms of admBG (p<0.0001; SH/NG p<0.0001; SH/T2DM p=0.444, ns; SH/ndT2DM p=0.13, ns), and HbA1c-based glycemic variables (SHR, p=0.0001; SH/NG p<0.0001; SH/T2DM p=0.001; SH/ndT2DM p=0.002; mSHR, p<0.0001; SH/NG p<0.0001; SH/T2DM p=0.011; SH/ndT2DM p = 0.009; GG, p=0.0003; SH/NG p=0.0001; SH/T2DM p=0.001; SH/ndT2DM p=0.007). In contrast to admBG, glycemic variables reflecting relative

Table 2. Characteristics of patients with NG, SH, T2DM, and ndT2DM.

Variable	NG (n = 62)	SH (n = 15)	T2DM (n = 27)	ndT2DM (n = 10)	F/H, p Value
Age (years), median (IQR)	74 (65.5–81.25)	75 (74–85)	74 (67–78)	71 (66.75–86.25)	H = 2.434, p = 0.487
NIHSS 1, mean (SD)	10.63 ± 6.12	15.33 ± 8.39	11.33 ± 6.51	8.7 ± 5.21	**F = 2.69, p = 0.0497**
NIHSS 2, median (IQR)	6 (3–10.25)	5 (1.75–14.75)	5 (3–8)	3.5 (3–4.75)	H = 1.6, p = 0.66
Cortisol (nmol/L), mean (SD)	701.7 ± 380.8	1039 ± 668	630.7 ± 305.1	615.9 ± 271.6	**F = 3.761, p = 0.013**
admBG (mmol/L), median (IQR)	6.23 (5.7–6.9)	8.4 (7.9–9.9)	9.4 (7.2–13.4)	8.35 (5.32–19.55)	**H = 43.431, p < 0.0001**
SHR, median (IQR)	0.96 (0.87–1.05)	1.31 (1.14-1.4)	0.95 (0.8–1.28)	0.96 (0.65–1.28)	**H = 20.775, p = 0.0001**
mSHR, median (IQR)	1.1 (0.99–1.18)	1.46 (1.33-1.65)	1.2 (0.98-1.67)	1.18 (0.79–1.77)	**H = 24.566, p < 0.0001**
GG, median (IQR)	-0.26 ((-0.82)-0.3)	1.89 (1.0–2.95)	-0.48 ((-2.2)–2.97)	-0.31 ((-2.82)–4.72)	**H = 18.586, p = 0.0003**

hyperglycemia demonstrated the highest levels specifically in the SH group.

In patients with SH, we established a significantly lower proportion of moderate AIS (score 5–15) (SH/NG p=0.017; SH/T2DM p=0.027; SH/ndT2DM p=0.011), as well as a higher proportion of moderate-to-severe and severe AIS (score 16–42) (SH/NG p=0.005; SH/T2DM p=0.016; SH/ndT2DM p=0.014) (Fig. 2).

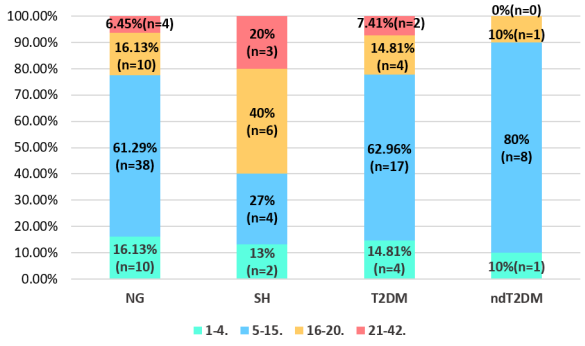
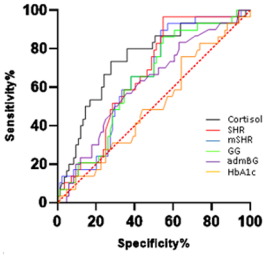


Fig. 2. Distribution of AIS severity at admission (NIHSS1) by groups.

Analyzing the indicators according to AIS severity at admission (Table 3), a tendency for their progressive increase was found with the severity of stroke. We observed a significant difference in terms of NIHSS2 (p<0.0001), cortisol (p=0.001), and glycemic variables (SHR, p=0.011; mSHR, p=0.014; GG, p=0.046), but not in admBG (p=0.19, ns).

Additionally, both NIHSS2 (r_s=0.916, p<0.0001) and cortisol (r=0.391, p<0.0001), as well as glycemic variables (SHR, r_s = 0.222, p=0.018; mSHR, r_s=0.232, p=0.014; GG, r_s=0.197, p=0.037), but not admBG (r_s=0.155, p=0.098, ns), showed a positive association with AIS severity at admission. We established a direct relationship between glycemic indicators and the level of cortisol, stronger for glycemic variables (SHR, r_s=0.301, p=0.001; mSHR, r_s=0.272, p = 0.004; GG, r_s = 0.288, p = 0.002) compared to admBG (r_s=0.218, p=0.02).

The ROC analysis performed demonstrated the greatest area under the curve (AUC) for cortisol, followed by glycemic variables, in relation to the development of moderate-to-severe and severe AIS (NIHSS1 >15) compared to admBG and chronic glycemic control (HbA1c) (Fig. 3).



	AUC	95%CI	p value
Cortisol	0.74	0.634–0.8459	**0.0001**
SHR	0.6521	0.5459–0.7583	**0.0149**
mSHR	0.6646	0.5611–0.7681	**0.0084**
GG	0.6357	0.5258–0.7455	**0.0298**
admBG	0.6187	0.5040–0.7333	0.0544
HbA1c	0.5025	0.3823–0.6226	0.9685

Fig. 3. ROC analysis of cortisol, glycemic variables, admission BG and chronic glycemic control (HbA1c) for the development of moderate to severe and severe AIS (NIHSS1 > 15).

Table 3. Indicators according to AIS severity at admission (NIHSS1).

Variable	1–4 (n = 17)	5–15 (n = 67)	16–20 (n = 21)	21–42 (n = 9)	F/H, p Value
Age (years), median (IQR)	74 (63–77)	75 (67–81)	75 (70.5–85)	82 (71.5–85.5)	H = 4.798, p = 0.187
NIHSS 2, median (IQR)	2 (1–2.75)	5 (4-9)	13 (6–15)	16 (13–25)	**H = 44.259, p < 0.0001**
Cortisol (nmol/L), median (IQR)	443.9 (323.3–636.1)	594.9 (424.2–772)	777.9 (624.4–1091)	1055 (759.1–1224)	**H = 17.603, p = 0.001**
admBG (mmol/L), median (IQR)	6.7 (5.45–8.45)	6.8 (5.8–7.9)	7.5 (6.15–9.0)	8.6 (6.6–15.05)	H = 4.765, p = 0.19
SHR, mean (SD)	0.98 ± 0.27	1.02 ± 0.34	1.1 ± 0.2	1.42 ± 0.69	**F = 3.879, p = 0.011**
mSHR, mean (SD)	1.13 ± 0.32	1.2 ± 0.41	1.28 ± 0.23	1.66 ± 0.8	**F = 3.702, p = 0.014**
GG, mean (SD)	-0.15 ± 1.96	0.31 ± 2.99	0.55 ± 1.57	3.04 ± 4.85	**F = 2.757, p = 0.046**

Fatal endpoint was found in 28 patients—19.35%, 53.33%, 22.22%, and 20% in the NG, SH, T2DM, and ndT2DM groups respectively, with the proportion of deceased being significantly higher in the SH group compared to NG (p=0.008) and T2DM (p=0.043). Table 4 presents patient characteristics according to stroke outcome.

Table 4. Characteristics of patients with fatal and favorable outcome.

Variable	Survivors (n = 86)	Non-Survivors (n = 28)	t/U, p Value
Age (years), mean (SD)	71.74 ± 11.34	78.18 ± 7.57	**t = 2.801, p = 0.006**
NIHSS 1, mean (SD)	9.72 ± 6.31	15.93 ± 5.31	**t = 4.69, p < 0.0001**
Cortisol (nmol/L), mean (SD)	610.5 ± 284.8	1060 ± 572.1	**t = 5.494, p < 0.0001**
admBG (mmol/L), median (IQR)	6.75 (5.7–8.07)	7.45 (6.61–9.35)	U = 966, p = 0.118
SHR, median (IQR)	0.99 (0.85–1.17)	1.12 (0.92–1.3)	U = 949, p = 0.11
mSHR, median (IQR)	1.14 (0.99–1.33)	1.31 (1.09–1.5)	U = 931.5, p = 0.086
GG, median (IQR)	-0.07 ((-1.06)–1.06)	0.89 ((-0.58)–2.14)	U = 974, p = 0.152
mean BG (mmol/L), mean (SD)	6.83 ± 2.31	7.98 ± 2.11	**t = 2.312, p = 0.023**

We found that patients with a fatal outcome were significantly older than survivors (total sample, p=0.006; NG, p=0.36, ns; SH, p=0.012; T2DM, p=0.149, ns; ndT2DM, p=0.117, ns), presented with significantly more severe AIS (total sample, p<0.0001; NG, p=0.011; SH, p=0.755, ns; T2DM, p=0.001; ndT-2DM, p=0.007), corresponding to significantly higher serum cortisol levels (total sample, p<0.0001; NG, p=0.001; SH, p=0.047; T2DM, p=0.072, ns; ndT-2DM, p=0.216, ns). However, we did not observe a significant difference in terms of admBG, as well as glycemic variables. On the other hand, the calculated mean fasting morning BG (mean BG) during the first three days of hospitalization demonstrated significantly higher values in patients with an unfavorable outcome compared to survivors in the total sample, as well as in the NG and SH groups (total sample, p = 0.023; NG, p = 0.004; SH, p = 0.004; T2DM, p=0.104, ns; ndT2DM, p=0.782, ns).

Correlation analysis found a moderately strong association between fatal outcome on the one hand and AIS severity (r_s=0.441, p<0.0001), cortisol level (r_s=0.39, p<0.0001), and mean BG (r_s=0.329, p=0.0004) on the other.

DISCUSSION

Ischemic stroke, as an acute and life-threatening condition, is often accompanied by SH (15,16), which according to various publications affects between 8% and 35% of this patient population (15). It is generally accepted to be more common in individuals with more severe stroke (15), although not all researchers find such an association (16).

In our study, we observed a similar distribution of SH in AIS, which is consistent with published data. The SH group demonstrated the greatest AIS severity at admission, accompanied by the highest serum cortisol levels, with a significant difference in both indicators compared to the NG control group. In contrast to admBG, HbA1c-based glycemic variables also showed the highest values in patients with SH, which corresponded to cortisol levels and the severity of AIS. Additionally, we found that both cortisol and glycemic variables, but not admBG, positively correlated with AIS severity at admission.

Cortisol levels are known to be elevated in the acute phase of stroke, due to activation of the hypothalamic-pituitary-adrenal axis in response to stress. The positive association of cortisol with the severity of AIS confirms that its levels reflect the severity of stress response. The corresponding values of the HbA1c-based glycemic variables lead us to conclude that, excluding the influence of background glycemia, they are better determinants of stress response than admBG. This statement is also supported by the results obtained from the ROC analysis.

We found significantly higher mortality prevalence in the SH group compared to those with NG and T2DM, which allows us to speculate that SH is associated with an increased risk of adverse outcome. We did not establish significant difference in glycemic variables of stress response between survivors and deceased though. However, the observed tendency for significantly higher mean morning BG values in patients with fatal outcome could link persistent hyperglycemia to adverse outcome in patients without DM.

Furthermore, in patients with a fatal outcome, we observed significantly more severe AIS, as well as higher cortisol levels. However, it is likely that cortisol not only correlates with stroke severity but is also independently associated with adverse outcome in these patients, as evidenced by data that prolonged exposure to elevated cortisol levels exerts a neurotoxic effect (17). Some (18, 19) but not all studies (20) have found high cortisol levels to be an independent predictor of adverse outcome, including death. A recent study by an Indian team shows that baseline serum cortisol can be considered a marker of severity, short- and long-term prognosis, as well as mortality after AIS (21).

CONCLUSION

In summary, we found that serum cortisol levels could be used to adequately assess the severity of AIS and identify high-risk patients. Additionally, we observed that HbA1c-based glycemic variables provided better evaluation of stress response than absolute BG value, which is consistent with most observations worldwide. Finally, yet importantly, we confirmed that SH was present in patients with more severe stroke, and observed higher mortality in the SH group, but did not establish a direct association of SH with fatal outcome.

ETHICS

Approval from the Research Ethics Committee of Medical University of Varna, decision No.92/02.04.2020, and consent from all participants was obtained.

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