

## POSTION STATEMENT

from ass. Prof. Antoaneta Trifonova Gateva, DMedSci  
Clinic of Endocrinology and Metabolic Diseases,  
UMBAL "Alexandrovska", Department of Internal Medicine, MF, MU- Sofia

about a dissertation

for the award of an educational and scientific degree "doctor" on the topic  
«GLYCEMIA IN ACUTE ISCHEMIC CEREBRAL STROKE – PROGNOSTIC  
SIGNIFICANCE AND RELATIONSHIP WITH METABOLIC AND INFLAMMATORY  
MARKERS »

of Dr. Zhaneta Atanasova Yaneva  
Second Department of Internal Medicine at the Faculty of Medicine,  
MU "Prof. Dr. Paraskev Stoyanov" – Varna

### I. Structure of the dissertation

The presented dissertation work covers 143 standard typewritten pages, is illustrated with 38 tables, 28 figures and 4 schemes and is structured as follows:

1. Literature review – 33 pages
2. Aims and objectives – 1 page
3. Materials and methods – 7 pages
4. Results – 53 pages
5. Discussion – 19 pages
6. Conclusions – 1 page
6. References – 1 page
7. The bibliography contains 285 titles, of which 9 in Cyrillic and 276 in Latin.

The content is presented correctly and in detail. The most frequently used abbreviations are listed. The individual chapters and sub-chapters are properly formatted, which provides clarity and readability of the dissertation.

The structure of the dissertation and the independent participation of the dissertation candidate in its preparation comply with the requirements according to the regulations on the conditions and procedure for acquiring scientific degrees and occupying academic positions at MU-Varna.

## **II. Relevance, significance and practical focus of the topic**

Cerebrovascular diseases occupy a leading place among socially significant diseases due to the high incidence of morbidity, mortality and severe disability associated with acute cerebrovascular accidents. Worldwide, ischemic stroke is among the main causes of mortality and permanent disability, with Bulgaria ranking second in stroke morbidity and mortality.

Acute ischemic stroke, as a stressful condition for the body, is often accompanied by stress hyperglycemia, which can affect the course and outcome of the disease. Modern studies associate stress hyperglycemia with higher mortality and morbidity among critically ill patients, regardless of the reason for hospitalization. Its harmful effect is observed especially in patients without a previous diagnosis of diabetes mellitus. Stress hyperglycemia is thought to be associated with a more severe course of the disease and increased short-term mortality, but it is still unclear whether it is only a marker of the severity of the condition or a direct cause of the adverse outcomes. Unraveling the mechanisms of its occurrence and its adverse effects is of particular interest in view of making therapeutic decisions in emergency settings.

Stress hyperglycemia tends to occur more frequently in patients with severe stroke, with higher blood glucose levels being associated with worse functional outcomes. It may enlarge the ischemic zone, increase the risk of hemorrhagic transformation, and reduce the effectiveness of recanalization after thrombolysis, leading to worse clinical outcome, stroke progression, and higher mortality. In addition, there is evidence of an increased risk of stroke recurrence and cognitive impairment within three months of the incident. Hyperglycemia has several adverse effects that may worsen the prognosis in patients with acute ischemic stroke. It leads to increased lactate formation, tissue acidosis, and direct neurotoxicity. Potential mechanisms by which hyperglycemia damages the brain include changes in cerebral metabolism, decreased



cerebral blood flow, increased cerebral edema due to oxidative stress, and neuroinflammatory processes.

The high incidence of ischemic stroke and the development of stress hyperglycemia in it, as well as the serious adverse consequences of elevated blood sugar in stressful conditions, makes the topic of the dissertation particularly relevant and justifies the search for new markers that support the correct diagnosis and optimal therapeutic options.

### **III. Components of the dissertation**

**The literature review** is purposefully constructed, with emphasis placed on the relevant aspects of the main topic. Stress hyperglycemia, its various definitions, pathogenetic mechanisms and clinical significance are discussed in detail. The various theories related to the possibility that stress hyperglycemia is a manifestation of a more severe course of the underlying disease, that hyperglycemia itself is the cause of more complications from it, or that the critical illness reveals latent insulin resistance and/or impaired beta-cell function, which subsequently identifies patients at risk of subsequently developing diabetes are analyzed. Of particular interest from a practical point of view are the original indices for stress hyperglycemia based on HbA1c-based glycemic variables, since it turns out that relative hyperglycemia is much more closely related to the risk of mortality than absolute hyperglycemia. By eliminating the possible influence of chronic hyperglycemia on acute hyperglycemia, glycemic indices have a greater discriminative power than the absolute value of blood sugar, allowing to distinguish acute fluctuations in CG as a result of critical illness.

The pathogenesis of stress hyperglycemia is next examined, analyzing the role of various counterregulatory hormones and cytokines in its occurrence. Particular attention in the literature review is paid to the mechanism of action of the hypoglycemic effect, which in the past was considered as a useful physiological adaptive response in stress conditions, but on the other hand is associated with a poor prognosis in a wide range of critically ill patients. The severity and duration of hyperglycemia are of great importance for the prognosis of stroke, with moderately elevated blood sugar levels being rather favorable, as they allow increased energy flow to immune cells and the CNS by changing the activity of various glucose transporters in individual tissues, promoting antiapoptotic pathways and favoring angiogenesis, thus protecting against

cell death after ischemia. On the other hand, however, glucose leads to increased expression of inflammatory markers, increased oxidative stress and endothelial dysfunction, which is especially pronounced in acute hyperglycemia due to the lack of adaptation.

It turned out that stress hyperglycemia is common in patients with ischemic stroke regardless of diabetic status and is associated with a worse outcome of the disease, regardless of other risk factors, with its adverse effects being especially pronounced in patients without diabetes mellitus. However, it should be borne in mind that both hyperglycemia and hypoglycemia resulting from treatment and glycemic variability in general can also have adverse effects in critically ill patients, which should be taken into account when setting goals for glycemic control in the early stages of ischemic stroke treatment.

In summary, the aspects of stress hyperglycemia and its relationship with ischemic stroke covered in the literature review represent an adequate justification of the goal and objectives and logically justify the motivation for developing the dissertation topic.

The formulation of **the goal and objectives** is clear and precise and concerns the assessment of the relationship between the level of glycemia and the outcome in patients with acute stroke, as well as the association with metabolic and inflammatory markers. There are five tasks that adequately reflect the set goal.

The section "**Material and Methods**" provides a detailed description of the study design; method of recruiting patients with inclusion and exclusion criteria; indicators studied. The strict selection of the covered contingent according to standardized criteria guarantees the reliability of the results obtained. The methods of the individual clinical and laboratory indicators, as well as the definitions used, are precisely described.

The "**Results**" section contains the individual aspects of the dissertation work and is presented following the logic of the tasks set to achieve the goal. The first stage of the study is a retrospective study covering 555 patients with acute ischemic stroke. It was found that patients with stress hyperglycemia are characterized by higher blood sugar on admission and higher levels of serum creatinine and leukocytes, with blood sugar being significantly higher in patients with moderate non-fatal stroke compared to those



with mild, but there is no additional increase with the severity of the stroke. In patients with higher glycemia (stress hyperglycemia and diabetes mellitus), higher mortality is also found compared to those with normoglycemia, and there is a relationship with serum creatinine and leukocyte count. All this confirms the relationship between blood sugar levels in stroke patients and the severity and prognosis of the disease.

The second stage of the study is cross-sectional and includes 114 patients with acute stroke, and the very high frequency of carbohydrate disorders is striking - diabetes mellitus (known and newly diagnosed), stress hyperglycemia and prediabetes, with only a quarter of the participants included in the study not having any deviations in the glycemic status. In addition, the majority of patients with diabetes mellitus demonstrate poor control - 56%. As expected, a very high frequency of existing cardiovascular risk factors is found in patients affected by ischemic stroke - first of all, arterial hypertension in almost all, followed by dyslipidemia, obesity, heart failure, etc. An interesting fact is that with advancing age, the relative share of women increases, which is probably related to differences in life expectancy between the two sexes.

Similar to the retrospective study, a relationship was found between the severity of stroke and the presence of stress hyperglycemia, with the severity and mortality being highest in the group of stroke survivors, exceeding that in patients with known and newly diagnosed diabetes mellitus. This fact is consistent with the theory that adaptation to high blood sugar levels in patients with diabetes mellitus reduces the harmful effects of hyperglycemia under stress conditions. A particularly interesting part of the study is the monitoring of blood sugar dynamics during hospitalization, taking into account normalization over time in patients with stress hyperglycemia, but not in patients with diabetes. In addition, HbA1c-based glycemic indices as markers of acute stress hyperglycemia also turned out to be higher in the HF group, which suggests that it is not the severity and duration of hyperglycemia, but rather the large variations in blood sugar levels under stress conditions that have an unfavorable prognostic value for the outcome of ischemic stroke. Similar to glycemia, cortisol as a stress hormone, analogous to glycemic indices and severity of acute stroke on admission, is significantly higher in the stress hyperglycemia group compared to the control group with normoglycemia and that with T2DM. A progressive increase in these indicators with increasing stroke severity was also observed.

The studied markers progranulin and TNF- $\alpha$  also turned out to be highest in the stress hyperglycemia group, despite the lack of statistical significance. On the other hand, an



increase in the value of PGRN was found with increasing severity of oMI and vice versa - the highest values of TNF- $\alpha$  were registered in the group with mild oMI and lower ones in patients with higher degrees of stroke severity, with no differences in the two markers depending on mortality.

Particularly valuable from a practical point of view are the presented linear regression analysis for predicting the severity of acute stroke and logistic regression analysis for predicting mortality. They show that the stress hyperglycemia index contributes most to the prediction of the severity of acute stroke, followed by the leukocyte count and serum progranulin, while for the mortality outcome - NIHSS 1, mean blood sugar and serum cortisol, with mean blood glucose having the greatest weight - an increase in meanBG by 1 SD increases the chance of mortality by 1.241 times. The ROC analysis conducted subsequently demonstrated the largest area under the curve for predicting the development of moderate to severe and severe acute stroke for serum cortisol, followed by the various glycemic indices. The optimal threshold values for cortisol and stress hyperglycemia index derived from it are also indicated, above which the risk of developing moderate to severe and severe acute stroke increases significantly. A similar analysis was also conducted for the risk of death, where the largest area under the curve is found for the severity of acute stroke on admission, followed by cortisol, the Neutro/Lympho ratio and the neutrophil count, and the optimal threshold value of NIHSS1, above which the risk of death increases, is determined to be 9.5 points.

The **discussion** is logically structured and examines the results in the context of the literature available to date on the subject. The text demonstrates good knowledge of the problem and insight into the hypotheses set forth in the scientific paper

The **conclusions** are presented separately for the different tasks and specifically and accurately and reflect in a summary the results related to the main and most important aspects of the paper.

The **contributions** are divided into those of an original and confirmatory nature. Most of the contributions are original and contribute to the enrichment of the overall knowledge in the field of the relationship between acute ischemic stroke and stress hyperglycemia.

The **bibliography** covers 285 literary sources and meets the requirements while being sufficiently comprehensive and up-to-date.

The dissertation candidate has 4 **publications** in connection with the dissertation, 1 participation in an international scientific forum and 3 participations in national congresses and symposia, as well as participation in one scientific project.

**CONCLUSION:** *The dissertation work of Dr. Zhaneta Atanasova Yaneva "GLYCEMIA IN ACUTE ISCHEMIC CEREBRAL STROKE – PROGNOSTIC SIGNIFICANCE AND RELATIONSHIP WITH METABOLIC AND INFLAMMATORY MARKERS" is up-to-date and properly structured. The design of the individual studies and the overall structure of the work correspond to the set goals and objectives. The dissertation meets all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation and the Regulations for the Conditions and Procedure for Acquiring Scientific Degrees and Holding Academic Positions at MU-Varna for acquiring the educational and scientific degree "Doctor" in the doctoral program "Endocrinology".*

*I give a positive review and strongly recommend that the members of the esteemed scientific jury vote positively to award the educational and scientific degree "Doctor" to Dr. Janeta Atanasova Yaneva.*

07.04.2025 г.  
Sofia

Signature :  
/A.Gateva/

Заличено на основание чл. 5,  
§1, б. „В“ от Регламент (ЕС)  
2016/679