

STATEMENT

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"Dr. G. Dr. Stransky",
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On dissertation:

**Glycemia in acute ischemic stroke - prognostic significance and relationship
with metabolic and inflammatory markers**

Developed by **Dr. Zhaneta Atanasova Yaneva**

for the award of the educational and scientific degree "**Doctor**"

Scientific supervisor: **Assoc. Prof. Dr. Mila Boyadzhieva**, MD, PhD

Medical University "Prof. Paraskev Stoyanov"

Varna,

Medical Faculty

Second Department of Internal Medicine

1.Information about the procedure:

According to the decision of the Faculty Council of the Faculty of Medicine of MU-Varna with Protocol No. 36/10.03.2025. a procedure for the defense of the educational and scientific degree (OSD) "Doctor" of Dr. Zhaneta Atanasova Yaneva is opened. By order No. R-109-160/14.03.2025 of the Rector of MU-Varna, Prof. Dr. D. Raykov, MD, PhD, MSc, the composition of the Scientific Jury (SJ) for the procedure was determined and the decision of the first absentee meeting of the SJ was to present a statement as an external member for MU-Varna.

The required set of documents, submitted on electronic media, was submitted on time and meet all the requirements of the Academic Staff Development Act in the Republic of Bulgaria (ASDA in RB) (<http://mon.bg>, as of 05.05.2018), the Regulations for its Implementation (RI ASDA) and the Regulations for the Conditions and Procedure for the Acquisition of Scientific Degrees and Academic Positions at MU - Varna.

2.Professional data about the candidate:

Dr. Zhaneta Atanasova Yaneva was born in 1988 and completed her secondary education at the Ist Language High School, with excellent grades. She is a Master of Medicine, graduated from the Medical University - MU "Prof. Paraskev Stoyanov" Varna, Faculty of Medicine in 2013 as the top of her class. Since 2014 started working at the Endocrinology Clinic at the University Hospital "St. Marina" as a doctor, later as a specializant-doctor and currently as a specialist doctor - endocrinologist at the same Clinic. She was a part-time assistant professor at the Endocrinology Clinic in the period 2016-2017, and from 2017 until now she is a full-time assistant professor in Endocrinology, carrying out medical, teaching and research activities at the Medical University of Varna. She is enrolled as a full-time doctoral student at the Second Department of Internal Medicine in the Doctoral Program: "Endocrinology".

She has a completed Master's degree in Health Management, graduated in 2022.

The publication activity of Dr. Janeta Atanasova Yaneva to date is represented by **11** total **publications** on various topics, of which **4** publications in the WoS and Scopus databases, **7** full-text scientific articles published in the national reference list and **one** co-authorship in a textbook on Internal Medicine.

Dr. Yaneva's scientific activity includes **8 scientific reports** on various topics and communications with printed summaries, of which **4** were presented in English at international and **4** at national scientific forums.

She has participated in **16** foreign training seminars and conferences.

She has participated in **two scientific projects related to the topic of the dissertation.**

Dr. Zhaneta Atanasova Yaneva has excellent written and spoken English (B2) and German (B2) languages and Russian at a very good level (B1).

3. Relevance of the problem developed in the dissertation work

The chosen topic for scientific development by Dr. Zhaneta Atanasova Yaneva is aimed at studying the role and prognostic significance of glycemia, with the participation of specific metabolic and inflammatory markers, in the conditions of acute ischemic stroke (aIS). This problem is of sustained scientific interest in the world and national literature and is refracted through the prism of the extremely high incidence of aISS in Bulgaria, which ranks it in second place in the world. In-depth study of changes in glycemia, under stressful conditions (SH) and of the associated elevated biomolecules of various origins, characteristic of aISS, is of essential importance for the course, prognosis, outcome of the disease, as well as the manifestation of adverse long-term consequences. These underlying metabolic, hormonal and proinflammatory pathophysiological mechanisms are poorly studied in Bulgaria and partly in the world. This argumentation defines the scientific work of Dr. Yaneva as timely, relevant and significant.

4. Structure of the work

The presented dissertation work is structured according to generally accepted criteria and requirements and contains all necessary sections. The dissertation work contains a total of 143 pages, is illustrated with 38 tables, 283 figures and 4 schemes. It is written in clear, precise and easy-to-read professional and grammatically correct Bulgarian language.

The bibliography contains 285 literary sources, of which 9 are in Cyrillic and 276 in Latin.

The layout of the dissertation as a whole, as well as the attached abstract, is in full compliance with the requirements of the Regulations of MU-Varna.

5. Essence of the dissertation

5.1 The title is clearly and precisely formulated and emphasizes in a summarized form the scientific significance of the problem.

5.2 The Literature Review describes the unfavorable role of variable blood glucose levels in conditions of acute stress, such as acute ISS. Particularly valuable are the explanations of the role of relative hyperglycemia and their relationship with mortality in hospitalized patients, as well as the description of HbA1-c based glycemic variables. The significance of various metabolic,

inflammatory and hormonal factors influencing the glycemic status, and thus the damaged brain tissue, is presented in detail. The role of some neuroactive steroids is described, with cortisol being examined in detail as a simultaneous cause of SH and brain neurotoxic damage and as the most promising prognostic indicator in aMI. The significance of some inflammatory biomolecules is monitored as a manifestation of a complex interaction between the immune system and the CNS in the context of aMI. Progranulin (PGRN) is presented as a biomarker for assessing the severity of neuro-tissue destruction and its presumed role as an adipokine associated with the occurrence of pathological insulin resistance (IR) and contributing to the pathogenesis of type 2 diabetes mellitus (T2DM). In summary, the statement that the study of these indicators would be an extremely useful assessment of the functional outcome of the disease is required.

5.3 The aim of the dissertation is to search for a relationship between the prognostic significance of the level of glycemia and the outcome of aMI, as well as an association with metabolic and inflammatory markers. It corresponds to the title and capabilities of the study.

By fulfilling the **five specific tasks set**, the formulated goal is fully met.

5.4 Material and methods: A two-stage study was conducted on a cohort of hospitalized patients with acute IS. The first stage of the study was retrospective, with data selected from the electronic patient registration system for a total of 555 participants in the time period 2016-2017.

The second stage of the study covers the time period 2021-2023. The scientific study, by its design, is cross-sectional, covering 114 selected patients with aIS, followed up in the first 24 hours of hospitalization. The selection of patients is based on well-chosen inclusion and exclusion criteria.

All ethical requirements for conducting a scientific study have been met.

Scoring systems for assessing the severity of stroke of the National Institutes of Health and for assessing the degree of disability after AMI upon dehospitalization using the modified Rankin scale were used.

The characteristics of the anthropometric, clinical-laboratory and hormonal studies performed are presented. The methods for testing HbA1c, cortisol, insulin, PGRN and tumor necrosis factor alpha are very precisely described. The formulas by which HbA1c-based glycemic indices were calculated, as indicators of stress hyperglycemia (SH), are presented.

The reliability of the obtained results has been proven by using modern methods of statistical processing, namely: Descriptive statistics, Hypothesis testing methods, Correlation analysis and Multiple regression analysis. A significant part of the data was processed with GraphPad Prism 7.03 (for stage I) and 8.3.0 (for stage II) for Windows, and another part of the data - using IBM SPSS Statistics Version 26.0 for Windows 10.

5.5 Results and discussion: For the purposes of the first stage of the study, the studied population was divided into three subgroups: without known T2DM, with SH and with known T2DM. The patients were comparable in age and all other baseline parameters, differing only in blood glucose levels at admission, leukocyte count and serum creatinine. For the purposes of the second part of the study, the patients were divided into four subgroups according to blood glucose levels and HbA1c values at admission: normoglycemia, SH, known T2DM, newly diagnosed T2DM and a subgroup of normoglycemic patients – with prediabetes.

It is established that glycemic disorders are widespread in patients with aIS, which proves the existence of an association between glycemic status and the occurrence of aIS and requires careful examination, monitoring and treatment of dysglycemia.

It is proven that HbA1c-based glycemic variables are better determinants of aIS compared to the absolute value of blood glucose.

When examining the relationship between changes in glycemia and the severity of aIS, it is found that there are differences in the groups with T2DM and aIS between surviving and deceased patients, with aIS being observed more often in patients with more severe aIS. This result proves the unfavorable role of aIS in the poor functional outcome of aIS with a fatal outcome. It is also confirmed the unfavorable role of persistent hyperglycemia, regardless of the diabetic status of the patients, in the occurrence of a lethal outcome of aIS.

The analysis of the estimated value of cortisol levels during aIS proves that high cortisol levels are independently associated with poor functional outcome and fatal outcome from aIS.

Cortisol levels among deceased patients were significantly higher, which proves its associativity with aIS severity and lethal outcome.

The regression analysis performed, which distinguishes aIS severity at hospitalization, cortisol and mean fasting blood sugar as indicators that statistically significantly predict fatal outcome, also proves the unfavorable role of cortisol, confirming that its levels can be an adequate measure of the stress reaction in aIS.

Tracking changes in proinflammatory biomarkers confirms the role of the inflammatory status, proven by high values of the Neutro/Lympho ratio, for the occurrence of aIS, for its more severe form of manifestation and shows an independent relationship with the unfavorable outcome of the disease, in the direction of fatal outcome.

The assumption that PGRN is involved in the regulation of glucose metabolism and its levels are increased in patients with T2DM has not been confirmed. A single correlation of PGRN with the severity of aIS at discharge was found. This gives grounds to argue that PGRN can be accepted as

an assessment indicator of the severity of aIS, but its prognostic role in determining the outcome of the disease remains uncertain.

5.6 Conclusions: In accordance with the results obtained, as well as the data from the literature review, 9 conclusions have been formulated, each of which is of exceptional importance.

5.6 Contributions and significance of the work for science and practice:

The self-assessment of Dr. Janeta Atanasova Yaneva is expressed in outlining a total of 6 contributions. **Three** of the formulated contributions are original in nature, and the remaining **three** contributions are confirmatory in nature. 6.

Publications on the topic of the dissertation:

A list of 4 publications on the topic of the dissertation is presented, of which **one** original article was published in an international journal in English and **three** (one original article and two reviews) were published in journals in Bulgarian.

Dr. Janeta Yaneva has presented parts of her work in **four** scientific forums, **three** in Bulgaria with international participation and one foreign **one**.

Conclusion: The dissertation work of **Dr. Janeta Atanasova Yaneva on the topic "Glycemia in acute ischemic cerebral insult - prognostic significance and relationship with metabolic and inflammatory markers"** is a thorough and complete study, the first of its kind in Bulgaria, which is based on an extensive literature analysis and presents an original research approach. It develops a not sufficiently well-studied scientific and socially significant problem, connecting changes in glycemia during the course of aIS. The set goal, tasks and achieved results convincingly prove the adverse impact of stress hyperglycemia in patients without previously diagnosed T2DM, as well as in those with good control, as a cause of a higher incidence of increased morbidity and mortality among critically ill aIS patients and highlight the advantage of HbA1-s based glycemic indices as markers for assessing the severity and prognosis of the disease. The adverse role of hypercortisolemia in the first 24 hours, the severity and fatal outcome of the stroke have been proven.

The most important results of the dissertation work have been published in renowned highly specialized national and international journals, which is a real assessment of its value.

The volume and quality of the scientific work, the original results, the in-depth analyses, the conclusions made and the contributions presented fully meet the requirements for developing a dissertation work for acquiring the educational and scientific degree "**Doctor**".

The dissertation and the abstract thus presented are in compliance with the formal requirements of the Law on the Development of the Academic Staff of the Medical University

of Varna, the Regulations on the Development of the Academic Staff of the Medical University of Varna.

Given this, I confidently give my positive assessment and vote "YES" the award of the educational and scientific degree "**Doctor**" in medicine to **Dr. Janeta Atanasova Yaneva** in the professional field "**Medicine**" in the scientific specialty "**Endocrinology**".

Pleven, 04.04.2025

Assoc. Prof. Dr. Katya Todorova MD, PhD

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