

To  
The Chair of the Scientific Jury  
Pursuant to Order No. R-109-171 / 28.03.2025  
of the Rector of the Medical University  
"Prof. Dr. Paraskev Stoyanov" – Varna  
Prof. Dr. Dimitar Raikov, DSc

## **Review**

by **Prof. Dr. Maria Mitkova Orbetzova, PhD**

Scientific specialty: Endocrinology and Metabolic Diseases  
Head, Department of Endocrinology and Metabolic Diseases, Faculty of Medicine,  
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Executive Director, University Specialized Hospital for Active Treatment in Endocrinology  
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of the dissertation submitted in application for the educational and scientific degree "Doctor"  
by **Dr. Ivan Georgiev Enev**, PhD student in full-time training  
entitled: **"Micronutrient Supplementation in Patients with Type II Diabetes Mellitus  
Treated with Metformin"**  
within the doctoral program: **"Hygiene (incl. Occupational, Environmental, School,  
Radiation Hygiene, etc.)"**  
under the scientific supervision of **Prof. Dr. Darina Naydenova Hristova, PhD**

### **I. Procedural Requirements**

I was appointed as an external member of the Scientific Jury by Order No. R-109-171 / 28.03.2025 of the Rector of the Medical University – Varna, regarding the defense of the dissertation submitted by Dr. Ivan Georgiev Enev for the award of the educational and scientific degree "Doctor" in higher education field 7. *Healthcare and Sports*, professional field 7.1. *Medicine*, and scientific specialty *Hygiene* (including Nutrition and Dietetics), for the needs of the Department of Hygiene and Epidemiology, Faculty of Public Health, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

As a full-time PhD student, Dr. Ivan Georgiev Enev has submitted all required materials for review in accordance with the Regulations for obtaining the educational and scientific degree "Doctor", including: the dissertation manuscript, abstract, curriculum vitae, administrative documentation, and relevant publications.

### **II. Biographical Data**

Dr. Ivan Georgiev Enev completed his secondary education at the High School of Foreign Languages "Henri Barbusse" in Vratsa (1979–1984). He graduated in Medicine in 1992 from the Higher Medical Institute – Sofia.

Between 1992 and 1998, he specialized in Pediatrics at the Medical University – Sofia and successfully obtained the specialty in Pediatrics. From 2002 to 2005, he undertook further specialization in General Medicine. Additionally, between 1993 and 1995, he pursued training in homeopathy at the London College of Classical Homeopathy, obtaining the relevant certificate. From 1995 to 1999, he completed a clinical homeopathy specialization at the Medical University – Sofia and CEDH – France, earning a diploma of competence in Clinical Homeopathy.

Dr. Enev initially worked as a pediatrician at the Regional Hospital – Vratsa (1998–2000), and subsequently as a general practitioner and pediatrician in ambulatory care from 2000 to 2020.

He has been a lecturer in Clinical Homeopathy since 1997 and has served as a pedagogical coordinator since 2011.

In 2019, Dr. Enev was admitted as a full-time PhD student at the Medical University – Varna, specializing in *Hygiene* (including Nutrition and Dietetics). Since 2022, he has been a member of the Management Board of the National Association for Practical Dietetics and Integrative Medicine.

He is fluent in Russian, English, and French.

Dr. Enev is a member of the following scientific and professional organizations:

- Bulgarian Medical Association (BMA)
- National Association of General Practitioners in Bulgaria
- Bulgarian Pediatric Association
- Bulgarian Medical Homeopathic Organization – Chair (2001–2002);  
Chief Scientific Secretary (2002–2024)

### **III. Relevance of the Topic**

The dissertation is dedicated to micronutrient supplementation in patients with type 2 diabetes (T2D). The topic is highly relevant, considering the global pandemic of diabetes—particularly type 2—and the widespread use of metformin as a first-line treatment for a large proportion of patients, despite the emergence of newer therapies focused on cardiovascular risk. It is well known that while metformin has relatively few significant side effects, it is associated with certain nutritional deficiencies—most notably vitamin B12, but also folic acid and other micronutrients.

Given the long-term treatment and common comorbidities among individuals with T2D, maintaining optimal nutritional status is essential for overall health, glycemic control, the prevention of diabetes-related complications, and quality of life. Investigating micronutrient deficiencies and the effects of appropriate supplementation in this population holds important clinical significance in forming an effective therapeutic approach.

Although there are some international publications on the topic addressed by the dissertation, targeted studies on micronutrient imbalances based on a national population sample and within the framework of our healthcare system are lacking. The results obtained from this research could be implemented in clinical practice and serve as a basis for recommendations regarding the routine monitoring and supplementation of certain trace elements and vitamins in people with type 2 diabetes in general, and particularly those treated with metformin.

Based on the above, I evaluate the topic, as well as the general idea of the dissertation, as timely and of clear theoretical and practical significance.

### **IV. Structure of the Dissertation; Aim and Objectives; Materials and Methods; Results, Discussion, Conclusions**

The dissertation consists of 163 standard typewritten pages and is appropriately structured in terms of its main components. The material is illustrated with 15 figures, 30 tables, and 9 appendices.

*The literature review* (52 pages) is focused and examines all antidiabetic medications in the context of their use according to modern consensus guidelines, with a particular emphasis on metformin. The role of several micronutrients in carbohydrate metabolism and the progression of hyperglycemia in diabetes mellitus (DM) is discussed. This includes B group vitamins – thiamine (vit. B1), riboflavin (vit. B2), niacin (vit. B3), pantothenic acid (vit. B5), pyridoxine (vit. B6), biotin (vit. B7), folic acid (vit. B9), and cobalamin (vit. B12) – which are known not to be stored in the body and thus must be regularly supplied through the diet. Deficiency of B vitamins is one of many factors that may contribute to the development of diabetic neuropathy. The review also systematically covers the fat-soluble vitamins – vitamins A, D, E, and K – providing valuable and up-to-date data on their effects on beta-cell function and pancreatic activity, as well as mechanisms by which they influence various metabolic processes. This also applies to different electrolytes – sodium, potassium, calcium, phosphorus,

magnesium, chromium, iron – and their typical imbalances in diabetes, which are presented in detail.

A key component of the review is the limited but existing data on current knowledge and recommendations regarding micronutrient supplementation in type 2 diabetes. At present, there is no globally accepted model for supplementation in individuals with type 2 diabetes concerning the diagnosis of potential micronutrient deficiencies or the type of supplementation – whether monocomponent or multicomponent formulations. It is emphasized that the personal assessment of nutritional and health status should be the basis for developing an appropriate supplementation approach in clinical practice.

*In summary*, the review is professionally structured, scientifically substantiated, and up to date, meeting the requirements for a dissertation. It provides valuable information and guidance for clinical practice in its own right.

The *aim of the dissertation* is to determine the micronutrient status in individuals with type 2 diabetes on metformin monotherapy, by assessing their dietary habits and the need for supplementation. The aim is clearly defined, and the approach to the topic is in-depth, combining fundamental and clinically relevant aspects in a balanced manner.

The *objectives* are formulated as seven in total, logically aligned with the main aim, and cover all the key aspects necessary to achieve it – from identifying deficiencies and analyzing their relationship with clinical parameters, to evaluating the effect of supplementation and developing practical recommendations for clinical practice. A particular strength of the formulation is the integration of an interdisciplinary approach, including medical nutrition science, clinical practice, and health education. The overall research concept demonstrates systematic thinking and scientific justification, offering the potential for a practical contribution to the management of people with type 2 diabetes treated with metformin.

The approaches used in *designing* the clinical study, as well as the *materials and methods*, are appropriate for the aim and the stated objectives.

The dissertation presents a prospective, open-label study conducted from March 20, 2021, to March 26, 2024, involving outpatients diagnosed with type 2 diabetes, treated with metformin and following a dietary regimen. The study was carried out during routine quarterly follow-up visits at a general medical practice within DCC 2 – Vratsa. Out of a total of 190 patients with type 2 diabetes in the investigator's outpatient practice, 48 individuals meeting clearly defined inclusion criteria were selected. Throughout the study, a total of 1,410 follow-up visits were conducted for all patients with type 2 diabetes, with 172 individual visits performed for the 48 participants in the active sample. The methodology aligns with real-world clinical practice, ensures traceability of observations, and enables the integration of clinical, laboratory, and behavioral (dietary) data into a unified analytical model.

The design includes a pre- and post-treatment comparative model, where participants serve as their own controls. During the regular follow-up visits, various metabolic and biochemical indicators are measured, including micronutrient levels and glycated hemoglobin. The study employs a serial approach, where patients undergo sequential visits during which treatment, nutritional status, and laboratory tests are assessed. A food diary and a food frequency questionnaire were developed and completed by the study participants after receiving training.

*Statistical analysis* was conducted at a high contemporary level using Jamovi software, version 2.6.

The presentation of the *results* spans 43 pages and is well-structured and well-illustrated. The data from the study show that vitamin D deficiency is observed in 58% of the participants. However, only half of these individuals respond to the standard dose of 2000 IU of vitamin D3—some patients require higher doses (5000 IU) to achieve normal levels. Among the participants with type 2 diabetes treated with metformin, 68.75% have a vitamin B12 deficiency, which may be linked to the long-term use of this medication, known to impair vitamin B12 absorption. Oral supplementation with 1000 µg of vitamin B12 is effective in only half of the patients; for the rest, intramuscular administration is necessary due to the difficulty

in restoring adequate levels. Folate deficiency was identified in 16.67% of the subjects, but treatment with 5 mg daily successfully corrected the deficiency in 75% of them, indicating that standard supplementation is generally effective. Magnesium deficiency was found in 66.67% of the patients, and correction required a high dose of magnesium orotate (3 tablets per day).

The doctoral candidate also identified a low level of awareness regarding the importance of therapeutic nutrition and the micronutrient content of foods in maintaining a healthy lifestyle. In response, they developed clinically applicable tools including: a questionnaire assessing nutritional awareness, a dietary habits survey, and a simple nutritional guide for healthy eating in type 2 diabetes, including a checklist.

The **discussion section** is logically constructed and follows the structure of the results presentation. It reflects a strong understanding of the topic, insight into the underlying concepts, and a focused analysis of the indicators, with the ability to interpret them and compare findings with the literature.

The **final conclusions** are presented in 10 points, offering a concise summary of the key findings in relation to the main aspects of the dissertation. Overall, the conclusions indicate that micronutrient deficiencies are common in patients with type 2 diabetes on metformin monotherapy, highlighting the need for targeted and precise monitoring and individualized supplementation to prevent complications.

The **bibliography** is comprehensive and meets academic standards—it includes 315 sources, of which 4 are in Cyrillic and 311 in Latin script.

## V. Contributions

With the results of this pioneering dissertation—first of its kind in our country—the author makes a significant contribution to expanding the overall knowledge on micronutrient status in an unselected sample of individuals with type 2 diabetes (T2D) on metformin monotherapy in outpatient care, supporting the conclusions with reliable evidence. The data demonstrate a high prevalence of deficiencies in vitamin D (58.3%), vitamin B12 (68.75%), vitamin B9 (16.67%), and magnesium (66.67%), which substantiates the need for active screening and monitoring of these parameters in clinical practice. This constitutes a contribution of original character, as no similar study has been conducted in Bulgaria to date. Moreover, the research identified substantial differences in the prevalence of micronutrient deficiencies compared to studies conducted in other populations. For example, this study reports a twofold higher prevalence of vitamin B9 and magnesium deficiencies, and a several-fold higher prevalence of vitamin B12 deficiency among individuals with T2D on metformin therapy, compared to data in the existing literature.

The findings have both scientific-theoretical and clinical-applied significance, particularly the observation that once deficiencies in vitamins B9, B12, and magnesium are present, nutritional intervention alone (i.e., increased intake of specific food groups) is insufficient, and adequate supplementation is required. Moreover, in a significant portion of the patients, higher-than-standard doses are necessary to correct the deficiencies, underscoring the importance of a personalized approach beyond standard protocols.

Of notable practical importance are the pioneering results and conclusions that have led to the development of recommendations for the diagnosis, monitoring, and appropriate supplementation of micronutrient deficiencies in individuals with T2D, particularly those on long-term metformin therapy. The study proposes specific guidelines for routine assessment of micronutrient status during follow-up visits, including the use of MCV as an accessible laboratory marker for probable vitamin B12 deficiency. In addition, structural changes are proposed, such as the updating of the laboratory test package covered by the National Health Insurance Fund (NHIF) to include vitamin D, B12, and B9 at least once a year for patients on metformin.

Equally valuable are the proposed tools for implementation in outpatient care, such as: a questionnaire assessing patient awareness of dietary nutrition, a dietary habits survey, and

educational materials for physicians and a self-monitoring nutrition guide for patients, all tailored to the realities of outpatient care in Bulgaria.

*In summary*, this dissertation highlights one of the relatively underexplored yet clinically important aspects of modern type 2 diabetes management: micronutrient status and the role of supplementation during metformin therapy. The author rightly emphasizes that medical nutrition therapy for T2D should take into account not only macronutrient composition, but also the adequate intake of vitamins and trace elements involved in numerous metabolic processes disrupted in this chronic disease. In Bulgaria, systematic and representative studies on nutrient deficiencies in people with type 2 diabetes—especially those treated with metformin, a drug known to induce vitamin B12 and other B-vitamin deficiencies—are lacking. In this context, the current work stands out for its high degree of relevance, scientific value, and potential for practical contribution to the fields of clinical diabetology and medical nutrition.

I accept Dr. Ivan Enev's self-assessment of the contributions of this dissertation as having both original and confirmatory-applied character.

## VI. Publication Activity

In relation to the dissertation, Dr. Ivan Enev cites three publications as first author in Bulgarian scientific journals and four participations in national scientific forums (being first author in three of them). *I recommend the publication activity to be further expanded based on the results obtained in the dissertation.*

## VII. Abstract

The submitted abstract is properly structured, includes all required components, and reflects the essential aspects of the dissertation. It complies with the content and formatting requirements of the Regulations of the Medical University of Varna.

## VIII. Conclusion

Based on the above, I consider that the dissertation of Dr. Ivan Georgiev Enev represents a timely and necessary contribution to the fields of diabetology and nutrition science, with clear potential for direct application in clinical practice. The work constitutes an original scientific research study with clearly defined and accomplished objectives and tasks, in full compliance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), its Implementing Rules, as well as the Regulations of the Medical University – Varna for the acquisition of the educational and scientific degree "Doctor" under the doctoral program *Hygiene (including Nutrition and Dietetics)*.

I hereby issue a **positive review** and strongly recommend to the esteemed members of the Scientific Jury to cast a **favorable vote** for the successful completion of the procedure for awarding the doctoral degree to Dr. Ivan Georgiev Enev, based on his submitted dissertation.

Dr. Enev is a physician with long-standing clinical experience and professional expertise in general medicine, pediatrics, clinical homeopathy, and dietetics, which significantly contributes to the practical implementation of his scientific work.

May 20, 2025  
Sofia

Signature: .

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