

OPINION

By Prof. Dr. Ludmila Borislavova Ivanova, MD

Faculty of Medicine, Sofia University "St. Kliment Ohridski" - Sofia

on the PhD thesis: "Micronutrient supplementation in patients with type II diabetes treated with metformin"

for awarding the educational and scientific degree "Doctor"

field of higher education: 7. Health and Sports

professional field: 7.1. Medicine, scientific specialty "Hygiene" (incl. Nutrition and Dietetics")

PhD Candidate Ivan Georgiev Enev, MD

Scientific supervisor: Prof. Darina Naydenova Hristova, MD, PhD, Department of Hygiene and Epidemiology, Medical University -Varna

The opinion has been prepared according to Order No. R-109-171/ 28.03.2025 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, and on the Protocol No. 1 /10.04.2025, in compliance with the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations on the Conditions and Procedure for Acquiring Scientific Degrees and Academic Positions at MU-Varna.

1. General information about the PhD candidate

The PhD candidate Ivan Georgiev Enev, MD is a Master of Medicine, graduated in Medicine from the Higher Medical University – Sofia (diploma No. 010630/13.10.92). He is a specialist in Pediatrics (Certificate of Acquired Specialty, 1998), Clinical Homeopathy (Diploma, 1999). Specialization of General Medicine (2002-2005). Dr. Enev is a General Practitioner and Pediatrician.

From 2011 to the present, he is a Coordinator of Pedagogical Activities and a lecturer in clinical homeopathy at the Center for Clinical Homeopathy.). Since 2019, he has been a specialist in "Nutrition and Dietetics" and a doctoral student at the Department of "Hygiene" at Medical University -Varna.

His scientific activities includes one monograph, more than 20 scientific articles and scientific reports and co-authoring in two textbooks. He is a member of a number of professional organizations - Bulgarian Medical Union (BLS), National Association of General

Practitioners in Bulgaria (NSOPLB), Bulgarian Pediatric Association (BPA) and Bulgarian Medical Homeopathic Organization (BMHO).

He is actively involved in social and volunteer work in the field of healthcare and preventive medicine. Dr. Enev has good language skills in Russian, French, and English.

2. Relevance of the dissertation topic

The subject of the dissertation is particularly relevant due to the widespread prevalence and high incidence rate of type 2 diabetes mellitus (T2DM), which is increasingly "rejuvenating". Not only is the trend of increasing the number of people with diabetes worrisome, but also the large proportion of undiagnosed cases in which treatment is delayed. Unidentified and neglected micronutrient deficiencies are another serious problem related to the development and treatment of Type 2 diabetes. Micronutrient deficiencies are a common problem among the general population not only in developing countries, but also in countries with a high economic status of the population. This is a result of deficient and unbalanced nutrition associated with inadequate dietary intake, consumption of processed foods and impaired absorption and metabolism in some disease states. The relationship between micronutrient deficiencies and diabetes is two-way and raises several questions. On the one hand, existing deficiencies can affect glucose metabolism and insulin signaling pathways, potentially leading to the onset and development of type 2 diabetes (T2D), and on the other hand, individuals with diagnosed diabetes are at high risk of developing micronutrient deficiencies.

Metformin is a preferred drug for the treatment of patients with type 2 diabetes with a good effect on glycemic control, but with prolonged use it can cause deficiencies of vitamin B12 and folate and a number of other micronutrients, which can remain unrecognized and uncorrected. All this outlines the relevance of the dissertation with a strong impact for medical practice.

3. Evaluation of the dissertation, results and contributions

The dissertation is structured by the standards adopted in our country for a dissertation for the scientific degree of "doctor". It includes on 163 pages an introduction, a review of the literature, a goal and objectives, material and methods, results, discussion, conclusions, and recommendations, contributions, publications related to the dissertation, limitations of the present work, appendices and cited literature which includes 315 sources, four of which are in Cyrillic and 311 - in Latin. Three papers and four presentations at conferences are related to the PhD thesis are included.

The content of the dissertation demonstrates a thorough understanding of the problem by the candidate. The terms are used correctly, the text is structured logically, the layout of the dissertation is adequate, the figures and tables are of good quality. The titles of the tables and figures could be improved by making them more informative and placing them before the table itself

The review of the literature includes 52 standard pages examines in detail the mechanism of action of various antidiabetic drugs, the role of a several micronutrients in glucose metabolism and the course of type 2 diabetes, the risk of deficiencies and correction of deficiency states. Particular emphasis is given to drug therapy, which could focus more on the action of metformin and the risks of its prolonged use.

The aim and objectives of the study are to establish the micronutrient status of patients with type 2 diabetes in outpatient settings treated with metformin, to analyze their dietary habits and to apply supplementation with vitamins and minerals, if necessary. The doctoral fellow sets himself the task not only to identify the presence of the most common deficiencies (vitamin D, B12, magnesium, and iron) in diabetics, but also to look for a relationship between the identified deficiencies and metabolic control, as well as to monitor the effect of supplementation. It was an adequate task to make a general assessment of nutrition of patients and to develop recommendations for monitoring micronutrient status in diabetics as a standard procedure in medical practice.

Subject of the study and applied methods: The criteria for inclusion of patients in the study as well as the applied methods are well described. The individuals were selected personally by the doctoral student in compliance with the described criteria. Despite the small number of patients – 48 in total, the group is evenly balanced by gender and includes 27 women and 21 men. I believe that the follow-up of each patient and individualization of the dose of supplements gives a particular advantage to the study.

The laboratory assessments, survey and statistical methods are adequate, described in detail and thus the study can be reproduced. It would be an advantage of the study if information was presented about the duration and course of diabetes, metformin treatment and relations with the existing micronutrient deficiencies.

Results and discussion: the results achieved correspond to the objectives of the study. The doctoral student identified a significant prevalence of micronutrient deficiencies among the studied group - B12 (68.8%), magnesium (66.7%), vitamin D (58.35%), folic acid (27.1%) and iron (14.6%). Effective supplementation improves micronutrient status, with statistically significant improvements at the second visit being found in vitamins B12, D, and magnesium. Regarding metabolic control and micronutrient levels, a number of dependencies have been established, some of which are well known (glucose-Hb1Ac, iron-hemoglobin, GFK-iron), while others would need to be confirmed in a larger number of patients. A negative correlation was found between body weight in women and serum levels of vitamin D, but not in men. This may be due to differences in total fat mass between the two sexes. The doctoral student correctly noted that due to the small number of patients, some relationships cannot be generalized. Assessment of anthropometric status, nutrition, and readiness to receive nutritional advice is an advantage of the development, as it allows for the identification of specific complex future interventions. The presented results support the thesis of the dissertation.

4. Scientific and practical contribution of the dissertation

The presented dissertation has a significant scientific applied impact. The results of the complex approach show significant micronutrient deficiencies in type 2 diabetes treated with metformin, the effect of supplementation and the importance of monitoring of the micronutrient status in outpatient practice. From a practical point of view, the inclusion of testing for specific micronutrients in the package of laboratory tests paid for by the National Health Insurance Fund for diabetics can prevent future complications for patients and reduce the burden on the healthcare system.

5. Conclusion

The dissertation "Micronutrient supplementation in patients with type II diabetes treated with metformin" written by Dr. Ivan Georgiev Enev is dedicated to an important medical problem and represents an in-depth study with scientific value and practical application. When discussing the results, the professional maturity and scientific competence of the doctoral student are impressive. The work establishes the author as a reliable researcher and practitioner who can conduct independent research and interpret scientific results that have a special contribution to preventive medicine and public health.

All this gives me a reason to suggest to the respected members of the Scientific Jury to award the educational and scientific degree "Doctor" to Dr. Ivan Georgiev Enev.

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Prepared by:

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