To the Scientific Council
of "ACHIBADEM CITY CLINIC UMBAL TOKUDA" EAD

BRIEF REVIEW

by **Assoc. Prof. Rumyana Boykova Dimova-Draganova, MD, PhD**
Department of Endocrinology, Faculty of Medicine, Medical University of Sofia,
University Hospital of Endocrinology "Acad. Ivan Pentchev", Division of Diabetology

on the doctoral thesis of **Desislava Ivanova Gorcheva, MD**
doctoral fellow at "ACHIBADEM CITY CLINIC UMBAL TOKUDA" EAD
Clinic of Internal Medicine,
on the topic: "Role of GDF-15 as a prognostic marker for diabetic cardiomyopathy in patients with type 2 diabetes mellitus and diabetic kidney disease",
with scientific supervisor: Assoc. Prof. Lachezar Boyanov Lozanova, MD, PhD

for an educational and scientific degree, *Doctor of Philosophy*, area of higher education code *7. Health care and sports*, professional division code *7.1 Medicine*, doctoral program *Internal Medicine*

According to order No. 15-03-96H2/16.04.2026 from the Executive Director of "Acibadem City Clinic MBHAL Tokuda" EAD, I have been appointed as an external member of the scientific jury. As decided at its first meeting, I have been assigned to prepare a brief review of the aforementioned doctoral thesis.
I declare full registration in NACID and no conflicts of interest.
The review has been prepared based on a full set of submitted documents, in accordance with 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 on the conditions and procedures for acquiring scientific degrees and holding academic positions at "Acibadem City Clinic MBAL Tokuda" EAD.

1. Relevance of the topic

The topic of the doctoral thesis focuses on one of the most severe, debilitating, and life-threatening complications of diabetes mellitus—diabetic cardiomyopathy. Despite its high occurrence, it often remains undiagnosed in the early stages, and diagnosing it later poses serious treatment challenges. Therefore, the search for new methods of prediction, prevention, and early diagnosis is a key focus of scientific research and a current issue in clinical practice.

2. Structure

The presented doctoral thesis comprises 158 pages of standard typewritten text and is organized as follows: Introduction – 3 pages, Literature review - 46 pages, Aims and objectives - 2 pages, Materials and methods - 17 pages, Results - 27 pages, Discussion - 30 pages, Conclusions and recommendations for clinical practice – 4 pages, References - 4 pages, and a Bibliography of 23 pages with 203 literary sources, including 5 in Cyrillic and 198 in Latin. Of these sources, 14 (7%) are from the last 5 years and 41 (20%) from the last 10 years.

2.1 The literature review is well organized with clear bullet points and sub-bullets. Diabetic nephropathy is thoroughly discussed, covering epidemiology, risk factors, pathogenetic mechanisms, diagnosis, staging, and its role—especially albuminuria—as a cardiovascular risk

factor. Diabetic cardiomyopathy is also comprehensively examined as a significant medical and social issue, with definitions, epidemiology, risk factors, and diagnostic methods all thoroughly covered. Diastolic dysfunction is defined and described in detail as the earliest marker of diabetic cardiomyopathy, and the main echocardiographic parameters for detecting diastolic dysfunction are examined in depth. Various established biomarkers, such as troponin, natriuretic peptide, interleukin-6, and apolipoprotein B, are examined separately. Additionally, growth differentiation factor-15 (GDF-15) is evaluated in a separate section, focusing on its role in various physiological and pathophysiological conditions, including diabetes mellitus, obesity, and inflammation. Emphasis is placed on its relationship with diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy. A separate subsection discusses the role of GDF-15 in the atherosclerotic process, its potential as a marker in heart failure, and its role in cardiomyopathy. The available data on the relationship between GDF-15 and obesity, mortality, and its role in tumorigenesis are also presented.

The literature review is thoroughly written, demonstrating a strong understanding of the problem. The sections are logically organized with clear presentation and demonstrate the doctoral candidate's broad theoretical background. Leading experts in diabetic nephropathy and diabetic cardiomyopathy are cited, along with current recommendations from international societies and scientific works related to Bulgarian collectives.

2.2 The aim and the tasks – the aim is clearly defined, and seven tasks are outlined, which follow logically and align with the achievement of the set aim.

2.3 Material and methods are presented comprehensively. The study design is clearly described, and each group is properly characterized. The instrumental methods used to examine the heart serve as the foundation for assessing diastolic function in the dissertation. Appropriate statistical methods in medicine are applied, ensuring the reliability of the results and the validity of the conclusions.

2.4 The results are presented in detail, well structured, and are visualized in tables and figures.

Most of the results are confirmatory. As expected, when comparing participants with type 2 diabetes mellitus and healthy controls, a significant difference is observed in the studied indicators of cardiometabolic risk. Although there was a significant age difference between the groups, which could influence the results, this was taken into account and analyzed by the doctoral candidate.

Of particular interest are the results regarding the frequency of diastolic dysfunction, which in this study even surpass those reported in the literature. The data on diastolic dysfunction are presented in subgroups by age, sex, body mass index, glycemic control, duration of diabetes mellitus, and antidiabetic therapy, showing a trend toward worsening diastolic dysfunction with increased body mass index, poorer glycemic control, and longer duration of diabetes mellitus.

The results regarding diabetic nephropathy do not confirm a relationship between albuminuria levels and diastolic dysfunction. The level of albuminuria is associated with GDF-15 and IL-6 when diastolic dysfunction is present, indicating increased cardiovascular risk related to low-grade inflammation.

The correlation analysis confirms the well-known age-related changes in the studied biochemical markers and their associations with body mass index and gender.

The results regarding GDF-15 are contributory, as the literature on this topic in populations with type 2 diabetes mellitus and diastolic dysfunction is limited. A high percentage of participants with type 2 diabetes mellitus were found to have elevated GDF-15 levels, which tended to increase with the duration of the disease. The predictive value of GDF-15 for diastolic

dysfunction was not confirmed, and this was also observed in subgroup analyses by albuminuria status. A relationship was found between GDF-15 levels and NT-proBNP, IL-6, and eGFR.

2.5 Discussion and Conclusions. The discussion somewhat repeats the results and even includes additional visualization with tables and figures, which should be part of the results section. The analysis and interpretation of the results are skillful and thorough, with the findings clearly placed in the context of existing knowledge.

The conclusions are clearly and moderately formulated, logically based on the results obtained. A key strength of the study is its practical focus, as it provides recommendations for clinical practice and proposes an algorithm for early stratification of cardiorenal risk and diagnosis of subclinical diabetic cardiomyopathy in patients with type 2 diabetes mellitus.

2.6 Contributions. The present study is described as pioneering in Bulgaria regarding the role of GDF-15 in diabetic cardiomyopathy and diabetic nephropathy, and it proposes a new practical algorithm for risk stratification in patients with type 2 diabetes mellitus.

3. Publications

Regarding her doctoral thesis, the doctoral candidate has published two articles in Bulgarian scientific journals, one of which is in a peer-reviewed Bulgarian journal. Dr. Gorcheva is the first author on these publications, demonstrating her leadership in the research. Parts of the dissertation have been presented at four scientific events - two national and two international, with Dr. Gorcheva as the lead author at three of them.

4. Personal contribution

The documentation clearly shows the doctoral candidate's personal involvement in the research conducted.

5. Summary

The summary of the doctoral thesis highlights the main results and complies with the regulations of "Acibadem City Clinic MBHAL Tokuda" EAD.

6. Remarks and recommendations

As recommendations for current and future research, I would suggest:

- Unification of terminology and abbreviations used – "тип 2 ЗД, диабет, ЗД т2, диабет тип 2"; "Diabetic kidney disease = diabetic nephropathy", "ХБЗ and ХБН". The term microalbuminuria should be replaced in the study material with mild, moderate and severe increased albuminuria, and subsequently the subgroups are correctly classified according to albuminuria in the "methods" section, page 68. "БМИ" – should be replaced with the Bulgarian version „индекс на телесна маса /ИТМ/"
- Adding the different subgroups that are the subject of research and analysis, such as type 2 diabetes with and without diabetic nephropathy, ensures that the tasks fully meet the defined goal of the scientific research.
- The sample size in the present study is standard, but it is not representative for determining the frequency of cardiomyopathy in the population being studied.
- Definition of groups based on renal function using estimated glomerular filtration rate (eGFR) and analysis of the albumin-to-creatinine ratio in first morning urine as a standard for assessing albuminuria according to KDIGO.
- Method for testing glycated hemoglobin – ELISA method was used, with the gold standard being the NGSP-certified method
- Inaccuracy was present in the statistical methods – Chi-square test is used for comparing 2 groups, but it does not evaluate relationships between 2 groups for categorical variables

- P values between 0.05 and 0.10 should not be considered borderline, as they indicate a trend but do not represent a statistically significant difference.
- Given the statistically significant difference between age groups, which reflects overall cardio-metabolic risk, and considering the literature data indicating that GDF-15 is strongly influenced by age—with increases mainly after 50 and especially after 65 years—the age group in which over 80% of individuals with type 2 diabetes fall, a subanalysis of the data should be performed in age-matched groups.
- The statement about healthy individuals with HbA1c <7% is incorrect - it needs correction
- The concepts of abnormal HbA1c (41%) and severely elevated HbA1c (17%) are not defined
- The description of Table 10 in the Results section does not match the table's content - it only shows data for the group with type 2 diabetes mellitus, not for the working groups
- It is appropriate to reorganize the results in section 2 on cardiomyopathy by presenting them with sub-bullets that reflect the sub-analyses within the individual subgroups. These should be described along with their main characteristics, such as age, BMI, HbA1c, and duration of diabetes mellitus, etc.
- The subgroups based on BMI for cardiomyopathy incidence are too small, which increases the risk of significant statistical bias
- The relationship between long-term glycemic control and cardiomyopathy incidence is hard to interpret – conflicting results, likely due to the small sample size
- The figures should display p values for statistical significance
- The analysis of the results suggesting a trend towards a higher incidence of cardiomyopathy with longer duration of diabetes mellitus should be reconsidered due to the inconsistency of findings in the groups with less than 1 year and 1-8 years of duration. It is unclear whether the Chi-square test reflects a difference between these two groups or simply indicates a trend
- It is speculative to establish a connection between cardiomyopathy and antidiabetic therapy given the study design, as this is a secondary endpoint not included in the study's aims and objectives. Additionally, there is a lack of data on the duration of the treatment regimen, the doses used, and whether the therapy was adjusted in the short term before conducting the present study
- The description of Table 3 and Figure 13 does not match the content and should be corrected
- The group with three participants /Table 12/ should not be included in the data analysis
- Given the lack of a statistically significant association between the presence of diastolic dysfunction and the level of GDF-15 /text after Figure 15/, the use of ROC curve analysis is inappropriate
- Figure 16 illustrates the ROC curve analysis
- It is advisable to prevent repeated presentation of data in both tables and figures
- Figure 17 and Table 17 contain conflicting data, which should be re-examined and interpreted
- Tables from 19 onward and Figures from 21 onward should be included in the results, as the discussion involves positioning the findings from the current study relative to existing and emerging knowledge in the literature

- It is appropriate to re-examine the results shown in Figure 22, as the observed trend reflects differences in the number of participants rather than the ratio or distribution of diastolic dysfunction by albuminuria, since it can be seen that, regardless of albuminuria, the number of participants with elevated GDF-15 is higher in each group.

CONCLUSION

In conclusion, I state that the presented doctoral thesis is relevant, addresses a highly important interdisciplinary problem, is well-organized, and includes detailed, credible analysis, interpretation, and summary of results. The recommendations do not lessen the merits of the doctoral thesis.

The candidate has the required in-depth theoretical knowledge in the relevant field and, as demonstrated by the presented work, the ability to conduct independent scientific research.

A key strength of the work is its clinical focus and the clear practical relevance and applicability of its conclusions.

The doctoral thesis fully complies with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations on the Terms and Procedure for Acquiring Scientific Degrees and Holding Academic Positions at "ACHIBADEM CITY CLINIC TOKUDA HOSPITAL" EAD.

Based on the above stated, I declare my positive review and recommendation to the other members of the scientific jury to award the educational and scientific degree *Doctor of Philosophy* to Desislava Ivanova Gorcheva, MD.

20.05.2026
Sofia

Respectfully
Assoc. Prof. Rumyana Dimova-Draganova, MD, PhD