

REVIEW

By: Assoc. Prof. Dr. Milena Krasimirova Nikolova-Vlahova, MD, PhD
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Subject: Dissertation of Dr. DESISLAVA IVANOVA GORCHVA, for the acquisition of the
educational and scientific degree "Doctor" (PhD) in the doctoral program "Internal Medicine"
on the topic: "ROLE OF GDF-15 AS A PROGNOSTIC MARKER FOR DIABETIC
CARDIOMYOPATHY IN PATIENTS WITH TYPE 2 DIABETES AND DIABETIC
KIDNEY DISEASE".

Field of higher education: 7. Health and Sports

Professional field: 7.1 Medicine

Scientific specialty: Internal Medicine" Scientific supervisor: Assoc. Prof. Dr. Lachezar
Boyanov Lozanova, MD

I have developed this review in my capacity as a Member of the Scientific Jury, determined on
the basis of the relevant Order (№15-03-96-H2 / 16.4.2026) and in accordance with the
legislation of the Republic of Bulgaria and the Regulations for its implementation of the
Scientific Unit.

I have no conflict of interest as a member of the esteemed Scientific Jury, I have no common
publications with the dissertant. I have no evidence of plagiarism.

Introduction

Type 2 diabetes mellitus is a socially significant disease, the incidence of which has increased
significantly in the last decade and affects no less than 10% of the world's population. It is often
asymptomatic and is detected only when serious organ damage of the disease is present. The
frequent and severe complications of diabetes mellitus and their treatment are associated with
enormous health and social costs and have a major impact on the personal and professional
lives of both affected patients and their families and loved ones. Diabetic cardiopathy and
diabetic nephropathy are among the severe organ damage of diabetes mellitus, affecting
survival and morbidity in these patients.

Growth differentiation factor - 15 (GDF-15) is a cytokine that is secreted by various tissues in
response to cellular stress, including hypoxia, inflammation or mitochondrial dysfunction. In
physiological conditions, it is secreted during pregnancy, after strength exercises, as well as
under drug effects (metformin). Its levels correlate with endothelial dysfunction and
microvascular damage in cardiovascular diseases (such as hypertrophy, heart failure and
atherosclerosis), in obesity, insulin resistance and prediabetes, in diabetic retinopathy and
nephropathy, oncological diseases, etc. Increased levels of this cytokine are associated with
faster progression of both vascular and organ damage in diabetes mellitus.

Presentation of the Dissertation

The Dissertation project presented by Dr. Gorcheva is fully prepared and meets the
requirements for developing a dissertation for acquiring the scientific degree "Doctor" (PhD).
It represents an in-depth study on the levels of GDF-15 in patients with type 2 diabetes with
kidney damage and examines the prognostic significance of this marker in the presence of
diabetic cardiopathy. The topic of this work is topical and evaluates a new marker for both
Bulgaria and the world, which makes the studies particularly valuable. The topic of the

dissertation is not only topical, but also aimed at a socially significant disease requiring a multidisciplinary approach - type 2 diabetes mellitus, in which vascular damage and the processes of inflammation, oxidation and fibrosis occurring in the vessels and organs are of leading importance for the prognosis.

The dissertation is presented on 158 pages, contains 31 figures and 29 tables. It is structured correctly, including all parts generally accepted for this type of scientific work: introduction, literature review, goals, objectives, materials and methods, results, discussion, conclusions, conclusion, contributions, literature review (containing over 200 sources, including in Cyrillic). The dissertation work was discussed and proposed for defense by an extended scientific collegium of the Clinic of Internal Medicine at "Acibadem City Clinic University Hospital Tokuda".

The introduction and literature review present the current knowledge about the importance of inflammation, incl. GDF-15, for the development of diabetic complications with a focus on diabetic nephropathy and cardiopathy. They introduce the reader in an extremely elegant way to the complex subject described in this way, demonstrating the profound knowledge of the dissertation author.

The abbreviations used and six scientific communications and publications in connection with the Dissertation work are mentioned (representing only a small part of the publication and scientific activity of the dissertation author).

The aim of the dissertation is: through a comparative analysis and assessment of some known cardiovascular risk factors and metabolic abnormalities in patients with type 2 diabetes mellitus (T2DM), with and without diabetic kidney disease (DKD), to determine the frequency of diabetic cardiomyopathy (DCM) and the importance of GDF-15 in the diagnostic algorithm for early myocardial dysfunction in these patients, with a view to a wider and routine use of GDF-15 in the diagnostic process and clinical practice.

To achieve this goal, Dr. Gorcheva sets the following 7 Tasks:

1. To investigate and compare metabolic, inflammatory and cardio-renal parameters in the two groups: healthy controls and individuals with T2DM.
2. To investigate the incidence of DCM in patients with T2DM, without known cardiovascular disease to date, and its relationship with some demographic, anthropometric and glycemic control indicators.
3. To investigate and compare the incidence of diabetic renal disease in patients with T2DM, with and without DCM, and to compare the incidence of diastolic dysfunction (DD) in the different degrees of diabetic renal disease.
4. To investigate and compare the levels of various cardiovascular risk markers (NTproBNP, troponin, GDF-15, eGFR, hsCRP) as well as some metabolic parameters (HbA1c, apoB, lipid profile) in patients with T2DM, without and with diabetic renal disease, with established and absent DD.
5. To investigate the relationship of the same cardiovascular risk markers and metabolic indicators from task 4, with some demographic, anthropometric and glycemic control indicators.
6. To investigate the frequency of elevated GDF-15 in patients with type 2 diabetes, with and without DD, with and without diabetic nephropathy (DN) and to compare it with the results of other cardiac and metabolic indicators.

7. To develop and propose a diagnostic algorithm with the participation of GDF-15 for the study and early diagnosis of diabetic cardiomyopathy in patients with type 2 diabetes according to the degree of diabetic renal disease.

Materials and methods

A large group of patients (131 patients, divided into 4 subgroups) and 21 healthy subjects were studied, with clearly stated inclusion and exclusion criteria. The study was conducted in accordance with the Rules for Good Clinical Practice and the Declaration of Helsinki, after obtaining written informed consent from the participants. A thorough history and physical status were taken from all patients and both clinical and laboratory and instrumental examinations and studies of new markers, such as GDF-15, NTproBNP, hsCRP, apoB, as well as standard biochemical and other laboratory indicators, were performed. Instrumental examinations were also performed, including ECG and echocardiography. Modern and generally accepted statistical methods were used.

The results are presented clearly and accurately. The development is excellently illustrated with 31 figures and 29 tables, which contribute to the easier understanding of the text even for a reader unfamiliar with the subject.

The discussion is written in easy-to-read and correct Bulgarian. It represents a comparison of the results obtained by the dissertation candidate with the data in the literature so far and explains the noted interrelationships and dependencies, becoming the basis for defining a total of 11 conclusions by Dr. Gorcheva:

1. Patients with type 2 diabetes have a distinct metabolic, inflammatory, and cardiorenal profile of impairment compared to healthy controls. Cardiorenal “aging” (NT-proBNP, GDF-15, eGFR) is observed as diabetes progresses.
2. Diastolic dysfunction is a common first manifestation of diabetic cardiomyopathy — up to 60% in patients with type 2 diabetes without other cardiovascular diseases (except hypertension), especially in albuminuria >30 mg/24h.
3. There is a relationship between diastolic dysfunction and the degree of albuminuria, most pronounced in AU >300 mg/24h, although not statistically significant. Diastolic dysfunction can also be detected in the absence of nephropathy (55% vs. 45%).
4. The occurrence of diastolic dysfunction depends on age and duration of diabetes, but can be detected even in diabetes < 1 year. Gender, weight, HbA1c and antidiabetic therapy do not have a significant impact.
5. The combination of albuminuria >30mg/24h and elevated hsTroponin I may be an early predictor of subclinical myocardial damage.
6. Elevated GDF-15 and IL-6 in diastolic dysfunction signal progression of systemic damage.
7. The GDF-15 marker in patients with type 2 diabetes may be associated with:
 - Myocardial damage and diabetic cardiomyopathy
 - Higher albuminuria or Reduced renal function (eGFR)
 - Elevated inflammatory markers (IL-6)
 - With heart failure (NT-proBNP)
8. GDF-15 is an indicator of systemic stress and damage, not metabolic control.
9. Nephropathy has a stronger effect on GDF-15 than myocardial damage.
10. GDF-15 values are highest in the combination of diastolic dysfunction and diabetic nephropathy - a prognostic marker for cardiorenal metabolic syndrome.
11. Can be used for risk stratification in patients with diabetes, hypertension or CKD without known vascular pathology.

Furthermore, based on the results obtained and after discussing the literature data, Dr. Gorcheva gives five recommendations for Clinical Practice and defines a diagnostic-prognostic algorithm for the use of GDF-15 in patients with diabetes mellitus for the assessment of cardiorenal damage. GDF-15 is defined as an integrative biomarker for early stratification of cardiorenal risk and diagnosis of subclinical diabetic cardiomyopathy and can be included in the diagnostic-prognostic algorithm for diabetic cardiomyopathy in patients with T2DM.

The recommendations for the Clinician are:

1. Early echocardiographic screening in patients with type 2 diabetes, especially in patients with albuminuria above 30 mg/24 h and with a longer duration of diabetes.
2. Use of GDF-15 as a biomarker for stratification of cardiorenal risk as part of the routine assessment of patients with T2DM.
3. Combined assessment of cardio-renal biomarkers for early detection of subclinical myocardial damage through integrated use of albuminuria, hsTroponin I, NT-proBNP and GDF-15 for earlier therapeutic intervention.
4. Integrated multidisciplinary approach to follow-up of diabetic patients without cardiac pathology with elevated values of GDF-15, albuminuria and NT proBNP jointly by an endocrinologist, cardiologist and nephrologist, to ensure timely detection of combined cardio-renal damage and optimization of the therapeutic strategy.
5. Diagnostic - prognostic algorithm for the application of GDF-15 in patients with type 2 diabetes mellitus, for the assessment of cardio-renal damage.

Dr. Gorcheva states a total of 7 contributions of the development – both scientific and scientifically applied/practical in nature:

1. For the first time in Bulgaria, an in-depth clinical study has been conducted on the role of the biomarker GDF-15 in the diagnosis and prognostic assessment of diabetic cardiomyopathy in patients with type 2 diabetes, depending on the degree of albuminuria.
2. An association has been proven between elevated levels of GDF-15 and the presence of diastolic dysfunction, as well as with the severity of albuminuria, which confirms its role as a biomarker for early combined cardiorenal injury in people with diabetes.
3. It has been shown that GDF-15 has a stronger dependence on nephropathy than on isolated myocardial injury. The discovery supports the concept of a cardiorenal continuum and the role of GDF-15 as an integrative indicator of systemic stress and injury.
4. It was revealed that the combination of albuminuria >30 mg/24 h and elevated GDF-15 can be an early predictor of cardiorenal dysfunction, even before the clinical manifestation of diastolic dysfunction. The discovery has direct clinical significance for the early identification of high-risk patients.
5. The correlation between GDF-15 and markers of inflammation (IL-6), heart failure (NT-proBNP) and renal function (eGFR) was confirmed, which confirms GDF-15 as a multisystem biomarker reflecting the degree of systemic damage in diabetes.
6. A new approach for risk stratification is proposed by including GDF-15 in a diagnostic algorithm for diabetic cardiomyopathy, which builds on the classical biomarkers (NT-proBNP, hsTroponin I, IL-6) and allows a more precise assessment of subclinical damage, applicable in clinical practice.
7. The dissertation also contributes to the national scientific community, as it represents the first systematic study of GDF-15, conducted by a specialist endocrinologist in Bulgaria, contributing to the introduction of modern biomarkers in the assessment of diabetic complications.

A total of 6 publications and scientific contributions in connection with this dissertation are mentioned.

Dr. Gorcheva's gratitude to her colleagues and relatives is particularly impressive.

The abstract is developed in accordance with all requirements and clearly and accurately reflects the main parts of the dissertation in a summary.

Thus, I believe that the presented work is extremely interesting. I have no comments on the substance. I have no evidence of plagiarism on the part of the dissertation candidate.

Personal impressions

I have known Dr. Gorcheva for more than 20 years, since the beginning of her career as a doctor, and I have excellent personal impressions - the dissertation candidate is a complete specialist internist and endocrinologist with extensive experience in both Internal medicine and Endocrinology, a teacher with a strong bias towards scientific activity, which is also evidenced by her publication activity.

I have no joint publications with Dr. Gorcheva.

There is no conflict of interest in connection with the current review.

In conclusion, based on everything mentioned so far - the emphasized innovation of the development, the well-formulated goal and tasks, the large group of patients, the modern methods of research and statistical data processing used, the clear results leading to clear conclusions, recommendations to the clinician and conclusion, I declare my POSITIVE opinion on the presented dissertation work and recommend, I vote with conviction "FOR" the awarding of the scientific degree "DOCTOR" (PhD) to Dr. Gorcheva and I would like to recommend to the other Members of the esteemed Scientific Jury to vote positively.

May, 2026
Sofia
MD

Respectfully:

Assoc. Prof. Dr. Milena Krasimirova Nikolova-Vlahova,

