

# OPINION

## OF DISSERTATION WORK

**To Dr. Petar Plamenov Petrov, topic: "Monitoring and evaluation of nutritional status and markers of the inflammatory process in patients with chronic kidney disease" for the award of educational and scientific degree "Doctor" in higher education 7 Health and Sports", Professional field 7.1 "Medicine" in scientific specialty 01.03.14. "Nephrology".**

Scientific adviser: **Prof. Dr. Svetla Vasileva Staykova, Ph.D, DSc**

### REVIEWER

**Assoc. Prof. Dr. Irina Ivanova Ivanova, Ph.D.**

An internist and gastroenterologist at the Clinic of Gastroenterology, University Hospital "St. Marina"

Head of the Second Department of Internal Medicine, Medical University "Dr. Paraskev Stoyanov" - Varna

By decision of the Chairman of the Scientific Jury (Protocol No. 1 of 13.01.22) and in accordance with order R-109-596 / 31.12.21 of the Rector of MU-Varna, I have been appointed to present this opinion.

#### **1. Brief biographical and professional data of the doctoral student:**

Dr. Petar Petrov graduated High School "Hristo Botev" in Popovo. He completed his training in Medicine at the Medical University, Varna in 2015. In 2020 acquires the specialty "Nephrology". Since 2015 he has been working as resident doctor at the Clinic of Nephrology at St. Marina University Hospital, and since 2017 he has been an assistant physician at the Department of Internal Medicine at the Medical University of Varna. Since 2018 he has been a full-time doctoral student at the Second Department of Internal Medicine at the Medical University of Varna.

## **2. Relevance of the dissertation topic**

Chronic kidney disease (CKD) is a significant health problem, given the high incidence and the possibility of progression to the final stage with the need for renal replacement therapy and kidney transplantation. Many studies suggest that chronic inflammation in patients with advanced CKD causes a catabolic state of increased protein breakdown and decreased protein synthesis. Malnutrition predisposes to complications of CKD, including infections. Thus, chronic inflammation and nutritional imbalance are important concomitant conditions of CKD, which should be detected early and possibly prevented.

Visfatin (visceral fat derived adipokine, visfatin, named by Fukuhara and team in 2005) has many functions. It is produced by visceral adipose tissue, but also by other cells in response to inflammatory stimuli. Visfatin plays a role in the nonspecific immune response as a ligand for the TLR-4 receptor. Its role as a cytokine is considered due to its ability to stimulate B-cell differentiation and inhibit the apoptosis of polymorphonuclear cells. Visfatin also has enzymatic activity as it is described as identical to extracellular nicotinamide phosphoribosyltransferase. This adipokine generates reactive oxygen species by activating NADPH oxidase. Studies show that visfatin can directly induce vascular inflammation and endothelial dysfunction. Elevated levels of visfatin have been reported in obesity and related diseases. Also, visfatin increases in proportion to the retention of nitrogen products, given its impaired urinary clearance. Elevated levels of visfatin correlate with high levels of C-reactive protein and interleukin-6. On the other hand, there is clinical evidence of a protective effect of visfatin in diabetic nephropathy, as well as an insulin-mimetic effect, lowering blood sugar and improving insulin resistance. At this stage, scientific arguments keep the discussion of the pathophysiological effects of visfatin open. Thus, the idea of the dissertation arouses interest and is substantiated with relevance.

## **3. Characteristics, volume, structure and evaluation of the dissertation**

The dissertation of Dr. Petar Petrov consists of 149 pages and follows the traditional structure: introductory words - 1 page; literature review - 41 pages; purpose and tasks - 1 page; research methods - 6 pages; results - 35 pages; discussion - 12 pages; conclusions - 1 page; conclusion and contributions - 1 page and a reference from 183 sources. The dissertation has a balanced content and the style of Dr. Petrov is clear and good.

In the literature review, both the following and the most up-to-date publications are presented in a concise and understandable way, in view of the topic. The presentation begins with the definitions of renal impairment and staging of CKD, continues with risk and pathogenetic factors for CKD, followed by a description of the clinical manifestations of CKD and a discussion of current epidemiological data on increasing incidence of CKD, which defines the need for informative biomarkers for monitoring the

natural course of CKD, respectively early diagnosis and assessment of the risk of progression to the final stage of CKD. A strong part of the review is the analysis of current non-invasive markers for assessment, staging and prognosis of patients with CKD. For a well-arranged literature data, it would be further helpful to illustrate the material with a graph of the multifaceted effects of visfatin and tabular analysis of publications related to the topic.

The aim of the dissertation is ambitious and clinically orientated: to look for a connection between the level of visfatin and indicators of inflammation and nutritional status in patients with CKD. The tasks follow the possible hypotheses for association between the non-invasive marker visfatin and the described conditions. It should be noted the clearly formed of tasks 1, 2 and 4, which allows overlapping results on each of them.

The proposed study is a prospective non-interventional protocol conducted in a reference center for diagnosis, follow-up and with the ability to provide in full all modern methods of treatment of patients with CKD. The Clinic of Nephrology and Dialysis at the University Hospital "St. Marina" has a long tradition and achievements in clinical and scientific work. Patients with CKD (80) were included without follow-up, divided according to the type of therapeutic intervention as predialysis and dialysis patients. Excluding criteria, the dissertation does not take into account the existence of current infection, sepsis and conditions associated with the activation of the non-specific immune response. The disadvantage is the lack of a control group of healthy people. The indicated research methods are: laboratory; questionnaire approach with a questionnaire on quality of life in patients with kidney disease with 36 questions and statistical. In the dissertation I did not find results of multifactor regression analysis and risk assessment analysis registered in the chapter "methods".

The results are well illustrated with 6 tables and 42 figures. Thus, assuming a physiological level of visfatin of 10-15 ng / ml in healthy people (according to literature data), it can be assumed that in the analyzed patients with CKD. Dr. Petrov found an increase levels in serum visfatin. However, the study found no association between visfatin and urea and creatinine levels. In the pre-dialysis phase, patients had higher levels of visfatin (mean 26 ng / ml) than patients undergoing hemodialysis (mean 21 ng / ml), but the difference was not statistically significant. In the predialysis stage, Dr. Petrov found an important moderately proportional relationship between glomerular filtration rate (GFR) and visfatin levels. The highest level of visfatin was found in hypertensive nephropathy (mean 31 ng / ml) and lower in chronic glomerulonephritis (22 ng / ml) and diabetic nephropathy (16 ng / ml). A key point in the study was the comparison of visfatin and C-reactive protein (CRP) levels. In the present analysis, CRP was normal in 9 patients and had low levels of visfatin, ie. below the threshold of 15 ng / ml. On the

other hand, in the dialysis group, which is characterized by significantly higher CRP values, visfatin above 15 ng / ml does not correspond to a statistical difference in CRP. The nutritional status of patients with CKD is assessed by body mass index (BMI) and levels of folic acid and vitamin B12. As expected, hemodialysis patients have significantly lower BMI, but visfatin levels do not differ between overweight / obesity compared with normal and low BMI. Low levels of visfatin have been associated with longer than 5 years of hemodialysis treatment. Patients with low levels of visfatin have a reduced assessment of their health and quality of life.

In the chapter "Discussion" Dr. Petrov competently analyzes the published data from studies of visfatin in patients with CKD and correctly compares them with their own results. A logical consequence of the above results and discussion are 5 conclusions and 5 summarized contributions. The literature reference from 183 sources meets the requirements for completeness and timeliness.

In connection with the dissertation, Dr. Petar Petrov offers 3 full text publications, 2 of which he is the lead author.

#### **Evaluation of the contributions of the dissertation**

I accept the above conclusions and contributions to the dissertation. Thus, this study of a reference center for our country for patients with chronic kidney disease and with an excellent initial register is important with the confirmatory and original nature of the conclusions.

#### **4. Critical remarks**

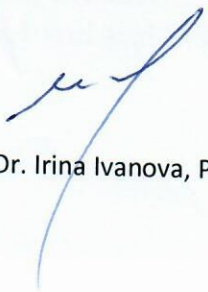
There are no grounds for significant critical remarks.

#### **5. Conclusion**

The review of the dissertation and the proposed publications, as well as my personal impressions of the clinical work of Dr. Petar Petrov justify my positive opinion. I would like to recommend to the esteemed Scientific Jury to award Dr. Petar Plamenov Petrov the educational and scientific degree "Doctor" in the scientific specialty "Nephrology".

4 February 2022

Varna

  
/ Assoc. Prof. Dr. Irina Ivanova, Ph.D /