

R E V I E W

by Assoc. Prof. Georgi Nikolaev Valchev, MD, PhD

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**of the dissertation for awarding the educational and scientific title of
"Doctor of Philosophy":**

**"QUANTITATIVE MEASUREMENT OF EPICARDIAL ADIPOSE
TISSUE AND CORRELATION WITH OTHER MARKERS FOR
INCREASED CARDIOVASCULAR AND METABOLIC RISK IN
PATIENTS WITH LONG-TERM DIABETES MELLITUS TYPE 1"**

Thesis by

Dr. Samar Ala Hasun El Shemeri

Doctoral student in the Scientific Specialty "Medical Radiology and Roentgenology
(Including Use of Radioactive Isotopes)",
Professional Heading "Medicine" (7.1)

By written order of the Rector № P-109-107/09.03.2022 I have been appointed as an Internal Member of the Scientific Jury judging on the aforementioned thesis. In accordance with protocol № 1 / 17.03.2022 of the conducted first session of the Scientific Jury I have been appointed to formulate a review.

I. BRIEF BIOGRAPHIC DATA AND CAREER DEVELOPMENT

Dr. Samar El Shemeri is born on the 28.01.1990 in Burgas. In 2015 she graduates her education in Medicine at Medical University "Prof. Dr. Paraskev Stoyanov" Varna.

Professional Development

- From 2016 – appointed as resident doctor at the Clinic of Diagnostic Imaging at UMHAT “Sveta Marina” Varna.
- From 2017 to 2021 – specialist in training at the Clinic of Diagnostic imaging at UMHAT “Sveta Marina” Varna.
- In 2021 – acquires “Diagnostic Imaging” specialty.

Academic Development

- From 2017 – teaching assistant at the Department of Diagnostic Imaging, Interventional Radiology, and Radiotherapy of Medical University “Prof. Dr. Paraskev Stoyanov” Varna.
- From 2020 to 2022 – doctoral student at the Department of Diagnostic Imaging, Interventional Radiology, and Radiotherapy of Medical University “Prof. Dr. Paraskev Stoyanov” Varna.

The doctoral student is fluent in English and German. Dr. Samar El Shemeri is a member of the Bulgarian Association of Radiology, of the Bulgarian Medical Association, and the European Society of Radiology. She is a participant in the organizational committee of the XVIII National Congress of the Bulgarian Association of Radiology in 2019 in Varna.

II. RELEVANCE OF THE DISSERTATION’S TOPIC

The metabolic syndrome is a combination of interconnected cardiovascular risk factors such as abdominal obesity, disruptions in the glucose metabolism, dyslipidemia, and others. It is a socially significant condition with an increasing frequency in recent years, which necessitates optimization of the algorithms for its early detection and proper treatment. One of the primary components of metabolic syndrome is diabetes mellitus type 1. It affects about 10% of all diabetes patients and requires introduction of exogenous insulin. Type 1 diabetes mellitus is among the most frequent metabolic diseases and its morbidity is gradually increasing. Obesity is associated with a range of atherogenic factors,

while fatty tissue on its own can also have a proatherogenic effect by expressing pathologic cytokines. Studying the relationship between the fatty depot of interest (epicardial fat) and other markers (imaging, clinical, and laboratory ones) of increased cardiovascular risk is a relevant scientific pursuit, with its results potentially aiding in elucidating at least some of the complex molecular mechanisms that determine this risk. Additionally, the findings can be used as a basis for future research in metabolic disease.

III. STRUCTURE OF THE DISSERTATION

Dr. El Shemeri's work encompasses 119 pages, from which: Introduction – 2 pages, Literature Review – 20 pages, Aim and Tasks – 1 page, Material and Methods – 13 pages, Results – 34 pages, Discussion – 8 pages, Conclusion – 1 page, Inferences – 1 page, Contributions – 1 page, Publications, Associated with the Dissertation – 2 pages, Bibliography – 28 pages, Addendums – 3 pages.

The dissertation is richly illustrated with 40 figures (27 of which annotated as “graphics” and 13 as “figures”) and 29 tables.

The writing style is accessible, the structure – classic.

IV. CHAPTER BY CHAPTER ANALYSIS OF THE DISSERTATION

Literature review: The review of literature is concise (20 pages), with excellent structure. The reader is introduced into the topic with historical data of the development of the medical concept of metabolic syndrome. Epicardial fat is discussed comprehensively – special attention is given to its anatomy, physiology, and to the cytokines and chemokines it secretes – substances, which potentially play a role in the genesis of cardiovascular disease. The factors which determine the amount of epicardial fat in an individual are described, as well as its thermogenic function. Special attention is given to the link between epicardial fat and diabetes, as well as between epicardial fat and atherosclerosis. A thorough description is given of the features, advantages, and disadvantages of the various diagnostic imaging methods employed

in the quantification of epicardial fat, further supporting the choices of modality delineated in the “Materials and Methods” chapter.

The review cites 260 sources, of which 5 in Bulgarian (4 of which autocitations) and 255 in English. Of the international sources 72 are from the last 5 years (2 from 2022, 8 from 2021, 11 from 2020, 18 from 2019, 16 from 2018, and 17 from 2017), comprising 27,7% of them. When adding the sources in Bulgarian, all of which dating between 2020 and 2022, the overall percentage of sources from the last 5 years is 29,6%. In view of this I determine that the presented selection of sources is sufficiently up to date. Additionally, the large number of articles cited demonstrates the doctoral student’s broad and detailed thematic knowledge.

Aim of the study: The doctoral student aims to “study the ways of imaging assessment of epicardial fat, its role as a biomarker, as well as its significance as a factor for increased cardiovascular risk in correlation with other known factors”. The goal is ambitious and multi-staged.

Tasks: In order to achieve the aim Dr. El Shemeri formulates a total of 7 tasks with varying degrees of difficulty and clinical relevancy. Of greatest importance for the clinician one would classify tasks 1, 2, 3, 5, and 6, which look for correlations helpful in restratifying risk. Tasks 4 and 7 are primarily practical, aiming to optimize epicardial fat quantification by applying a specially-developed, deliberate, and easily-reproducible algorithm for segmentation of medical images, as well as comparing the accuracy of CT and MRI quantification results.

Material and Methods: The work presents prospectively acquired data from a multidisciplinary scientific project “Cardiovascular and Metabolic Risk, Associated with Visceral Fat, In Diabetes Mellitus Type 1 Patients”. A total of 183 participants have been examined – 124 patients with at least a 15-year duration of diabetes mellitus type 1 and 59 healthy controls, matching the patient population by sex, age, and BMI. The number of patients and controls is sufficient for the purposes of the study. The selection is adequate and assures maximum accuracy of the results. It should be noted that the participating patients have poor control of their diabetes – a fact that differentiates the studied cohort significantly from other similar international studies, adding to the author’s study’s value.

The author describes in detail the utilized technical tools, imaging protocols, as well as the types of analyzed clinical and laboratory data. Special attention is given to the custom easily-reproducible algorithm for semi-automatic and manual segmentation of epicardial fat,

additionally promoted via a pointed article published by a collective with the participation of the doctoral student. A concise and clear recapitulation and argumentation of use are made of the used statistical methods, without unnecessary mathematical detail, which would only serve to distract the reader.

Results: The results are diligently ordered and presented, separated by tasks, and supported with corresponding graphics and tables. In favor of greater precision of the conclusions and inferences, the patient and control cohorts are further separated into subgroups. The author notes a statistically significant strong agreement between planimetric and volumetric data on epicardial fat, acquired with CT and MRI. This finding is of practical significance for further research in this field, allowing for the two methods to be employed interchangeably. A significant positive correlation between BMI and epicardial fat volume in diabetes patients and healthy controls is proven. Correlations are also found between interleukin-6 and tumor-necrosis-factor-alpha and the epicardial fat thickness, measured by CT and MRI in certain points. Epicardial fat, measured volumetrically and planimetrically, demonstrates a varying degree of association with the values of waist circumference in the different subgroups. Additionally, a correlation is found in diabetic patients between CT- and MRI-measured epicardial fat and DEXA-measured abdominal fat. The doctoral student does not find a correlation between the epicardial fat volume and the duration of diabetes.

Discussion: The conclusive discussion is thorough and well-supported with comparisons with analogous international scientific works – similar and opposing results are pointed out. Dr. El Shemeri presents a concise conclusion, which denotes the future significance of segmentation as a tool for medical research, as well as pointing out the necessity for additional studies for further elucidating the role of epicardial fat in cardiovascular risk restratification.

Inferences: Eight inferences are presented – they are ascertained based purely on the results of the statistical analysis.

Contributions: The doctoral student points out 5 contributions, which have a scientific, applied, and practical character. I concur with the author's defined contributions.

V. PUBLICATIONS, ASSOCIATED WITH THE DISSERTATION

Dr. Samar El Shemeri presents the following scientific publications, associated with the dissertation:

- Full text publications in referred and indexed journals – 3 items
- Full text publications in non-referred peer-reviewed journals – 5 items
- Non full text publications in referred and indexed journals – 1 item

Additionally, Dr. Samar El Shemeri has a total impact factor of 41.414, acquired from three full text articles, published between 2019 and 2021. Among these articles one concerns the topic of the dissertation. The value is exceptionally high for a young researcher, which should be interpreted as an indicator for the high quality of the doctoral student's works.

The doctoral student presents a Thesis Summary in Bulgarian comprising 69 pages, which sufficiently well presents the results of the dissertation. The Thesis Summary is also available in English.

The aforementioned materials completely satisfy and exceed the scientific metric criteria for the acquisition of the title of "Doctor of Philosophy" in Medicine.

Dr. Samar El Shemeri has active scientific profiles in *Google Scholar*, *ResearchGate*, and *ORCID*.

The candidate has participated in a multitude of national and international scientific forums.

Dr. Samar El Shemeri is a participant in the interdisciplinary project "Cardiovascular and Metabolic Risk, Associated with Visceral Fat, In Diabetes Mellitus Type 1 Patients", led by Prof. Dr. Violeta Yotova, MD, PhD, active in the span 2017 – 2021.

The works of Dr. Samar El Shemeri possess scientific, theoretical, and practical significance. They encompass cutting-edge topics in diagnostic imaging and new technologies in medical image processing. A special accent on multidisciplinary scientific collaboration with endocrinologic and cardiologic focus is to be noted. The exceptionally high value of two oncologically-oriented publications regarding breast cancer in males is to be taken into consideration because of their high impact factor contribution. The publications are varied and demonstrate the broad scope of the doctoral student's interests and competences.

VI. CONCLUSION

The dissertation “Quantitative Measurement of Epicardial Adipose Tissue and Correlation with Other Markers for Increased Cardiovascular and Metabolic Risk in Patients with Long-Term Diabetes Mellitus Type 1” is an exhaustive study with substantial clinical value and practical applications. The topic is current and of great significance, pertaining to the restratification of cardiovascular risk in diabetes mellitus type 1 patients. The conducted study is thorough and excellently structured, while the inferences are logical and substantiated by the results. I deem that the doctoral student demonstrates the ability for assiduous and competent work with scientific information and data, as well as the capacity to formulate a scientific thesis and defend it with evidence. The work satisfies the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria, as well as those of the Rules for the Development of Academic Staff of MU “Prof. Dr. Paraskev Stoyanov” Varna, legitimizing the author as a reliable researcher.

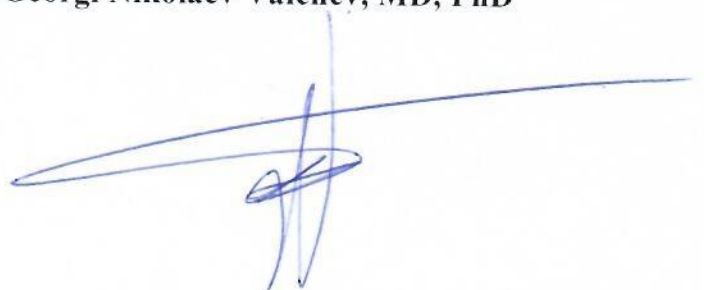
I confidently express my **positive** assessment of Dr. Samar Ala Hasun El Shemeri. I propose to the honorable members of the Scientific Jury that they also **vote in favor** of Dr. Samar Ala Hasun El Shemeri being awarded the educational and scientific title of “Doctor of Philosophy” in the higher education field of “Medical Radiology and Roentgenology (Including Use of Radioactive Isotopes)”, Professional Heading “Medicine” (7.1).

02.04.2022

Varna

Regards,

Assoc. Prof. Georgi Nikolaev Valchev, MD, PhD

A handwritten signature in blue ink, consisting of a long horizontal stroke with a loop and a vertical stroke crossing it.