

**"VICTOR BABEȘ" UNIVERSITY OF
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DOCTORAL SCHOOL
MEDICINE**



HABILITATION THESIS

DIABETES INTEGRATIVE AND TRANSLATIONAL CLINICAL RESEARCH: BETWEEN EPIDEMIOLOGY, IMPACT AND INTERVENTIONS

A B S T R A C T

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ABSTRACT

The Habilitation Thesis contains the most important professional achievements, obtained after receiving the title of *Ph D* in 2004 with the thesis entitled “Clinical, nosological, evolutive and therapeutical aspects of type 2 diabetes mellitus”, awarded after its public defense.

This Habilitation Thesis is divided in three major sections: in the first section, the main academic, professional and scientific achievements are presented; the second section briefly describes the future academic, professional, and scientific perspectives; the last section of the thesis contains the references used for the research and documentation work presented in the first two sections.

My post-doctoral research and my professional path are in a close relation to the two positions appointed: senior specialist physician in Diabetes Mellitus, Nutrition and Metabolic Diseases and in Internal Medicine, respectively Associate Professor at the Discipline of Internal Medicine – Diabetes, Nutrition, Metabolic Diseases and Systemic Rheumatology. I had the opportunity to be part of some multidisciplinary teams, being able to expand the research beyond the narrow field of diabetes and metabolic diseases to a much larger one. Therefore, together with the teams I worked with, I was able to find some connections between diabetes mellitus and liver disease, between dietary habits and the serum level of some metabolites and so on. The teams consisted of clinicians (diabetologists, nephrologists, gastroenterologists, psychiatrists), as well as fundamental science specialists (physiologists). The research teams focused its research on Diabetes Mellitus, its complications, and co-morbidities as well as on nutrition. The importance of this research is emphasized in the context of the global public health issue generated by diabetes, being a disease affecting approximately 537 million adult persons, having a worrying increasing trend of in-time incidence, having a major impact on both the individual's health as well as on the public health systems.

At the moment of writing this thesis, I have disseminated my research work in 45 papers indexed in Clarivate's Web of Science (27 in extenso papers and 18

meeting abstracts), which received a total of 180 citations from 174 different citing articles indexed in the Web of Science. In September 2022 I had a Hirsch index of 9 in Web of Science and of 10 in Google Scholar

The research was published in scientific journals with high impact on the research community.

To summarize, my research was disseminated in:

- 14 *in extenso* articles indexed in Clarivate's Web of Science as principal author
- 13 *in extenso* articles indexed in Clarivate's Web of Science as co-author
- 6 *in extenso* articles indexed in international scientific databases as principal author
- 15 *in extenso* articles indexed in international scientific databases as co-author
- 18 abstracts or proceedings after conferences in supplements of journals indexed in Clarivate's Web of Science, as principal author, or co-author
- 129 abstracts in supplements of recognized scientific journals

A part of the research done was funded by two international and one national scientific grants which were won in a competitive process. In these grants I was local project director or member. I was involved in global projects of state-of-the-art medical research, being an active participant in major clinical trials from the area of diabetes holding positions of principal or co-investigator in several clinical trials.

Also, I participated in the publishing of 24 books in which I was author, co-author, or chapters co-author.

In this Thesis, my main scientific achievements are underlined by presenting the results of 11 of the most important studies in which I have participated.

The first important subject I have focused my research on was the epidemiology of type 1 diabetes mellitus.

1. The time-related evolution of type 1 diabetes incidence in Romania.

The purpose of this paper is to indicate the trends in evolution of the incidence of type 1 diabetes mellitus between 1996 and 2015, in pediatric patients 0 to 14 years of age, focusing on possible differences among different age groups, gender, regions or season. Results show a steeper rise in incidence than the global norm, in both genders and across all age groups, an increase which if maintained would cause a doubling of disease incidence every 14 years. Significant differences among geographic regions and seasons of diagnosis for type 1 diabetes mellitus have been shown in all age groups apart from the 0-4-year group.

2. Type 1 Diabetes in Romania: an emerging public health issue in Romanian children.

The purpose of this study was to extend research to a more comprising age group (0-17 years) and to study the time-related influences in the incidence of type 1 diabetes mellitus in this pediatric population from 2002 to 2011, being the first study that analyses the time-related trends in the incidence of type 1 diabetes mellitus in the Romanian pediatric population (0-17 years of age) that comprises the entire country. The overall incidence marked a significant increase during the study period especially in those aged 0 to 14 years, however a shift to a younger diagnostic age is a possibility.

3. The incidence of Type 1 Diabetes in special epidemiological settings: the COVID-19 pandemics.

There is a well-known link between type 1 diabetes mellitus and COVID-19, the two diseases influencing each other: patients with diabetes mellitus present with more aggressive forms of COVID-19, and the evolution of diabetes is more severe in those who have SARS-CoV-2 infection. Furthermore, there has been a surge in cases of diabetic ketoacidosis, frequently as inaugural ketoacidosis. To date, however, there is little data regarding the incidence of type 1 diabetes mellitus in the context of the pandemic, the immune implications of the viral infection making the increase of type 1 diabetes mellitus cases

very likely. The Romanian National Organization for the Protection of Children and Adolescents with Diabetes (ONROCAD) represent Romania's centralized system through which Romanian children with diabetes receive medical care. ONROCAD established the Romanian National Diabetes Register in 1996, a registry which has been renewed annually thereafter, based on data provided by physicians treating children with type 1 diabetes mellitus. ONROCAD continued to gather information on the incidence of type 1 diabetes mellitus in children after the last published data on Romanian children ages 0 to 14, in 2015. The data we gathered regarding the incidence of type 1 diabetes mellitus suggests that SARS-CoV-2 might have a role in the triggering of the disease.

- 4. Biomarkers' particularities in the Romanian population of children with Type 1 Diabetes.** The aim of this study was to characterize a group of Romanian children with type 1 diabetes mellitus focusing on pancreatic autoimmunity (evaluated by pancreatic autoantibody positivity) and endogenous insulin secretion (estimated using the levels of fasting C peptide). Specifically, the intent was to assess the percentage of children with type 1 diabetes mellitus that are positive for pancreatic autoantibodies and their level of insulin secretion (low or normal C peptide values) in relation to the child's age, gender and disease, as well as the influence of endogenous insulin secretion on glycemic control (estimated by the value of HbA1c) and on daily insulin dosage. Another point of focus was represented by the correlation between pancreatic autoantibodies positivity and fasting C peptide. The intent of the study was to contribute to the global effort of revealing the pathogenic mechanisms implicated in type 1 diabetes mellitus, with the ultimate purpose of developing a precise algorithm that would permit a more efficient prevention process. The conclusions that can be drawn from the study are as follows: in the majority of cases serum pancreatic autoantibodies are absent, the most frequently encountered pancreatic autoantibody is represented by IA-2A, the most efficient means of late diagnosis of pancreatic autoimmunity is represented by determining GADA and especially IA-2A, given their longer persistence in the patient's serum, while ICA positivity decreases after 2

years from diagnosis. In the majority of cases, fasting C peptide levels are low. A more important β cell destruction and a lower pancreatic insulin secretion are encountered at younger ages, given a more active pancreatic autoimmunity. 1 year after diagnosis, fasting C peptide levels decrease. A better glycemic control, obtained with a lower insulin dose is obtained by maintaining endogenous insulin secretion.

The second important subject I have focused my research on was the emerging associations of type 2 diabetes mellitus.

5. Non-alcoholic liver disease in Type 2 Diabetes. Nonalcoholic Fatty Liver Disease (NAFLD) is a condition characterized by excessive fat accumulation in the form of triglycerides (steatosis) in the liver. NAFLD appears in the liver of patients with no history of alcohol abuse (<10 g of pure alcohol per day in women and <20 g per day in man). NAFLD is defined as 5% or greater hepatic steatosis without hepatocellular injury or fibrosis. The aim of the study was to assess the prevalence of fatty liver in a group of patients with type 2 diabetes mellitus and to evaluate the influence of obesity on the presence of NAFLD in these patients. The presence of fatty liver was evaluated by abdominal ultrasonography. Our study showed that liver steatosis is a very frequent liver disease in patients with type 2 diabetes mellitus and also, we observed that obesity increases its prevalence. In the future, in Romania, given the increasing prevalence of obesity, it is possible for NAFLD to become the leading cause of liver disease, especially now when we have potent drugs to treat chronic hepatitis. The elevated prevalence of NAFLD had no significant differences between women and between men. Body mass index, abdominal circumference, and serum triglyceride levels had an impact on developing NAFLD, and we observed that the development of liver steatosis is not influenced by the HbA1c level. In our group, 23.9% of the cases had elevated aminotransferases along with NAFLD, meaning that these patients already presented an impairment of the liver function, also having an augmented risk of progression toward cirrhosis.

- 6. Emerging methods for steatosis and fibrosis diagnosis in patients with Type 2 Diabetes.** Usually type 2 diabetes mellitus patients are overweight and obese and have increased levels of serum triglycerides. These three factors are risk factors for significant and severe fibrosis. The aim of this study was to evaluate a population of diabetic patients regarding the severity of liver steatosis using ultrasound and of liver fibrosis using a non-invasive method – TE. Frequently patients with type 2 diabetes mellitus associate liver steatosis, diagnosed by ultrasound. As assessed by ultrasound more than half of the patients from the studied group had moderate or severe steatosis. In more than 30% of these patients we found a significant increase in liver stiffness. The practical applicability of the study is that we should perform systematic liver stiffness assessment in type 2 diabetic patients in order to identify those with significant fibrosis.
- 7. Epicardiac fat and heart function after SGLT2i intervention in patients with Type 2 Diabetes.** In the past years, epicardial fat has risen interest as a marker of cardiovascular dysfunction, but also as a therapeutic target. The aim of this study was to evaluate the dynamics of epicardiac fat and heart function after an up to one year treatment with a sodium glucose transporter 2 inhibitor in a group of type 2 diabetes patients and to evaluate the relation between epicardiac fat, type 1 diastolic dysfunction, obesity indices and metabolic outcomes. Our results show the beneficial effect of dapagliflozin on type 1 diastolic dysfunction, in association with a reduction of epicardiac adipose tissue in patients with type 2 diabetes mellitus, independent of glycemic control.
- 8. Predictors for diastolic dysfunction remission after SGLT2i therapy in patients with Diabetes.** The diastolic dysfunction of the left ventricle is a pathological condition preceding left heart failure, characterized by altered relaxation and compliance of the left ventricular myocardium. In type 1 diastolic dysfunction the impaired relaxation of the left ventricle is reversible. The aim of this study was to evaluate the possible predictors associated with the remission of type 1 diastolic dysfunction in patients with type 2 diabetes mellitus after one year of treatment with dapagliflozin.

Although the mechanisms by which this molecule improves diastolic dysfunction are not fully understood, our study research showed significant associations between the remission of type 1 diastolic dysfunction and the improvement of liver stiffness, the increase of estimated glomerular filtration rate, the increase of HbA1c, and the volume of the epicardial adipose tissue, with no association with age, body mass index, or abdominal visceral adiposity.

The third important subject I have focused my research on was the nutrition therapy interventions in metabolic diseases.

9. Evaluating the energy intake habits in patients with obesity. This study aims to establish if persons with obesity, treated by health care professionals for their metabolic diseases have an adequate intake of macro- and micronutrients, according to the published recommended dietary allowances (RDAs), per either United States Department of Agriculture (USDA) or European Food Safety Authority (EFSA), in the absence of proper nutritional assessment for intakes and of structured dietary advice and follow-up throughout the period when subjects attempt to lose weight. The study showed that, in a Romanian population, specifically in persons with obesity attempting a hypocaloric diet there are various micronutrient shortages and unbalanced fatty acid intakes. The patients in the study were under medical monitoring for obesity-related disorders but did not receive dietary counseling or supervision from a trained dietician.

10. Opinions regarding low carb diets in nutrition therapy. Nutrition has become a major research topic, not only for the purpose of losing weight, but also for the benefits of acquiring a state of well-being by adopting a healthy lifestyle. The difficulty regarding the adoption of a healthy diet consists not only in the existence of the multitude of trends regarding the dietary options but also, in the totality of the information appeared in both, the specialized literature and in ordinary articles offered to the general population through social media. Therefore, multiple debates have been generated regarding the optimal type of diet, but one thing is certain, there

is no general diet composition valid for the whole population, the adoption of a healthy nutrition is necessary to be personalized and done with the help of a specialized nutritionist. One of the debated types of diet is the low carb diet with all the subtypes included. Limiting carbs in the diet has been shown to have positive effects in numerous papers, studies, reviews, and meta-analyses, but we must be aware that when we reduce the percentage of one of the energogenic macronutrients, we always increase the percentage of the others, and this may rise other issues. Still, low carb diet may be a beneficial approach in reducing insulin resistance.

11. Healthy eating – is it possible? Probably the most important link between eating and disease is obesity, but there are many other diseases being influenced by lifestyle. Since it has been recognized by the medical community that lifestyle is a very important part of disease management, there is a continuous work to find the best solution, the best diet, the best recommendation for nonpharmacologic management. And the conclusions of this work are numerous sets of guidelines. After reading all these guidelines, one can conclude that there is no optimal distribution of macronutrients and therefore, a dietary plan should be based on individualized eating habits and preferences. The recommendation to include high amount of fruits, vegetables, whole grains products and dietary fibers is still true. It is worth to mention that the quantity of food is an important issue and that the attention traditionally paid to the glycemic index should be rather addressed to the glycemic load, a more accurate measure.

The second part of the Habilitation Thesis focuses on my future perspectives, from academic, professional, and scientific perspectives. From an academic point of view, I would like to develop the current existing teaching and knowledge base regarding diabetes, metabolic diseases, and nutrition. I aim to develop new lectures for medical students, students in nutrition and dietetics and master students broadening the spectrum of the existing topics and integrating them in the context of state-of-the art medical research areas.

From the researcher's point of view, I aim to continue the research topics already started, a work in which PhD students will have a central place being pro-actively involved in applied and theoretical state-of-the-art medical research. Part of the approached areas of research will be continuing the already started ones: insights of the epidemiology and pathogenesis of Diabetes, the pro-active search for unforeseen complications or co-morbidities.

Of course, this short list of further perspectives doesn't intend to comprise the entire area of future research since the development of science rises unforeseen new areas of research and new perspectives regarding metabolic diseases and nutrition.

Finally, having the premises of my previous training and experience and considering my future plans, I hope that by achieving the previously mentioned goals I will be a member of the academic staff who will reach the expectations of the University which formed me, my Alma Mater, the "Victor Babes" University of Medicine and Pharmacy from Timisoara.

LIST OF THE 10 REPRESENTATIVE PAPERS

1. Vlad, A.; Serban, V.; Timar, R.; **Sima A** (autor corespondent); Botea, V.; Albai, O.; Timar, B.; Vlad, M. Increased Incidence of Type 1 Diabetes during the COVID-19 Pandemic in Romanian Children. *Medicina* 2021, 57, 973. EISSN 1648-9144, IF = 2,948 <https://doi.org/10.3390/medicina57090973>, <https://www.mdpi.com/1648-9144/57/9/973>
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