„VICTOR BABEŞ” UNIVERSITY OF MEDICINE
AND PHARMACY FROM TIMIŞOARA
DOCTORAL SCHOOL
MEDICINE DOMAIN

HABILITATION THESIS

PREVENTION AND EARLY INTERVENTIONS IN THE DIAGNOSIS AND TREATMENT OF PEDIATRIC ENDOCRINE AND METABOLIC DISEASES

A B S T R A C T

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ABSTRACT

For successful results in academic medical school, perseverance and the desire for continuous education are necessary to keep up with the latest achievements and actual research directions in the field. The biggest challenge for a medical teacher is the successful combination of the academic, professional, and scientific research

I had the chance to complete my medical training in a university clinic with concerns in endocrine and metabolic diseases in children, which is why, it stimulated my curiosity and desire to know more in this field. Thus, even since the beginning of my activity in the 2nd Department of Pediatrics, in 1997, I have started my research activity within the PhD work, focused on anterior pituitary insufficiency in children.

After completing my PhD training and public presentation of my PhD thesis, I continued my research work, because of my interests in different subjects in the field. During my post-doc research I focused myself on the study of the endocrine disease in children, mainly pediatric obesity, (genetics and simple tools for diagnosis, early diagnosis methods and prevention of complications in pediatric obesity) and also the role of imaging in diagnosis of thyroid diseases.

Given my activity of more than 25 years within the UMFTVB, I decided that is the right time to write a habilitation thesis, which describes my entire scientific, professional and academic post-doc activity.

The thesis entitled ““Prevention and early interventions in the diagnosis and treatment of pediatric endocrine - metabolic diseases” is elaborated according to the recommendations of the Ministry of Education and Research (Order of Ministry of Education and Research nr. 3121/27.01.2015) and also of the Guide of preparation and writing of Habilitation Thesis of "Victor Babeș" University of Medicine and Pharmacy, Timișoara, elaborated according to the recommendations of the National Council for Attestation of University Degrees, Diplomas and Certificates (CNATDCU), approved by H.S. Nr.201/18470/18.12.2020.

The habilitation thesis presents the results of my scientific, academic and medical activity, starting from 2004 after being awarded the title of Doctor in Medicine (Ord. MEC nr 5237/2004).

The thesis is organized in four parts: (i) first part is dedicated to scientific work, (ii) second part presents the academic activity (iii) third part is dedicated to professional activity and (iv) last part includes future plans concerning the academic career development. The habilitation thesis in ends with References.

I was awarded with Licence Diploma in Medicine in 1996, when I graduated the Faculty of Medicine, Specialization General Medicine, within the Victor Babeș" University of Medicine and Pharmacy, Timișoara. I chose pediatrics as my specialty and I had the opportunity to start a teaching career in the UMFT, even since 1997,as a Junior Teaching Assistant (Preparator) at IInd Pediatrics Discipline, Department of Pediatrics, after winning the position by exam in February 1997. In the same time I have completed my professional training, as a resident doctor in Pediatrics, within the 2nd Pediatric Clinic, Clinical Emergency County Hospital, Timișoara.

In October 1997, I started my PhD training programme within UMFT, in a field that I was passionate about even since I was a Medical student, Pediatric Endocrinology, focused on anterior pituitary insufficiency in children, mainly the management of the child with growth hormone deficit. I completed my PhD research in 2004, with the public presentation of my PhD Thesis which for I was awarded Doctor in Medicine.

Given my training in two medical specialties Pediatrics and Endocrinology, my post-doctoral scientific research activity, focused, mainly on subjects in the field of pediatric endocrinology: growth and puberty, pediatric obesity and its complications, diagnosis and management of the thyroid disorders in children, rickets and vitamin D deficiency etc. The multidisciplinary approach of this pathology in children in collaboration with colleagues within UMFTVB, and, not only, including also research grants, was the basis of the results obtained. The results were published as articles in different high impact journals. I have participated, as a member, in two national research CNCSIS grants, and, one international research grant.

The main directions of my postdoc research activity included child’s obesity and imaging in thyroid disorders. In conclusion, my habilitation thesis presents three main study directions

1. Contributions to the study of obesity in children: genetics and nutrigenetics in child's obesity and simple evaluation methods of obesity in children.
2. Early diagnosis methods and prevention of the complications in obese children.
3. The role of imaging in the diagnosis of thyroid disorders in children

Within the research grant I was co-opted in 2015, *Use of nutrigenomic models for personalization of dietary treatments in obesity (NUTRIGEN)* I have participated to the elaboration of the articles, including the one published in *Applied Sciences, in 2021,"Docosahexaenoic acid and eicosapentaenoic acid intakes modulate the association of FADS2 gene polymorphism rs526126 with plasma free docosahexaenoic acid levels in overweight children" (principal author)*

In this study we observed the association between FADS2 gene variants and free plasma levels of polyunsaturated free fatty acids (PUFA) in a group of 200 overweight and obese children, taking into consideration their into account their dietary intake. The results of the study revealed that FADS2 genes polymorphism impacts plasma levels of n-3 PUFA and the presence of rs526126 low frequency allele in FADS2 gene is associated with higher plasma levels of free DHA, difference being more evident when the dietary intake of n-3 PUFA was low.

In the second study we analyzed the utility of the ultrasound method for the measurement of the subcutaneous adipose tissue thickness in the overweight and obese children. The results revealed that method is useful, both for clinical and research purposes, if tricipital and supraspinal sites are considered for evaluation. The results included in the article *„A novel method for measuring subcutaneous adipose tissue using ultrasound in children – interobserver consistency"* were published in the Romanian Journal of Morphology, in 2017.

Later on, the research regarding pediatric obesity focused on cardiovascular assessment methods, including CIMT for subclinical atherosclerosis and surrogate markers like pulse wave velocity, augmentation index, and blood pressure levels for arterial stiffness. It explores their synergy, investigates insulin resistance's role in vascular issues, and examines serum trimethylamine N-oxide (TMAO) as a potential biomarker in obese children. This research consists of four studies.

The first research direction focused on the investigation of relevant risk factors impacting the status of subclinical atherosclerosis and of arterial stiffness in obese children. The research was structured on in three research directions.

The observational study entitled “Subclinical Atherosclerosis Progression in Obese Children with Relevant Cardiometabolic Risk Factors Can Be Assessed through Carotid Intima Media Thickness” was published in Applied Sciences. The study was conducted from January 2021 to May 2021 and involved 60 children, aged 6 to 17 years old. This study focused on cardio-metabolic risk factors using clinical evaluations and targeted patient anamnesis. We concentrated on factors acknowledged for their influence on adult vascular health but not extensively explored in pediatric populations. These factors encompassed age, gender, puberty development, Body Mass Index, waist circumference, and blood pressure, all of which correlated with vascular health. Furthermore, we analyzed risks associated with pregnancy, birth weight, postnatal nutrition, family history of cardiometabolic ailments, sedentary behavior, and exposure to smoking. Our objective was to furnish additional scientific proof regarding the impact of childhood obesity and other risk factors on the advancement of subclinical atherosclerosis.

The research regarding arterial stiffness had a similar design, investigating additional risk factors in obese children. Two original papers were published, one in The Journal of Clinical medicine - “The Oscillometric Pulse Wave Analysis Is Useful in Evaluating the Arterial Stiffness of Obese Children with Relevant Cardiometabolic Risks”, and one in Children - “Evaluating the Arterial Stiffness as a Useful Tool in the Management of Obese Children”. The observational study involved 60 children, aged 6 to 18 years old. The Pulse Wave Analysis was performed in each subject using an oscillometric arteriography device, rendering surrogate markers of arterial stiffness, such as pulse wave velocity, augmentation index, and peripheral and central blood pressure levels, which were consequently introduced in the formal analysis. The same easily identifiable cardio-metabolic risk factors were examined through clinical evaluations and targeted interviews. The impact of unhealthy sleep was investigated in addition to the aforementioned risk factors.

Having confirmed the connections between these vascular biomarkers and weight excess in children, as well as having identified the most prominent cardio-metabolic risk factors for the progression of vascular damage, the second research direction was designed to analyze the synergy between these two assessment

approaches, CIMT and Pulse Wave Analysis. The original paper was published in Biomedicines under the title “Unveiling the Silent Danger of Childhood Obesity: Non-Invasive Biomarkers Such as Carotid Intima-Media Thickness, Arterial Stiffness Surrogate Markers, and Blood Pressure Are Useful in Detecting Early Vascular Alterations in Obese Children” The study involved 84 children aged 6 to 18 years old and was conducted from June 2022 to December 2022. Clinical markers such as the Body Mass Index, waist circumference, waist-to-height ratio, puberty development, the presence of acanthosis nigricans, and irregular menstrual cycles in adolescent girls were examined. Blood tests investigating metabolic and hormonal alterations were also considered. The study also focused on determining the impact of insulin resistance on these early vascular disruptions by investigating the connections between obesity, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and vascular biomarkers.

The third research direction focused on examining the value of a gut-derived metabolite previously connected to multiple disorders in adult populations, including cardiovascular and metabolic alterations: serum trimethylamine N-oxide. The study was published in Frontiers in Endocrinology and was entitled “Connections between serum trimethylamine N-Oxide (TMAO) a gut-derived metabolite vascular biomarkers evaluating arterial stiffness subclinical atherosclerosis in children with obesity”. The role of TMAO in childhood obesity has not been established, and its connections to non-invasive biomarkers of vascular health, such as the CIMT, PWV, AIx, and peripheral and central blood pressure levels, have never been studied before in children. Therefore, the study focused on establishing the extent of the connections between TMAO, subclinical atherosclerosis, and arterial stiffness in obese children. Seventy children aged 4 to 18 were involved in the research from November 2022 to May 2023.

The next research topic focused on the imaging diagnosis methods in thyroid disorders in children. At first we analyzed the usefulness of strain elastography in the evaluation of chronic autoimmune thyroiditis (CAT) in both adults and children..

The purpose of this study was to assess strain elastography's efficacy as a supplementary method to traditional ultrasound in the detection of CAT. The study involved 250 patients, of whom 180 were diagnosed with CAT. The control group consisted of 70 healthy people. it was discovered that a mean strain ration (SR) value over 1.64 was predictive of the presence of CAT. Furthermore, CAT patients

had considerably higher mean values for SR as compared to the controls. We concluded that elastography does offer useful information for the US (ultrasound) assessment of patients with autoimmune thyroiditis. (*The value of strain elastography in predicting autoimmune thyroiditis.* Diagnostics, 2020).

We continued our research following the usefulness of strain elastography in detecting chronic autoimmune thyroiditis in children. The aim of this study was to compare the elastographic characteristics of thyroid parenchyma in children with and without CAT. 52 children with CAT diagnoses and 22 children without thyroid pathology were included in our research. It was determined that a mean value of SR over 0.9 was predictive for CAT. Our findings support previous research on adults by demonstrating that SE is a helpful evaluation method for children with CAT.("*Is Strain Elastography Useful in Diagnosing Chronic Autoimmune Thyroiditis in Children?",* Applied Sciences. *2022).*

Our next research subject focused on the usefulness of shear-wave elastography in the evaluation of chronic autoimmune thyroiditis in children. 50 children with a verified diagnosis of CAT were included in the study group, and they were compared to 50 children in the control group who had no thyroid pathology and 50 adult individuals with CAT. The children in the CAT group had mean TS values that were considerably higher than those of the healthy aged-matched controls and lower than those of adults with CAT SWE elastography seems to be a method that holds great potential for the assessment of children suffering from autoimmune thyroid disease. Evaluation of TS SWE proved to be a useful supplementary diagnostic technique for people with CAT. (*Shear-wave elastography-diagnostic value in children with chronic autoimmune thyroiditis* , Diagnostics,2021)

The following research study aimed to establish a systematic diagnostic approach using multiparametric ultrasound (MPUS) to diagnose hyperthyroid diffuse thyroid disease (DTD). We conducted a retrospective study from June 2021 to June 2023, enrolling 218 subjects presenting with clinical hyperthyroidism confirmed through biochemical assessment, subgrouping various pathologies such as subacute thyroiditis, Graves' disease, painless thyroiditis, Hashimoto's thyroiditis, iatrogenic, as well as healthy controls. Using the Mach 30 Aixplorer ultrasound equipment, evaluations were performed initially in B-mode US, followed by Color Doppler and Spectral Doppler measurements, and finally, 2D Shear wave elastography (SWE). Our study offers a step-by-step evaluation algorithm for DTD diagnosis, with a very

good overall diagnostic performance (Multiparametric Ultrasound-Based Assessment of Overt Hyperthyroid Diffuse Thyroid Disease, Frontiers in Endocrinology 2023)

The summary of my scientific activity includes the elaboration of a total number of 38 ISI Web of Science indexed articles (10 as principal author, 15 as co-author) with a total of 153 citations and a Hirsch Index 6 and a cumulated impact factor as principal author FCIAP=36.

The second chapter of the thesis includes the **academic achievements** I had during my teaching career, from the position of junior teaching assistant to associate professor. My activity including practice and courses for students, to bachelor licence coordination, and, other educational activities and post university training courses, is mentioned in this chapter. I have mentioned here, also, the educational materials for medical students and resident doctors, that I have collaborated at, but, also, monographs and specialty textbooks to which I have also contributed. In the meantime, I have mentioned may activity as a reviewer for articles in journals Web of Science indexed.

In the same time, I am carrying out my **professional activity**, as a Consultant in Pediatrics / Specialist in Pediatric Endocrinology within the 2nd Pediatric Clinic, „Pius Brînzeu" Emergency Clinical County Hospital, Timișoara, I am certified on complementary studies in Diabetes, Nutrition and Endocrine diseases and Competence in General Echography.

In the last chapter, I presented the **future plans for the academic and scientific development.** Considering my professional and academic training, but, also my experience achieved during more than 25 years of teaching, medical and scientific research activities within our university, my plans aim to a continuous development in all directions.

One of my objectives is the development of the Department and the Specialty Pediatrics and, especially Pediatric Endocrinology, so necessary in our country. I propose that we succeed in developing a School of Excellence in Pediatric Endocrinology, in Timișoara, at UMFTVB.

In the long-term, I will continue my academic and scientific research activity in my field of preoccupations, developing interdisciplinary collaborations, which should allow the development on many directions. The multidisciplinary involvement of young researchers is essential, for the academic development. Together with the students and resident doctors in Pediatrics and Endocrinology, but also, through

collaborations with colleagues from other specialties, we have succeeded to build a team with very good results, materialized in papers presented in national or international scientific meetings, or, published in journals with high impact factor. I hope, some of them will be co-opted in the future team of scholars and future specialist doctors, and members of the academic community of UMFTVB, that I would be happy to guide in Pediatrics and Pediatric endocrinology.

LIST OF 10 REPRESENTATIVE SCIENTIFIC PAPERS

1. Chiriță Emandi A., Papa M.C., Abdrudan .L, Dobrescu M.A., Puiu M., Velea I.P., Paul C. - A novel method for measuring subcutaneous adipose tissue using ultrasound in children – interobserver consistency. Rom. J. Morphol. Embryol 2017, 58(1): 115-123. ISSN print – 1220-0522, ISSN online - 2066-9279, IF: 1,033

2. Mihuța M.S., Paul C., Ciulpan A., Dacca F, Velea I.P., Mozos I., Stoian D. - Subclinical Atherosclerosis Progression in Obese Children with Relevant Cardiometabolic Risk Factors Can Be Assessed through Carotid Intima Media Thickness. Applied Sciences 2021;11(22):10721 ISSN:2076-3417 IF:2,7 https://doi.org/10.3390/app112210721 WOS:000726023900001

3. Mihuța, M.S., Paul C., Borlea A., Cepeha C.M., Velea I.P., Mozos I., Stoian D. - The Oscillometric Pulse Wave Analysis Is Useful in Evaluating the Arterial Stiffness of Obese Children with Relevant Cardiometabolic Risks. J. Clin. Med. 2022, 11, 5078 ISSN: 2077-0383 IF:4,9 https://doi.org/10.3390/jcm11175078 WOS 000852832200001, PubMedID: 36079009.

4. Mihuța, M.S., Stoian D., Borlea A., Roi C.M., Velea-Barta O.-A., Mozos I., Paul C. - Evaluating the Arterial Stiffness as a Useful Tool in the Management of Obese Children. Children 2023, 10, 183. ISSN: 2227-9067 IF:2,4 https://doi.org/10.3390/children10020183 WOS:000938349400001; PubMedID: 36832311.

5. Mihuța, M.S., Paul C., Borlea A., Roi C.M., Velea-Barta O.-A., Mozos I., Stoian D. - Unveiling the Silent Danger of Childhood Obesity: Non-Invasive Biomarkers Such as Carotid Intima-Media Thickness, Arterial Stiffness Surrogate Markers, and Blood Pressure Are Useful in Detecting Early Vascular Alterations in Obese Children. Biomedicines 2023, 11,1841. ISSN: 2227-9059; IF 4,7; https://doi.org/10.3390/biomedicines11071841 WOS:001034965300001; PubMedID: 37509481.

6. Mihuța M.S., Paul C., Borlea A., Roi C.M., Pescari D., Velea-Barta O.-A., Mozos I. and Stoian D. - Connections between serum Trimethylamine N-Oxide (TMAO), a gut-derived metabolite, and vascular biomarkers evaluating arterial stiffness and subclinical atherosclerosis in children with obesity. Front. Endocrinol.2023;14:1253584 ISSN: 1664-2392, IF 5.2; http://doi: 10.3389/fendo.2023.1253584 WOS 001082885100001; PubMedID: 37850094

7. Cepeha C.M., Paul C., Borlea A., Borcan F., Fofiu R., Dehelean C.A., Stoian D. - The value of strain elasography in predicting autoimmune thyroiditis. Diagnostics, 2020, 10,874; (eISSN: 2075-4418) IF: 3,607 doi:10.3390/ diagnostics10110874

8. Cepeha C.M., Paul C., Borlea A., Fofiu R., Borcan F., Dehelean C.A., Ivan V., Stoian D. - Shear-wave elastography-diagnostic value in children with chronic autoimmnue thyroiditis. Diagnostics, 2021, 11, 248. (eISSN: 2075-4418) IF: 3,607 https://doi.org/103390/diagnostics11020248

9. Cepeha C.M., Paul C., Borlea A., Bende R., Mihuța M.S., Stoian D. - Is Strain Elastography Useful in Diagnosing Chronic Autoimmune Thyroiditis in Children? Appl. Sci. 2022, 12, 8881. (IF: 2,838) DOI 10.3390/app12178881

10. Stoian D., Borlea A., Moisa-Luca L. and Paul C. - Multiparametric ultrasound-based assessment of overt hyperthyroid diffuse thyroid disease. Front. Endocrinol. 2023,14:1300447.(IF 5,2) https://doi: 10.3389/fendo.2023.1300447