Universitatea
Transilvania
din Brașov

HABILITATION THESIS

SUMMARY

Title: "THROMBOSIS AND INFLAMMATION: FROM EVIDENCE-BASED MEDICINE TO PERSONALIZED MEDICINE"

Domain: Medicine

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BRAŞOV, 2024

Abstract/Summary

The habilitation thesis "THROMBOSIS AND INFLAMMATION: FROM EVIDENCE-BASED MEDICINE TO PERSONALIZED MEDICINE" includes my scientific, professional, and academic achievements, as well as my personal plans for further career development. In preparing this thesis, I started from the principle that habilitation in the field of medicine represents the recognition of having reached a high level of professional, academic, and scientific training.

Inflammation and thrombosis are two essential physiological processes that, when out of control, become major factors in the development of cardiovascular diseases, antiphospholipid syndrome, and other associated conditions. A multidisciplinary and interdisciplinary approach is crucial for understanding these mechanisms and their interactions, with the potential to revolutionize how we assess thrombotic risks and develop personalized therapies.

By identifying specific biomarkers and exploring the interaction between inflammation and thrombosis, early diagnosis and therapeutic interventions are achieved, having a direct impact on patient prognosis. An integrative approach involving various medical and scientific fields will offer personalized solutions for preventing and managing risks, thereby strengthening the contribution of personalized medicine to improving patients' quality of life. Addressing these topics makes an important contribution to the medical field, as it can guide the development of more effective prevention and treatment strategies based on the individual profile of patients, reducing thrombotic and inflammatory risks in cardiovascular, infectious, neuropsychiatric, and other conditions.

The first section of the habilitation thesis encompasses the main results of my professional, academic, and research activities, closely correlated with the level of knowledge in the respective research fields at the time. It highlights the most significant scientific contributions in the field, both from a classical perspective and in terms of interdisciplinarity and integrative medicine.

Chapter 1 presents the primary results of the scientific research, systematically organized into the main research domains: the assessment of recurrent thrombosis risk in patients with antiphospholipid syndrome, the role of low-grade inflammatory markers and platelet activation as predictors of thrombotic events in patients with antiphospholipid syndrome, and the evaluation of the inflammatory response in the progression of patients with various pathologies, with a brief mention of other research domains at the end.

The first research domain focused on assessing the risk of recurrent thrombosis in patients with antiphospholipid syndrome (APS), a condition characterized by the presence of antiphospholipid antibodies (aPL), associated with thrombotic events and pregnancy morbidity. This area has been a central focus of my professional and scientific career, culminating in my doctoral thesis: *“Platelet Activation Markers in Antiphospholipid Syndrome.”The primary objective of the research was to evaluate the prognostic value of P-selectin and sCD40L levels for predicting recurrent thrombotic events in patients with APS. Published results revealed that patients with APS (whether primary or secondary to systemic lupus erythematosus or other rheumatic diseases) had significantly higher levels of P-selectin and sCD40L compared to healthy controls, with these markers correlating with the occurrence of acute and recurrent thrombotic events. Statistical analysis demonstrated that P-selectin was an independent predictor of recurrent thrombosis in APS patients. Furthermore, increased platelet activation was observed in APS patients, supporting the role of P-selectin and sCD40L as critical markers for thrombotic risk assessment. These markers could be utilized to identify patients at higher risk of recurrent thrombosis and to develop new prophylactic strategies.

The second research domain explores the role of low-grade inflammatory markers and platelet activation as predictors of thrombotic events in patients with antiphospholipid syndrome (APS). Although APS is characterized by vascular thrombosis in the absence of overt inflammation, recent evidence suggests the presence of a pro-inflammatory state. The results demonstrated that APS patients exhibited significantly increased levels of hs-CRP, P-selectin, and sCD40L compared to the control group. Furthermore, hs-CRP and aCL were identified as independent predictors of recurrent thrombotic risk, while elevated P-selectin levels were associated with recurrent thrombosis. These findings suggest a more personalized approach to thrombotic risk management, based on the assessment of these markers.

The third research domain addressed in the first chapter focused on the inflammatory response and outcomes of patients with schizophrenia undergoing long-term antipsychotic treatment who were infected with SARS-CoV-2. Patients with schizophrenia exhibit significant comorbidities, such as diabetes, hypertension, and chronic pulmonary diseases, which could increase the risk of severe COVID-19. However, schizophrenia patients had a lower risk of severe COVID-19 and reduced mortality compared to the control group, despite having more comorbidities. Inflammatory markers (CRP and fibrinogen) were significantly lower in schizophrenia patients than in the control group. A potential explanation for these findings could be the rapid access to care and constant monitoring of hospitalized patients, as well as the potential effects of antipsychotics on the inflammatory response. Schizophrenia patients on long-term antipsychotic treatment demonstrated a reduced risk of severe COVID-19, and antipsychotic therapy might play a protective role in SARS-CoV-2 infection. These results highlight the need for further studies to better understand these effects.

In the fourth research domain, I explored integrative medicine, focusing on studies analyzing various natural extracts, covering two major areas with potential applicability in cardiovascular pathology and its comorbidities. The review titled “New Therapeutic Strategies in Diabetic Kidney Disease examines current and emerging therapeutic approaches for managing patients with diabetic kidney disease, emphasizing the prevention of disease progression and the reduction of cardiovascular risk. Diabetic kidney disease is one of the main complications of diabetes mellitus (DM) and a leading cause of chronic kidney disease (CKD), affecting approximately 20–40% of diabetic patients. Renal damage associated with DKD is multifactorial, involving metabolic, hemodynamic, pro-inflammatory, and pro-fibrotic factors. These include advanced glycation end-products, reactive oxygen species, activation of the renin-angiotensin-aldosterone system (RAAS), growth factors (e.g., TGF-β), and pro-inflammatory cytokines (e.g., TNF-α, IL-6). Current therapeutic strategies focus on slowing the progression of DKD and preventing cardiovascular complications. First-line pharmacological therapies used in DKD management include RAAS inhibitors (ACE inhibitors and angiotensin receptor blockers) and sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors). Therapeutic strategies in DKD are continually evolving, with novel molecules such as SGLT2 inhibitors and mineralocorticoid receptor antagonists showing promising prospects for renal and cardiovascular protection. A multimodal approach, integrating both existing and emerging therapies, is essential to optimize the treatment of patients with DKD and DM.

Chapter 2 summarizes my professional and academic achievements. My academic career began in 1995 as a teaching assistant at the Faculty of Medicine, Transilvania University of Brașov, where I conducted practical sessions in internal medicine under the supervision of Professor Dr. Mariana Rădoi. In 2000, I was promoted through a competitive process to university assistant. In 2012, I advanced to lecturer and delivered courses for the following undergraduate programs at the Faculty of Medicine: Internal Medicine (4th and 5th years), General Nursing (2nd and 3rd years), Clinical Laboratory (2nd year), and Balneophysiokinetotherapy (3rd year).

Since 2017, as a recognition of the quality of my teaching and scientific activity, I have been appointed Associate Professor.

During this time, I conducted teaching activities, delivering courses and practical sessions in Internal Medicine with students from the Medicine, Clinical Laboratory, and General Nursing programs, as well as Rheumatology with students from the Balneophysiokinetotherapy program. My doctoral thesis was developed under the supervision of Professor Dr. George Ioan Pandele from “Gr. T. Popa” University of Medicine and Pharmacy, Iași. The research evaluated the relationship between the presence of platelet activation markers and the occurrence of recurrent thrombotic events (arterial, venous, and multiple) in patients with primary and secondary antiphospholipid syndrome (APS). Special attention was also given to assessing inflammation markers such as fibrinogen and hsCRP. The results suggested the presence of a low-grade inflammatory state in APS, despite the disease being defined as a non-inflammatory autoimmune disorder. My international recognition is reflected in the number of scientific papers published in high-visibility journals indexed in international databases: 15 articles in ISI Web of Science, with 116 citations and a Hirsch index of 6.

I demonstrated management and leadership experience during the period 2015–2019, when I was elected as the Medical Director of the Brașov County Emergency Clinical Hospital. During this mandate, I coordinated the hospital's team responsible for drafting projects funded through the 2014–2020 Regional Operational Program, focusing on equipping the Outpatient Clinic and the Emergency Unit. The project "Equipping the Integrated Outpatient Clinic of the Brașov County Emergency Clinical Hospital with Medical Equipment", funded through the 2014–2020 Regional Operational Program, was developed and implemented in collaboration with representatives of the Brașov County Council. The project had a total value of 10,699,095.67 RON.

The evaluation of thrombotic risk in patients with antiphospholipid syndrome is a complex and continually evolving topic, given the heterogeneous nature of the disease, which I intend to further develop. **Emerging new research directions** will focus on integrating biological markers, advanced imaging techniques, and genetic profiles, including:

-Defining advanced biomarkers and multimarker profiles (subtypes of antiphospholipid antibodies: specific evaluation of IgA antibodies or antibodies against domain 1 of beta-2-glycoprotein I, evaluating the significance of diagnostic biomarkers in seronegative patients) to better stratify thrombotic risk.

-Evaluating inflammatory and procoagulant biomarkers such as thrombomodulin, tissue factor, neutrophils, and extracellular traps (NETs) in association with aPL.

-Identifying metabolic profiles associated with hypercoagulability in patients with APS.

-Studying genetic variants associated with coagulation (e.g., factor V Leiden, prothrombin) or inflammatory response.

-Analyzing epigenetic modifications (DNA methylation, miRNA) associated with thrombotic risk.

-Integrating thrombotic risk in the context of other autoimmune diseases (e.g., systemic lupus erythematosus) or in association with cardiovascular risk factors.

-Identifying infectious or environmental factors that may trigger thrombotic events.

-Using integrated risk models and artificial intelligence (AI) to develop algorithms that combine clinical, imaging, and biomarker data to predict thrombotic risk more accurately by analyzing complex data and identifying risk patterns.

My personal development and professional evolution plans are based on the history of my educational and professional activities so far, and obtaining the right to supervise doctoral theses represents the key to success in my future professional and scientific career, coordinated by prominent figures in the academic community at the helm of the Doctoral School of Transilvania University in Brașov. This achievement will allow my future personal development and, in addition, will offer me the opportunity to guide young doctors toward a successful academic career, ultimately integrating them into the academic elite of Transilvania University in Brașov.

September 2024

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