

**"VICTOR BABEŞ" UNIVERSITY OF
MEDICINE AND PHARMACY TIMIŞOARA
DOCTORAL SCHOOL
MEDICINE**



HABILITATION THESIS

INTERDISCIPLINARITY AND HOLISTIC APPROACH IN INTERNAL MEDICINE

A B S T R A C T

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ABSTRACT

I graduated from the Faculty of General Medicine, within the "Victor Babeș" University of Medicine and Pharmacy in Timisoara, class of 1984, MAGNA CUM LAUDE. Currently I practice medicine as a primary internal medicine physician, specialist in gastroenterology and hepatology, with competence in general and vascular ultrasound. In 2000 I presented my PhD thesis entitled *"Research on clinical, biochemical and morpho-immunohistochemical elements with prognostic value in viral chronic hepatopathies"*, under the scientific coordination of Prof. Univ. Dr. Gheorghe Dancău, at UMF "Victor Babeș" in Timișoara, being confirmed as a doctor of medical sciences in 2001, with the qualification MAGNA CUM LAUDE.

The topic of my Doctoral thesis started from the challenges related to the diagnosis and treatment of patients with chronic viral hepatitis, being at that time a national approach for the first time to this current and interesting topic. The studies of the doctoral thesis were complex associating to the laborious clinical examination, the peak paraclinical explorations and a top morphological exploration that included morphological evaluations with usual and special staining as well as immunohistochemical type with different monoclonal antibodies. All these allowed to finally result, in the chapter of conclusions, the elements with prognostic value in chronic viral hepatitis.

The habilitation thesis entitled **"Interdisciplinarity and holistic approach in internal medicine"** is in fact the synthesis of professional, scientific and academic activity, referring especially to the achievements obtained after presenting the doctoral thesis, respectively from 2000 until now.

The theme of the habilitation thesis started from the idea of highlighting the essential attributes of internal medicine, namely, the concept of interdisciplinary approach having as a corollary that of the holistic vision, that integrates unity in diversity, being structured as follows:

The first part of the habilitation thesis includes the main scientific, professional and academic achievements.

Chapter 1 extensively presents the main postdoctoral scientific achievements.

In subchapter 1.1, a short introduction is made in which it is discussed about the role and place of internal medicine in the modern era, about the necessity of regaining its pivotal position and overcoming its identity crisis in the millennium overspecialization, digitalization and over-technology. The following are presented the scientific achievements in chronological order, which are structured on several directions of research.

Thus, the first direction of research was presented in subchapter 1.2.1 comprising internal medicine at the intersection with hepato-biliary pathology, which at least in the first years of postdoctoral period continued to pursue directions of doctoral studies, subsequently acquiring new valences. There are presented in this subchapter 14 papers in extenso: in the form of review or original studies. They have been published in journals with ISSN, B+, BDI or ISI with impact factor. Thus, the first study in this category, where I was the first author, referred to the clinical-morphological correlations in portal hypertension syndrome in patients with cirrhosis of the liver, demonstrating characteristic morphological changes depending on the severity of the underlying disease. The next study, where I was the first author, was a review that started from the personal experience gained from the specializations in liver transplantation centers, having as theme the liver transplantation and the risk of viral infections at the graft level, a topic still current, representing even today a relatively difficult problem to manage, which can jeopardize the prognosis of transplanted patients. Then followed two clinical-morphological studies as the first author, regarding patients with chronic viral hepatitis, namely: the study of hepatocytic iron as well as the study of steatosis and ductular lesions, as prognostic factors, proving that iron overload and lesions of the biliary ducts present in patients with chronic hepatitis C virus, are negative prognostic factors. The next study, in which I was the first author, focused on the role of liver regeneration macro-nodules and dysplastic lesions in liver cirrhosis, as risk factors in hepatocellular carcinoma, a study that based on establishing the proliferative index at the level of nodular-type lesions, with the help of immunohistochemical staining with specific monoclonal antibodies, can specify the level of risk of these formations. It follows two morpho-clinical studies, as the first author, about autoimmune manifestations in chronic hepatitis C virus, addressing the correlations between mixed cryoglobulinemia and some less studied autoimmune manifestations such as peripheral polyneuropathies. The two studies demonstrate that patients with autoimmune manifestations characterized by the

presence of mixed cryoglobulinemia IgG-IgM generally associate histological forms with higher lesion grading and more reserved prognosis. Another of clinical-morphological design, where I was the first author, was referring to nonalcoholic steatohepatitis (NASH), is presented below in a group of diabetic patients with cholelithiasis who have been cholecystectomized, in whom a close concordance between liver damage and the degree of steatosis has not been observed, or the intensity of cytolytic syndrome. The next original study, where I was also the first author, deals with a topic of great interest related to the risk of atherosclerosis and the appearance of atheroma plaques at the carotid level assessed by imaging, in cirrhotic patients. This study demonstrated that cirrhotic patients have a high cardio-vascular risk, thus emphasizing the need for early diagnosis of atherosclerosis. Autonomic neuropathy and the associated disorders of motility of the gallbladder (GB), a paper in which I was the first author, were the topic of interest for the next study, in which the ejection fraction of GB and the dyspeptic manifestations were tracked, as well as their behavior after the administration of gabapentin, bringing into question some hypotheses related to the mechanisms involved in biliary dyskinesias in diabetics. The next study, to which I was the first author, was about comparing antibiotics vs. probiotics in the treatment of encephalopathies in liver cirrhosis. It is a study that demonstrated even 11 years ago the role of the intestinal microbiome in hepatic encephalopathy in cirrhotic patients. Biliary suffering and migraine often intersect. These aspects were analyzed in a study, in which I was the first author, in which biliary motility was tracked - evaluated noninvasively by ultrasound methods - in a group of migraine patients treated with triptanes. The NASH theme was repeated in the following study, from the therapeutic perspective, where I was also the first author. This theme was materialized in the idea of a prospective study that followed clinical, biochemical and imaging parameters in the evolution of a group of patients treated with phytoproducts with a hepatoprotective role, with encouraging results. The next study, where I was the first author, had as topic the thrombosis of the portal vein in cirrhotic patients and the possible involvement of the intestinal microbiome in this type of complication by maintaining a constant level of subclinical inflammation that can favor thrombogenesis. NASH in diabetic patients, to whom I was the author of correspondence, was the topic of the next paper in which possible correlations between intestinal dysbiosis and serum markers of inflammation were studied, with a close correlation between these variables being found. The last two studies, from this

subchapter, in which I was the first author, were dedicated to cholelithiasis and its complex connections with the intestinal microbiome, studied by NGS-type genetic sequencing techniques. The multiple implications of intestinal dysbiosis were evaluated in gallstones patients, including postcholecystectomy syndrome, were analyzed.

Subchapter 1.2.2 incorporates 6 papers published in BDI and ISI journals with impact factor, having as a research direction interdisciplinarity in digestive functional pathology, the intestinal microbiome representing a possible bridge. This part of the habilitation thesis mainly includes clinical studies related to irritable bowel syndrome either from a pathogenic perspective, from a therapeutic perspective, or in connection with particular clinical aspects related to functional pain that can often complicate the clinical picture, such as chronic pelvic pain, fibromyalgia or migraine. Only one study in this category concerned nonmotor digestive manifestations in Parkinson's disease. All these studies have as connecting points the highlighting of the involvement of the intestinal microbiome in certain pathogenetic mechanisms associated with digestive functional disorders and or the use of probiotics as a treatment method in various pathologies designed to restore the balance of the intestinal microbial ecosystem. Thus the first clinical study addresses the role of probiotic treatment in patients with irritable bowel syndrome with the predominance of constipation. In this study I was the first author, and the results obtained were satisfactory. The next study, in which I was also the first author, was also addressed to patients with irritable bowel syndrome but this time it aimed to investigate intestinal bacterial overproduction (SIBO) using respiratory tests with the determination of H₂ in exhaled air. Extra-digestive manifestations in irritable bowel syndrome can sometimes be extremely disturbing, as happens in chronic pelvic pain. As the first author, I approached this topic in the following study, where the role of gabapentin in improving some of the evaluated symptoms is evaluated, namely: cystalgia, dyspareunia and urinary urge. The next clinical study, where I was the first author, addressed the nonmotor manifestations of digestive type in elderly patients with Parkinson's disease emphasizing as early as 2016 the importance of probiotics as an alternative method of treatment, based on the restoration of the pathologically modified intestinal microbiome. The association of irritable bowel syndrome and migraine has been studied in the following paper. As the first author in this study, I thought about the approach of irritable bowel syndrome from the perspective of intestinal dysbiosis, noting that dysbiotic patients had more severe

forms of migraines as well as associations of other extra-digestive functional pathologies such as fibromyalgia, dysfunction of the temporomandibular joint or chronic pelvic pains. In the same idea is the following work, where I was the first author, which punctually addresses the relationship irritable bowel syndrome- chronic pelvic pain, against the background of pathogenetic intervention of intestinal dysbiosis that favors a latent chronic inflammation syndrome with all the consequences that derive from it.

Subchapter 1.2.3 includes a number of 9 papers on interdisciplinarity in clinical trials from various perspectives, the papers being published in BDI and ISI journals with impact factor. The first study in which I was the first author, addresses the depression/anxiety disorders often associated with irritable bowel syndrome and the extent to which certain phytoproducts could influence the general condition and quality of life of these patients of great clinical complexity. The second clinical study presented in this subchapter, to which I was the first author, refers to the study of gastric motility evaluated by non-invasive imaging methods and the related symptoms of dyspeptic type in a group of patients with Parkinson's disease. from the point of view of treatment with trimebutine as a regulator of motility of the digestive tract. The next work, where I was the first author, is a review relative to a thorny problem of current medicine, namely overspecialization. Even from the title, attention is drawn to excessive overspecialization, or "how not to see the forest for the trees". The work goes through some contemporary situations relatively frequently encountered in practice, emphasizing the limits of overspecialization in the medical field. Osteoprotegerine (OPG) and cardio-vascular diseases are the theme of the next study, where I was a co-author. The study was intended to make some correlations between OPG, vitamin D₃ and vascular rigidity indices in patients with heart failure. Diabetes mellitus tends to become pandemic and with it in the package appear more and more problems of pathology. That is why great efforts are currently being made on the prevention side of it. This category also includes the next study in which I was a co-author, which aimed to investigate whether the assessment of the percentage of body fat, carried out with dedicated equipment, associated with FINDRISC, as a predictive score for diabetes mellitus, could improve the predictability of the occurrence of diabetes mellitus to a group of apparently healthy young students. The next study started from the idea that migraine with aura is considered a cardio-vascular risk factor, but little is known about this possibility in young women without known cardio-vascular risk

factors and suffering from migraine without aura. In this study I was the first author and I followed this idea from the perspective of the involvement of intestinal dysbiosis. The study demonstrated good correlations of intestinal dysbiosis with intimate-medium thickness, measured imaging at the carotid level, as a marker of subclinical atherosclerosis and with the severity and age of migraine syndrome in women studied. The next two studies in this subchapter, where I was a co-author, had as a research topic the involvement of psychological factors in different medical situations. Thus, a paper focused on emphasizing the importance of studying psychological stress factors in coronary patients with or without coronary revascularization, as a type of therapy, drawing attention to giving increased importance to the psychological evaluations of these patients, before their inclusion in cardio-vascular rehabilitation programs. The 2nd study targeted a problem related to excessively high alcohol consumption among young people in Romania, from the perspective of psychological factors. Thus, the study highlighted the types of alcohol consumption among the young population while also analyzing the psychological factors that contributed to this abusive behavior. Another study in this subchapter, to which I was the last author, had as a research topic the behavior of the medical staff in Romania in the conditions of the Covid-19 pandemic, from the perspective of the personal and institutional stress, as well as of the numerous bioethical problems generated by it. The last study in this subchapter, to which I was the last author had aimed to present a rare and atypical case of a young, pregnant woman, who suffered from a particular form of encephalitis, often underdiagnosed, that initially was mistaken for a psychiatric disease. The case was particularly challenging because it was accompanied by a persistent, severe hypokalemia of unknown origin and put the clinicians many therapeutic problems.

Subchapter 1.2.4 comprises 7 papers and had as research direction collaborations in various pharmaco-clinical studies. They were published in ISI journals with an impact factor, between 2016-2022. A study, where I was the author of correspondence, has aimed to analyze the effects of aqueous solutions of phytoextracts in malignant melanoma. Then 2 studies on betulinic acid, conducted a few years apart, where I was the corresponding author to one and to the other I had equal contribution, in which the effectiveness of some types of extracts starting from certain phytoproducts was highlighted, demonstrating the ability to mitigate the harmful effects of ultraviolet radiation on the skin. Other 2 studies in which I was a co-author demonstrated the effectiveness of thermodynamic methods in assessing compounds

from certain medicinal formulas. Then came a study, in which I was a co-author where the role of rutin as -type flavonoids as an anti-inflammatory and antitumor factor in tumor cells in malignant melanoma was studied. And the last study in this subchapter, where I was a corresponding author, had as topic of research alternative therapeutical approach in oncology highlighting the role of certain phytoextracts from the spontaneous flora of Romania as antitumor agents in skin and breast tumors.

Subchapter 1.2.5 includes several mini-reviews, published as the first, only or last author, over time in Family Medicine, a journal with ISSN, which aimed at a methodological activity of continuous medical education of the family doctor, targeting numerous topics of medical interest. Such were approached themes such as: TIPS as a method of therapy in HTP syndrome; chronic hepatitis B mutated form, Ag HB e negative; Meckel, diverticulum, as an obscure source of digestive bleeding in adult; clinical significance of serum viral markers in liver diseases; mechanisms involved in the chronicling of viral hepatitis C; Barrett's esophagus and its long-term problems; some complications of liver cirrhosis of the type of hepato-renal syndrome diagnostic and therapeutic aspects and the last study in this category in relation to NASH, relative to diagnostic methods and treatment possibilities.

Subchapter 1.2.6 includes 7 titles of books and monographs where I contributed as an editor, first author or co-author.

Subchapter 1.2.7 comprises postdoctoral grants. I participated in 2 national grants type CNCSIS and CEEEX, as a member having as main research topic nutraceuticals and their beneficial effects in different pathologies. I was also the project manager of 2 research projects such as a workshop for young people.

Subchapter 1.3 includes the list of papers presented in the country and abroad and published in summary in journals with impact factor or volumes of congress summaries. Thus, I had 39 papers as first author published in summary in journals with impact factor, 4 co-author papers, published in summary in journals with impact factor, 10 papers as first author published in summary in volumes of international congresses, 22 papers presented at national congresses with international participation, as first author or co-author, published in summary in volumes of congress and 16 papers presented at national congresses and published in journals without ISI quotation or volumes of abstracts.

Chapter 2 deals with academic activity, consisting of the following subchapters: 2.1 as an introduction in which I presented the motivation for choosing the academic

career; 2. 2 in which I presented the academic path since entering the UMFT in 1992 as an assistant professor at the Discipline of Medical Semiology I and until now, in the same discipline,; as a associate professor, passing also through the stage of senior lecturer for a long time; 2.3 which refers to the courses for students developed over time, a total of 10 of which some in new directions. At some I have been editor, first author, co-author or author of chapters, 2.4 includes a list of support for practical works for students; 2.5 includes the list of postgraduate courses that we have organized in the discipline; 2.6 includes the list of students bachelor thesis conducted over the years; 2.7 contains the list of scientific student activities; 2.8 includes the list of various other academic activities such as participation in various examinations and commissions, organization of medical events for doctors and nurses.

Chapter 3 refers to the professional activity comprising the following subchapters: 3.1 formulated as an introduction to the professional activity in which reference is made to aspects related to the motivation to do medicine and the way in which over the years I have understood to carry out this activity; 3.2 in which I have detailed the professional path from the completion of medical studies at the University of Medicine and Farmacy “V Babeş” in Timisoara until now, pointing out the main stages of professional development, related to obtaining professional titles, specialties, skills and various professional capabilities, participation in various, trainings and workshops, which gave me the possibility to progress in terms of professional level.

Chapter 4 includes the plan of personal development, having the following subchapters: 4.1, the plan of academic career development; 4.2, the plan of scientific career development and 4.3, the plan of professional career development.

The 2nd part of the habilitation paper includes the Bibliography with all the references related to the text of the thesis, as well as the List of the 10 representative papers.

LIST OF THE 10 REPRESENTATIVE PAPERS

1. **DOINA GEORGESCU**, Ioana Ionita, Ana Lascu, Emil-Florin Hut, Simona Dragan, Oana-Elena Ancusa, Mihai Ionita, Despina Calamar-Popovici, Liviu-Andrei Georgescu, Daniel-Florin Lighezan. Gallstone disease and bacterial performance of gut microbiota in middle aged and older people. *INT J GEN MED* 2022;15: 5513 ISSN: 1178-7074 **IF 2,445** doi: 10.2147/IJGM.S350104
2. **DOINA GEORGESCU**, Alexandru Caraba, Ioana Ionita, Ana Lascu, Emil Florin Hut, Simona Dragan, Oana Elena Ancusa, Ioana Suceava, Daniel Lighezan Dyspepsia and gut dysbiosis in female patients with postcholecystectomy syndrome. *IJWH* 2022;14:41 ISSN: 1179-1411 **IF 2,59** doi: 10.2147/IJWH.S342882
3. Daniela Reisz, Iulia Crișan, Andrea Reisz, Raluca Tudor, **DOINA GEORGESCU**. Stress and bio-ethical issues perceived by romanian healthcare practitioners in the Covid-19 era. *IJERPH* 2021,18,12749 ISSN 1660-4601 **IF3,39**
4. Pah, A. M., Buleu, N. F., Tudor, A., Christodorescu, R., Velimirovici, D., Iurciuc, S., Rada, M., Stoichescu-Hogea, G., Badalica-Petrescu, M., **GEORGESCU D.**, Nutiu, D., Iurciuc, M., Dragan, S. Evaluation of psychological stress parameters in coronary patients by three different questionnaires as pre-requisite for comprehensive rehabilitation. *BRAIN SCIENCES* 2020;10(5):316; ISSN 20763425. **IF 3,394** <https://doi.org/10.3390/brainsci10050316>
5. **DOINA GEORGESCU**, Mircea Stefan Iurciuc, Ioana Ionita, Simona Dragan, Mihaela Muntean, Oana Elena Ancusa, Daniela Reisz, Mihai Ionita, Daniel Lighezan Migraine without aura and subclinical atherosclerosis in young females: is gut microbiota to blame? *MEDICINA* 2019;55(12):786 ISSN 1648-9144 **IF 1,205** <https://doi.org/10.3390/medicina55120786>
6. **DOINA GEORGESCU**, Mircea Iurciuc, Ioana Ionita, Liviu-Andrei Georgescu, Mihaela Muntean, Ana Lascu, Mihai Ionita, Daniel Lighezan. Portal vein thrombosis

and gut microbiota: understanding the burdem. *REV CHIM* 2019;70(6): 2181-2185
ISSN 2668-8212 **IF 1,6** <https://doi.org/10.37358/RC.70.19>

7. **DOINA GEORGESCU**, Mircea Stefan Iurciuc, Izabella Petre, Liviu Andrei Georgescu, Florin Szasz, Ioana Ionita, Oana Elena Ancusa, Mihai Ionita, Daniel Lighezan Chronic pelvic pain and irritable bowel syndrome: is subclinical inflammation bridging the gap? *REV CHIM* 2019;70(10): 3634-3637 ISSN 2668-8212 **IF 1,6** <https://doi.org/10.37358/RC.70.19>
8. Buleu FN., Luca CT, Tudor A, Badalica-Petrescu M, Caraba A, Pah A, **GEORGESCU D**, Christodorescu R, Dragan S. Correlations between vascular stiffness indicators, OPG and 23-OH vitamin D3 status in heart failure patients. *MEDICINA*. 2019; 55(6) ISSN 1648-9144. **IF 1,205** <https://doi.org/10.3390/medicina55060309>
9. **DOINA GEORGESCU**, Daniela Reisz, Camelia Vidita Gurban, Liviu Andrei Georgescu, Ioana Ionita, Oana Elena Ancusa, Daniel Lighezan Migraine in young females with irritable bowel syndrome: still a challenge. *NEUROPSYCHIATRIC DISEASE AND TREATMENT* 2018;14:21-28 ISSN 1178-2021. **IF 2,426** doi: 10.2147/NDT.S144955
10. **DOINA GEORGESCU**, Ancusa OE, Georgescu LA, Ionita I, Reisz D. Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope? *CLINICAL INTERVENTION IN AGING*, 2016; 11:1601-1608; ISSN 1178-1998. **IF 2.3** doi: 10.2147/CIA.S106284