"IULIU HAȚIEGANU" UNIVERSITY OF MEDICINE AND PHARMACY CLUJ-NAPOCA
DOCTORAL SCHOOL

HABILITATION THESIS

Field: MEDICINE

Clinical and biological effects of artificial and natural physical factors. Answers and challenges in medical rehabilitation

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ABSTRACT

The current habilitation thesis is a synthesis of an important part of my profesional, academic and scientific activity after having obtained the title of Doctor in Medicine in 2012, and also includes future plans and projects for further development of my profesional career and research activity.

The habilitation thesis is structured in five sections, the last one including the references.

The first chapter (A) briefly presents data related to medical rehabilitation and research areas: balneology, human bioclimatology, physical medicine by pulsed electromagnetic field waves, neurological rehabilitation.

The second chapter (B), with two subchapters, presents the evolution of my professional and academic career.

My medical and professional career in the specialty of rehabilitation, physical medicine and balneology, started with the residency period (2002-2007), the confirmation as a specialist by Order of the Ministry of Health no. 2140/2007, continued as a specialist (2007-2012) and subsequently as a consultant (2012-present, June 2012 by Order of the MH no. 848/2012). My clinical activity in the field of medical rehabilitation has been carried out since 2013 to the present at the Clinical Rehabilitation Hospital Cluj-Napoca, where since 2018 I have been a member of the Scientific Board and since 2019, a member of the Coordination Commission for revaluating hospital accreditation.

I obtained by examination many professional competences: certificate in general ultrasound, musculoskeletal ultrasound in 2009, certificate in health service management in 2010, certificate in osteodensitometry, International Osteoporosis Fundation, 2007, certificate of project manager in 2012, 2016, certificate of mediator 1 (analysis of conflict, negotiation techniques, mediation techniques, mediation legislation and ethics) in 2013, a course attendance certificate in "Botulinum toxin injection", in 2016.

From May 2015 to February 2017, I was a member of the Medical Rehabilitation Commission, by Order of the MH 345/2015. One of my priorities, which was subsequently materialized, was the reintroduction of training programs for specialty residents in spa resorts, especially that some of them will carry out their professional activity here.

In 2018, I received the Diploma of Ambassador of Romanian Balneology, at the National Congress of Rehabilitation, Physical Medicine and Balneology, organized in Cluj-Napoca in the period 22-26 May 2018, a distinction offered for my entire activity of research of natural therapeutic factors and promotion of spa resorts. In 2018, I also had the honor of receiving the Prize of Scientific Excellence in Balneology for the study in balneology entitled "STRUCTURAL AND ULTRASTRUCTURAL CHANGES IN EXPERIMENTALLY INDUCED ALCOHOLIC LIVER INJURY AFTER CONSUMPTION OF CARBONATED MINERAL WATER FROM BAILE TUSNAD". At the Days of UMPh Cluj-Napoca, 2018, I obtained the First Prize in the poster section, surgical specialties. Authors: Daniel Oltean Dan, Gabriela Bombonica Dogaru et al. Presentation – Using pulse short waves (Diapulse) facilitates bone reconstruction in vivo.

Through collaboration with Băile Tuşnad spa resort, I developed a "Program of therapeutic education and medical rehabilitation for patients with chronic obliterating arteriopathy" and I conducted studies on carbonated mineral waters, mofettes, and studies of human bioclimatology. In Ocna Sibiului resort, I initiated studies related to the effects of salt mineral waters, sapropelic mud, in degenerative articular diseases, and in Băile Govora, studies of aerosol therapy-inhalotherapy with iodine, sulfur, bromine mineral waters in the rehabilitation of respiratory diseases. Also, in 2019 I initiated the campaign "Training for effective spa treatment and consolidation of spa treatments".

In 2019, through the Romanian Association of Balneology, I was a partner in the organization of the event "Discover Romania - Balneotherapy in Romania", a Conference of the Joint Research Center (JRC) – General Directorate of the European Commission, based in Ispra, in the context of the taking over by Romania of the Presidency of the Council of the European Union. I had the honor to represent Romania, with the presentation "Research clusters, prevention and health facilities in balneological centers of Transylvania" http://bioclima.ro/Ispra2019.php. Since 2016, I have been the Vice-President of the Romanian Association of Balneology, the founding President of the Cluj branch, and since 2015, the Vice-President of the Romanian Society of Physical Medicine, Rehabilitation and Balneoclimatology. In 2008, I obtained my diploma of Bachelor of law and legal sciences.

My entire medical training activity was based on my desire to acquire and develop the knowledge and skills of a specialist in medical rehabilitation and balneology. At present, my professional expertise in this specialty has been recognized nationally and internationally, and I have been invited as a speaker in national and international meetings and courses.

My academic activity started in 2011, when following competition I obtained the position of instructor at the Discipline of Medical Rehabilitation of the Faculty of Medicine of "Iuliu Haţieganu" University of Medicine and Pharmacy, and in 2016, following my academic and research activity, I obtained the title of assistant professor by competition.

My teaching activity is currently dedicated to the 5th year students of the Faculty of Medicine, through medical rehabilitation courses and practical work, as well as courses and training of balneophysiokinetotherapy, courses of the master program "Techniques and methods of rehabilitation of patients with rheumatic diseases", courses of the master program "Medical assistance specialized in intensive care". From November 2015 to the present, I initiated and coordinated the first postgraduate course on intra-articular infiltrations and ultrasound as part of the discipline, from 2017 to the present I initiated postgraduate courses of balneology, balneo-prophylaxis, and since 2015 I initiated and coordinated postgraduate courses of neurological rehabilitation. I have been a coordinator and refounder of the student scientific group "Medical rehabilitation" since 2012 to the present. I am a supervisor of bachelor theses, a supervisor of dissertation theses (finalized and defended 61), a member of many specialty examination boards. Since 2019, I have been involved in the Online English Master Course in Balneology, Balneo-Prophylaxis and Spa Tourism - Educational Program Coordinator.

Since 2016 I have been a deputy editor-in-chief, a member of the peer review board of the Balneo Research Journal, Emerging Sources Citation Index ESCI - Science Thomson Reuters. My research activity has materialized by the publication of 18 articles in ISI rated journals with impact factor – 4 articles in Q1 journals, 2 articles in Q2 journals, 64 articles in ISI rated journals without impact factor, 33 articles in IDB journals, articles published as abstracts in journals and volumes of scientific meetings with ISBN or ISSN 63 abstracts. Participations in national and international scientific meetings, as an invited speaker/speaker, more than 40.

In 2018, through the Romanian Association of Balneology, whose current Vice-President I am, I became a member/partner of the InnovaSPA interregional cooperation project - Innovative health solutions for thermal spa regions, financed as part of the interregional cooperation program of the European Commission - Interreg Europe, Priority Axis 1: Research, technological development and innovation of the Regional Operational Program, implementation period 2018-2022 – Promotion of technological transfer in the spa sector, No. PGI05018.

During the activity with students, the main objectives have been to pass on knowledge and to train the skills required for the medical profession, to inspire the interest in medical rehabilitation and to create an academic environment where students can express themselves.

The third chapter (C) is divided into two subchapters, and the second subchapter is subdivided into seven sub-subchapters (C.2.1-C.2.7).

In section C.1., the scientific studies and achievements in the pre-doctoral period are briefly described. The first research directions were in the field of physical medicine and medical rehabilitation, materialized in the elaboration of the doctoral thesis entitled "Experimental and clinical contributions regarding the role and place of high-frequency pulsed currents in the rehabilitation of patients with rheumatic diseases" (Order of the MH 6508/19.12.2012). As a result of the three studies of the thesis, with clinical applicability, I can mention the evidencing of structural and ultrastructural changes in the adrenal glands, with alterations of the hormonal synthesis and secretion function, highlighting in this way the usefulness of the application to the lumbar area, before application to the somatic area, at different pulsed short wave parameters, used in our clinical activity. Also, we can mention the influence of pulsed short waves on bone metabolism, following determinations of the biochemical markers of bone formation turnover, with a role in bone remineralization, alkaline phosphatase and osteocalcin. Rehabilitation treatment should be initiated as early as possible in patients with algoneurodystrophy; pulsed short waves can influence the clinical and functional picture, bone structure changes, having a role in the improvement of quality of life in these patients. Our studies demonstrated the local as well as the general, systemic influence of pulsed short waves, the changes induced being mostly strictly dependent on the parameters used. In 2015, I elaborated the monograph "Cellular studies regarding pulsed short wave treatment" published by Editura Balneară, Bucharest, 2015.

Section C.2 presents the scientific research activity in the post-doctoral period (since 2013), which continues the initial directions and develops new research areas.

Section C.2.1. **Experimental studies regarding bone consolidation facilitation methods by using pulsed electromagnetic field waves and titanium implants covered with biomimetic composites.** As a conclusion to the two studies, it can be said that our results indicate the fact that high-frequency pulsed electromagnetic field waves (HF-PEMF) generated by a Diapulse device facilitate bone healing by reducing the duration of consolidation, particularly in the early stage of fracture healing. Further studies should elucidate the molecular mechanisms of the stimulating effects of HF-PEMFs on fracture healing, and more clinical studies are needed to see the impact of HF-PEMFs on fracture healing in humans. Moreover, the concomitant use of HF-PEMF waves, along with the covering of titanium implants with hydroxyapatite (HAPc) promotes a synergistic effect on fracture healing. Consequently, these methods used concomitantly can be employed in clinical applications, proving a superior approach to changing the biomedical implant surface.

Section C.2.2. **Contribution of pulsed electromagnetic field waves in the remineralization of maxillary alveolar bone structures – efficacy in oral rehabilitation.** Pulsed electromagnetic field waves used in oral rehabilitation represent a valid physical therapeutic method, which has allowed obtaining results in alveolar bone regeneration in the case of patients with periodontal disease. The protocol proposed by application of pulsed short waves for the treatment of alveolar bone loss in diabetic patients represents a less invasive alternative compared to periodontal flap surgery, even when aggressive bone loss is present.

Section C.2.3. **Crenotherapy – Cellular and subcellular effects, biochemical effects.** The objective of the two experimental studies was to investigate the effects of mineral water from spring 3 in Băile Tușnad, indicated in chronic hepatic diseases. We attempted to evidence potential changes in the liver following

administration of ethyl alcohol in experimental animals, the differences in the anatomopathological picture by electron and optical microscopy between animals that drank tap water and those that drank mineral water from spring 3 in Băile Tuşnad, after cessation of alcohol administration, as well as to study the biological effects, and possibly the hepatoprotective effects of mineral water from spring 3 in experimentally induced alcoholic liver disease on hepatic tissue, biochemical aspects. The conclusion of these studies was that following optical and electron microscopy analyses, mineral water from spring 3 in Băile Tuşnad has potential hepatoprotective properties, through its capacity to diminish the toxic action of alcohol in hepatocytes and to maintain the liver structure and function extremely close to normal. Further clinical studies are required; at present, there are only clinical observations. The general picture regarding the chemical components of a therapeutic spring should always be kept in mind, an important role being played by the absorption of these components.

Section C.2.4. **Human bioclimatology studies regarding the perception and influence of meteorological conditions on rheumatic pain in Romania.** The main objective was to analyze the perception of the influence of various weather conditions on patients with degenerative rheumatic pathology. We also investigated which of the meteorological parameters is perceived by patients as influencing the most the intensity of articular pain. In this study, we aimed to examine the different concepts of human biometeorology (meteosensitivity, meteotropism) applied to persons with rheumatic diseases. The conclusion of the study shows that most of the interviewed persons (more than 75%) consider that their pain is influenced by weather, which is in accordance with other results reporting that 92% of the respondents consider that their symptoms are influenced by weather. For the majority of the patients, pain becomes unbearable when air temperature drops (73.79% of the subjects reporting this), when relative humidity increases suddenly (65.81%), when fog/foggy air is present (46.72%), when nebulosity increases suddenly (69.80%). The study shows that the meteorological factors which mostly influence the intensification of articular pain are: low atmospheric pressure, low temperature and high humidity.

Section C.2.5. **Efficiency of medical rehabilitation treatments/balneotherapy in neurological diseases.** My interest in this field is supported by the many published articles, my involvement in the development of a medical telerehabilitation project, participation in conferences, the development of new neurological rehabilitation programs, such as the introduction of virtual therapy, robotics in spa resorts. I conducted a number of studies aimed at monitoring the clinical efficiency of natural therapeutic factors in Băile Tuşnad for the continuation of rehabilitation treatment in patients with Parkinson's disease and post-stroke patients in a spa and climatic resort. The conclusion of the studies was that natural therapeutic factors, such as carbonated mineral water baths, mofette therapy, aerotherapy, along with kinetotherapy, massotherapy, electroanalgesia, indicated in treatment, influenced the clinical and functional picture, inducing a significant improvement in the quality of walking, balance, the independence and quality of life of the patients. The results of these studies are in agreement with international studies that showed the fact that the mid-term and long-term beneficial effects of CO2 baths and spa treatments can be obtained only by serial applications that determine their final efficacy. It was demonstrated that balneotherapy methods do not only lead to favorable motor changes, but also to a positive effect on patient's mental state. Public health/prophylaxis policies should take into consideration the possibility of subsidizing two rest and treatment tickets per year so that the most vulnerable persons can benefit from two treatment courses per year, in order to maximize the beneficial effect of balneotherapeutic treatments. Continuing the medical rehabilitation treatment in the absence of contraindications in spa and climatic resorts is extremely important and necessary for patients with chronic neurological diseases.

Section C.2.6. **Balneotherapy – Effect of natural carbonated mineral water and mofette on the oxidative stress/antioxidant balance in experimental myocardial ischemia.** The aim of these studies was to

observe and quantify the effect of carbonated mineral water from spring 7 in Băile Tuşnad and mofette on oxidative stress markers in myocardial ischemia induced in rats and to histologically evaluate myocardial tissue, in order to assess whether there is a beneficial effect of these non-pharmacological treatments. The composition of the mineral water used in this experimental study is rich in carbon dioxide, this property being important in reducing the ischemic effects that occur after isoproterenol administration, demonstrated by a significant improvement of all oxidative stress parameters and also, the improvement of characteristic histopathological changes as a result of myocardial ischemia. The results also showed the positive effects of exposure to natural mofette therapy in Băile Tuşnad, through a reduction of oxidative stress, a significant improvement of the antioxidant status, an amelioration of inflammatory infiltrate and the repair of necrotic areas by collagen proliferation, on histological examination. However, periodic analysis of the physical and chemical properties of mineral waters and natural mofettes is important. Experimental studies regarding the biological effects and the action mechanism, as well as other clinical studies of the therapeutic effects are also necessary. These are the first studies performed regarding the therapeutic efficacy of treatment with carbonated mineral water and natural mofette in experimental myocardial ischemia.

Section C.2.7. **The antioxidant and anti-inflammatory activity of the nutraceutical compounds liposomal curcumin and epigallocatechin gallate in experimental models.** This study offers a new perspective for therapeutic strategies to improve hepatic lesions related to acetaminophen overdosage. Our results provide evidence that liposomal curcumin can exert a protective effect against hepatotoxicity induced by acetaminophen, through a reduction of NOx and MDA production, an improvement in thiol and catalase levels and a decrease in serum concentration of TNF-α, MMP-2 and MMP-9. Consequently, the liposomal curcumin formula can be a promising therapy for acetaminophen-induced hepatic lesions, with beneficial effects on oxidative stress and associated inflammation. Studies on the antioxidant and anti-inflammatory properties of the epigallocatechin gallate (EGCG) compound, incorporated in liposomes (L-EGCG) have opened a new research direction regarding the efficiency of natural compounds incorporated in nanoliposomes, in experimentally induced diabetes mellitus in rats.

The fourth chapter (D) describes the future professional development plans and the research perspectives.

My permanent aim was and will be to dedicate my entire professional experience to patients and to the improvement of professional recognition by individual study and participation in scientific events. The main objectives of my future professional development are the continuous updating of the most recent achievements in the field of medical rehabilitation and balneology, the rapid adoption and the application of the new therapeutic options for the benefit of patients. I will continue my collaboration regarding the clinical and research activity, the organizational activity in spa resorts. I consider that spa resorts are a place of HEALHTY and ACTIVE aging!

Within the department, I will ensure the academic environment that creates the premises for didactic and scientific performance. In faculty and university, I will support all actions aimed at promoting performance in education and medical research.

The teaching activity intended for students and the training of resident doctors are essential components of academic activity. I will permanently ensure the quality of courses, practical work, the student group, the application of modern methods in education allowing students to develop practical skills, the free expression of personal concepts and clinical judgements, all in the general context of empathy and respect for patients.

Scientific research will represent an important part of future activity. My research activity will take several directions. In the first place, it will be focused on topics related to neurological prevention and rehabilitation, cardiovascular rehabilitation, e-health systems, the study of medico-legal aspects in persons with disabilities.

I will continue the idea of implementing a telerehabilitation platform for monitoring and increasing the quality of life of patients with neuromotor disabilities, extended to some spa resorts through research projects. I will continue research on the biological effects, the cellular and subcellular action mechanism of various forms of currents used in physical medicine, in our clinical activity. Another research area in which I will continue to work is balneology, the scientific research of natural therapeutic factors, clinical studies, experimental studies, research/structural projects, development of spa tourism. In balneology, the importance of the study of natural resources is essential, providing information about the therapeutic properties of natural factors, their contribution to our health, the biological mechanisms by which they act on the organism. Both mofettes and carbonated mineral waters are used in the rehabilitation treatment of cardiovascular, neurological, rheumatic diseases. We started all the procedures to find eligibility solutions for the development of a research center to study the therapeutic effects of mofettes/carbonated mineral waters in Băile Tuşnad area.

I will participate in the organization of scientific meetings, conferences, round tables, in the application of research projects. I will provide assistance and support to all my colleagues who wish to develop research and to publish important papers, as well as to doctoral students, who should complete their doctoral research years with papers published in ISI journals.

Our specialty of rehabilitation, physical medicine and balneology is extremely generous in offering interesting and extremely useful research areas. A valuable study requires a team of valuable researchers. Training and coordinating such a team are a permanent challenge, and also an important task that I wish to accomplish in order to address important topics and studies, which will increase the national and international visibility of our Faculty and University.