“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY
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CONTRIBUTIONS TO THE BIOLOGY AND THE PATHOLOGY OF THE MUSCULOSKELETAL SYSTEM IN ROMANIA

-SUMMARY-

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SUMMARY

My habilitation thesis was a welcomed opportunity to explain my interest and my dedication with which I have served for over three decades on all levels of my activities as a university associated doctor- scientific, academic and professional- two issues that I am very fond of: metabolic bone diseases and parathyroid gland disorders. As a matter of fact, Professor Parhon has made significant and little-known experimental contributions on animal models to hypocalcemia related disorders.

The thesis is structured on these dimensions and also on the most important achievements of my university career, in chronological order.

The fundamental pillar of my entire subsequent evolution is my PhD thesis regarding postmenopausal osteoporosis, one of its first kind to address this topic in Romania, under the guidance of the extraordinary scientist who was acad. St. Milcu. In this thesis I have capitalized the existing equipment in the National Institute of Endocrinology in Bucharest- the bone X-ray densitometer- a tool that diagnoses osteoporosis through the DXA technique, the only one existing in the country in those times, and the large number of patients who came in our institution. I have also included in my thesis my personal experience and researches conducted in several international scholarships: the first measurements of 25 OHD in Romanian patients performed in the Chapuy MC laboratory (at INSERM Lyon) and the demonstration in bone cell cultures that glucocorticoids directly stimulate bone resorption (Umea University, Sweden). These results were published in the prestigious American journal of bone metabolism-JBMR (49 international citations) and brought me the membership of the American Society of Bone and Mineral Research in 1996.

Meanwhile, with the consent of Professor C. Dumitrache, I lectured probably the first courses dedicated to bone metabolism and postmenopausal osteoporosis. Keeping in touch with international experts I understood the need of two decisive organizational structures for the development of the field of bone metabolism disorders on an international scale: a dedicated study center and a scientific society.

The development of the National Center for Clinical and Biological Research in Osteoporosis (2000) was possible as a result of a national grant obtained through competition (Project Director- Professor C. Dumitrache, Executive Director- Dr. D. Grigorie) and included essential substructures needed for the study and clinical approach of patients with postmenopausal osteoporosis and secondary osteoporosis: the first laboratories in Central and Eastern Europe for bone densitometry and bone markers and calciotropic hormones measurements.

Using the CNCCBO infrastructure, I contributed to the continuous medical education of doctors in various specialties (rheumatology, gynecology, orthopedics etc.), chemists, biologist and undergraduate students who were able to write their original theses and articles. In the CNCBO undergraduate students, PhD students, residents and specialists were trained and taught to capitalize their research through publications. In my turn, with the help of the team I have created, I was able to produce original national and international contributions on the pathogenesis and treatment of postmenopausal osteoporosis and secondary osteoporosis. Among the absolute international priorities, I could cite: the first international demonstration of age-related increase in osteoprotegerin levels (55 international citations), one of the largest European epidemiological study regarding vitamin D in Romania (2008-29 citations), the first familial genetic screening in a family with primary hyperparathyroidism-jaw tumor syndrome- a national priority which also highlighted a new mutation that additionally increases the risk of parathyroid carcinoma. The mutational analysis was performed in collaboration with Professor ML Brandy from University of Florence. The use of Denosumab as a treatment in primary hyperparathyroidism was also the first observational study published in 2014 and served as a "proof of concept" for introducing it since 2022 in the international treatment guidelines.

One special interest of mine is and has been the epidemiology of hip fractures in Romania. My team together with International Osteoporosis Society (IOF) experts have developed the Romanian FRAX model based on the epidemiology of hip fractures in Romania. This placed our country on the 9th place in the EU in 2011 (www.shef.ac.uk/FRAX). This Romanian risk model was published in a prestigious American journal in 2013, with 66 international citations, and served as a model for other countries. Based on the Romanian FRAX I have published, in an international journal, the Romanian diagnostic and treatment guidelines for osteoporosis. By developing the Romanian FRAX model, we have made available to general practitioners a free and simple tool for

identifying patients at high risk of fracture. I have held at least a hundred conferences in all major cities promoting the FRAX model in over a decade. In 2019 we published one of the largest European studies so far on the epidemiology of hip fracture (194. 369 patients) and we were able to demonstrate that in Romania, the standardized incidence of hip fracture increased by 30% in the last decade, unlike other European countries. This data, although national, were also presented at the American Congress of Osteoporosis in 2021. This year I will present to the ASBMER the Romanian data of the epidemiology of hip fracture in the pandemic years (2020-2021), also an original contribution, as the publishing countries have data for only one year (2020).

In 2019 I was welcomed in the group of experts of the International Society of Osteoporosis as a recognition of my activity in the field of Romanian and international osteoporosis epidemiology. As a member, I have contributed to the development of a guideline on screening for increased risk of fracture in EU countries, which has been accepted for publication this year in Archives of Osteoporosis and will be submitted for acceptance to the EU Health Commission.

The other strong pillar for the education in osteoporosis provided for Romanian specialists with an interest in bone metabolism was founding of the Romanian Society of Osteoporosis and Musculoskeletal Diseases (SROBMS) in 2009. Under my presidency, this interdisciplinary society has been carrying out for over 10 years a nationally and internationally recognized activity of promoting education in osteoporosis and training of various specialties doctors through courses, symposiums and a strong, active social media. SROBMS is regularly followed by many major national and international osteoporosis societies. Every year, famous European and American experts have spoke at the national symposium, which makes SROBMS a school of ideas and collaboration. Born out of those collaborations were the mutational analysis for PHT-JT syndrome with Professor ML Brandi, a project of residents exchange with Professor Andrea Palermo (Rome) and numerous published studies and a scholarship for a biologist with Professor Ulf Lerner (Chairman of the PhD Committee in Sweden).

The Romanian Society for Osteoporosis and Musculoskeletal Diseases elaborates guidelines based on national epidemiological data thus making national risk criteria and placing Romania in the elite of EU countries. At the last year`s symposium, the criteria I have proposed for defining the very high risk category of fracture were adopted, the

epidemiological data they were based on being national data and using the Romanian FRAX model.

In 2009 SROBMS was one of the few national and international societies that was reflecting the new concept of musculoskeletal diseases, a concept that was first devised two decades ago by accumulating evidence on the age-related reduction of muscle mass and strength-sarcopenia- and highlighting the role of falls in the pathophysiology of fractures. In a 2013 editorial I suggested the need for an operational definition of the age-related musculoskeletal decline and I also developed the Romanian criteria of some sarcopenic criteria.

Besides the study of osteoporosis, the other topic to which I have dedicated three decades of research, didactic and professional activity, are parathyroid gland disorders. Starting with a solid research training achieved during two scholarships in the molecular biology of PTH (Harvard University and Massachusetts General Hospital) and vitamin D (INSERM, Paris), I have conducted fundamental and clinical studies of parathyroid physiology and pathology, especially regarding PHPT.

These studies allowed me to highlight the particularities of PHPT in Romania, often a completely different disease from the Western and North American PHPT in terms of heterogeneity, the absence of biochemical screening, delays in diagnostic, the limitation in imaging localization and high prevalence of severe vitamin D deficiency. We have also identified the first Romanian family with PHPT-JT syndrome and performed the first familial genetic screening (in collaboration with University of Florence) and we pointed out that the identified genetic mutation confers the highest risk of carcinoma (66%) in comparison with international published known mutations. As recognition of my research I was welcomed in the European Society of Endocrinology expert group dedicated to parathyroid disorders-PARAT 2021. In this capacity I have contributed to the Parathyroid Diseases European Guideline published this year in the European Journal of Endocrinology.

Regarding my academic activity of teaching osteoporosis I merged the lectures for students and residents, the advanced course of Endocrinology with the courses organized by SROBMS alone or in collaboration with IOF. I also coordinated the practical work in CNCCBO which included demonstrations of bone densitometry, methods of measurement and clinical interpretation of bone metabolism markers, identification and classification of vertebral fractures on plain X-rays.

The content of osteoporosis lectures has evolved, including not only endocrine osteoporosis, but also other metabolic bone diseases as a necessity in clinical medical practice. In recent years, in line with the international trend of evolution regarding the concept of rare diseases I have perfected myself by participating in courses and webinars organized by the international societies of which I am a member and I brought in light the subject of rare metabolic bone disorders in lectures for residents, pediatric endocrinology courses for pediatricians, at SROBMS symposiums but also in the clinical activity in my department.

For over two decades I am leading the endocrine ultrasound training program and I have trained (by lecturing and practical work and also by establishing a curricula) and examined probably all the Romanian endocrinologists and from then on all the residents assigned to the National Institute of Endocrinology.

Regarding my professional activity, I am the head of the Endocrinology and Metabolism department in the National Institute of Endocrinology, a department created in order to increase the evaluation of patients with different types of osteoporosis to modern standards. One of the main priorities has been the clinical management of different forms of PHPT which led to a well-known expertise and an increased addressability of patients facing difficulties in diagnosis and treatment. In recent years, more and more patients with rare metabolic bone diseases have turned to our department. As a chairman of the Institute`s Committee for Diagnostic Protocols, I coordinated the development of 50 new diagnostic protocols during the first pandemic year.

I have been the manager and medical director of the National Institute of Endocrinology and I contributed to the modernization of the patient care and general institutional management. As an example I would include the introduction of hormonal measurements (aldosterone, renin, new methods for measuring cortisol, FGF23, P1NP, C-telopeptide and calcitriol), promoting ultrasound evaluation and fine needle aspiration as a standard of care in endocrinology, the elaboration of the first ROF of the medical council and transforming the ICU compartment in a fully operating department. I have also coordinated, locally and nationally, the National Health Program of Endocrinology (CNAS) which included the National Osteoporosis Program developed over a decade ago (probably the first program of its kind) which progressively evolved among with the recommendations of the

International Society of Osteoporosis (IOF) using modern criteria adapted according to my expertise and experience in CNCCBO and epidemiological research.

My personal development is an extension of my pursuits for over three decades. My future research will focus on identifying fracture risk factors that are not included in the FRAX model, based on Romanian epidemiology and in collaboration with national and international expert groups. In collaboration with SROBMS and general practitioners societies I will coordinate the screening of the high fracture risk in the elder population, using a methodology elaborated with the IOF expert group. I will also implement the already-approved project of prospective diagnosis in parathyroid carcinoma.

Academically, I will continue lecturing on musculoskeletal biology and pathology and I will proceed for this to become a subspecialty, as recommended by the European and International Societies.

Professionally, I am currently working on the set up of a department of expertise in rare metabolic bone diseases and I am also promoting the establishment of a laboratory for the study of bone quality.

In conclusion, I would like to thank those who taught and guided me, those whom I collaborated with and those who will kindly evaluate this thesis.