

CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST



The Habilitation thesis Abstract

Renal disorders: from pathological observations to clinical studies

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2019

This habilitation thesis summarizes my main scientific contributions after graduating the doctoral school of the "Carol Davila" University of Medicine and Pharmacy in Bucharest, entitled "Assessment of the risk of thromboembolic events in patients with primitive nephrotic syndrome" (Scientific coordinator: Prof. Dr. Gabriel Mircescu, publicly defended in April 2013, order of confirmation MEC 3930 / 20.06.2013). All the articles referred to in the habilitation thesis were published after the completion of this doctoral thesis.

The main areas of interest in my scientific research work derive from the complexity of the treated cases and the nature of the medical specialty I am working in the Department of Nephrology of the Fundeni Clinical Institute, one of the largest tertiary care units in the country to which all of the difficult cases that are not addressed in other hospitals are redirected and the medical center with the highest tradition and expertise in Romania in solid organ transplantation (kidney, liver, pancreas) as well as in medullary or hematopoietic stem cell transplantation.

Considering these, the main areas of interest in kidney diseases that I have addressed can be grouped into four major areas: 1. aspects of epidemiology, diagnosis and treatment of primitive and secondary glomerular diseases, 2. diagnosis and treatment of renal transplant specific pathology, 3. epidemiology, diagnosis and treatment of hereditary renal diseases, 4. the interrelationship between kidney diseases and other organs and systems disorders.

The actual thesis is structured in three sections.

The first part, "Professional, Academic and Scientific Achievements", consists of three distinct chapters, one for each of the three areas of activity.

Professionally, I have been doing all my medical work so far in the Clinical Departments of the Center for Internal Medicine and Nephrology at Fundeni Clinical Institute, Bucharest. Subsequently, (including after 2013 when I obtained my PhD in Medicine), I continued to work in the Clinical Nephrology Department of the Institute, where I provided highly specialized medical services to patients with various renal pathology admitted for continuous hospitalization or day hospitalization (about 2500 admissions/year, of which more than 30% are patients diagnosed with different primary and secondary glomerulopathies at different evolutionary stages). I have always been concerned, along with the other colleagues in the department, to provide the best conditions for patient care and I have pursued my own uninterrupted training to meet the standards of healthcare specific to a specialized tertiary center. This results from obtaining the title of senior physician in Nephrology, as well as from the approximately 50 professional manifestations credited with hours of continuing medical education in which I participated in the country and abroad (10 of them took place after finishing doctoral studies, in 2013), most of them addressing various topics regarding Kidney Diseases and its multiple related issues - the subject of this Habilitation Thesis. Recognition of professional prestige is supported by my co-optation in the Nephrology Advisory Committee of the Ministry of Health (since 2013) and in the executive committee of the Romanian Society of Nephrology (since 2017), as well as by the distinctions received from national professional and academic societies, as would be the *Ștefan S. Nicolau* Prize of the Romanian

Academy for the work "Glomerulonefritele" in 2018 and the Honorable Medal of the Romanian Society of Nephrology in 2014.

On the educational level, during the 16 years passed from joining the medical higher education, I have successively come by competition through the stages of didactic degrees from assistant professor to university lecturer (since October 1st 2013) and I have been involved in all aspects of the theoretical and practical education process for students and resident doctors. I have directed and coordinated more than 50 graduate papers of UMF "Carol Davila" graduate students, I participated in the medical students scientific sessions and congresses. In the years 2014 and 2015, I participated as a long-term expert for counseling and professional guidance in the POSDRU / 161 / 2.1 / G / 135802 project; 2014 "Partnership for a successful career in the medical specialties involved in renal pathology", UMF "Carol Davila" Bucharest, a project that has been very successful. A major responsibility of my teaching activity was and still is guiding and supporting resident physicians and specialists in their post-graduate professional training. Thus, since 2017 I have been working as a Scientific Director within the FEDURO - POCU / 91/4/8/105910 project, a project born of the desire to be involved in the training of physicians working in Romania as specialists in the uro- and nephro-oncology who want an improvement in their professional activity in line with current standards of practice and intervention in oncology. Also, during 2014-2017, I coordinated the CERO project - career profile: Romanian researcher UMF Carol Davila / POSDRU / 56 / 1.2 / S / 31081. The CERO project benefited from considerable European funding and its overall objective was to improve the personal development opportunities of doctoral students and researchers in the field of renal pathology as well as in related fields.

Regarding editing teaching materials, I contributed as author and coauthor to the publishing of two monographs and to over 5 chapters in specialty books (1 of which - in an international monograph). The vast majority of these publications were made after obtaining the Doctor of Medicine degree/PhD.

In the field of scientific research, I have participated in 22 international multicentre clinical trials as principal investigator (10) and sub-investigator (12), numerous unicentric research projects carried out within the Discipline where I work, as well as 12 grants financed by project competition (two of which as a manager). I have published 25 full text articles in international ISI-indexed journals with IF (of which 12 as lead author - first, last or corresponding author) and 39 full text articles in other journals (26 are indexed in international databases). My articles are quoted/cited by over 145 publications in ISI indexed journals (source: Web of Science). My current Hirsch index is 6 according to the Web of Science core collection (and 11 in Google Scholar, respectively).

The chapter on scientific achievements is divided into 5 subchapters, which summarize the most important personal contributions structured in 4 major areas of scientific interest:

- Aspects of epidemiology, diagnosis and treatment of glomerular primitive and secondary diseases, a field which continued the theme addressed in the doctoral thesis (entitled "Assessment of the risk of thromboembolic events in patients with primitive nephrotic syndrome " - Supervisor:

Prof. Dr. Gabriel Mircescu). Following implementation of separate research protocols on subjects diagnosed with primitive and secondary glomerular diseases, the following parameters were analyzed: severity of histopathological lesions, risk factors for the progression and response to specific treatment, and various therapeutic protocols. The value/the quality of the results obtained in this area of research is substantiated by 9 articles published in scientific journals with ISI Thomson impact factor > 1 as lead author, by presenting more than 15 papers/reports at congresses of renown international scientific societies and the publication of 2 monographs as a co-author on the topic of primitive and secondary glomerular diseases. Among the conclusions drawn from my own research, I mention the following: 1. identification of extracapillary proliferation lesions and of segmental glomerulosclerosis are of great importance in identification of patients at high risk of progression and the presence of IgG deposits does not correlate with renal survival in patients with IgA nephropathy. 2. In patients with IgA nephropathy, the presence of endocapillary hypercellularity lesions was associated with favorable renal prognosis in the subgroup of patients who received immunosuppression, suggesting the reversibility of this type of lesion to immunosuppressant therapy. 3. Treatment with Rituximab, through its dual mechanism of action (mature lymphocyte B depletion and stabilization of podocyte cytoskeleton) in patients with IgA Nephropathy and cortico-resistant nephrotic syndrome may be effective in achieving nephrotic syndrome remission and renal function stabilization. 4. In patients with IgA nephropathy and high risk of progression, budesonide was superior to methylprednisolone treatment in terms of decreasing proteinuria, while decline in renal function was similar in the two groups. 5. Anti-PLA2R antibody dosing is an extremely useful tool both in the diagnosis of primitive membranous nephropathy and in personalizing the management of this glomerular nephropathy with often severe development. 6. In lupus nephritis, extracapillary proliferation lesions, global glomerulosclerosis, capsular adhesion and tubulitis along with eRFG and proteinuria as risk factors for renal evolution, independent of the classification of the International Society of Renal Pathology. Our data suggest that quantitative assessment of active and chronic glomerular and tubulo-interstitial lesions is necessary to accurately assess renal prognosis in patients with lupus nephritis. 7. The effectiveness of new treatments with direct antivirals in HCV-associated cryoglobulinemic glomerulonephritis is not yet demonstrated. Immunosuppressive adjuvant treatment should be used in severe forms of HCV-associated cryoglobulinemic glomerulonephritis, and continuous clinical, immunological and histopathological monitoring is required even with sustained virologic response post-treatment with direct antivirals. In addition, in this subchapter, I also presented several study protocols in which I am involved as leader of the research team on IgA nephropathy and lupus nephritis.

- ***Aspects of diagnosis and treatment of renal graft pathology***, a priority research area at Fundeni Clinical Institute; I presented five studies that analyzed both the diagnosis of graft dysfunction and the infectious, metabolic or urological complications of renal transplantation, the results of four studies being published in ISI-indexed international journals. Among the results, I mention the following: 1. For patients with graft dysfunction, dd-cfDNA is associated with the

histopathological diagnosis of acute humoral rejection when specific donor antibodies are present. The level of dd-cfDNA correlates with the presence of characteristic histopathological lesions for humoral mediated rejection (peritubular capillaritis, glomerulitis, transplant glomerulopathy), being a marker of endothelial dysfunction. 2. The use of a cyclosporin + mycophenolate mofetil immunosuppressive regimen and pre-transplant HCV infection have been identified as independent risk factors for the occurrence of post-transplantation diabetes. 3. The histopathological picture of BK nephropathy is difficult to distinguish from that of cellular or humoral rejection outside/beside of highlighting viral inclusions. The prognosis of this complication of renal transplantation is still reserved in the absence of etiological treatment. 4. Patients in whom the extravesical Lich-Gregoire technique has been used had a lower rate of urological complications. In addition, compared to the transvesical Leadbetter-Politano technique, the extravesical Lich-Gregoire technique is simpler and faster, does not require separate cystostomy or a long ureter of the renal graft, which recommends it as a superior ureteroneocystostomy technique. At the end of this subchapter I presented the protocol of a prospective study conducted in collaboration with the Center for Urological Surgery and Renal Transplantation, Fundeni Clinical Institute led by Prof. Dr. Ioanel Sinescu and the Renal Transplantation Center of the Nephrology Department of Washington University, Seattle, USA, on the role of angiotensin II type 1 anti-receptor antibodies in humoral mediated rejection and the impact on graft survival.

- ***Aspects regarding the diagnosis and treatment of renal impairment in patients with genetically transmitted kidney diseases***, in this subchapter I presented the studies conducted on the diagnosis and treatment of some of the most frequent and severe genetic diseases with renal impairment such as Autosomal dominant polycystic kidney disease or Fabry disease. One of these is the first published study on the efficacy of metabolic reprogramming with metformin in human subjects with autosomal dominant polycystic kidney disease. The conclusions drawn from the research in this field, I mention the following: 1. We confirmed the presence of elevated serum levels of the soluble receptor for urokinase-type plasminogen activator in patients with Fabry disease. The serum level of this biomarker has been identified as a risk factor in the progression of Fabry disease. 2. Metformin has a good tolerance and safety profile, even in patients with advanced stages of autosomal polycystic kidney disease and has been associated with a slow decline in renal function. Also in this subchapter I presented the protocol of a study conducted with the Department of Pathology of the University of Washington and the Department of Pediatrics, University of Minnesota, USA, study entitled Podocyte structural studies in Fabry patients with a late onset variant of the disease.

- ***Aspects on the interrelationship between kidney disease and other organ and system disorders*** - in which I studied the interrelationship between renal diseases and endocrine, haematological or marginal periodontium disorders. In this subchapter we briefly presented four of the representative studies in this research area and a general review, all published in ISI indexed international journals. Some of the findings of this research include: 1. The plasma level of the free fraction of metanephrine and normetanephrine in patients with CKD was frequently above the

upper normal limit. Patients with CKD in renal replacement therapy (hemodialysis or continuous peritoneal ambulatory dialysis) had a comparable level of the free fraction of metanephrine with that of patients with pheochromocytoma and this was associated with duration in the dialysis program. 2. *T.denticola*, *T.forsythia* and *P.micros* are periodontal pathogens with increased frequency of detection among patients with CKD and moderate or severe forms of periodontal disease (PD). Also, age and *T.forsythia* are independent risk factors for PD in those diagnosed with CKD. 3. Acute kidney injury complicated 10.3% of autologous haematopoietic stem cell transplantation performed for multiple myeloma and / or amyloidosis. Independent risk factors for acute renal injury during the first 30 days after autologous medullary transplantation were: high serum β_2 microglobulin, pre-transplant CKD and post-transplantation mucositis grade 3 or 4. In this subchapter also I presented the protocol of a study, conducted in collaboration with the Department of Bone Marrow Transplantation, Fundeni Clinical Institute regarding renal complications occurred post-transplantation of autologous / allogeneic /stem cells in patients with lymphoproliferative diseases.

The last subchapter of the first part summarizes a list of the main scientific papers on which this thesis is based, as well as a list of other personal publications that are relevant to the habilitation thesis.

Altogether, this thesis presents the summaries of 12 original papers and 2 general reviews, which I published as lead author or co-author in the last 6 years (after graduating from the doctorate) and which have been published in main, peer-reviewed ISI indexed with impact factor scientific journals. In 9 of the original articles I was the lead author (first, last or corresponding).

The second section of the habilitation thesis, "**Professional, Didactic and Scientific Perspectives**", was reserved for the exposure of the strategic objectives and specific activities of the career development plan on the three fundamental directions.

In terms of medical care, the major objectives are to permanently improve my own training as development of medical knowledge and to continue to provide highly specialized healthcare services to a large number of patients with complex renal pathology. As a specific activity, I aimed to identify new directions of development and to develop the existing ones with the support of Fundeni Clinical Institute management, such as: Center for Expertise in Genetic Renal Disease Management, by affiliating our Center to other European Centers of Expertise in Rare Genetic Diseases.

On the didactic level, I believe that a constant effort to update the medical information that is available to students and residents is necessary because the level of knowledge in nephrology (and medicine in general) is changing rapidly. That is why I propose to intensify my own contribution to the editing of teaching materials. For students and resident doctors, it is important both the theoretical training by attending courses and the practical preparation at the patient's bed. Therefore, in the coming years, I propose to elaborate a manual of clinical cases for students and resident doctors, which will be updated every two-three years. For the residents in nephrology

in the Department of Nephrology, Fundeni Clinical Institute, I will continue to organize nephropatology sessions, case presentations, lectures on key themes in clinical nephrology as well as practical sessions (methods of renal replacement therapy, apheresis methods, vascular approach, renal biopsy, etc.). I will continue to encourage the best residents to engage in clinical research and to develop/write and publish articles in national and international impact journals. In the next years, I will continue my work as a Scientific Director within the FEDURO - POCU / 91/4/8/105910 project, I will also use my experience in attracting new European non-reimbursable funds into medical education projects for students and young doctors.

In terms of perspectives in scientific research, I will try to identify new research directions, develop the existing ones and raise funds by continuing to participate in national, European and international project competitions in collaboration with national research institutes (National Institute of Pathology Victor Babes, Bucharest, University of Agronomic Sciences and Veterinary Medicine, Bucharest) and with international research partners (Washington University, USA, Temple University, Philadelphia, USA, etc.). I propose to continue to organize research teams including clinical nephrologists, residents, students, specialists in paraclinical investigations (imaging, ultrasound, nephropathologists, etc.) and specialists in complementary fields (other medical specialties).

The third part of this habilitation thesis contains the complete list of bibliographic references used in the first two parts.

