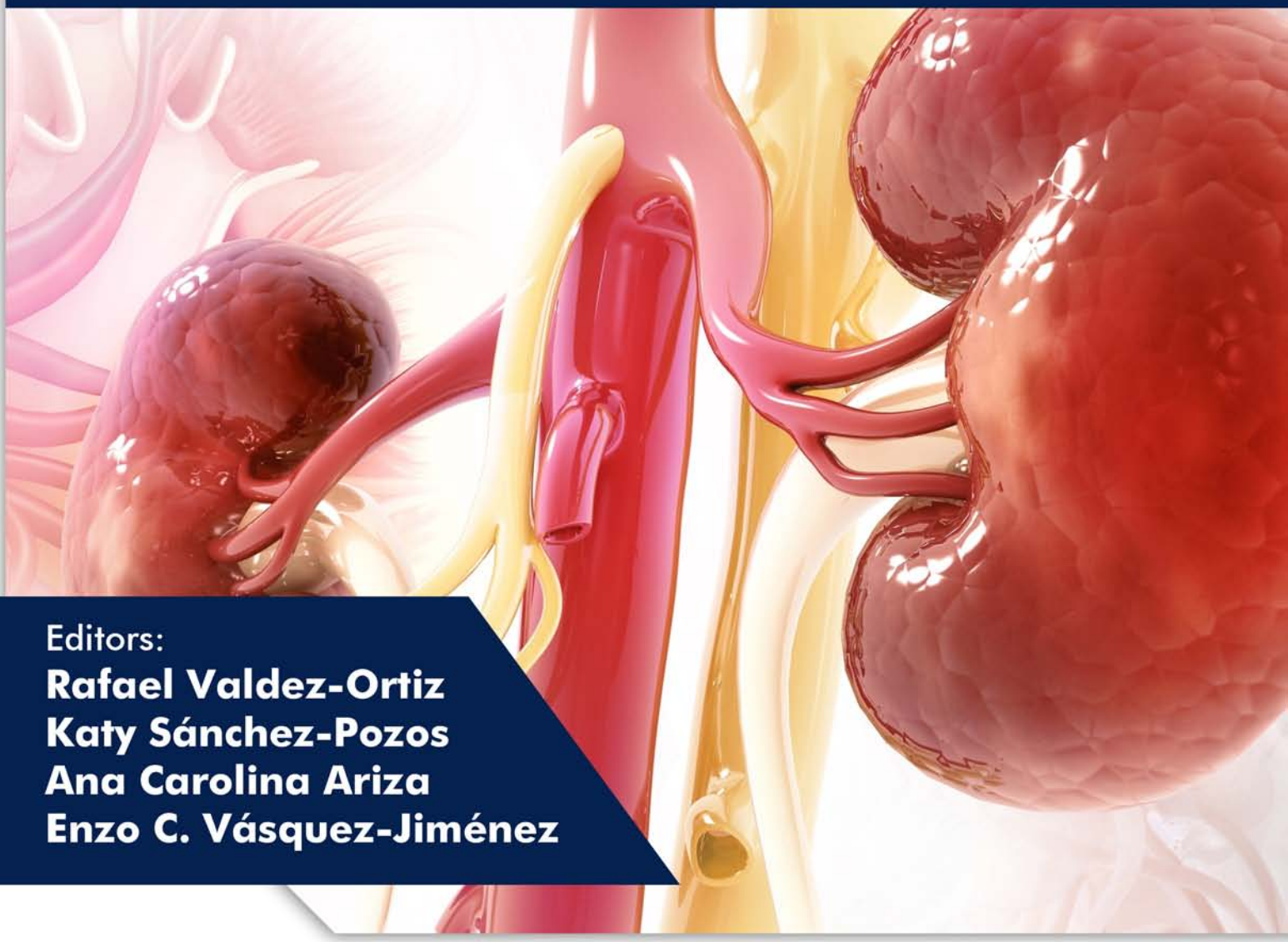
CURRENT TOPICS ON RENAL DYSFUNCTION

FROM BASICS TO CLINIC



Editors:
Rafael Valdez-Ortiz
Katy Sánchez-Pozos
Ana Carolina Ariza
Enzo C. Vásquez-Jiménez

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Current Topics on Renal Dysfunction: From Basics to Clinic

Edited by

Rafael Valdez-Ortiz
Department of Nephrology
Hospital General de México
Dr. Eduardo Liceaga, Mexico City
Mexico

Katy Sánchez-Pozos
Research Division, Hospital Juárez de México
Mexico City, Mexico

Ana Carolina Ariza
Center for Nutrition and Health Research
National Institute of Public Health
Cuernavaca, Morelos, Mexico

&

Enzo C. Vásquez-Jiménez
Department of Nephrology
Hospital Juárez de México
Mexico City, Mexico

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Editors: Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez

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Singapore
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FOREWORD

I want to start this chapter by telling you a story: how and why I have been continually amazed and enthusiastic about learning every day a new issue about kidney physiology and pathophysiology and how this book starts a new era in Mexico by demonstrating how basic science can improve from using the laboratory results in our understanding of Kidney's health and the earliest identification and effective treatment of kidney diseases.

My interest in the kidneys started in my early days at medical school 53 years ago, since 1979, during and after my postdoctoral studies at the laboratory of nephrology and Mineral Metabolism at Washington University School of Medicine in Saint Louis, Missouri, where two outstanding professors Dr. Saulo Klahr and Eduardo Slatopolsky involved me under the tutorial of Kevin Martin and Ezequiel Bellorin-Font in the development of the area on mineral, bone metabolism and the intracellular pathways of action of parathyroid hormone throughout their proximal tubular receptors and intracellular signaling. After returning to the Nephrology and Mineral Metabolism at the National Institute of Nutrition, I coordinated and developed the mineral metabolism laboratory and clinical services.

A lifetime perspective of the last 5 decades in Mexico

Let me start a journey remembering some examples of the teaching strategies of my mentors, Dr. José Carlos Peña and Jaime Herrera, in the nephrology specialty training in the late 1970s: for example, to have a precise determination of glomerular filtration rate (GFR), we did use the inulin clearance rate if the clinical decision making needed such precision. The urinary collection during a 24-hour interval was used in several decision-making processes, including the Creatinine Clearance, to not only determine GFR but to define the fractional excretion of different substances or the metabolic balance of several substances in specific protocols conducted in an excellent clinical research service. Except for inulin determination, most tests performed lacked specificity, and their scientific basis was derived mainly from observational and metabolic studies. Looking at the conclusions we derived from their results in those days, I feel that they allowed us to use very intuitive reasoning due to their design. Their precision and reproducibility were difficult to standardize and, therefore, to perform in any clinical setting. Nonetheless, we made an excellent diagnosis, mainly with respect to the physiology and metabolic aspects of KD.

The characterization of the immune system was also in its very early years. Therefore, its role in CKD etiology and evolution was suspected, and the evidence was merely observational. During these decades, an enormous change has been achieved, and it is a consequence of basic research translated to clinical nephrology under the leadership of Dr. Donato Alarcon, Federico Chavez Peon, coworkers, and many groups in the transplant community.

In the early 1980s, the science of membrane receptors, membrane channels, transporters, and co-transporters was another considerable progress when applied to clinical nephrology. The mineral and bone metabolism system, the acidification system, and arterial hypertension, among other areas, greatly benefited from this research, and there are important groups around Mexico developing this area.

From 1990 to date, another big area of development in nephrology was the genomic, transcriptional, metabolomic, and microbiome research areas.

In this route of more than half a century, nephrology as a specialty of internal medicine was started around the world, and in Mexico, it happened in 1972. Not to forget are the advances in dialysis procedures and the quality-of-life improvements made possible since 1979 by fundamental scientific research on peritoneal membrane physiology and its adaptations to the procedure. The hemodialysis efficacy was also improved due to the development of biocompatible membranes, up-to-date purification of water, and better dialysates.

This book comes together as an example of the collaboration and enthusiasm of at least 10 different institutional groups around the country; they work as a community where CKD, AKD, ESRD, and transplantation are potent stimuli for their work.

The renal circulatory system is pivotal for these mechanisms to act in precise coordination

Over these decades, the kidneys have always been a great laboratory where the multiple functions covered by the two kidneys are paramount to the whole-body economy and health. The anatomic place where nature allocated them is strategic. Humans, a species that stands on two feet and in a vertical position and walks as a bipod, need a barometric sensor system and a unique propulsion of blood. This peculiarity, combined with the non-permeable characteristics of our skin, is also related to the volume control of the intra and extracellular compartments. In a few words, the Kidney, the central nervous system, and the heart have evolved in the human species with a very complex system for precisely regulating fluid and volume control. The strategic position of the kidneys in the retroperitoneum and under the diaphragm allows them to have an excellent mechanism for sensing and adjusting both fluid and volume, with a super specialized mechanism: a. the renin-angiotensin; b. the vasopressin; and c. renal innervation is also an essential component.

Another consequence of humans is having non-permeable skin, which obligates the body to have precise water and mineral homeostasis conservation mechanisms. The role of the kidneys in this area is of great importance; a precise balance between ingestion, metabolic needs, and excretion depends on the coordinated function of many different systems for secretion, reabsorption, transport, and cotransport of the monovalent and divalent ions coordinated with glucose, nitrogen, and ammonium either in the proximal or distal tubule where acidification is also regulated and, therefore, the metabolic acid-base balance of the whole body.

The urine concentration and sodium/chloride balance are coordinated in the renal medulla where the loops of Henle and distal /collecting ducts are to be studied.

Also, the kidney interstitium was elucidated and understood in the last two decades, along with the role of erythropoietin and anemia of CKD, inflammation, fibrosis , and tissue death.

Hence, this book is a unique opportunity to invite you to focus our attention on the great opportunity that the contemporary clinical practice of nephrology already has in several areas, namely earliest detection of Kidney Diseases (KD) and the mechanisms involved in the damage of kidney tissues, acute kidney injuries, the effect of different toxic exposures on kidney function, the mechanisms of tissue death and fibrosis as well as the mechanisms of action of specific treatments/therapeutic interventions among others, thanks to the advances generated by the results of very well focused basic scientific research.

The kidneys are bright organs; they play a role in the human body's health

You will enjoy analyzing the contributions of my co-authors, which can be addressed considering the focus of their interest in some of the issues summarized in the contents table.

A group of chapters are focused on genomic sciences and the Kidney, namely the pleiotropic aspects of CKD, the genetic influence on cell differentiation, kidney/urinary tract cancers, epigenetics of CKD, and their relationships with microbiota. A fascinating area related to stem cell science is the integration of new organs, including functional kidneys, and forecasting a new era in successful organ transplantation.

Examples of how inflammation and metabolic syndromes affect energy utilization are exemplified by the chapters analyzing mitochondria and oxidative stress (oxygen and ROS), for example, in diabetic kidney damage.

Arterial hypertension, sodium balance, acid-base metabolism, and nephrolithiasis are also areas where co-authors had incursion and generated new insights into the pathophysiology and treatment options.

An emerging area regarding mechanisms of kidney damage is related to the toxic effects of different chemicals to which people are exposed, either due to the natural contamination of the habitat or anthropogenic activities.

Regarding clinical nephrology, this book discusses the science related to the diagnosis and association of CKD with metabolic syndrome, type 2 diabetes mellitus, systemic arterial hypertension, nephrolithiasis, renal tubular acidosis, polycystic kidney disease, and acute kidney injuries.

CKD in Mexico and the world;A global burden lacking fundamental strategies to be controlled, diminished, or ideally avoided

When getting accurate data on the number of Mexican citizens living with CKD, we will face the results of small population studies from which only a gross estimation can be done. This latter is explained by the complexity of our fragmented health system, which makes it almost impossible to adopt a uniform policy for early detection, classification, and, very importantly, successful intervention of this disease.

Therefore, the Mexican scenario shows late identification and ineffective intervention of CKD, leading to a growing and uncontrolled number of patients facing the irreversible end stage of kidney disease (ESKD) and the need for the high cost of dialysis treatment to survive. This resource does not cover the whole ESKD population.

There is enough international evidence of the catastrophic costs implied of the yearly expenses of the different options to treat ESKD when hemo and peritoneal dialysis are unavoidable treatments for survival.

In Mexico, these data are available only for the significant health provider system: the Mexican Institute of Social Security (IMSS), where formal workers are covered, and a significant percentage of ESKD patients receive either hemo and/or peritoneal dialysis. Note that there is a significant and underestimated ESKD population of IMSS beneficiaries who do not receive dialysis.

The direct and indirect expenses of such programs are catastrophic for the IMSS. If they are extrapolated to the estimated ESKD population not covered by IMSS, it is easy to realize that they are catastrophic for the whole country. What do we mean when considering a cost catastrophic for any health system? There is an example for you to analyze before you go through this publication. In 2020, the direct cost of the IMSS dialysis programs, just the costs related to the treatment session or the peritoneal supplies for approximately 60,000 ESKD

patients, equals the expenses to attend all the millions of births attended at IMSS facilities in the whole IMSS population. In addition, there are indirect costs bearableby this population, namely of the complications of treatment, hospitalizations, and death. They almost cost three times more than the direct cost just described.

I hope these examples provide enough reasons to be enthusiastic about fostering the kind of scientific research presented throughout this book, which is focused on the early identification of renal tissue damage, the options to prevent it and stop deterioration, and lastly, avoiding fibrosis and tissue death.

In the last three decades, a significant effort has been made to identify the presence of CKD in high-risk populations; there are many worldwide spread programs with this purpose, one of which has been active in Mexico, the Kidney Early Evaluation Program (KEEP) of the International Kidney Foundation which allows estimating the "remnant glomerular reserve." This program is well designed to identify clinical antecedents correctly to establish the kind of risk present, correlating with clinical anthropometry, classifying the stage of CKD estimating glomerular filtration rate using standardized determination of serum creatinine and different validated formulas as well as glomerular integrity through the albumin/creatinine ratio in one sporadic urine sample.

Although it is very "glomerulocentric," it has been demonstrated to be very useful as a clinical tool to conscientize the patient and, in very few cases, to provide a photograph of the size of the CKD problem to a specific health system, which ultimately is responsible for providing access to effective treatment options; all oriented to stop the deterioration of such glomerular remnant function and to slow the need of dialysis, ideally to recover functional glomerulus.

Using this model in the year 2010 in the Mexican state of Jalisco, it became evident that we were able to screen nearly 8000 citizens with type 2 diabetes (DM2) covered by the public health state services in only two weeks, adapting a validated version of the KEEP protocol. As a result of this campaign, we did generate consciousness of the kind of care that the individual patient needs to have according to the CKD remnant "kidney" reserve, as well as those that did not have CKD; in this case, the patients became aware that they can develop this undesirable complication of DM2 if they do not adhere to appropriate medical care and control of their disease.

We also established and finished a course online designed to train general practitioners (GPs) in taking medical care of this DM2 population in their primary care clinics; the course was peer-reviewed, and the intervention protocol was validated to treat each deterioration stage. These GPs identified approximately 100 CKD patients in their own DM2 registry. We also asked for the nephrologist evaluation online in a very well-programmed schedule.

The Health Care Authorities of Jalisco stopped the program because there were several logistical problems regarding accessibility to laboratory testing and medications. Nonetheless, the program yielded a model to be pursued at the non-IMSS covered population affected by DM2, which is most of the population in the country, nearly 60% of the adult population older than 20 years old.

These results were compared with those obtained in other Mexican States where the Mexican Kidney Foundation (FMR) openly invited the public to participate in KEEP testing events. Those with known risk factors for developing CKD were accepted, regardless of whether they have IMSS or other insurance coverage. The results were significantly similar, if not almost identical, to those we obtained in the Jalisco scenario.

With these data, it is easy to speculate on how many people are affected by one or more of the Metabolic Syndrome components identified by the Nationwide Health and Nutrition Survey conducted by the National Institute of Public Health (INSP, ENSANUT), which may have developed CKD and classify them according to the KDOQUI/EPI criteria in the whole country.

Although imprecise, the figure is of millions of cases with CKD in the 20-year and older adult group, which are affected by CKD, of which 96% are in the early stages of the disease. Therefore, a significant opportunity exists to establish a fundamental public policy to face this challenge through systematic early identification, classification, and protocolized interventions, briefly a cost-efficient policy that should decrease the burden to the nation represented by CKD and ESKD.

Let us finish this section by mentioning that many new biomarkers identified and understood by recent scientific research can identify when a kidney starts deteriorating its integrity; KEEP accepts a patient as having CKD.

Which will be the best-case scenario for CKD in Mexico?

As we have reviewed in this chapter, I hope you became aware of the significant avenues opened today for the research community regarding the importance of kidney integrity in the health sustainability of anyone, with a large emphasis on people with one or more components of metabolic syndrome as several chapters of this book endorse.

Let's drive the route on the contemporary issues that syndemic entities like metabolic syndrome present to an integrated science community to develop effective and sustainable public policies to solve these problems; it is mandatory to acknowledge that they have conditionings that are not only related to a specific disease state but also include many socio-economic, ambient, and geographical factors. Therefore, the research on these multifactorial human conditions needs to establish a compelling inter- and transdisciplinary approach .

The interinstitutional and interdisciplinary nature of the present publications must encourage their institutions to promote transdisciplinary involvement; this is more feasible in universities where many disciplines and specialties are available. Recent efforts by the National Council of Science and Technology (CONACyT) have encouraged this approach, which has been demonstrated to be particularly cumbersome but necessary if feasible; long-term policies are to be implemented.

Meanwhile, the example given in this publication is excellent; basic scientists working on specific mechanisms of CKD and AKD and interacting with nephrology specialists have made a tremendous effort that is unique to my knowledge in Mexico.

Juan Alfredo Tamayo y Orozco
Accessalud, Mexico City, Mexico

PREFACE

Renal dysfunction includes a wide range of diseases affecting kidney function. But what are the common factors in development and disease progression? What do we know so far? and what are the most recent discoveries in this matter? One thing we know is that the common outcome is chronic kidney disease, end-stage renal disease, and finally the need for a transplant.

The kidney is a multifaceted organ, with its main function being the removal of excess water and toxins from the body as urine. Among the other functions are, the production of hormones, the regulation of fluid and mineral levels, the production of vitamin D, the regulation of blood pressure and the maintenance of the acid-base balance. Structured by a complex network of cellular interactions such as mesangial, parietals, podocytes and endothelial cells. Thus, any imbalance in whichever of their functions will have a detrimental effect on the systemic physiology.

Also, kidney failure can reach other organs, such as the heart, circulatory system, mineral balance, bones, muscles and joints, the gastrointestinal system as well as the immune system, at least in part through the suggested crosstalk between renal dendritic cells and T cells as suggested by some authors, causing maintained systemic inflammation and immunodeficiency.

Lately, new available approaches like the next generation sequencing, microbiota analysis, and epigenetics, are contributing to novel perspectives on physiological and pathological conditions of the kidney.

This e-book aims to address the current studies in kidney diseases, from basics to clinic, and from environmental factors to genetics, integrating the convoluted systems involved in kidney disease.

Rafael Valdez-Ortiz
Department of Nephrology
Hospital General de México
Dr. Eduardo Liceaga, Mexico City
Mexico

Katy Sánchez-Pozos
Research Division, Hospital Juárez de México
Mexico City, Mexico

Ana Carolina Ariza
Center for Nutrition and Health Research
National Institute of Public Health
Cuernavaca, Morelos, Mexico

&

Enzo C. Vásquez-Jiménez
Department of Nephrology
Hospital Juárez de México
Mexico City, Mexico

List of Contributors

Ana Carolina Ariza	Center for Nutrition and Health Research, National Institute of Public Health Mexico, Cuernavaca, Morelos, Mexico
Ana Laura Calderón-Garcidueñas	Neuropathology Department, Research Direction, Instituto Nacional de Neurologia y Neurocirugía, Manuel Velasco Suarez, Tlalpan 14269, Mexico City, Mexico
Ana Ligia Gutiérrez-Solís	Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico Centro de Investigación y de Estudios Avanzados del IPN (CINVESTAV-IPN) Mérida, Yucatán, Mexico
Azalia Ávila-Nava	Research Division, Hospital Regional De Alta Especialidad De la Península De Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico
Claudia J. Bautista	Department of Reproduction Biology, Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico
Consuelo Plata	Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
Cristino Cruz	Department of Nephrology, Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico
Enzo C. Vásquez-Jiménez	Department of Nephrology, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico
Estefani Yaquelin Hernández-Cruz	Chemistry School, Department of Biology, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico Posgrado en Ciencias Biológicas, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico
Estefany Ingrid Medina-Reyes	Chemistry School, Department of Biology, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico
Fabio Solis-Jiménez	Instituto Nacional de Cardiología Ignacio Chávez, Tlalpan 14080, Mexico City, Mexico
Guadalupe Ortiz-López	Research Division, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico
Isabel Medina-Vera	Methodology of Investigation, Instituto Nacional de Pediatría, Mexico City, Mexico
Iván Calderón-Lojero	Research Division, Hospital Juárez de México, Mexico City, Mexico
Jazmin Marlen Pérez-Rojas	Research Division, Instituto Nacional De Cancerología, Tlalpan 14080, Mexico City, Mexico
José Pedraza-Chaverri	Chemistry School, Department of Biology, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico
Joyce Trujillo	Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI) - División de Materiales Avanzados-Instituto Potosino de Investigación Científica y Tecnológica - (SECIHTI-IPICYT), San Luis Potosí, Mexico

Juan Carlos Diaz Núñez	Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico
Juan Reyna-Blanco	Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico
Karina Robledo-Márquez	Facultad de Ingeniería, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México
Katy Sánchez-Pozos	Research Division, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico
Laura Elena Zamora- Cervantes	Department of Nephrology, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico
María De Los Ángeles Granados-Silvestre	Research Division, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico
Martha Medina-Escobedo	Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico
Mercedes Aguilar-Soto	Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico
Nayeli Goreti Nieto-Velázquez	Research Division, Hospital Juárez de México, Mexico City, Mexico
Nina Mendez-Domínguez	Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico
Rafael Valdez Ortiz	Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico
Roberto Lugo	Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico
Victoria Ramírez	Department of Experimental Surgery, Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico
Yadira Ramírez	División de Materiales Avanzados, Instituto Potosino de Investigación Científica y Tecnológica (IPICYT), San Luis Potosí, Mexico

CHAPTER 1

Metabolism in Kidney Disease

Azalia Ávila-Nava[1], Isabel Medina-Vera[2] and **Consuelo Plata[3,*]**

[1] *Research Division, Hospital Regional De Alta Especialidad De la Península De Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico*

[2] *Methodology of Investigation, Instituto Nacional de Pediatría, Mexico City, Mexico*

[3] *Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

Abstract: The kidney contains numerous types of cells; this cellular heterogeneity and functional diversity make the kidney an organ with great metabolic activity. Most solute reabsorption occurs in the proximal tubules, so much energy is used to recover them. The proximal tubules use fatty acid oxidation as their preferred metabolic pathway to carry out this process. The kidney plays a central role in glucose reabsorption, production, and utilization. However, it is important to note that the proximal tubules of the nephron prefer fatty acids as energy. Much of the glucose in the glomerular filtrate is reabsorbed in the proximal tubules by the two isoforms of glucose/Na+ transporters (SGLT1 and SGLT2) located in the apical zone of the tubular epithelium. It is well known that the human kidney is a key organ for maintaining systemic glucose homeostasis through gluconeogenesis. The only organs that can synthesize and release glucose into the bloodstream are the kidney and the liver because both synthesize glucose 6-phosphatase, which is necessary to form glucose from glucose-6-phosphate. Remarkably, the kidney produces approximately 25% of all glucose delivered into the blood. Several studies have demonstrated that lactate is the primary substrate of gluconeogenesis in the kidney. However, after kidney injury, metabolism is impaired, resulting in increased lactic acid generation and decreased fatty acid oxidation.

Keywords: Amino acid metabolism, Fatty acid oxidation, Gluconeogenesis, Glycolysis, Metabolic activity.

INTRODUCTION

To successfully carry out their functions, the kidney contains numerous types of cells that constitute the functional units known as nephrons, which react to diverse

* **Corresponding author Consuelo Plata:** Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; E-mail: consueloplata@hotmail.com.

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

hormonal, neuronal, inflammatory, and intra- and intercellular stimuli. Various cell populations are in well-defined and specific microenvironments, such as hypoxic and hypersaline areas, where they perform many functions to maintain kidney homeostasis and, in turn, systemic balance. The communication and functional coordination between the nephron cells is responsible for the three important functional processes of the kidney: filtration, reabsorption, and secretion [1]. This cellular heterogeneity and functional diversity make the kidney an organ with great metabolic activity that depends on 20 highly specialized epithelial cells in charge of reabsorbing almost all the solutes and water infiltrated [2]. The proximal tubules of the nephron reabsorb more than 70% of the glomerular filtrate, so the cells need a large amount of energy to facilitate the absorption of different solutes. Under physiological conditions, the cells of the proximal tubules obtain this energy mainly through the oxidation of fatty acids since they produce a more significant amount of adenosine triphosphate (ATP) molecules than glycolysis. Nonetheless, after kidney injury occurs, energy metabolism is modified, favoring an increase in lactate due to the activity of anaerobic glycolysis and a decrease in the oxidation of fatty acids [3].

Kidney damage or injury is caused by various situations, such as ischemia, infections, or the consumption of various substances, such as toxins and drugs, or by secondary damage to chronic diseases, such as diabetes, hypertension, glomerulonephritis, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) and a history of cardiovascular disease. In general, renal tubules are susceptible to acute kidney injury (AKI) and chronic kidney disease, though specifically proximal tubules, which are more sensitive to injury. Therefore, it has been hypothesized that metabolic disturbances observed during AKI or CKD can be corrected, attenuating injury or improving recovery. Below, we briefly discuss general aspects of renal tubular metabolism under physiological conditions and the metabolic changes reported during kidney damage [4].

FATTY ACID OXIDATION (FAO)

As previously mentioned, the proximal tubules in the nephrons recover most of the glomerular filtration (70%). Various solutes and water transport systems are present in this zone, and many ATP molecules are needed to accomplish their functions. The cells of the proximal tubules are rich in mitochondria that generate the necessary ATP in a very similar way to that of cardiomyocytes. Therefore, the proximal tubules depend on the oxidation of fatty acids to produce a greater quantity of ATP than glucose. In this sense, the kidney consumes most of the oxygen it receives to generate energy through the oxidation of fatty acids [4].

The reabsorption of long-chain fatty acids (LCFAs) in the renal tubules occurs through fatty acid transport proteins (FATPs), the membrane CD36 receptor, and fatty acid binding proteins (FABPs) [5 - 7]. Fatty acids are used for energy or other metabolic requirements and are obtained from the diet. Some are obtained from phospholipids through phospholipase A2, and others are synthesized by the enzyme fatty acid synthase in the cytosol. The catabolism of LCFAs, such as palmitate, occurs in the mitochondria through beta-oxidation for the synthesis of ATP. In order to cross the mitochondrial membrane, fatty acids must bind to carnitine [3]. The fatty acid is linked to CoA by Acyl-CoA-synthetase, forming an acyl-CoA to interact with carnitine palmitoyl transferase 1 (CPT1) in the outer mitochondrial membrane. This enzyme will exchange CoA for carnitine; that is, CPT1 transforms acyl CoA to acyl-carnitine, which allows the movement of the molecule toward the internal mitochondrial membrane where acyl-CoA is reconstituted with the enzyme carnitine palmitoyltransferase-2 (CPT2), allowing the entry of acyl-CoA into the mitochondrial matrix for oxidation. The acetyl-CoA resulting from beta-oxidation is oxidized in the tricarboxylic acid (TCA) cycle; in both metabolic pathways, reduced coenzymes (NADH and $FADH_2$) are obtained, which are responsible for donating electrons in the electron transport chain to form the proton gradient necessary for the synthesis of ATP molecules [8]. CPT-1 is the rate-limiting enzyme in fatty acid oxidation in mitochondria. CPT-1 deficiency results in energy failure and kidney disease. Three isoforms of CPT1 have been described (a, b, and c). The three isoforms are mainly expressed in the organs with high metabolic rates, such as the kidney and liver (CPT1a); skeletal muscle, heart, and adipose tissue (CPT1b); and brain and testes (CPT1c) [9].

In eukaryotes, principally in mammals, peroxisomes in conjunction with mitochondria constitute a tactical collaboration in the interplay of energy metabolism in cells. Usually, short- and medium-chain fatty acids are transformed mainly by mitochondria, while very long-chain fatty acids (VLCFAs) with more than 22 carbons are metabolized by peroxisomes. The VLCFAs in the peroxisomes are shortened and later transported to mitochondria, where they are oxidized to acetyl-CoA. Fatty acid oxidation in peroxisomes generates H_2O_2, a byproduct of oxidative reactions. In peroxisomes, the energy is released as heat because these organelles do not contain respiratory chain enzymes coupled to the generation of ATP. Fatty acid oxidation enzymes differ between peroxisomes and mitochondria. The first reaction in peroxisomal fatty acid oxidation is catalyzed by an acyl-CoA oxidase (ACOX), followed by reactions catalyzed by a bifunctional enzyme and 3-ketoacyl-CoA thiolase. The impaired activity of peroxisomal enzymes, mainly the rate-limiting enzyme ACOX, is responsible for unmetabolized fatty acids that promote lipoperoxidation and cellular damage, increasing oxidative stress and apoptosis [10].

CHAPTER 2

The Role of Mitochondria and Oxidative Stress in Renal Disease

Ana Carolina Ariza[1] and **Consuelo Plata**[2,*]

[1] *Center for Nutrition and Health Research, National Institute of Public Health Mexico, Cuernavaca, Morelos, Mexico*

[2] *Department of Nephrology & Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan 14080, Mexico City, Mexico*

Abstract: The role of mitochondrial disorders in kidney diseases is receiving increasing attention since evidence indicates that mitochondrial structure, dynamics, and crosstalk within the local environment are related to physiological homeostasis for adequate kidney function. In particular, in acute kidney disease (AKI), there are well-established alterations in mitochondrial structure and function. These changes included decreased mitochondrial abundance in proximal tubule cells, swelling of individual organelles, and disturbance of tightly stacked cristae. In this chapter, we discuss how disturbances in mitochondria exacerbate the production of reactive oxygen species (ROS), aggravating renal dysfunction, particularly AKI, and increasing the risk of developing chronic kidney disease (CKD). In this context, this review of the role of mitochondria in renal disease revealed that knowledge concerning changes in the redox ratio caused by NADH/NAD in renal cells and cellular compartments is limited and needs further investigation.

Keywords: Amino acid metabolism, Chronic kidney disease, Mitochondrial dysfunction, NOX, Renal dysfunction.

INTRODUCTION

Renal disorders, like many other diseases that share some underlying metabolic mechanisms, are usually treated when the clinical manifestations are evident. However, a better prognosis could be achieved by preventing or ameliorating unsighted first signs such as inflammation and oxidative stress. The role of mitochondrial disorders in kidney diseases is gaining attention since evidence relates mitochondrial structure, dynamics, and crosstalk within the local environment to physiological homeostasis for adequate kidney function. In this

* **Corresponding author Consuelo Plata:** Department of Nephrology & Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan 14080, Mexico City, Mexico;
E-mail: consueloplata@hotmail.com.

chapter, we discuss how disturbances in mitochondrial function and, consequently, the augmented generation of reactive oxygen species (ROS) can cause renal dysfunction, particularly acute kidney disease (AKI), which in turn increases the risk of developing chronic kidney disease (CKD). Understanding the cellular mechanisms that lead to increased ROS production, including mitochondrial dysfunction, with the subsequent establishment of systemic inflammation and oxidative stress, unlocks a novel era for advancing new drugs for treating kidney disorders.

MITOCHONDRIA AND OXIDATIVE STRESS

Mitochondria are bilayer-membrane-bound organelles that differ in morphology, quantity, and targeted functions among mammalian cells [1]. Since the late 1940s, mitochondria have been recognized as the "microscopic power plants" of cells due to their vital function in energy production [2]. These organelles possess their DNA (mtDNA), and besides ATP generation, they actively participate in other physiological processes such as ROS and heat production, cytosolic calcium homeostasis, and apoptosis regulation. Each mitochondrion has two membranes: an outer membrane (MOM) and an inner membrane (MIM). The outer membrane is porous since it contains VDACs (voltage-dependent anion channels).

In contrast, the inner membrane is tightly folded into structures called cristae, which increase the surface area and make energy production more efficient. The mitochondrial membranes create two main spaces: the matrix, which is inside the inner membrane and where important chemical reactions occur, and the intermembrane space (IMS), located between the inner and outer membranes. The shape and folds of the cristae are important because they help control the diffusion dynamics along the mitochondria, affecting their function [3, 4]. Therefore, alterations in the local or external cell environment or mitochondrial external and internal structures due to impaired physiological mechanisms can profoundly affect the functional state of these organelles and their surroundings. Regarding cellular stress, microenvironment plays an important role in mitochondrial dynamics, particularly the redox state achieved by substrate availability. Conditions such as hypoxia and hyperglycemia modify healthy adenosine triphosphate production to exacerbate ROS production, which in turn contributes to cell damage [5].

In the early 1980s, Professor Helmut Sies introduced the term oxidative stress to describe the effects on animal cells and tissues produced by altering the balance between cellular defense mechanisms and various conditions that promote oxidation reactions. After over 30 years, oxidative stress has been described as a disequilibrium between oxidant and antioxidant molecules in favor of the former,

promoting a disorder in redox control and signaling and/or generating molecular damage [6]. ROS are highly reactive molecules that are produced physiologically as part of redox metabolism and include radical anions (O_2*), nitric oxide (*NO), radical anion superoxide (HO*), and hydrogen peroxide (H_2O_2) [7]. ROS react with lipids, proteins, DNA, RNA, and even carbohydrates when generated excessively, causing cell damage. The body has an antioxidant system composed of various enzymes to counteract the damage, such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (Gr), as well as cofactors (vitamins or inorganic nutrients) that inactivate ROS or transform them into inert metabolites [8]. Several biomarkers for assessing an individual's redox or oxidative stress status include ROS, intermediate metabolites, final metabolites, and damaged molecules from diverse compartments. The quantification of free radicals or ROS is complicated due to their high reactivity and short half-life. Thus, NO can be measured only indirectly by quantifying nitrates and nitrites. Currently, the most internationally accepted biomarkers include isoprostanes, 8-hydroxy-deoxyguanosine, protein carbonyls, lipid hydroperoxides, and malondialdehyde (MDA), the latter of which are thiobarbituric acid reactive species (TBARS). Similarly, the quantification of antioxidant enzymes (SOD, CAT, and GPx), inorganic nutrients, and vitamins with antioxidant functions (mainly retinol, tocopherols, magnesium, and ascorbic acid) or the total antioxidant capacity can be used to assess the state of the antioxidant system. Using two or more biomarkers is recommended due to their high intra- and inter-variability, obtaining a more accurate picture of the state of systemic oxidative stress [9].

Along with ROS production, cells produce cytokines and tissue-specific hormones that promote the attraction and activation of macrophages, generating a state of underlying chronic inflammation. This state of inflammation, in turn, promotes the generation of ROS, establishing a continuous cycle with chronic detrimental consequences to the tissue if not disrupted. Furthermore, oxidative stress activates multiple intracellular signaling pathways, which induces apoptosis, cell overgrowth, and endothelial dysfunction. Overall, oxidative stress contributes to heart failure and pancreatic, pulmonary, and renal dysfunction, causing hypertension, glucose intolerance/diabetes mellitus, pulmonary disorders, and CKD [10]. Importantly, once oxidative stress is established, a cascade of events that predict the rapid progression of damage and the development of complications occurs; this suggests that oxidative stress can be an initial risk marker of kidney disease.

CHAPTER 3

Inflammation in Kidney Diseases

Azalia Ávila-Nava[1], Nayeli Goreti Nieto-Velázquez[2] and **Isabel Medina-Vera[3,*]**

[1] Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico

[2] Research Division, Hospital Juárez de México, Mexico City, Mexico

[3] Methodology of Investigation, Instituto Nacional de Pediatría, Mexico City, Mexico

Abstract: Inflammation is a complex network of interactions between renal parenchymal cells and resident immune cells, such as macrophages and dendritic cells, in conjunction with the recruitment of circulating monocytes, lymphocytes, and neutrophils. Inflammation is an important defense mechanism intended primarily to detect and fight pathogens; resident and circulating immune cells can interact with renal parenchymal cells to trigger the inflammatory response when subjected to stress, leading to irreversible tissue damage and organ failure. Although more evidence of the impact of exercise and omega-3 supplementation on the inflammatory status of these patients has yet to be generated, current evidence suggests that these types of interventions could have a beneficial impact on reducing inflammatory reactions in this population.

Keywords: Adaptative immune system, Dendritic cells, Immune cells, Innate immune system, Interleukins.

INTRODUCTION

The immune system plays an important role in renal homeostasis throughout life. Aging leads to immunosenescence, which is associated with a decrease in the capacity for tissue regeneration and increased susceptibility to kidney disease due to defective immune responses and increased systemic inflammation [1]. Changes in the availability of nutrients and biomolecules, such as cytokines, growth factors, and hormones, initiate cell signaling events involving energy-sensitive molecules and other metabolism-related proteins to coordinate the differentiation, activation, and function of immune cells. The homeostasis alteration causes the metabolic reorganization of immune cells and kidney cells, promoting inflammation and tissue damage [2].

[*] **Corresponding author Isabel Medina Vera:** Methodology of Investigation, Instituto Nacional de Pediatría, Coyoacán 04530, Mexico City, Mexico; E-mail: isabelj.medinav@gmail.com

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

The inflammation is defined as a complex network of interactions between renal parenchymal cells and resident immune cells, such as macrophages and dendritic cells, in conjunction with the recruitment of circulating monocytes, lymphocytes, and neutrophils [3]. The stimulation of these cells, in turn, can activate other specialized structures, and upon detection of danger-associated molecules, receptors activate the main pathways of innate immunity. An example of this is the activation of Nuclear Factor Kappa-B (NF-κB), Nuclear Factor of Activated T cells (NFAT), or Activator Protein 1 (AP-1). This process causes metabolic reprogramming and phenotypic changes of immune and parenchymal cells, triggering the secretion of inflammatory mediators that are signaled as inflammatory biomarkers: cytokines, Tumor Necrosis Factor-α (TNF-α), Interleukins 1, 6 and 8 (IL-1, IL-6, IL-8), Monocyte Chemotactic Protein 1; or other enzymes and proteins, such as Cyclooxygenase-2 (COX-2), 5-Lipoxygenase (5-LOX), C-Reactive Proteins, Vascular Endothelial Growth Factor (VEGF). Activation of these pathways promoted irreversible tissue damage and functional loss [4]. Kidney inflammation can cause kidney tissue injury and progressive fibrosis, which contributes to the development of glomerulonephritis, acute or chronic kidney disease, and finally end-stage renal disease (ESRD). Kidney inflammation can be caused by several factors, including infection, ischemia/reperfusion, tissue damage, and prolonged exposure to toxic agents [5].

Inflammation: Acute Kidney Injury to Chronic Kidney Disease Progression

The underlying mechanisms in acute kidney injury (AKI) and chronic kidney disease (CKD) are different, but both conditions are interconnected by inflammation. Inflammation is an important defense mechanism intended primarily to detect and fight pathogens; resident and circulating immune cells can interact with renal parenchymal cells to trigger the inflammatory response when subjected to stress, leading to irreversible tissue damage and organ failure [6].

The pathophysiology of AKI is generally characterized by a common pathway, including a cascade of cell death and inflammation induced by injury. The first progression approach from AKI to CKD has been reported as a function of tubule injury, an important source of proinflammatory cytokines. Renal tubular cells recruit immune cells to the tissue. Some of the immune cell populations that are recruited to kidney tissue are mucosal-associated invariant T cells (MAIT), neutrophils, monocytes/macrophages, NK cells, dendritic cells, and T and B lymphocytes, essential components of the innate and adaptive immune response, which play a crucial role in the pathophysiology of kidney disease [4, 7 - 9].

MAIT cells are a subpopulation of unconventional T lymphocytes because they express a minimal repertoire of T cell receptors (TCR) defined by the invariant

TCR Va7.2 (iTCR) alpha chain. They can be activated for their iTCR, which mainly recognizes metabolites derived from vitamin B through the protein related to the major histocompatibility complex class I (MR1). Once activated, they can secrete cytokines of the Th1 type, such as interferon-gamma (IFN-γ), or the Th17 type, such as interleukin 17 (IL-17), in addition to cytotoxic proteins such as granzymes and perforins so that they can protect the host from invasive pathogens and the growth of malignant cells [10].

Although discovered in the mucosa, MAIT cells are distributed in various tissues. Its protective function is limited to barrier tissues; when MAIT cells migrate from peripheral blood to these tissues, their function is tissue repair, the proliferation of other cell types, and the regulation of their activation. In the kidney, a population of MAIT cells that produce IL-17 (MAIT17) with anti-inflammatory properties resides. Such MAIT cells are activated when an inflammatory process such as glomerulonephritis begins. MAIT17 cells can interact with proinflammatory myeloid cells of the kidney, neutrophils, and macrophages, through the CXCR6/ CXCL16 axis, suppressing their destructive capacity. However, the persistence of MAIT17 cells in other tissues can drive the development of chronic and metabolic diseases, which is why they are still being studied since their plasticity is of particular interest [4, 9].

Renal infiltration by neutrophils can be detected in the first hours after ischemia-reperfusion injury. Upon reaching the renal parenchyma, neutrophils are exposed to damage-associated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs), leading to the activation of pattern recognition Toll-like receptors (TLRs) and Nod-like receptors (NLRs), as well as to the secretion of inflammatory factors such as proteases, reactive oxygen species (ROS) and lytic enzymes that alter the homeostasis of the vascular endothelium. DAMPs and PAMPs also induce one of the defense mechanisms against pathogens of neutrophils, which is the formation of extracellular traps (NETs). These network-shaped chromatin structures trap pathogens and eliminate them. However, although NETosis is efficient if not adequately regulated, it can cause damage to the surrounding tissue by itself or by increasing the proinflammatory response; this could be one of the mechanisms by which neutrophils cause tissue damage during the AKI. In removing NETs, macrophages play a leading role [11].

Macrophages are monocyte-derived phagocytic cells that act as important mediators of inflammation and immune modulation. Usually, once they are activated, they can have two phenotypes: proinflammatory macrophages or M1 and anti-inflammatory macrophages or M2. Interestingly, it is known that the phenotype of macrophages can change depending on the microenvironment; in such a way they can contribute to both the pathophysiology and the maintenance

CHAPTER 4

Metabolic Syndrome as a Risk Factor for Chronic Kidney Disease

Ana Ligia Gutiérrez-Solís[1,2,*] and **Nina Mendez-Domínguez**[1]

[1] *Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico*

[2] *Centro de Investigación y de Estudios Avanzados del IPN (CINVESTAV-IPN) Mérida, Yucatán, Mexico*

Abstract: Recent evidence suggests that MetS significantly increases individuals' risk of developing CKD. Among individuals with CKD, the MetS incidence can reach 70%. Epidemiological studies have reported an independent and positive association between MetS and CKD; accordingly, patients with MetS have up to a 2.6-fold greater risk of CKD than individuals without MetS. On the other hand, the presence of microalbuminuria is also more frequent among patients with MetS. This chapter aims to explore the association between MetS and precursor factors of kidney disease, including prevalence, pathophysiology, and clinical and laboratory diagnosis, including progression monitoring. The factors contributing to kidney injury onset in MetS patients may include oxidative stress and systemic inflammation, endothelial dysfunction, altered renal hemodynamics, excessive renal sodium reabsorption, activation of the RAAS and sympathetic nervous system, an atherogenic lipid profile, and even physical compression of the kidneys by adipose tissue. In conclusion, measures for broadly addressing the impact of CKD and MetS may not be understood as separate approaches but may be complementary. The need to ensure effective primary prevention based on nutritional and lifestyle approaches is fundamental.

Keywords: Chronic kidney disease, Inflammation, Metabolic syndrome, Microalbuminuria, Renin-angiotensin system.

INTRODUCTION

Chronic kidney disease (CKD) is defined as an alteration in renal function characterized by the excretion of urinary albumin between 30-300 mg/dL and/or a decrease in the estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m2 that persists for at least three months, independent of its origin, whether structural

* **First and Corresponding author Ana Ligia Gutiérrez Solís:** Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Altabrisa, 97130 Mérida, Yucatán, Mexico;
E-mail: ganaligia@gmail.com

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

or functional. CKD is a widespread health problem worldwide and is associated with increased morbidity and mortality. CKD decreases the quality of life by generating disability and loss of independence and involves social and psychological burdens for caregivers. These factors, taken together, result in a high economic impact on families and institutions [1].

The worldwide prevalence of CKD is estimated to be close to 10.6%, including patients in 3-5 stages, with CKD being greatest among females (12.1%) [2]. The prevalence varies with geographic region: in China, a prevalence of 1.7% has been reported [3]; with 3.1% in Canada [4]; 5.8% in Australia [5]; and 6.7% in the United States [6], while in Europe, the prevalence varies from 2.3% to 5.2% [7, 8]. Moreover, in America, the prevalence from 2015 to 2016 was 15.3% [9]. According to the Renal Data System of the United States, Taiwan, Mexico (Jalisco), and the United States contributed the most significant number of patients with terminal CKD in 2015 (CKDT, glomerular filtration rate < 15 mL/min/1.73 m^2), with 378-476 patients per million of the general population [10].

The disturbances in CKD correlate with several clinical manifestations, such as insulin resistance (IR), hypertension, central obesity, and/or dyslipidemia, which are the main manifestations of metabolic syndrome (MetS). Overall, the main risk factors for CKD are T2D (57.6%) and systemic arterial hypertension (SAH) (3.2%). An increase in body mass index (BMI) (26.6%), a diet rich in sodium (9.5%), and an unintentional consumption of lead (3.6%) can increase the risk of CKD [11, 12]. Additionally, MetS is linked to aging and unhealthy lifestyles, such as a lack of physical activity and smoking, and it has been well established that MetS is a good predictive factor for T2D and cardiovascular disease (CVD) [13].

MetS is defined as a combination of risk factors, including abdominal obesity based on waist circumference (WC), increased blood pressure (BP), low levels of high-density lipoprotein-cholesterol (HDL-C), and elevated glucose and triglyceride levels. MetS occurs when three or more risk factors are met [13]. Although global data regarding the prevalence of MetS are unavailable for each country, several studies have reported high variation among populations due to differences in demographic characteristics such as ethnic backgrounds, locations, and clinical conditions. The estimated prevalence of MetS in 2011-2016 in the United States was 34.7% in adults [14]. In African populations, the MetS incidence is as high as 50% [15]. Furthermore, in Mexico, a recent meta-analysis reported a MetS prevalence of 41% among adults [16].

Recent evidence suggests that MetS significantly increases individuals' chances of developing CKD. The MetS incidence among individuals with CKD can reach

70% [17]. Several studies have reported an independent and positive association between MetS and CKD; accordingly, patients with MetS have up to a 2.6-fold greater risk of CKD than individuals without MetS [18, 19]. On the other hand, the presence of microalbuminuria is also more frequent among patients with MetS [20]. Furthermore, individuals with advanced CKD have higher prevalence rates of MetS components than individuals without CKD [21].

The increase in CKD incidence has emerged simultaneously with the rise of the obesity epidemic and obesity-related diseases, including MetS. Thus, it is unsurprising that CKD may be more prevalent in regions where MetS has a high incidence. In addition, both conditions share physiopathological pathways; therefore, CKD and MetS may also have common approaches to decrease their burden. Among the reliable strategies may be those that help to prevent and control obesity and its related diseases, promoting multilevel approaches to healthier lifestyles [22]. In this context, favorable outcomes in patients with CKD can be achieved with dietetic and lifestyle changes [23]. However, adopting these changes toward healthier nutrition and active lifestyles depends not only on patients' commitment but also on societal, economic, and political factors. Food insecurity, social violence, production chains, and costs of healthy food and medication are thus limiting factors related to MetS and renal failure progression worldwide [24].

There is an incipient impairment in renal function in patients with MetS long before clinical diagnosis, as microvascular changes are found to be present before metabolic components are integrated as a syndrome. Tubular atrophy, along with increased microvascular disease, interstitial fibrosis, and global and segmental arterial sclerosis occur gradually, and all of these processes, in combination with the presence of inflammatory cytokines (interleukin 6, IL-6; tumor necrosis factor-alpha, TNF-α; and other cytokines), potentiate kidney damage, leading to renal fibrosis [20].

Patients at early stages of CKD can be asymptomatic until the illness is advanced, and renal function deteriorates by more than 50%. This latter favors the accumulation of uremic toxins, alterations in the production of erythrocytes, calcium and phosphorus metabolism, metabolic acidosis, hydro electrolyte alterations, and immune system dysfunction. Together, these factors can contribute to the occurrence of comorbidities and gradual worsening of general conditions, leading to patient death without adequate management [25].

Several studies from different populations have linked MetS to CKD progression. A cohort study of 15,605 patients with stage 3 and 4 CKD (eGFR=15–59 mL/min/1.73 m^2) revealed that MetS was associated with end-stage renal disease

CHAPTER 5

Current Definitions, Biomarkers, and Treatments for Acute Kidney Injury

Juan Carlos Diaz Núñez[1] and **Rafael Valdez Ortiz**[1,*]

[1] *Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico*

Abstract: An unexpected reduction in renal function during the first seven days after a triggering event is known as acute kidney injury (AKI). AKI is diagnosed when serum creatinine increases by 0.3 mg/dL in 48 h, or an increase ≥ 50% in the first seven days of follow-up or a urinary volume < 0.5 mL/kg/h for six hours. AKI affects between 7% and 20% of hospitalized patients, and the incidence in the community is estimated to be between 20 and 200 per million inhabitants. Among critically ill patients, the incidence of AKI varies between 30% and 70%. AKI is multifactorial and can develop in a heterogeneous population in terms of genetics, age, previous renal function, and different comorbidities. The limitations in classifying and diagnosing AKI lie in the scarce variable specificity since serum creatinine and urine output do not always represent the severity of damage and are only markers of excretory function. Hence, owing to a lack of evidence of kidney damage in some cases (patients who did not present increased creatinine or decreased urine volume at the time of evaluation) and despite patients meeting the criteria for AKI, timely detection of functional changes with more precise and effective biomarkers is urgently needed.

Keywords: ADQI, Acid-base balance, Glomerular filtration rate, KDIGO, Metabolic acidosis.

INTRODUCTION

Acute kidney injury (AKI) is characterized by a sudden reduction in renal function during the first seven days after a triggering event [1]. AKI causes the accumulation of waste products derived from protein metabolism (urea, urea nitrogen, and creatinine) in conjunction with an alteration in acid-base balance (metabolic acidosis) and fluid and electrolyte homeostasis [2, 3]. AKI spectrum is broad, fluctuating from minor changes in biochemical markers of renal function to a total impaired kidney function, which demands the beginning of life-supporting treatments that involve renal replacement therapy (RRT) [4].

* **Corresponding author Rafael Valdez Ortiz:** Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico; E-mail: rafavaldez@gmail.com.

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The name of this abrupt decrease in renal function has transformed over time from "insufficiency" to "failure" to "injury." Hence, to obtain better outcomes for patients with AKI, in 2007, the report of the Acute Kidney Injury Network (AKIN) group recommended the word "injury," except for other terms that dichotomously suggest either normal kidney function or organ failure [2]. Later, the International Consensus of the Kidney Disease Improving Global Outcomes (KDIGO) group used the AKIN initiative and published the operational concept of AKI in 2012. Therefore, AKI is defined as a rise in serum creatinine (>0.3 mg/dL in 48 h), an increase oϕ ≥50% in the first 7 days of follow-up, or a urinary volume < 0.5 mL/Kg/h for six hours [5]. Table **1** shows the categorization of AKI based on the serum creatinine level and urine volume.

Table 1. KDIGO severity classification of AKI.

Stage	Serum Creatinine Concentration	Urine Volume Output
1	sCr basal value increase ≥ 1.5 to 1.9 times in 7 days or baseline increase ≥ 0.3 mg/dL in 48 h	<0.5 mL/Kg/h for 6 h
2	Baseline sCr rise > 2 to 2.9 times the baseline value	<0.5 mL/Kg/h for 12 h
3	sCr ≥4 mg/dL or baseline sCr increase ≥ 3 times the baseline value or need for RRT	<0.3 mL/Kg/h for 24 h or anuria for 12 h

Abbreviations: AKI, Acute Kidney Injury; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, Renal Replacement Therapy; sCr, serum creatinine.

The importance of classifying the spectrum from AKI to chronic kidney disease (CKD) was advertised in the Working Group of the Acute Disease Quality Initiative (ADQI) report [1, 6]. The acute kidney disease (AKD) concept was first proposed to delineate the course of the disease after patients were affected with AKI and progressed to advanced stages. Moreover, regardless of the severity of AKI, the complete and continuous reversal of an episode within 48 hours of its onset is known as "transient AKI" [5, 7]. Other methods to classify AKI have used the concepts of community-acquired AKI and hospital-acquired AKI. The last proposed classification system considers the origin of AKI and the prognosis and survival of patients [8]. Table **2** shows the definitions proposed by the latest ADQI consensus for AKI, AKD, and CKD.

EPIDEMIOLOGY

The importance of AKI lies in its consistent association with increased mortality, elevated progression risk to chronic kidney disease (CKD), and increased healthcare spending [9].

Table 2. AKI classification according to the Acute Disease Quality Initiative (ADQI).

-	AKI	AKD	CKD	Without kidney disease
Duration	**≤ 7 days**	**< 3 months**	**> 3 months**	**Not applicable**
Functional criteria	Oliguria for ≥ 6 h or sCr increased by ≥ 50% in 7 days, or sCr increased by ≥ 0.3 mg/dL in 2 days	GFR reduction ≥ 35% over baseline or sCr increase > 50% over baseline or AKI or GFR < 60 mL/min/1.73 m^2	GFR < 60 mL/min/1.73m^2	Unchanging sCr (no 50% rise in 3 months nor 0.3 mg/dL increase in 2 days), GFR ≥ 60 mL/min/1.73m^2, constant GFR (no 35% reduction in 3 months), no oliguria for ≥ 6 h
Either	Either	Either	Either	Either
Structural criteria	Not Defined	Increased albuminuria, hematuria, or pyuria, which are the most common biomarkers of kidney injury	Commonly elevated albuminuria	No marker of kidney damage

Abbreviations: AKI, Acute Kidney Injury; AKD, Acute Kidney Disease; CKD, Chronic Kidney Disease; sCr, serum creatinine; GFR, glomerular filtration rate.

The changes in the operational definitions of AKI have increased the incidence and reports of the disease to the extent that long-term economic and clinical impacts on health are recognized. Publications from upper-income countries have provided data for comparisons of incidence, course, and clinical settings. Nonetheless, this information is scarce in low- and middle-income countries, which has led to a deficient and restricted perspective of AKI as a pathology that affects only hospitalized and critically ill patients [10, 11]. In this context, the incidence and prevalence of AKI worldwide are very heterogeneous, not only among ethnic groups but also among different studies in the same population, mainly depending on the hospital and community setting. AKI affects between 7% and 20% of hospitalized patients, and the incidence in the community is estimated to be between 20 and 200 per million inhabitants [10, 12].

In the hospitalization setting, AKI affects mainly older adult patients, whereas outpatients with AKI tend to be younger and healthier. AKI incidence varies between 30% and 70% in critical care patients; moreover, it is estimated that around 5% of patients admitted to the intensive care unit (ICU) will need RRT [4, 5, 12].

In high-income countries, AKI is more prevalent in ICUs, where it occurs mainly in older patients with multiple organ failure. In this sense, the costs related to AKI are high, and prevention is difficult due to its unexpected appearance [8]. In

CHAPTER 6

Non-Anion Gap Metabolic Acidosis: Renal Tubular Acidosis

Juan Reyna-Blanco[1,*]

[1] *Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico*

Abstract: Renal tubular acidosis (RTA) is a condition in which there is a defect in the reabsorption of bicarbonate, the excretion of hydrogen ions, or both, generating a clinical syndrome characterized by normal anion gap metabolic acidosis, hyperchloremia, and impaired urinary acidification.

Keywords: Ammoniagenesis, Hyperchloremic acidosis, Metabolic acidosis, Reabsorption of bicarbonate.

INTRODUCTION

Renal tubular acidosis (RTA) is a condition in which there is a defect in the reabsorption of bicarbonate, the excretion of hydrogen ions, or both, generating a clinical syndrome characterized by normal anion gap metabolic acidosis, hyperchloremia, and impaired urinary acidification [1]. According to the site of tubular involvement, RTA is classified as RTA type 1 (distal), RTA type 2 (proximal), or RTA type 4 (aldosterone deficiency). Rarely, due to carbonic anhydrase II (CAII) deficiency, a mixed or type 3 RTA can be generated. However, some authors have removed it from the classification because most of these patients progress to a distal RTA. In these patients, bicarbonate reabsorption is characterized by a reduced renal threshold for bicarbonate reabsorption with developmental immaturity of the proximal tubule, which subsequently normalizes [2].

PHYSIOLOGY OF ACID-BASE BALANCE

The lungs and kidneys are primarily responsible for regulating the acid-base balance of the blood. They do so by independently controlling the two primary components of the body's central buffering system: CO_2 and HCO_3^-. Whereas the

* **Corresponding author Juan Reyna Blanco:** Department of Nephrology, Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico; E-mail: juanrb07@gmail.com.

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

lungs are responsible for excreting a large amount of CO_2 that is produced during the oxidation of carbohydrates, fats, and amino acids, the kidneys are responsible for removing nonvolatile acids such as sulfuric acid, phosphoric acid, oxalic acid, lactic acid, keto acids, and other organic acids. These molecules are generated through the following processes: oxidation of sulfur-containing amino acids, metabolism of phosphorus-containing compounds, oxidation of cationic amino acids, production of nonmetabolizable organic acids, and incomplete oxidation of carbohydrates and fats. In addition, metabolism generates nonvolatile bases, which are converted into HCO_3^-. Subtracting the metabolically generated base from the metabolically generated acid leaves a net endogenous H^+ production of ~40 mmol/day for a person weighing 70 kg. The strong acids in a typical Western diet (20 mmol/day of H^+ gained) and the loss of bases in the stool (10 mmol/day of OH^- lost) represent an additional acid load to the body of 30 mmol/day. Thus, the body faces a total load of nonvolatile acids of ~70 mmol/day (0.75-1.5 mmol/kg body weight) derived from metabolism, diet, and intestinal losses [3]. The kidneys face two problems in addressing this. The first problem is the need to excrete H^+, which implies the need to reabsorb all the HCO_3^-filtered through the glomeruli. Every day, 180 liters of blood are filtered through the kidneys. If each liter of blood contains 23 to 25 mmol of HCO_3^-, then the filtered load of HCO_3^- per day is 180 L x 24 mmol/L = 4,320 mmol of HCO_3^- (4140-4500 mmol) [4]. The kidneys solve this problem by secreting H^+ into the tubular lumen and titrating filtered HCO_3^- to form CO_2 and H_2O. According to the following chemical reaction, for each H^+ consumed, the HCO_3^- is reduced in the same proportion, ultimately generating the same amount of CO_2:

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows CO_2 + H_2O.$$

The carbonic anhydrase enzyme accelerates this process.

Second, 70 mmol of nonvolatile acids were excreted in the form of free H^+ in an "unbuffered" urinary volume of 1,500 mL per day, consequently producing urine with an H^+ concentration of 0.046 M (0.07 mol of H^+/1.5 L of urine). This latter would lead to a urinary pH of ~1.3 (pH = -log $[H^+]$). Physiologically, the lowest urinary pH that can occur is ~4.2, corresponding to an H^+ concentration of 0.000063 M, meaning that H+ is ~1000 times less concentrated than in "unbuffered" urine. The kidneys overcome this problem by binding H^+ with buffers such as phosphates and NH_3^+/NH_4^+ that maintain the urinary pH within a physiological range. Likewise, the H^+ secreted into the lumen has three destinations: the reaction with the filtered HCO_3^- to favor its reabsorption (80-85% is reabsorbed in the proximal convoluted tubule (PCT) and the rest in the thick ascending loop of the Henle and collecting tubules); titration with filtered phosphates ($HPO_4^{2-}/H_2PO_4^-$); and titration with secreted or, to a lesser extent,

filtered NH_3^+ to form NH_4^+. The net acid excretion (NAE) is defined with the following equation:

$$NAE= [titratable\ acid]u + [NH_4^+]u – [HCO_3^-]u \times urinary\ volume/day$$

Titratable acid is obtained as the amount of alkali needed to increase the urinary pH to 7.4. It is the excreted acid load in the form of phosphates ($HPO_4^{2-}/H_2PO_4^-$) or, to a lesser extent, H^+ bound to creatinine or uric acid. Under normal conditions, the amount of excreted HCO_3^- is negligible, and the amount of excreted titratable acid is almost constant. However, NH_4^+ excretion is variable and can increase to more than 300 mmol/day in severe nonrenal metabolic acidosis states. Therefore, an increase in the NAE is due to an increase in the amount of excreted NH_4^+, and conversely, a decrease in the NAE is due to a decrease in the amount of excreted NH_4^+ or an increase in HCO_3^- loss.

Acid-base Balance in Proximal Tubules and Ammonia Genesis

Bicarbonate is freely filtered through the glomerulus, so PCT indirectly reabsorbs most of the filtered HCO_3 load through H^+ secretion. The leading players in this process are the apical Na^+/H^+ exchanger (NHE3), luminal H^+ ATPase, carbonic anhydrase IV located at the brush border (CAIV), cytoplasmic carbonic anhydrase II (CAII), basolateral $Na^+/3HCO_3^-$ cotransporter (NBCe1) and Na-K ATPase, which supply the necessary Na^+ gradient. As shown in Fig. **1**, filtered HCO_3^- reacts with H^+, which is secreted through NHE3 (coupled with Na+ reabsorption) and to a lesser extent through H^+ ATPase, forming H_2CO_3 [5], and in a reaction catalyzed by CAIV, where water and CO_2 are released, which diffuse freely through the cell membrane. Once CO_2 is in the cytoplasm, it reacts with water to reform H+ and HCO_3^- through cytoplasmic ACII. HCO_3^- leaves the basolateral membrane along with Na+, through which the basolateral $Na^+/3HCO_3^-$ cotransporter (NBCe1) reaches the systemic circulation, while H^+ is recycled through NHE3 and H^+ ATPase, repeating the process.

PCT is also responsible for the synthesis and secretion of NH_4^+ through ammonia genesis. Glutamine metabolism leads to the formation of glutamate and, finally, α-ketoglutarate with the help of glutaminase (GS) and glutamate dehydrogenase (GDH). In the synthesis of α-ketoglutarate, 2 NH_4^+ ions are formed. Then, α-ketoglutarate enters gluconeogenesis or the Krebs cycle, forming 2 HCO_3^-, which are reabsorbed through the NBCe1 cotransporter in the basolateral membrane, whereas NH_4^+ can be dissociated intracellularly into H^+ and NH_3^+. Then, H^+ is secreted into the tubular lumen through the apical NHE3 exchanger or H^+ ATPase, and NH_3^+ diffuses across the apical membrane to join free H^+ in the lumen to form NH_4^+. Moreover, intracellular NH_4^+ can be secreted directly into the

CHAPTER 7

The Genetic Structure of Polycystic Kidney Disease (PKD)

Cristino Cruz[1], Claudia J. Bautista[2] and **Victoria Ramírez[3,*]**

[1] *Department of Nephrology, Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico*

[2] *Department of Reproduction Biology, Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico*

[3] *Department of Experimental Surgery, Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico*

Abstract: Polycystic kidney disease (PKD) is characterized by uncontrolled cellular proliferation, leading to fluid accumulation, extracellular matrix remodeling, and cyst formation with progressive kidney damage that leads to renal failure and death. Besides the kidney, other organs, such as the liver, the heart, and vasculature, are damaged.

Keywords: ADPKD, Autosomal dominant, Autosomal recessive, Heritage, Monogenic disease.

INTRODUCTION

Polycystic kidney disease (PKD) is a life-threatening disease with no cure or specific treatment. PKD is characterized by uncontrolled cellular proliferation, leading to fluid accumulation, extracellular matrix remodeling, and cyst formation with progressive kidney damage that leads to renal failure and death. However, in addition to the kidney, other organs, such as the liver, heart, and vasculature, are damaged [1 - 3].

PKD is a monogenic disease classified as heterogeneous. There are two known variants; the first is the most common and least severe variant present in adulthood, known as autosomal dominant polycystic disease (ADPKD). ADPKD is caused by mutations in the polycystin 1 (*PKD1* or *PC1*) and polycystin 2 (*PKD2* or *PC2*) genes. The second is autosomal recessive polycystic kidney disease (ARPKD), a rare and severe disease affecting people before birth or

* **Corresponding author Victoria Ramírez:** Department of Experimental Surgery, Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Tlalpan 14080, Mexico City, Mexico; E-mail: victoria.ramirezg@incmnsz.mx.

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childhood. It results from mutations in the fibrocystin or polycystic kidney and liver disease (*PKHD1*) gene. Both disease variants will result in progressive renal function loss until the development of end-stage renal disease (ESRD), and some patients will need replacement therapy or transplantation to survive (Fig. **1**) [4 - 7].

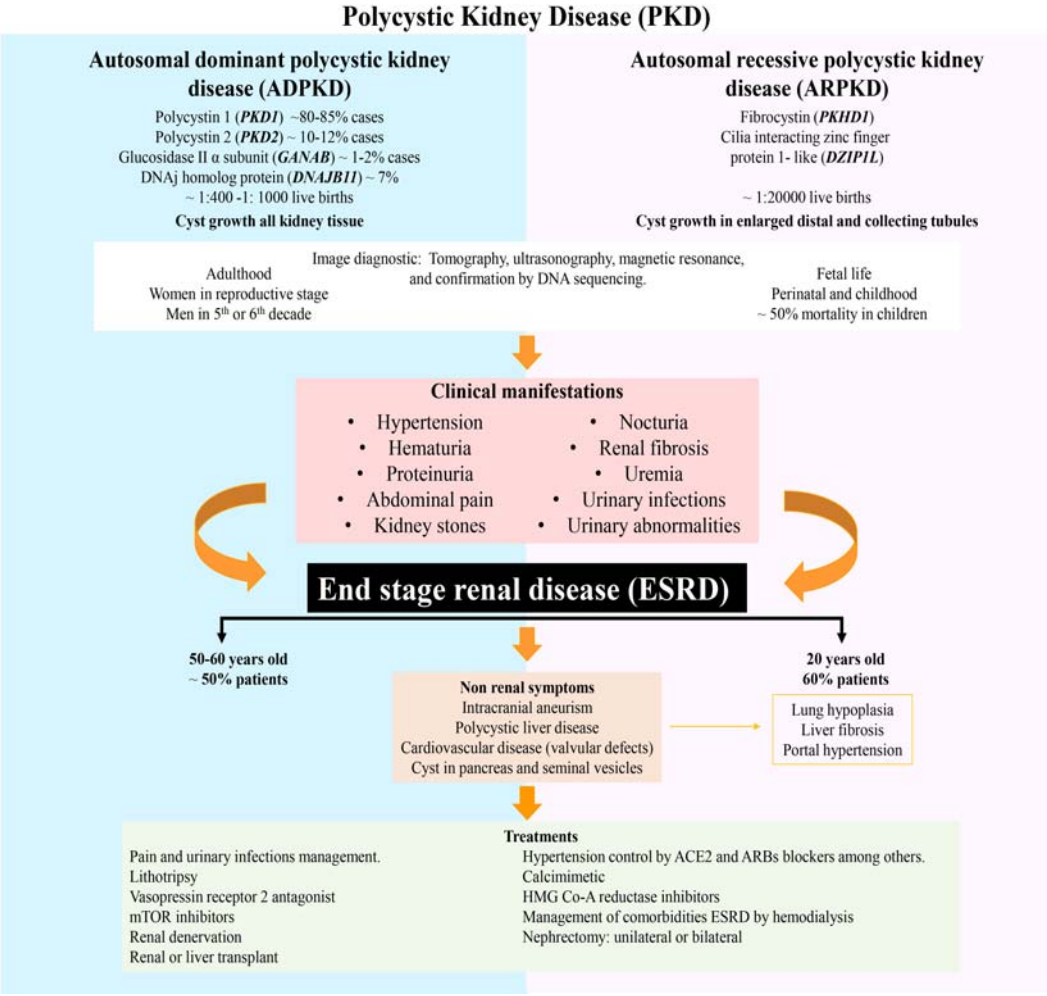

Fig. (1). Characteristics of polycystic kidney disease, gene mutations, prevalence, symptoms and treatments. (ACE2) Angiotensin converting enzyme, (ARBs) Angiotensin II receptor blockers, (mTOR) mammalian target of rapamycin.

Frequently, ADPKD patients present germline cell mutations in one allele in any *PKD1* or *PKD2* gene. Consequently, somatic inactivation of the remaining wild-

type alleles or loss of heterozygosity can initiate cyst formation. Loss-of-function mutations or truncating mutations determine the phenotypic variability of the disease. Many authors conclude that PKD severity depends directly on the type of mutation present or PKD genes' expression and remaining activity. Patients with truncating *PKD1* mutations develop ESRD faster than those without truncating mutations. Fewer severe cases are diagnosed after 60 years old. Although *PKD2* mutations are related to mild disease progression [8], *PKD1* and *PKD2* inactivating mutations are embryonically lethal. The variety of mutations will generate a different degree of disease or mosaicism, even in the same family members; some of them will have fast cyst growth and loss of renal function, and others will have slow progression with mild or imperceptible symptoms; also, age and hormones may have an essential role in ADPKD disease progression [5, 9, 10].

EPIDEMIOLOGY

The prevalence of PKD is controversial due to the lack of a standard criterion of ascertainment or symptoms; it may vary according to geographical location and ethnicity.

ADPKD

It has been estimated that ADPKD affects 1:400 to 1:1,000 live births [11 - 14]. In 2015, the National Ambulatory Medical Care Survey (NAMCS) in the USA described 170 million registered patients, with a prevalence of 4.3 per 100,000 people. The annual incidence was 0.62 per 10,000 people in the USA. Females were diagnosed early in the reproductive period. Men were diagnosed with comorbidities or complications at 65 years of age [15, 16]. Similar results were found in the European population; a meta-analysis of eight European studies revealed that the prevalence of ADPKD was 2.63:10,000 people; however, in Modena, Italy, the incidence was more than 4.6 per 10,000 people [17]. Comparable results were found in French and Japanese populations [5]. Systematic sequencing of publicly available databases, such as gnomAD and BRAVO, which include all ethnic groups, has shown that the prevalence is greater than the estimated 9.3 cases per 10,000 sequenced individuals; additionally, several new truncate mutations that could be a cyst modifier with clinical importance have been found [12]. In 2020, Suwabe T. *et al.* reported in a retrospective cohort that included data from 1980–2016 that the incidence of ADPKD was 2.2 times greater than that previously reported in the first five decades, which was 3.06 per 100,000 persons per year in Minnesota, USA [18]. As we mentioned before, ADPKD is caused by *PKD1* and *PKD2* mutations; 85% of ADPKD cases are caused by *PKD1* gene truncations (short amino or carboxyl

CHAPTER 8

Renal Lithiasis: Current Concepts about a Millenary Disease

Roberto Lugo[1,*] and **Martha Medina-Escobedo**[1]

[1] *Research Division, Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Mérida, Yucatán, Mexico*

Abstract: Renal lithiasis has been a disease afflicting humankind since ancient times; epidemiological data worldwide show that its prevalence varies in different geographical areas, with a higher prevalence in a belt mainly encompassing tropical regions.

Initially, medicine focused on searching for and developing surgical strategies for treating renal lithiasis; currently, the application of minimally invasive surgical procedures predominates. The predominant clinical symptoms are hematuria and acute and intense pain.

Because of its high recurrence rate, research on renal lithiasis has focused on determining its causes and risk factors. Diagnostic methods for pathology have evolved significantly; currently, there are accessible and inexpensive methods (renal and urinary tract ultrasound), as well as more sophisticated methods; however, computed tomography is the gold standard method because it offers high sensitivity and specificity and allows us to pinpoint the location of the stone and suggest its composition. Even so, a percentage of patients are asymptomatic, and the diagnosis is made fortuitously.

New approaches to treating this disease are focused on metabolic studies to improve medical and nutritional therapy, minimally invasive surgical procedures, and the development of new wireless laparoscopic devices to obtain real-time images and biopsies to reduce the recurrence of the pathology.

Keywords: Hounsfield units, Kidney stones, Lithiasis belt, Risk factors, Stone composition.

INTRODUCTION

Renal lithiasis is a millenary disease. In Ancient Egypt, the first evidence dates from El–Amrah. In 1991, Elliot Smith found stones in the bladder in a mummy

[*] **Corresponding author Roberto Lugo:** Research Division Hospital Regional de Alta Especialidad de la Península de Yucatán IMSS-Bienestar, Altabrisa, 97130 Mérida, Yucatán, Mexico; E-mail: roberto.lugo.gomez@gmail.com.

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from 4800 B.C. The discovery of the oldest kidney stone has been attributed to Shattock. His reports describe a stone located next to the spinal column of a mummy from 3000 B.C. The first reports about the symptoms and prevention of lithiasis are found in the medical books of Asutu in Mesopotamia (320-1200 B.C.) [1]. In addition, the book Sushruta Samhita (600 B.C.) describes the first surgical procedures, including perineal lithotomy, used to treat bladder stones. However, this document does not mention kidney and ureteral stones [2].

Hippocrates (46-377 B.C.) described kidney diseases and symptoms of bladder lithiasis. He mentioned that specialists must perform stone extraction surgeries due to the high risk of death and due to neural stimulation of the bladder. Similarly, he was the first to issue some theories about the formation of kidney stones; he carried out a detailed macroscopic analysis of alterations in the urine and provided diagnostic interpretations and concepts currently in use [3]. After Hippocrates, advances were slow for a long time until Celsus' investigations. He described surgical techniques for stone removal; nonetheless, the origin of the stones was unknown [4].

In the 7th century, the Arab Rhazes proposed the theory of stone formation due to excess salts in urine [5]. Hildegard (1098–1179) was the first to identify modern "metabolic syndrome" and urinary tract infections as the causes of lithiasis [6].

Later, in the 18th century, hypercalciuria was recognized as the principal cause of lithiasis, and the importance of diet in treating lithiasis caused by uric acid was established. At the same time, several strategies have been developed to dissolve stones using alkaline salts, potassium carbonate, and others. Advances in treating lithiasis are related to the surgical treatment of the stones [5].

Over time, the frequency of bladder stones has decreased, and that of kidney stones has increased [7]. However, in the 19th century, studies on the surgical treatment of lithiasis focused on treating the disease. Multiple studies on metabolic disorders and the medical management of kidney stones have been performed in the last century, the most relevant of which will be addressed in the appropriate sections of this chapter.

EPIDEMIOLOGY

Urinary tract lithiasis is a global problem and is the third most common type of urological disorder after urinary tract infections and prostate disease. The incidence and prevalence can vary according to the geographic area and the socio-demographic aspects of the population. The first signs of the disease documented in the ancient population revealed a predominance of bladder lithiasis. Decades later, a progressive increase in renal lithiasis was observed, especially in

industrialized countries, where significant changes in eating habits and lifestyle were established [8]. In the last 3-40 years, the prevalence of renal lithiasis has progressively increased globally. Between 1964 and 1972 [9], an increase of 200% was reported in the United States. Subsequent studies revealed an increase in the prevalence of 3.4% from 1976 to 1980 and an increase of 5.2% between 1988 and 1994 [10]. Between 2007 and 2010, an unadjusted prevalence of 8.8% was observed [11], and between 2013–2014, a 10.1% was reported [12].

An increase in the prevalence of renal lithiasis has also been reported in Europe. In Spain, the prevalence increased from 4.2% to 5.2% between 1986 and 2007. In Italy, renal lithiasis increased from 5.9% to 8.0% in 1986-1998. In Germany, the prevalence was 4.0% to 4.7% between 1979 and 2001 [13]. Reports from China showed a similar prevalence of renal lithiasis; they reported 6.0% in 1991–2000 to 10.6% in 2001–2011 [14].

A geographical belt of lithiasis has been identified, in which countries with the highest prevalence of renal lithiasis, such as Egypt, Sudan, Saudi Arabia, Iran, the United Arab Emirates, the Philippines, India, Pakistan, Thailand, Myanmar, and Indonesia, are found [7]. In 2015, Ahmad *et al.* reported the prevalence of urinary stones according to the origin of the patients. These countries included Egypt (29.5%), Pakistan (24.9%), India (23.3%), Yemen (20.5%), Sudan (17.6%), Bangladesh (16.2%), Eritrea (15.4%), and Saudi Arabia (7.4%). The mean prevalence in the population of this geographical area was 19.1%. Seventy-five percent of the urinary tract stones were found in the kidneys [15].

On the American continent, Canada has reported a greater prevalence of regional variations and a greater prevalence in New Brunswick than in other Canadian regions [16]. A similar situation has been reported in the United States, where a geographic belt in the southeast is also mentioned. It includes the states of Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and Kentucky [17].

In Mexico, there are few epidemiological studies on this topic. Gomez *et al.* reported that the national prevalence of renal lithiasis was 2.4 per 10,000 patients at the Instituto Mexicano del Seguro Social (Public Hospitals of the Mexico Government) in 1984; this region refers to the lithogenic geographic areas of Yucatan, Puebla, and Quintana Roo [18]. In addition, Medina-Escobedo *et al.* reported that the prevalence of lithiasis in Yucatan, Mexico, was 550 per 10,000 inhabitants in 2002 [19]. The results confirmed the findings of Ortegon-Gallareta et al., who reported that Yucatan has an annual hospitalization rate for lithiasis of 12.5 per 1,000 inhabitants, which is higher than the national average estimated at 4.4 per 1,000 inhabitants [20].

CHAPTER 9

Sodium Imbalance and Hypertension: An Old and Current Disease

Mercedes Aguilar-Soto[1] and **Fabio Solis-Jiménez**[2,*]

[1] *Instituto Nacional de Ciencias Médicas y Nutrición" Salvador Zubirán", Mexico City, Mexico*

[2] *Instituto Nacional de Cardiología Ignacio Chávez, Tlalpan 14080, Mexico City, Mexico*

Abstract: The global prevalence of hypertension in adults ranges between 30-40% of the population, with an age-standardized global prevalence between 24 and 20 in women and men, respectively. Individuals with hypertension face approximately 2,000 dollars higher annual healthcare expenditure compared to an individual who does not suffer from it. Although it is considered a disease of multifactorial origin, there is broad agreement that excess salt in the diet is the most important controllable factor in the increase in blood pressure. In the study of arterial hypertension and sensitivity to sodium, the sodium intake in humans in developed countries is subject to important variations from day to day. The balance in sodium is controlled almost entirely by the ability of the kidney to vary urinary sodium excretion. The immediate effect of ingested sodium in the diet is to modify plasma sodium and extracellular volume. The increase in plasma sodium is rapidly dampened by the increase in osmolarity that tends to move fluid from the intracellular space to the extracellular space. Small increases in plasma sodium also strongly stimulate the thirst center, causing increased water intake and vasopressin secretion. These mechanisms return sodium levels to baseline but increase extracellular volume, which stimulates other compensatory mechanisms involved in the regulation of vascular tone. More research with a better diagnostic definition and a higher number of participants should be conducted to improve outcomes in this group of patients.

Keywords: Cardiovascular disease, Diastolic blood pressure, Diet, Osmolality, Salt, Sodium, Systolic blood pressure.

INTRODUCTION

Hypertension is currently recognized as the leading cause of cardiovascular disease worldwide. Based on blood pressure measurements in 2015, it was estimated that approximately 1.13 billion people in the world suffer from hypertension [1]. The global prevalence of hypertension in adults ranges between

* **Corresponding author Fabio Solís Jiménez:** Instituto Nacional de Cardiología Ignacio Chávez, Tlalpan 14080, Mexico City, Mexico; E-mail: fabiosolisjimenez@gmail.com.

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30% and 40% of the population, with an age-standardized global prevalence between 24% and 20% in women and men, respectively [2]. The mortality of hypertension reaches approximately 10.4 million people a year [3]. The prevalence increases with age and is more frequent in older adults (over 60% of people over 60 years) [4].

The burden of disease varies widely according to the level of awareness, accessibility to treatment, and level of hypertension control when comparing developing and developed countries [5].

Individuals with hypertension face approximately 2,000 dollars higher annual healthcare expenditure than people with no hypertension; hence, it is also a burden for the health system [6]. In addition, it affects the global economy, as it implies a lower number of productive life years per individual, which translates into a decrease in gross domestic product [7, 8].

Although it is considered a disease of multifactorial origin, there is broad agreement that excess salt in the diet is the most important factor controlling the increase in blood pressure with age in our culture [9].

Until 5000 years ago, when the Chinese discovered that salt could serve as a food preservative, we used to ingest low amounts of salt since less than 500 milligrams of sodium is required in adults to maintain homeostasis [10]. The salt began to become popular and commercialized even at high costs, reaching a peak in consumption in approximately 1870 when it was estimated that each person was ingesting approximately 9 to 12 g per day [11]. This approximately 50-fold increase in basal sodium intake in such a short evolutionary period did not allow adaptive changes to emerge to excrete these amounts, which are produced through different routes, such as the sustained increase in blood pressure that we currently know [12]. Since the middle of the last century, epidemiological studies have shown that there is a strong correlation between the consumption of salt and the development of hypertension in individuals, as well as the incidence of hypertension in populations [13, 14]. It has also been shown that a restriction in sodium consumption substantially lowers blood pressure [15].

On the other hand, high salt intake is associated with an increased risk of cerebrovascular disease [16], left ventricular hypertrophy [17], chronic kidney disease progression, and proteinuria, independent of the effect of blood pressure on these complications [18].

The increase in blood pressure and the adverse cardiovascular effects resulting from the increase in salt intake in the diet are related, at least initially, to the kidney's inability to excrete excess sodium [19]. The study of this and other

pathophysiological mechanisms that explain the relationship between sodium consumption and hypertension led to the description of a condition called salt sensitivity, which is defined as the behavior of blood pressure parallel to changes in sodium intake; therefore, if salt intake increases, blood pressure increases, and the opposite occur when salt intake decreases [20].

Although the diagnostic criteria have not been well standardized, it is estimated that approximately 30% to 50% of hypertensive patients are sensitive to salt and that approximately 25% of normotensive patients are also sensitive to salt [21]. The clinical importance of salt-sensitive hypertension has been questioned for several years because there is a strong belief among some authors about whether it truly represents an abnormal condition. This finding contradicts the physiological basis that salt balance *via* natriuretic and antinatriuretic mechanisms is independent of blood pressure. However, more recent studies have shown that it is a risk factor for cardiovascular morbidity and mortality independent of blood pressure [22].

PATHOPHYSIOLOGY

In the study of arterial hypertension and sensitivity to sodium, sodium intake in humans in developed countries is subject to important daily variations. The balance in sodium is controlled almost entirely by the ability of the kidney to vary urinary sodium excretion. The immediate effect of ingested sodium in the diet is to modify plasma sodium and extracellular volume. These first changes are responsible for the immediate changes in blood pressure [23]. The increase in plasma sodium is rapidly dampened by the increase in osmolarity, which tends to move fluid from the intracellular space to the extracellular space. Small increases in plasma sodium also strongly stimulate the thirst center, causing increased water intake and vasopressin secretion, resulting in fluid retention. These mechanisms return sodium levels to baseline but increase extracellular volume, stimulating other compensatory mechanisms that regulate vascular tone [24].

Blood pressure must increase to increase the filtration pressure in the glomeruli and thus increase the filtered load and urinary sodium excretion. Under normal conditions, there is a balance between renal perfusion pressure (approximately 100 mmHg) and urinary sodium excretion (approximately 100-120 mEq). This balance is disrupted by the excessive consumption of sodium associated with different factors that affect the anatomical and functional integrity of the kidneys, resulting in hypertension [25].

When mineralocorticoids are given continuously, they cause sodium retention, which consequently causes natriuresis (sodium excretion through the urine) when sodium levels reach the cut-off point. This phenomenon is known as

CHAPTER 10

Diabetic Kidney Disease: A Versatile Disease

María De Los Ángeles Granados-Silvestre[1], Guadalupe Ortiz-López[1] and **Katy Sánchez-Pozos[1,*]**

[1] *Research Division, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico*

Abstract: Diabetic kidney disease (DKD) is a microvascular complication of diabetes characterized by elevated urine albumin excretion, a decrease in the glomerular filtration rate (GFR), or both. Type 2 diabetes (T2D) accounts for approximately 20%–40% of DKD cases. There are two main risk factors for progression to DKD: modifiable and nonmodifiable. Modifiable factors include hyperglycemia, a long duration of diabetes, a sedentary lifestyle, high blood pressure, obesity, metabolic syndrome, smoking, and dyslipidemia. Nonmodifiable factors include ethnicity, age, genetics, and sex. For many decades, albuminuria was considered the main clinical sign of DKD; however, many patients with diabetes do not follow the classic course of DKD. Approximately 9.0%-39.0% of patients with diabetes and a GFR < 60 mL/min/1.73 m2 do not present albuminuria. In this context, the effectiveness of diagnosis and early treatment for DKD is limited by the lack of accessible and safe biomarkers with high sensitivity. Hence, there is an urgent need to identify biomarkers to diagnose and monitor DKD. The use of different omics technologies can be helpful.

Keywords: DKD (Diabetic Kidney Disease), Diabetic nephropathy, Microvascular complication, Type 2 diabetes, Type 1 diabetes.

INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disease characterized by chronic hyperglycemia as a consequence of defects in insulin secretion, insulin action, or both [1]. According to the International Diabetes Federation (IDF), global diabetes incidence continues to increase, and projections predict that 745 million adults will have diabetes by 2045 [2]. Among affected people, 30% to 40% will develop diabetic kidney disease (DKD), and approximately 30% will progress to end-stage renal disease (ESRD) [3]. Compared with Caucasians, Native Americans, Hispanics, and African Americans have a greater risk of developing DKD [4].

[*] **Corresponding author Katy Sánchez Pozos:** Research Division, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico; E-mail: katypozos@gmail.com.

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According to the International Organization for Kidney Disease Improving Global Outcomes (KDIGO), DKD is defined as chronic kidney disease (CKD) in patients with diabetes. In contrast, diabetic nephropathy is the histological diagnosis of glomerular structural alterations detected through biopsy [5]. Therefore, DKD is a microvascular complication of diabetes characterized by elevated urine albumin excretion, a decrease in the glomerular filtration rate (GFR), or both [6]. DKD is infrequent if the duration of diabetes is less than one decade. An incidence of 3% per year occurs 10 to 20 years after diabetes begins, after which the incidence of DKD decreases (Table **1**). It is important to note that patients with 20 to 25 years of diabetes without clinical signs of DKD have a low risk of developing such complications. The progression of diabetes to DKD has become a health burden, not only because of costs but also because of the deterioration of patient quality of life and its consequences. As shown in Table **1**, the epidemiology of DKD in T1D and T2D patients is similar. T2D accounts for approximately 20%–40% of DKD cases [7 - 9].

Table 1. Epidemiology of DKD in patients with T1D and T2D.

-	T1D	T2D	References
Prevalence of DKD (%)	9.6 20.2 (After 30 years of postpubertal diabetes)	14.0-30.6 45.0 (40 years of duration of T2D)	[10 - 17]
Incidence of eGFR < 60 ml/min/1.73 m^2 (%)	2.1	2.2-4.3	
Prevalence of eGFR < 60 ml/min/1.73 m^2 (%)	11.4-15.0	28.0-29.6	
Microalbuminuria (%)	25.4-27.2	25.0-35.0	
Annual microalbuminuria and albuminuria incidence (%)	1.3-3.8	3.8-12.7	
Macroalbuminuria incidence (%)	1.1-1.8	1.0-4.8	
Macroalbuminuria (proteinuria) (%)	25.0-40.0	3.4-20.5	
Dialysis (%)	0.3 – 1.5	0.2 – 1.0	
Annual incidence of ESRD (%)	0.04-4.5		
ESRD (%)	3.3-7.8	19.5	
Microvascular complications (%)	35.5 – 60.1	38.8 – 65.1	
Macrovascular complications (%)	5.9 – 12.4	16.0 – 28.1	

There are two main risk factors for progression to DKD: modifiable and nonmodifiable. Modifiable factors included hyperglycemia, a long duration of diabetes, a sedentary lifestyle, high blood pressure, obesity, metabolic syndrome,

smoking, and dyslipidemia (Tables **2** and **3**). Hyperglycemia and hypertension, either in combination or separately, are the principal risk factors for DKD development. Nonmodifiable factors include ethnicity, age, genetics, and sex. Most of these factors are variable and depend on drugs or modifications in lifestyle. Consequently, controlling modifiable risk factors is crucial for preventing and delaying the decrease in renal function. Clinical guidelines recommend managing numerous risk factors concurrently to ameliorate kidney outcomes in patients with T2D. These measures include smoking cessation, weight loss, increased physical activity, glycemia, blood pressure, and dyslipidemia control [18 - 20].

Table 2. Causal factors of DKD.

-	Type 1 Diabetes	Type 2 Diabetes
Causal factors (frequency, %)	Hyperglycemia Glomerular hyperfiltration (70%)	Hyperglycemia Glomerular hyperfiltration (50%) Obesity Hypertension Dyslipidemia

Table 3. Risk factors for DKD.

-	Odd ratios	References
HbA1c variability	1.43 (1.24-1.64)	[21]
Hypertension	1.67 (13.1–2.14)	[22]
Obesity	2.87 (1.24–6.66), $P = 0.014$ 3.76 (1.88-7.53), $P < 0.001$	[23, 24]
Triglycerides ≥150 mg/dL	1.71 (1.35-2.16), $P < 0.001$ 1.20 (1.06–1.36), $P = 0.004$	[25, 26]
HDL-C <40 mg/dL (men) or <50 mg/dL (women)	1.20 (1.06–1.36), $P = 0.005$	[26]
Smoking	1.33 (1.22, 1.46), $P < 0.001$	[27]

PATHOPHYSIOLOGY

For many decades, albuminuria was considered the main clinical sign of DKD; however, many patients with diabetes do not follow the classic course of DKD, which includes hyperfiltration, which begins with microalbuminuria, followed by proteinuria and ongoing renal function decline, leading to ESRD [28]. Nonetheless, approximately 9.0%-39.0% of patients with diabetes and a GFR < 60 mL/min/1.73 m^2 did not present albuminuria [29 - 32]. Hence, DKD can occur independently of the prior proteinuria development and microalbuminuria's onset. In this sense, several studies have proposed two pathways for the progression to

CHAPTER 11

The Nephrotoxicity by Chemicals

Estefani Yaquelin Hernández-Cruz[1,2], Estefany Ingrid Medina-Reyes[1] and **José Pedraza-Chaverri[1,*]**

[1] *Chemistry School, Department of Biology, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico*

[2] *Posgrado en Ciencias Biológicas, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico*

Abstract: The amount of chemicals is constantly increasing, which increases the likelihood of exposure to toxic substances. The kidney is one of the organs most affected by exposure to these chemicals, medications, and environmental pollutants. Although the proximal tubules are the main target of a large majority of nephrotoxic agents, all kidney compartments can be affected by nephrotoxins, leading to one or more classic clinical renal syndromes. These include acute kidney injury, tubulopathies, proteinuric kidney disease, and chronic kidney disease. Different molecular mechanisms, such as oxidative stress, mitochondrial dysfunction, autophagy, necrosis, and apoptosis, can regulate these renal syndromes. It is important to note that the nephrotoxicity of chemicals is not always recognized due to the lack of identification of the causal link between chemicals and kidney damage; however, different clinical biomarkers have been used and discussed in recent years to determine nephrotoxicity at an early stage. This chapter provides an overview of chemical-induced kidney damage and details about relevant biomarkers for identifying nephrotoxicity. In addition, we discuss some promising therapeutic targets for the early identification of toxin nephrotoxicity.

Keywords: Acute kidney injury, Clinical markers, Chronic kidney injury, Kidney damage, Nephrotoxin, Protein disease, Tubulopathies.

INTRODUCTION

Nephrotoxicity is one of the most common kidney problems; it occurs when a drug, chemical, or toxin, which can be ingested, inhaled, injected, or a substance produced by the body, causes direct or indirect adverse effects on kidney function [1, 2]. Nephrotoxicity can affect function (e.g., acute renal failure) or structure (e.g., acute tubular necrosis). Various drugs and environmental pollutants can be included among the toxic chemical agents. Drugs that can induce nephrotoxicity

* **Corresponding author José Pedraza Chaverri:** Chemistry School, Department of Biology, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico; E-mail: pedraza@unam.mx

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

include cancer treatments, antibiotics, analgesics, anti-inflammatories, antineoplastics, immunosuppressants, and radiocontrast agents. Environmental pollutants include heavy metals, diglycolic acid, ethylene glycol, and hydrocarbons [3].

Additionally, toxic substances are constantly being discovered worldwide; for instance, in 1970, only 65,000 toxins were known, while by 2000, the number of toxins increased to more than 500,000, so we live in a world full of invisible molecules whose effects are poorly understood. Many of these toxins are eliminated *via* the kidneys, which could be related to several cases classified as idiopathic [4].

This is particularly relevant since the incidence of kidney disease caused by toxic substances has been increasing in recent years [5]. Additionally, the American Association of Poison Control Centers reported that over 6 years (2001-2007), there were approximately 16.8 million exposures to toxic substances, 16,444 of which showed kidney effects, while 55.2% of the subsequent exposures induced severe renal complications such as increased creatinine, oliguria/anuria, and renal failure [6].

Drug-induced nephrotoxicity is more common in hospitalized patients than in the community. In Latin America, only 2% of community-acquired acute kidney injuries are attributed to nephrotoxins in countries such as Argentina, Brazil, Colombia, Mexico, and Paraguay. On the other hand, 14% of hospital-acquired acute kidney injuries are due to nephrotoxins (13%) and radiocontrast agents (1%) in countries such as Argentina, Bolivia, Brazil, Colombia, Cuba, Mexico, Peru, Puerto Rico, and Uruguay [7]. Although community-acquired kidney injury is rare, the incidence is estimated to be 4.3% among all hospital admissions in the United Kingdom [8].

Several decades ago, in the 1970s, it was estimated that nearly four million workers in the United States were occupationally exposed to known or suspected nephrotoxins [9]. Although occupational exposure to high levels of nephrotoxins is becoming less common in industrially developed countries, it is well known that chronic exposure to low levels of nephrotoxins contributes to kidney damage and is a risk factor for developing chronic kidney disease [10]. For example, in a cohort of Native Americans (3,119 participants) exposed to low and moderate levels of arsenic through drinking water, the authors reported a positive relationship between arsenic concentration in urine and chronic kidney disease [11]. In addition, “prolonged” exposure to organic solvents, pesticides, and copper sulfate has been reported to be widely associated with renal cell cancer [12]. A relationship between kidney damage and high occupational exposure to

hydrocarbons has also been observed [13]. In addition, occupational exposure and people with high environmental exposure to cadmium have been reported to have an increased risk of chronic kidney disease [14, 15].

It is important to note that the general population is exposed to several nephrotoxic substances. Although physicians prescribe the vast majority of potentially nephrotoxic drugs, numerous are available as over-the-counter preparations, increasing the probability of exposure. As mentioned above, drug-induced nephrotoxicity is more common in hospitalized patients than in the community, particularly in intensive care units (ICUs).

According to a Chinese study on patients hospitalized in ICUs, the incidence of acute kidney injury was 51%, and the majority of cases occurred on the fourth day after admission [16]. Moreover, the incidence of nephrotoxicity associated with medication is approximately 18-27% of all patients with acute kidney injury in US hospitals [17]. In general, epidemiological studies on acute kidney injury have reported that the incidence of drug-induced nephrotoxicity in adults is approximately 14% to 26%, while in hospitalized children, it is 16% [18 - 22]. The global picture of acute kidney injury describes that one in five adults and one in three children will develop acute kidney injury during hospitalization [23]. Overall mortality in critically ill patients with acute kidney injury can be over 60% [21]. Several factors can contribute to acute kidney injury and to the progression of kidney failure in hospitalized patients, including cardiovascular and liver disorders, metabolic diseases, malignancies, hypovolemia, poisoning, anemia, and vascular and surgical interventions. In addition, many of these patients require nephrotoxic iodine contrast agents for computed tomography (CT) scans and other radiological examinations [24]. Multiple studies have shown that patients with diabetic nephropathy are at high risk for contrast drug-induced acute kidney injury [25]. The mortality rate associated with acute kidney injury induced by this type of drug could be greater than 30% in patients with diabetes who receive intravenous contrast media [26]. Nephrotoxicity problems have also been found in studies on drug development. In 2014, an AstraZeneca study reported that 82% of projects failed in the preclinical phase due to safety concerns, while 8% failed due to nephrotoxicity. Likewise, 52% of the projects failed in the clinical phase due to safety reasons, and 9% failed due to kidney problems [27].

PATHOPHYSIOLOGY

High drug and toxin delivery to the kidney is due to high blood irrigation, which exposes the kidney to significant concentrations of toxins [2, 28]. In addition, the kidney is exposed to chemicals through apical contact and cell uptake or transport

CHAPTER 12

Loss of Cellular Differentiation in Renal Carcinoma

Jazmin Marlen Pérez-Rojas[1,*]

[1] *Research Division, Instituto Nacional De Cancerología, Tlalpan 14080, Mexico City, Mexico*

Abstract: Renal cell carcinoma (RCC) is a silent cancer that has increased in prevalence in the last decade, in men older than 50 years old. Clear cell RCC is the most common type of renal cancer and the most lethal urogenital cancer with a mortality rate above to 40% of frequency. More than 30% of renal cancers develop which are increasing worldwide metastatic spread. The main risk factors related with this neoplasia are smoking, hypertension, chronic kidney disease, and obesity, which are increasing worldwide. RCC has a low response to chemotherapy and radiotherapy, which has led to the investigation of new pharmaceutical strategies, such as immunotherapy and/or its combination with chemotherapy and surgery, for the treatment of this neoplasia. Unfortunately, RCC is resistant to treatment, which complicates its management.

Keywords: Cancer, Cancer therapy, Metastasis, Risk factors, Treatment resistance.

INTRODUCTION

Cancer is a major public health problem and is the second or third leading cause of death worldwide. Renal cell carcinoma (RCC) is a urinary malignancy that represents 3-4% of all types of cancers. Approximately 431,519 new RCC cases and 179,368 RCC-related deaths are registered each year worldwide, with Asia and Europe having the highest incidence. According to data from the International Agency for Research on Cancer (IARC), the mortality rate continues to increase in low- and middle-income countries, with 15,831 deaths in Latin America and the Caribbean and 10,850 deaths in Africa. RCC occurs with a high frequency in the adult population between 50 and 70 years old and with a greater prevalence in males than in females (the incidence rate is 139,216 cases compared with an incidence rate of 71,622 cases, with a 2:1 relation between men and women) [1, 2]. Similar to mortality rate is prevalence rate, it is higher in men compared to

* **Corresponding author Jazmin Marlen Pérez Rojas:** Research Division, Instituto Nacional De Cancerología, Tlalpan 14080, Mexico City, Mexico; E-mail: jazminmarlen@gmail.com.

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

women. RCC has a high mortality rate because it is a "silent" tumor. Only 40% of cases present one of the three common symptoms for detection: hematuria, flank pain, or a palpable abdominal mass, while 60% of cases are detected accidentally when the patient undergoes a study of abdominal imaging for nonspecific musculoskeletal or gastrointestinal complaints. RCC metastasizes in more than 25% of patients, with a median survival of 13 months once detected [3]. The main sites where metastasis occurs are the lungs, lymph nodes, liver, bone, and brain. One factor associated with the rise in the incidence of RCC is due to the increased use of diagnostic imaging techniques, such as ultrasound and computed tomography (CT) [4].

PATHOPHYSIOLOGY OF RCC

The onset of loss of cellular differentiation of renal cells egins with the gain and/or deletion of genetic material, which triggers tumorigenesis. Deletions occur frequently on chromosomes 1, 2, 3p, 5q, 6, 7, 8p, 9p, 10, 13, and 17, while gains occur on chromosomes 5q, 7, 16, 17, and 22q [5, 6]. All of these modifications cause chromatin remodeling, which leads to alterations in the genetic products of different survival pathways, such as increases in cell growth [7]. Additionally, understanding the role of altered epigenetic states in these disturbances is important for understanding RCC behavior and, therefore, carrying out pharmacological studies.

Classification

RCC shows notable heterogeneity, both histopathologically and molecularly, with a high diversity of genetic and epigenetic abnormalities, making it difficult to establish a clear line of genetic events to define the process of tumorigenesis [8]. However, it has become essential to establish an order of cellular features to choose the most appropriate and effective therapeutic strategy. The classification of RCC encompasses the histological and functional origin of the cell, the basis of molecular disturbances, the cellular morphology, and genetic alterations. Hence, the most widely accepted categorization is the TNM staging system (T, tumor size; N, lymph node involved; M, metastasis) [9]. The RCC subtypes were classified as follows:

- In clear cell renal cell carcinoma (most common), the cell of origin is in the proximal convoluted tubule of the nephron and accounts for >70%.
- Papillary renal cell carcinoma originates in the distal convoluted tubule and accounts for 15% of total renal cell carcinoma (RCC) cases.
- Chromophobic renal cell carcinoma originates in the intercalary cells of the tubule manifold and represents 5-10% of the cases.

- Collecting duct carcinoma occurs in less than 1% of cases
- Renal medulla carcinoma
- Spindle tubular cell carcinoma
- Unclassifiable renal cell carcinoma
- Papillary adenocarcinoma
- Oncocytoma is considered a benign tumor that is derived from intercalary cells and has an incidence of 7 to 10%.

The Vancouver Classification of Renal Neoplasia by the International Society of Urological Pathology [10] includes new RCC:

- Tubulocystic renal cell carcinoma
- Acquired cystic disease-associated renal cell carcinoma
- Clear cell (tubule) papillary renal cell carcinoma
- Renal cell carcinoma associated with MiT family translocation renal cell carcinoma syndrome
- Renal cell carcinoma associated with hereditary leiomyomatosis renal cell carcinoma syndrome
- Thyroid-like follicular renal cell carcinoma
- Succinic dehydrogenase B deficiency-associated renal cell carcinoma
- ALK translocation in renal cell carcinoma

Risk Factors

Two forms of RCC have been reported, the sporadic and hereditary forms, with the sporadic form being the most common [11]. Several risk factors are associated with the occurrence of sporadic RCC, including smoking [12, 13], hypertension [13, 14] and obesity [13, 15]. Other factors associated with the risk of RCC include occupational exposure to certain carcinogenic agents, such as pesticides, asbestos, benzenes, crystalline silica, sun exposure, and tobacco smoke [16]. Some medical interventions that predispose patients to sporadic RCC are dialysis and/or hemodialysis treatment and kidney transplantation [17, 18].

Hereditary forms of RCC include patients with different syndromes, such as Von Hippel–Lindau syndrome (strongly associated with mutations in chromosome 3p), papillary hereditary carcinoma, Birt-Hogg-Dubés syndrome (a hybrid carcinoma oncocytoma-chromophobic), hereditary leiomyomatosis, germ cell mutation in the B subunit of the succinate dehydrogenase enzyme-encoding gene family, hereditary nonpolyposis colorectal cancer syndrome, PTEN-associated hamartomatous tumor syndrome, and tuberous sclerosis (germline mutations in the tumor suppressor genes TSCI or TSC2). There are other nonsyndromic hereditary forms of RCC, such as the translocation of constitutional chromosome

CHAPTER 13

Epigenetics in Renal Diseases

Karina Robledo-Márquez[1], Yadira Ramírez[2] and **Joyce Trujillo[3,*]**

[1] *Facultad de Ingeniería, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México*

[2] *División de Materiales Avanzados, Instituto Potosino de Investigación Científica y Tecnológica (IPICYT), San Luis Potosí, Mexico*

[3] *Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI) - División de Materiales Avanzados-Instituto Potosino de Investigación Científica y Tecnológica - (SECIHTI-IPICYT), San Luis Potosí, Mexico*

Abstract: AKI and CKD have been described as interconnected syndromes as CKD predisposes to AKI, and AKI, in turn, may accelerate CKD progression. Thus, they are considered as an integrated clinical syndrome. AKI and CKD remain incompletely understood. It is well known that environmental and genetic factors are involved in the process. Long-term environmental effects lead to alterations in gene expression, specifically epigenetic changes. Epigenetic mechanisms that might integrate these interactions include chromatin modification, DNA methylation and demethylation, covalent modifications of histones: methylation, acetylation, and crotonylation, and the expression of various non-coding RNAs. Recent advances in epigenetics and diagnostic tools have made the study of kidney dysfunction more efficient, as well as technological achievements that have allowed us to improve our understanding of epigenetics on the physiological and pathological state of the kidney.

Keywords: Acetylation, Chromatin, Crotonylation, Histones, Methylation.

INTRODUCTION

Acute kidney injury (AKI) and chronic kidney disease (CKD) are associated with high morbidity (13-20% of the population) and mortality in the general population. AKI is a transitory, rapid, and reversible reduction in renal function. Many risk factors, such as drugs, toxins, sepsis, ischemia-reperfusion (I/R), and COVID-19, generally cause AKI, leading to a reduced glomerular filtration rate and acute tubular damage [1 - 3] (Fig. **1**). Numerous studies have demonstrated through several different strategies [4, 5] that AKI is a leading cause of cardiovascular events and the development of CKD [6]. AKI can progress to

* **Corresponding author Joyce Trujillo:** Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI)-División de Materiales Avanzados-Instituto Potosino de Investigación Científica y Tecnológica - (SECIHTI-IPICYT), San Luis Potosí, Mexico; E-mail: daniela.trujillo@ipicyt.edu.mx.

Rafael Valdez-Ortiz, Katy Sánchez-Pozos, Ana Carolina Ariza & Enzo C. Vásquez-Jiménez (Eds.)

CKD, characterized by changes in the structure and function of the kidney [7]. CKD is irreversible and progressive and is associated with chronic comorbidities such as hypertension, cardiovascular disease, diabetes, anemia, and bone diseases [8]. CKD can progress to end-stage kidney disease, which is associated with renal replacement therapy and an increased risk of premature death (Fig. **1**) [9].

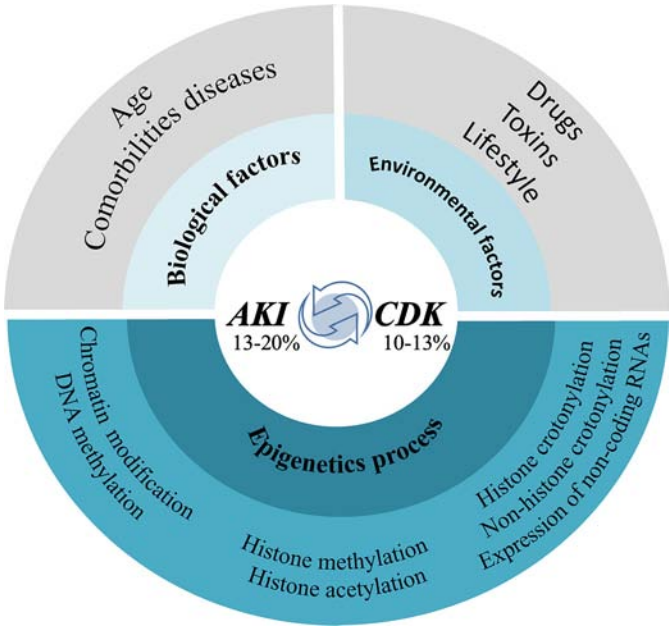

Fig. (1). Prevalence and factors involved in the development and progression of AKI and CDK. Acute kidney injury (AKI); Chronic Kidney Disease (CKD), the percentages refer to the prevalence of each pathological entity.

AKI and CKD have been described as interconnected syndromes because CKD is a risk factor for AKI, and AKI, in turn, may accelerate CKD progression; thus, they are considered integrated clinical syndromes [9]. Consequently, both entities share injury mechanisms, such as damage to vascular endothelial and/or tubular epithelial cells, cell death and proliferation, inflammation, and fibrosis [4, 10, 11]. Nonetheless, although the development and progression of AKI and CKD are incompletely understood, it is well-known that environmental and genetic factors are involved in this process (Fig. **1**) [12]. Long-term environmental effects lead to alterations in gene expression, specifically epigenetic changes [13]. Epigenetics refers to modifying and modulating gene expression without impairing the DNA sequence, which results in a modified phenotype [14]. Furthermore, epigenetics can facilitate the interconnection between genes and the environment [12]. Throughout cell division, epigenetic changes can be inherited but may be reversible and modified by age, disease, and the environment [9].

Currently, epigenetic mechanisms, including priming and tolerance, are known to be involved in all stages of AKI and CKD [11]. Therefore, this chapter aims to provide an overview of current and novel studies that explore the epigenetic mechanisms of AKI and CKD in human disease and animal models. In addition, we will discuss the implications of epigenetics in diagnosing and treating renal diseases of diverse etiologies.

PATHOPHYSIOLOGY, CURRENT AND NOVEL STUDIES

Epigenetics mechanisms include DNA methylation and demethylation, covalent modifications of histones (methylation, acetylation, and crotonylation), and the expression of various non-coding RNAs [9, 15]. There have been new efforts to investigate the contribution of epigenetic mechanisms in renal disease, concretely onset, progression, and treatment of AKI or CDK, as we will see below [14].

The principal pathological manifestations of the AKI-to-CKD transition are hypoxia and apoptosis, which are common pathways of the AKI-to-CKD transition. When renal injury is minor or short in duration (AKI), adaptive repair is initiated for renal function recovery. Nonetheless, when the injury is severe and persistent, maladaptive repair (inflammation and fibrosis) occurs to mediate CKD occurrence [15, 16]. In AKI, under hypoxic conditions, hypoxia-inducible factor 1 (HIF-1) binds to hypoxic response elements in the regulatory region of several target genes to regulate their expression under decreased oxygen conditions. These epigenetic changes have long-term effects and are called “hypoxic memory.” Changes induced by hypoxia promote the expression of inflammatory and fibrotic genes, such as monocyte chemoattractant protein 1 (MCP-1), transforming growth factor-beta 1 (TGF-β1), and type III collagen, all of which aggravate hypoxia, inflammation, and fibrosis, leading to CKD [15].

DNA Methylation and Demethylation

DNA methylation is catalyzed by DNA methyltransferases, which transfer a methyl group from the donor S-adenosyl-L-methionine (SAM) to the 5'-position of cytosine residues in the DNA, specifically in the CpG dinucleotides in the promoter region of DNA, to form 5-methylcytosine. DNA methylation in the promoter region is a silencing mechanism that inhibits the binding of transcription factors or the recruitment of proteins involved in gene expression [9, 15]. Methylated DNA can be demethylated or oxidized by a demethyltransferase, and the reaction progresses from 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) to regulate gene expression [15].

In particular, Pratt *et al.* were the first group to report changes in DNA methylation, specifically the demethylation of a cytosine residue in interferon-

CHAPTER 14

From Stem Cells to One Functional Kidney

Ana Laura Calderón-Garcidueñas[1,*]

[1] *Neuropathology Department, Research Direction, Instituto Nacional de Neurologia y Neurocirugía, Manuel Velasco Suarez, Tlalpan 14269, Mexico City, Mexico*

Abstract: Human pluripotent stem cells (hPSCs) have self-renewal capacity and can generate cells of all three germ layers of the embryo. After division, each newly produced cell can either remain a stem cell or differentiate to form any other cell type with more defined functions, such as muscle cells, blood cells, or neural cells. There are two types of stem cells: embryonic stem cells and somatic or adult stem cells. Specifically, embryonic stem cells are pluripotential stem cells that can differentiate into all body cell types. It is possible to induce pluripotent stem cells (iPSC). These cells are somatic stem cells genetically reprogrammed to become like embryonic stem cells by inducing expressions of specific genes and other components necessary for maintaining embryonic stem cell properties. The idea that renal progenitors can give rise to a functional kidney under certain experimental conditions has encouraged hundreds of researchers to achieve this goal. Nevertheless, obtaining a fully functional organ *in vitro* is still perceived as distant. However, we can get closer to this objective as we learn more about the factors that influence cell proliferation and differentiation.

Keywords: Bioartificial, Bioengineering, Bioprinting, Chip, Organoid.

INTRODUCTION

Once the kidney is insufficient to fulfill its functions, the patient and the health system face a series of problems: the cost and availability of hemodialysis, the lack of organ availability, and the morbidity and mortality of these patients. In addition, the annual health cost per patient increases with the degree of renal failure. Hence, searching for viable alternatives to overcome this serious health problem is mandatory.

TYPES OF CELLS IN THE HUMAN BODY

According to their functions, there are three types of cells: somatic, germinal, and stem cells. Somatic cells are diploid and contain two pairs of chromosomes. They

* **Corresponding author Ana Laura Calderón Garcidueñas:** Neuropathology Department, Research Direction, Instituto Nacional de Neurologia y Neurocirugía, Manuel Velasco Suarez, Tlalpan 14269, Mexico City, Mexico; E-mail: ana.calderon@innn.edu.mx

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are divided by mitosis, producing two daughter cells and constituting different organs and tissues with specific functions. Germinal cells are haploid, have a single set of 23 chromosomes, produce gametes, and are the only cells that can undergo meiosis and mitosis. The egg and the sperm are germ cells [1].

Human pluripotent stem cells (hPSCs) have self-renewal capacity and can generate cells from three embryo germ layers. Following division, newly produced cells can remain stem cells or differentiate into any other cell type with specific functions, such as muscle cells, blood cells, and neural cells. There are two types of stem cells: embryonic stem cells and somatic stem cells. Embryonic stem cells are pluripotent stem cells that can differentiate into any cell body type. On the other hand, somatic stem cells can differentiate only into different cell types present in the tissue of origin. However, it is possible to induce pluripotent stem cells (iPSCs). These cells are genetically reprogrammed to resemble embryonic stem cells through the induction of the expression of specific genes, together with other components required for maintaining embryonic cell properties. These latter cells are ideal candidates for restoring kidney function [2].

EMBRYOLOGY

The kidney has three important components: the nephron, interstitial stromal cells, and blood and lymphatic vessels. In a functional kidney, these elements are perfectly structured and coordinated. Embryologically, kidneys are formed with the participation of three types of cells: nephron progenitor cells (SIX2+), ureteric buds (GATA3+), and interstitial stromal progenitor cells (FOXD1+) [3 - 5]. The nephron is the functional unit of the kidney; it has two components: the glomerulus, which is responsible for filtering, and a system of tubules that perform selective secretion and reabsorption of numerous solutes and solvents. The kidney is a mesodermal organ that arises from the primitive streak (PS). The PS forms in the blastula and is an elongating groove at the caudal end of the embryo [6]. The mesoderm is formed from front to back by cells that migrate anteriorly from the stria. The pronephros and mesonephros form primitive nephrons in early embryogenesis to later give way to the metanephros that constitutes the functional kidney. In mice, the metanephros originate from the posterior area of the medial mesonephros [7]. Intermediate mesoderm cells also produce ureteric bud progenitor cells [8]. Feedback between both structures has been described since the metanephric mesenchyme produces fibroblast growth factor 20 (FGF20), and the ureteral buds secrete fibroblast growth factor 9 (FGF9) [9]. Finally, nephron progenitor cells (NPCs) can differentiate into functional nephron structures. However, another essential component of kidney function is the vasculature. The kidney receives 25% of the cardiac output. The embryonic vasculature originates with the constitution of a primitive vascular plexus.

Mesoderm-derived angioblasts differentiate in a process called vasculogenesis. Later, this network undergoes expansion and remodeling through angiogenesis [10].

However, it is not well known whether angioblasts arise from progenitors in the metanephros or migrate into them from the systemic circulation [11]. When the renal vesicle changes from a "coma" to an "s" shape, glomerular vascularization begins; then, a vascular cleft develops between the podocyte precursor and the proximal tubule [12]. Endothelial progenitor cells (VEGFR-2+) enter the vascular cleft under the influence of immature podocytes that produce VEGF-A (vascular endothelial growth factor, type A) and form capillary loops, which subsequently develop a lumen after excess TGF-β1-mediated "apoptotic pruning" of endothelial cells [13]. These capillary loops undergo branching and form the glomerular tuft with fenestrae [14].

VASCULAR ORGANIZATION

The renal artery, segmental artery, interlobar artery (cortex), arcuate artery (located at the border of the cortex and the medulla) (Fig. **1**), interlobular artery, afferent arteriole, glomerular hilum (which contains juxtaglomerular cells producing renin), glomerular capillary network, efferent arteriole, descending vasa recta (medullary microcirculation with continuous endothelium), and diaphragmed fenestrated ascending vasa recta constitute the complex renal vascular network [15].

Achieving this structural and functional complexity is one of the major engineering challenges of the kidney.

SIGNALING PATHWAYS AND REGENERATIVE PROCESS

The kidney's regeneration in the face of various insults involves the participation of renal progenitor cells as well as other cells, such as tubular epithelial cells, fibroblasts, and macrophages. These cells establish communication by activating several pathways, and it is important to know them.

PI3K/AKT/mTOR Pathway

HGF (hepatocyte growth factor**)**, IGF-1 (insulin-like growth factor-1), and EGF (epidermal growth factor) contribute to the recovery of ischemic renal damage by activating phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4-5-biphosphate to yield phosphatidylinositol-3-4-5-triphosphate, which activates Akt (protein kinase B). Activated Akt stimulates the mammalian

CHAPTER 15

Pleiotropic Effects of Renal Disease Management: Role of SGLT2 Inhibitors

Iván Calderón-Lojero[1], Rafael Valdez-Ortiz[2] and **Katy Sánchez-Pozos[1,*]**

[1] *Research Division, Hospital Juárez de México, Mexico City, Mexico*

[2] *Department of Nephrology, Hospital General de México, Mexico City, Mexico*

Abstract: Sodium-glucose cotransporter-2 inhibitors (SGLT2i), also called gliflozins, are a group of drugs to lower blood glucose in adults with type 2 diabetes (T2D) by inhibiting the reabsorption of glucose in the proximal tubules of the kidney and increasing glucose excretion in urine. Furthermore, some studies have demonstrated that SGLT2i increases insulin sensitivity and incretin-stimulated insulin secretion and reduces blood pressure, plasma lipids, and risk of cardiovascular events. SGLT2i have a low risk of hypoglycemia or serious events and have demonstrated other advantages. In general, SGLT2i, besides reducing glucotoxicity by decreasing glucose reabsorption in tubules, can reduce inflammation, oxidative stress, body weight, visceral adiposity, and arterial stiffness. Its beneficial effects go beyond glycemic control. Also, it is important to mention that the beneficial effects of SGLT2i are independent of ethnic origin, kidney function, doses, and age, which allows clinicians to expand their use. Furthermore, the SGLT2i provides a wide margin of safety.

Keywords: Adverse events, Beta cell, Glycemic control, Hyperglycemia, Insulin resistance, Renoprotection.

INTRODUCTION

As mentioned in previous chapters, the kidney contributes to glucose homeostasis through gluconeogenesis and renal glucose reabsorption. In this process, sodium-glucose cotransporters (SGLTs) play a crucial role. Specifically, SGLTs are responsible for the transport of glucose from the tubular lumen to epithelial cells by means of sodium electrochemical potential gradients sustained by sodium- and potassium-activated adenosine 5′-triphosphatase (Na+/K+-ATPase) [1]. There are two main isoforms of SGLT cotransporters: SGLT1 and SLGT2. SGLT1 is localized on the luminal side of the proximal tubular S1/S2 segments, while

* **Corresponding author Katy Sánchez Pozos:** Research Division, Hospital Juárez de México, Mexico City, Mexico; E-mail: katypozos@gmail.com

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SGLT2 is localized on the luminal side of the proximal tubular S3 segment [2]. Specifically, SGLT2 is responsible for 90% of glucose reabsorption in proximal tubules [3].

Sodium-glucose cotransporter-2 inhibitors (SGLT2is), also called gliflozins, are a group of drugs used to lower blood glucose in adults with type 2 diabetes (T2D) by inhibiting the reabsorption of glucose in the proximal tubules of the kidney and increasing glucose excretion in the urine [4, 5]. The FDA has approved SGLT2, which includes canagliflozin, dapagliflozin, and empagliflozin. Among the benefits of SGLT2 therapeutic management are reduced insulin resistance and improved pancreatic b-cell function, cell mass, and function [6, 7]. Furthermore, some studies have demonstrated that SGLT2i increases insulin sensitivity and incretin-stimulated insulin secretion and reduces blood pressure, plasma lipids, and the risk of cardiovascular events [8, 9]. In addition, SGLT2i impacts pancreatic a-cells, increasing glucagon and gluconeogenesis [10]. Current therapies for glycemic control improve the majority of risk factors; however, CV mortality is not decreased, in addition to adverse effects such as hypoglycemia and body weight alterations. Thus, glycemic control is not enough to ameliorate cardiovascular disease [11]. SGLT2i have been proposed as a good alternative to diminish these adverse effects, although they are accompanied by other metabolic responses, such as increased lipolysis, endogenous glucose, and ketone body production [6, 12, 13]. Nevertheless, SGLT2i are associated with a low risk of hypoglycemia or serious adverse events and have other advantages, as we will see below.

CARDIOPROTECTIVE EFFECTS

Cardiovascular disease is the leading cause of mortality among patients affected with end-stage renal disease (ESRD) [14]. Eighty-seven percent of adult patients aged 45 years or older with chronic kidney disease (CKD) reported cardiovascular disease at the time of ESRD [15]. There are well-known risk factors for cardiovascular disease, such as age, smoking status, hyperglycemia, hypertension, dyslipidemia, and obesity [16]. One decade ago, several studies revealed cardioprotection in patients with diabetes treated with SGLT2i therapy. Randomized clinical trials have shown that SGLT2i therapy reduces hospitalizations for heart failure and deaths, independent of glycemic control [17 - 19]. In the phase III placebo-controlled trial, 4,744 patients with class II, III, or IV heart failure and an ejection fraction of 40% were randomly assigned to receive 10 mg/day dapagliflozin or placebo. Patients treated with dapagliflozin presented a lower risk of worsening heart failure or death from cardiovascular causes than patients who received a placebo [20]. In the DEFENCE study, dapagliflozin add-

on therapy improved endothelial function compared with metformin, as assessed by the change in flow-mediated dilation.

Additionally, in the urine, the level of the biomarker of oxidative stress, 8-hydroxy-2'-deoxyguanosine, was significantly lower in the dapagliflozin group. The authors suggested that endothelial function improvement results from reduced oxidative stress [21]. The mechanisms underlying such cardioprotection are still not clear, but some theories have been proposed [22 - 24]. Another meta-analysis carried out by Yeong *et al.* showed that SGLT2i, compared with metformin and Glucagon-like peptide-1 receptor agonists (GLP1-RA) was superior in improving the left ventricular ejection fraction in diabetic patients and improving maximal oxygen consumption and serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels in non-diabetic patients. The investigators proposed that the benefits observed are mediated by increased hematocrit and positive effects on cardiac and renal metabolism [25, 26].

Despite numerous studies on SGLT2i effects in model animals and humans, the mechanisms involved in cardiovascular protection are still under investigation. These studies revealed that the cardioprotective effects include natriuretic, diuretic, and antihypertensive effects, as well as the regulation of plasma and interstitial fluid volume. The excretion of glucose in urine has an impact on osmotic diuresis and natriuresis, which in turn could be favorable for heart failure [17]. This latter is one of the main theories for the cardiovascular benefits of SGLT2i. The administration of SGLT2i resulted in plasma volume contraction and, in turn, volume reduction [27, 28].

Furthermore, high levels of serum uric acid have been associated with cardiovascular diseases [29, 30]. Hyperuricemia increases the risk of heart failure by 65% and 20% for every 1 mg/mL increase in serum uric acid [31]. Elevated serum uric acid levels stimulate smooth cell proliferation and release proinflammatory cytokines [32]. In addition, patients with heart failure and high levels of uric acid present impaired ventricular function, ventricular filling pressures and volumes, and limited functional capacity [33, 34]. SGLT2i reduce serum uric acid levels independently of therapy for regulating uric acid and independent of diabetes [35]. SGLT2i may influence uric acid levels through sirtuin 1 (SIRT1). As mentioned in previous chapters, sirtuins are deacetylases involved in many biological processes, including the regulation of cellular homeostasis, metabolism, inflammation, oxidative stress, and aging [36 - 39]. SIRT1 has been shown to ameliorate hyperuricemia in animal models [40 - 42]. Hence, SGLT2i promotes the activity of SIRT1, which in turn reduces oxidative stress and xanthine oxidase activity and, consequently, the formation of uric acid

CHAPTER 16

Dysbiosis in Acute Kidney Injury and Chronic Kidney Disease

Laura Elena Zamora- Cervantes[1] and **Enzo C. Vásquez-Jiménez**[1,*]

[1] *Department of Nephrology, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico*

Abstract: During acute kidney injury (AKI) and chronic kidney disease (CKD), dysbiosis is induced by mechanisms that alter intestinal homeostasis, leading to a persistent proinflammatory response. This alteration in the intestinal microbiota may regulate immunity, inflammation, and nutrition in patients with AKI and CKD. However, the therapies proposed to reestablish the microbiome balance remain limited and have not shown a benefit. It is possible to use different strategies to modulate the gut microbiota balance to improve kidney function in different renal diseases. Therefore, strategies can be used in combination with available treatment. Nevertheless, it is important to note that individual factors, comorbidities, medications, diet, and lifestyle limit current therapies. Thus, personalized strategies are needed, along with continued research, to achieve outcomes by altering the microbiome and its effects on the progression of kidney disease.

Keywords: Acute kidney injury, Chronic kidney disease, Gut microbiota, Microbiome, Prebiotics, Probiotics.

INTRODUCTION

Epidemiology of AKI and CKD

Acute kidney injury (AKI) and chronic kidney disease (CKD) are considered a continuum in the course of the disease and a failure of the adaptive mechanism after injury. The presence of either of these two entities is associated with high morbidity and mortality [1]. CKD affects more than 10% of the general population and affects more than 800 million people; in 2019, it was estimated that approximately 1.43 million people died from CKD [2]. Even if the estimated mortality of AKI improved compared to that in previous years, from 23% to 17.5% in those who did not require replacement therapy (2013 to 2020), 11.6% of

[1] **Corresponding author Enzo C. Vázquez-Jiménez:** Department of Nephrology, Hospital Juárez de México, Gustavo A. Madero 07760, Mexico City, Mexico; E-mail: enzo.vas.ji@gmail.com

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survivors were diagnosed with CKD upon discharge, and 24 months later, this percentage increased to 20.7%, with a 36.7% increase in mortality [3].

Both entities have common denominators, such as diabetes, and classic cardiovascular risk factors, such as obesity, hypertension, and dyslipidemia. However, the role of changes in the microbiome or dysbiosis is beginning to be a topic of interest in kidney pathology.

Microbiome and its Functions

The microbiome is composed of a community of microorganisms (microbiota) that cohabit in a specific microenvironment. Approximately 50% of the fecal mass is composed of bacteria, mainly *Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria* [4].

The gut microbiota plays a role in the regulation of immunity, inflammation, and nutrition, mainly through the following mechanisms:

- Lymphocyte regulation promotes $CD4^+$ T-cell differentiation to balance Th1 and Th2 populations, which maintains the balance of Th17 cells that secrete different cytokines, such as IL-17F, IL-21, IL-22, IL-23, and TNF-α, and produces an increase in IL-10 and IL-18 (GPR109A), resulting in an anti-inflammatory response.
- The production of short-chain fatty acids, which are the end products of the fermentation activity of the microbiota. With greater kidney relevance, the GPR109A receptor, which has anti-inflammatory activity and is implicated in gut homeostasis, is the GPR43 receptor, which induces the activation of FOXP3, resulting in cellular differentiation, in addition to rennin secretion, since it is expressed in the afferent arteriole and the juxtaglomerular apparatus, as well as the OLFR78 receptor [5 - 7].
- It also maintains homeostasis between the intestinal epithelial cells of the gastrointestinal tract by maintaining the intestinal barrier's permeability and polarity for lipid diffusion, preventing the passage of endotoxins [8, 9].

When a disturbance occurs in gut microbiota, it is known as dysbiosis. This disturbance includes the loss of beneficial organisms, the overgrowth of harmful organisms, and the loss of microbial diversity [10].

Altered Pathways in AKI and CKD

Upon the onset of renal damage, there is an extension phase, which, depending on adaptation or maladaptation, results in repair or progressive renal sclerosis [1].

Regardless of the process, various mechanisms that induce hypoxia are triggered, activating different pathways [11 - 13]:

- Cellular responses of neutrophils, macrophages, and T lymphocytes produce the secretion of proinflammatory cytokines and adhesion molecules, generating nitric oxide and reactive oxygen species by endothelial and mesangial cells, podocytes, and tubular cells.
- Sustained and exaggerated activation of the Wnt/β-catenin pathway, with continuous stimulation of vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β).
- Cellular senescence occurs in response to the activation of JNK (c-Jun N-terminal kinase) when renal tubular cells enter the G2/M phase. This allows them to resist apoptosis and secrete cytokines such as IL-6 and IL-8, which promote an inflammatory state.
- Fibrosis following mesangial expansion leads to collagen deposition with increased myofibroblasts and pericytes.

Role of Dysbiosis in Kidney Disease

A change in the microbiota composition may alter intestinal homeostasis (dysbiosis), promoting disturbances in cardiovascular and renal systems and the progression of various diseases, such as AKI and CKD [14, 15]. In CKD patients, it may induce greater dysbiosis. These alterations in the microbiota occur mainly through three mechanisms:

- The expansion of pathobionts (low amounts of commensal bacteria with harmful effects when outnumbering other commensals) can be triggered by various factors, such as genetics; changes in macronutrients, such as diets high in preservatives, which promote the overgrowth of proteobacteria; low-fiber diets that alter fermentation and reduce short-chain fatty acids due to shifts toward *Bacteroides* spp., *Akkermansia muciniphila*, and *Prevotella spp*.; and inflammatory states, such as obesity, which are associated with an increase in the *Firmicutes/Bacteroidetes* ratio [16 - 19].
- Leaky gut, which induces changes in proteolytic fermentation and short-chain fatty acid production, disturbs the junctions of intestinal epithelial cells, allowing more metabolites, including uremic toxins and lipopolysaccharides, to cross through. This latter leads to a subsequent proinflammatory response [20].
- Microinflammation subsequent to the release of lipopolysaccharides from gram-negative bacteria, such as proteobacteria. This causes the migration of macrophages and the nuclear transcription factor kappa B (NF-κB), leading to the synthesis of TNFα, IL-1, IL-6, and IL-8, thus inducing a persistent proinflammatory state [21].

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Rafael Valdez Ortiz

Dr. Valdez is an internist and nephrologist, a graduate of the Salvador Zubirán National Institute of Medical Sciences and Nutrition. He holds Master's and Doctorate degrees in Medical Sciences (UNAM), as well as a Master's in Organ, Tissue, and Cell Transplantation (Barcelona, Spain). He carried out a postdoctoral fellowship in kidney transplantation at Bellvitge University Hospital, Barcelona, Spain. He served as Head of the Nephrology Department at the General Hospital of Mexico City from 2014 to 2024. He is a professor of undergraduate and postgraduate courses at UNAM. He was formerly President of the Mexican Institute of Nephrological Research (2024) and a member of the Board of Directors of IMIN. Dr. Valdez's research has focused on acute and chronic renal disease.

Katy Sánchez-Pozos

Graduated in Pharmaceutical Biological Chemistry from the National Autonomous University of Mexico (UNAM). She holds a Master's and PhD in Biochemical Sciences from the National Autonomous University of Mexico in the area of Nephrology and Mineral Metabolism at the Peripheral Unit of the Biomedical Research Institute at the Salvador Zubirán Institute of Medical Sciences and Nutrition. She completed postdoctoral work at the School of Chemistry and the National Institute of Genomic Medicine in the Diabetes group of UNAM. Currently, she is a Researcher in Medical Sciences at the Juárez Hospital. She is a professor in the Postgraduate Program in Medical, Dental, and Health Sciences at the School of Medicine, UNAM, and in the Program in Health Sciences at the National Polytechnic Institute.

Ana Carolina Ariza

She holds a degree in Nutrition and Food Sciences, a Doctorate in Sciences, and completed postdoctoral fellowships. She is a two-time national first-place winner for best thesis in Nutrition and Biomedical Sciences. She is a tenured professor at the undergraduate and graduate levels. Part of her research objective has been the integration of basic and clinical sciences (biological factors, biomarkers, genetics) in epidemiological projects, especially those related to dietary factors and chronic diseases. Dr. Ariza's research has focused on various birth cohort studies related to early nutritional exposures, mechanisms associated with appetite and satiety, nutritional status assessment, sweet preferences, oxidative stress, and inflammation in chronic diseases.

Enzo C. Vásquez Jiménez

Dr. Enzo C. Vásquez-Jiménez is a distinguished physician specializing in Nephrology. He is currently Head of the Nephrology Service at the Juárez Hospital of Mexico City and Full Professor of Nephrology at the National Autonomous University of Mexico (UNAM). He completed his specialty training in Internal Medicine at the UMAE Hospital de Especialidades, Centro Médico Nacional La Raza (UNAM), and his specialty training in Clinical Nephrology at the Dr. Ignacio Chávez National Institute of Cardiology. He is an active member of the American Society of Nephrology, the Mexican Transplant Society, and the Mexican Institute of Nephrological Research. In the field of research, Dr. Vásquez-Jiménez is interested in the impact of chronic kidney disease in Mexico. He has focused on the study of renal replacement therapies and, more recently, on the study of complex infections in critical areas and antimicrobial resistance.