Nutrition in Kidney Disease

NUTRITION ◊ AND ◊ HEALTH

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Nutrition in Kidney Disease

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Dedications

Laura dedicates this book to her husband, Steven, and her daughters, Erin and Jillian. Jerrilynn dedicates this book to the thousands of patients with kidney disease who will benefit from the information embedded in these pages. The goal is to improve the health and well-being of patients with kidney disease through optimal nutritional practices.

Series Editor's Introduction

The Nutrition and Health™ series of books have, as an overriding mission, to provide health professionals with texts that are considered essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient /health professional questions that are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Nutrition in Kidney Disease edited by Laura Byham-Gray, Jerrilynn Burrowes, and Glenn Chertow is a very welcome addition to the Nutrition and Health™ series and fully exemplifies the series' goals. This volume is especially timely as over 10% of the US adult population currently suffers from chronic kidney disease and the number is expected to increase as the major comorbidities, obesity and diabetes, continue to increase around the world. As only one example cited in this critically important volume, even though 7% of the adult US population has diabetes, 54% of the patients on kidney dialysis have diabetes.

This text has many unique features, such as highly relevant case studies, that will help to illustrate the complexity of treating the patient with kidney disease and/or reduced kidney function. However, the volume is also relevant for the non-practicing healthcare providers as there are in-depth discussions of the basic functioning of the kidney, demographics of the different kidney diseases, and conditions that affect the kidney. There are also clear, concise recommendations about dietary intakes and use of drugs and supplements across the stages of kidney disease. Thus, this volume provides the broad knowledge base concerning kidney anatomy, physiology, and pathology required by the practicing health professional as well as those professionals who have an interest in the latest, up-to-date information on the consequences of loss of kidney function, treatment of kidney disease, and disease implications on morbidity and mortality.

Nutrition in Kidney Disease serves a dual purpose of providing in-depth focus on the nutritional aspects of treating individuals throughout the lifespan who have lost some or all of their kidney functions as well as examining the current clinical modalities used in treating kidney disease and the consequences of the treatments on nutritional status. The book is organized as a stand-alone text that provides the historic beginnings of nutritional interventions in patients and reflects upon the necessity of these historic practices even today in developing countries where dialysis and/or kidney transplants, expensive drugs, and other disease management tools are not readily available and medical nutritional support remains the primary care available to patients with kidney disease.

The three editors of this volume, Laura Byham-Gray, Jerrilynn Burrowes, and Glenn Chertow, are internationally recognized leaders in the fields of clinical nutrition and renal disease research, treatment, and management. Each has extensive experience in academic medicine and collectively, they have over 500 peer-reviewed publications and numerous awards for their efforts to improve the care of those with kidney disease. The editors are excellent communicators and they have worked tirelessly to develop a book that is destined to be the benchmark in the field of nutrition and kidney disease because of its extensive, in-depth chapters covering the most important aspects of the complex interactions between kidney functions, diet, obesity, cardiovascular disease, autoimmune disease, and diabetes as examples, and the impact of loss of kidney function on other disease states. Additionally, the nutritional consequences of loss of kidney function in infants, children, pregnant women, and the aged are examined in

depth in separate chapters that also include potential solutions to the nutritional deficits specific for those with kidney dysfunction.

Nutrition in Kidney Disease contains 25 chapters and each title provides key information to the reader about the contents of the chapter. In addition, each chapter begins with a list of concise learning objectives as well as key words. The introductory chapters provide readers with the basics so that the more clinically related chapters can be easily understood. The editors have chosen 46 well recognized and respected chapter authors who have included complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include the eleven case studies at the end of the relevant chapters and the inclusion of the answers to the case study questions at the end of the book. The volume includes over 100 detailed tables and informative figures, an extensive detailed index, and more than 1500 up-to-date references that provide the reader with excellent sources of worthwhile information. Moreover, the final chapter contains a comprehensive list of resources in print as well as via the internet including a complete listing of the practice guidelines that have been developed under the auspices of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI); protocols from the American Dietetic Association concerning nutrition therapy for the non-dialysis patient; tables of general as well as specific nutrient contents of foods for individuals with different stages of kidney disease; an extensive list of reliable internet sites as well as examples of relevant assessment tools for the health provider.

Unique to this volume is the inclusion of chapters dealing with prevention as well as treatment of kidney disease. The text is divided logically into five consistently organized parts: I. Foundations for clinical practice and overview that contains information about kidney function, historic perspective of nutritional support for kidney disease patients, demographics, and overall assessment tools; II. Chronic kidney disease (CKD) during stages 1–4 in adults that contains a first section on disease prevention and the role of hypertension, diabetes, and dyslipidemias in increasing the risk of kidney disease development and nutritional strategies that can reduce this risk. In section 2, nutritional and pharmacological treatment of individuals with stages 1–4 kidney disease is reviewed. Part III, Stage 5 chronic kidney disease, is also divided into two sections with treatment options of dialysis and transplant examined with respect to the nutritional needs and consequences. Section 2 looks at the most commonly seen management issues in patients with end stage renal disease and includes chapters on

protein-energy malnutrition, nutrition support, anemia management, bone and mineral consequences, and other chronic diseases seen in CKD patients. Part IV delves into the nutritional needs of patients that have CKD and become pregnant, those that have kidney malformations or malfunction in infancy, childhood, or adolescence, or at the end of life in section 1. Section 2 includes separate chapters on acute renal failure, nephritic syndrome, and kidney stones. The final Part V: Additional nutritional considerations in kidney disease contains individual chapters on dietary supplements, compliance with dietary programs, the value and complexities of outcomes research, and the extensive chapter on resources for the practitioner. Thus, there is no question about the comprehensive coverage of the complex field of nutrition and kidney disease that is found in this important volume.

In conclusion, *Nutrition in Kidney Disease* edited by Laura Byham-Gray, Jerrilynn Burrowes, and Glenn Chertow provides health professionals in many areas of research and practice with the most up-to-date, well referenced volume on the importance of defining the nutritional status of the patient with decreased kidney function regardless of cause and the critical value of medical nutrition evaluation, treatment support, and management for patients with CKD and related chronic diseases that can affect human health. This volume will serve the reader as the benchmark in this complex area of interrelationships between diet, supplements, specific nutritional products for enhancing kidney function, and the functioning of all organ systems that are intimately affected by renal disease. Moreover, these physiological and pathological interactions are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. The editors are applauded for their efforts to develop the most authoritative resource in the field of "Nutrition in Kidney Disease" to date and this excellent text is a very welcome addition to the Nutrition and Health™ series.

Adrianne Bendich, PhD, FACN

Foreword

The interrelationship between nutrition and chronic kidney disease (CKD) is one that has enticed scientists, physicians, and nutritionists from all over the world. No other disease entity draws the same intensity of study and interdisciplinary treatment as CKD. There are so many facets to address: definition of normal function and metabolism, identification of abnormalities and their consequences, what intervention to provide and how. Each component, basic science, medicine, and nutrition, involves a spectrum of investigation and/or treatment that is all encompassing, with the goal of forestalling progression of disease and allowing continuation of life. The interdisciplinary requirement for successful treatment and management of the individual with CKD is another unique attribute of this amazing field.

The text *Nutrition in Kidney Disease* edited by Byham-Gray, Burrowes, and Chertow well exemplifies this description of the CKD specialty. This outstanding book includes information from the many areas that impact the individual with CKD. There are sections on CKD epidemiology, pathophysiology, metabolism, and diet therapy. The chapters are written by experts in the field. The authors provide insight into these areas as well as state-of-the-art information for students, professionals, and other healthcare professionals interested in nutrition and kidney disease.

This complex discipline simplifies to one element: the individual patient. Individualizing the diet and the treatment leads to the response of maximizing positive outcomes. *Nutrition in Kidney Disease* provides vital information to provide exceptional care for extraordinary people: individuals living with CKD.

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Preface

The field of kidney disease has evolved over the years to encompass a broad and sophisticated knowledge base. There has been a proliferation of scientific information and technical advances in the field. The clinician involved in the care of patients with kidney disease must have a vast knowledge of nutrition management of the disease. The purpose of this book is to provide a comprehensive reference on the practice of nutrition in kidney disease. It is our belief that this book will become a useful reference and tool for the practicing clinician in the fields of nutrition and nephrology, as well as other disciplines whose research, practice, and education includes nutrition and kidney disease. This book will also be a current resource for undergraduate and graduate level nutrition and allied health profession students, medical students and residents, nutrition and allied health clinicians, including general practitioners, nephrologists, educators, and researchers.

ORGANIZATION AND CONTENT

Nutrition in Kidney Disease is organized into five sections with a variable number of chapters based on breadth and depth of information. Part I addresses kidney function in health and disease. It provides a historical perspective of the emerging science in nutrition in kidney disease over the past several decades, and it defines and forecasts health care trends and outcomes in kidney disease. A comprehensive review of the components of the nutrition assessment is also provided. In Parts II and III, in-depth information on the prevention of common disorders associated with chronic kidney disease, current treatment options based on the latest scientific evidence, and management of comorbidities such as protein-energy malnutrition, anemia, and bone disease are covered. Part IV presents the nutrition concerns of special needs populations such as through the life cycle–pregnancy, infancy, childhood, adolescence and the elderly, and nutrition management of disorders such as acute kidney injury, nephrotic syndrome, and nephrolithiasis. Part V addresses additional nutritional concerns in kidney disease such as complementary and alternative medicine, cultural issues affecting dietary adherence, and outcomes research.

In an attempt to make this volume as practical as possible, a wide variety of tables, resources, practical tools, clinical practice guidelines, and Internet websites are compiled into one chapter.

FEATURES

The chapters in this textbook have been designed with special features to enhance learning. Each chapter begins with an abstract, key words, learning objectives, and a content outline, and ends with a summary. Up-to-date references for more in-depth review are included at the end of each chapter. This list provides the clinician and student with an extensive source of reading for continued study. In addition, several chapters end with a case study, which can be used to assess knowledge of the content area within the context of didactic curricula. These provide thought-provoking, illustrative questions that will add to the student's learning and clinical application of the material. The answers to the case studies are provided at the end of the book. The problems posed in these chapters enable the clinician and the student to apply the chapter material to "real-life" nutrition-related problems.

The chapters have been written by a collaborative group of distinguished dietitians and physicians in the specialized field of kidney disease and clinical nutrition who have devoted their careers to the care of patients with kidney disease. This collaborative effort is a testament to the interdisciplinary approach that is used to provide care to this unique patient population. It is our belief that this book will be used to guide and enhance the care of the patients we serve.

Laura D. Byham-Gray, PhD, RD
Jerrilynn D. Burrowes, PhD, RD, CDN
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Disclaimer

Considerable attention has been taken to confirm the accuracy of the information presented and to describe generally accepted practices. However, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to currency, completeness, or accuracy of the contents of the publication. Use of such information in a particular patient care situation remains the professional responsibility of the respective practitioner.

The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage indicated in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs presented in this book have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health care provider to ascertain the FDA status of each drug planned for use in their clinical practice.

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I Foundations for Clinical Practice and Overview

1 Kidney Function in Health and Disease

Alluru S. Reddi and Kishore Kuppasani

LEARNING OBJECTIVES

1. Describe the gross and microscopic structure of the kidney.
2. Discuss the various functions of the normal kidney.
3. Define and discuss the various renal syndromes, such as acute kidney injury, chronic kidney disease, nephrotic and nephritic syndromes, tubulointerstitial diseases, and vascular diseases of the kidney.

Summary

The kidneys are paired organs located retroperitoneally in the lumbar region and perform three major functions: (i) maintenance of fluid and acid–base balance; (ii) removal of nitrogenous waste products; and (iii) synthesis of hormones, such as renin, erythropoietin, and active vitamin D_3 (calcitriol). The functional unit of the kidney is the nephron, which consists of a renal corpuscle, the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct. The renal corpuscle consists of the glomerulus and Bowman's capsule. Plasma is filtered in the glomerulus to form protein-free ultrafiltrate. About 60% of this ultrafiltrate is reabsorbed in the proximal tubule. The loop of Henle participates in countercurrent multiplication of urine concentration. The distal tubule generates hypotonic fluid in the tubular lumen, causing hypertonic medullary interstitium. The collecting duct plays an important role in potassium (K^+) secretion, urinary acidification, and water reabsorption in the presence of antidiuretic hormone. When the structure of the kidney is disturbed by a pathologic

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process, its functions are altered. These changes in the kidney result in an increase in serum creatinine levels (e.g., acute kidney injury, chronic kidney disease, or tubulointerstitial disease), proteinuria (e.g., nephrotic syndrome), and hematuria (e.g., glomerulonephritis). Also renal vasculature is affected, causing hypertension and thrombotic microangiopathies.

Key Words: Nephron; glomerulus; renal function; chronic kidney disease; nephrotic syndrome; nephritic syndrome.

1. INTRODUCTION

The kidneys perform three major functions *(1)*. As regulatory organs, the kidneys precisely control the composition and volume of the body fluids and maintain acid–base balance as well as blood pressure by varying the excretion of water and solutes. As excretory organs, the kidneys remove various nitrogenous metabolic end products in the urine. In general, the kidneys filter plasma in the glomerulus to form a protein-free ultrafiltrate. This ultrafiltrate passes through the various tubular segments where reabsorption of essential constituents and secretion of unwanted products occur. As endocrine organs, the kidneys produce important hormones, such as renin, erythropoietin, and active vitamin D_3 (calcitriol). In addition, the kidneys participate in the degradation of various endogenous and exogenous compounds. In order to understand these functions, it is essential to examine the gross and microscopic structure of the kidneys.

1.1. Anatomy of the Kidney

The kidneys are paired, bean-shaped structures located retroperitoneally in the lumbar region, one on either side of the vertebral column *(1–3)*. The lateral edge of the kidney is convex, while the medial aspect is concave with a notch called the hilum. The hilum receives the blood and lymphatic vessels, the nerves, and the ureter. The hilum contains a cavity, the renal sinus, where the ureter expands to form the renal pelvis. The normal adult kidney is about 10-12 cm long, 5-7 cm wide, and 2-3 cm thick, and it weighs 125–170 g.

Each kidney is composed of the parenchyma and the collecting system. The parenchyma consists of an outer cortex and an inner medulla. The medulla is divided into an outer (toward the cortex) and an inner medulla (toward the pelvis). The collecting system includes the calyces, renal pelvis, and the ureters. The major calyces unite to form the renal pelvis. The renal pelvis drains into the ureter, which connects the kidney to the bladder.

The basic structural and functional unit of the kidney is the nephron. There are about 600,000 (range 300,000–1,400,000) nephrons in each kidney. Each nephron contains specialized cells that filter the plasma, then selectively remove, reabsorb, and secrete a variety of substances into the urine. The nephron consists of a renal corpuscle, the proximal tubule, the loop of Henle, and the distal tubule. The collecting duct is not part of the nephron because it is embryologically derived from the ureteric bud, whereas the nephron is derived from the metanephric blastema. However, the collecting duct is commonly included in the nephron because of its related function.

1.2. Renal Corpuscle

The renal corpuscle consists of the glomerulus and Bowman's capsule. Generally the term "glomerulus" is widely used for the entire corpuscle. The glomerulus is composed of a capillary network lined by an inner thin layer of endothelial cells: a central region of mesangial cells surrounded by collagen-like mesangial matrix, and an outer layer of visceral epithelial cells. The endothelial and epithelial cells are separated by the glomerular basement membrane (GBM).

The GBM is a dense fibrillar structure, which is the only anatomical barrier between blood and urine. Biochemical studies of the GBM showed that it contains predominantly type IV collagen, proteoglycans, and laminin. Collagen provides the structural framework, whereas proteoglycans, such as heparan sulfate, confer a negative charge to the GBM. Because of this negative charge, filtration of albumin is curtailed. The Bowman's capsule, which is a double-walled cup surrounding the glomerulus, consists of an outer layer of parietal epithelial cells. Between the visceral epithelial and parietal epithelial cells is a space called Bowman's space. The glomeruli are located exclusively in the cortex, which undergo pathologic changes in several disease conditions.

The endothelial cells line the glomerular capillaries and are separated by large (70 nm) fenestrations. These fenestrations limit filtration of only cellular elements such as erythrocytes but not water or proteins. The epithelial cells, also called podocytes, represent the visceral layer of the Bowman's capsule. The podocytes have foot processes that cover the GBM. These foot processes are separated by a thin diaphragmatic structure called the slit diaphragm or slit pore.

The renal corpuscle is responsible for the ultrafiltration of the blood, which is the first step in urine formation. In this process, medium and small sized molecules are allowed to pass through into the Bowman's space, while large sized molecules, such as proteins, are left behind.

To enter the Bowman's space, the ultrafiltrate must pass through the fenestrae of the endothelial cells, the layers of the basement membrane, and the slit diaphragms of the foot processes.

1.3. Proximal Tubule

The Bowman's capsule continues as the proximal tubule, which is lined by cuboidal or columnar cells with a brush border on their luminal surface. The brush border consists of millions of microvilli, which markedly increase the surface area available for the absorption of solutes and water through cells (transcellular transport) or between cells (paracellular transport) or both. The proximal tubule reabsorbs about 60% of the ultrafiltrate. Several electrolytes (Na^+, K^+, Cl^-, HCO_3^-), minerals (Ca^{2+}, HPO_4^{3-}) amino acids, glucose, and water are reabsorbed in the proximal tubule. Also, secretion of organic acids and bases occur in the proximal tubule. The proximal tubule is susceptible to insults such as renal ischemia and nephrotoxins, resulting in altered kidney function.

1.4. Thin Limb of Henle's Loop

The proximal tubule continues into the medulla as the thin descending limb of Henle's loop. The loop then bends back and becomes the thin ascending limb of Henle's loop. The thin descending limb is more permeable to water and less permeable to NaCl. As a result, water moves into the interstitium and makes the ultrafiltrate more concentrated than in the proximal tubule. In contrast, the thin ascending limb is impermeable to water, but permeable to NaCl. Therefore, the ultrafiltrate becomes dilute and the medullary interstitium hypertonic. Thus, the thin descending and ascending limbs participate in the countercurrent multiplication of the urinary concentration process.

1.5. Distal Tubule

The distal tubule includes the thick ascending limb of Henle's loop and the distal convoluted tubule. The thick limb runs from the medulla into the cortex up to its parent glomerulus, where it forms the macula densa, a component of the juxtaglomerular apparatus that secretes renin. The thick ascending limb of Henle's loop is responsible for the reabsorption of Na^+, K^+, and Cl^- in the ratio of 1:1:2. The reabsorption of these electrolytes is dependent on the Na/K-ATPase located in the basolateral membrane. NaCl reabsorption also occurs in the distal convoluted tubule. Both segments of the distal tubule

are normally impermeable to water, and thus the fluid formed in the distal tubule is hypotonic. The impermeability of the distal tubule to water, combined with active transport of Na^+ and Cl^- out of the thick ascending limb, makes the medullary interstitium hypertonic. The distal tubule is connected to the collecting duct by the connecting tubule.

1.6. Collecting Duct

Depending on its location in the kidney, the collecting duct can be divided into the cortical, outer medullary, and inner medullary portions. The epithelium of the collecting ducts contains two types of cells: principal (65%) and intercalated (35%) cells. The principal cell is the predominant type of cell lining the collecting duct system. In the cortical collecting duct, principal cells are responsible for K^+ secretion and Na^+ reabsorption. This function is only partly regulated by aldosterone, because some of the cells are capable of K^+ secretion in the absence of this hormone. Intercalated cells are involved in H^+ ion and HCO_3^- secretion. Transport of water occurs in all segments of the collecting duct in the presence of the antidiuretic hormone or vasopressin. Figure 1 summarizes the functions of various segments of the nephron.

1.7. Interstitium

The renal interstitium, a space between tubules, is comparatively sparse. It increases from the cortex to the medulla. In humans, the fractional volume of the cortical interstitium ranges from 12% in younger individual to 16% in older subjects. In the medulla, the interstitial volume increases from the outer to the inner medulla in the range of 4 to approximately 30%.

Two types of interstitial cells have been described in the cortex: type 1 cortical interstitial cell, which resembles a fibroblast, and type 2 interstitial cell with mononuclear or lymphocyte-like structure. Between the cells is a space that contains collagen and fibronectin. It is believed that the peritubular fibroblast-like interstitial cells secrete erythropoietin. Type 2 interstitial cells are believed to represent bone marrow-derived cells. Three types of interstitial cells have been described in the medulla. None of these cells is the site of erythropoietin; however, some cells (type 1 medullary interstitial cell) contain lipid droplets, which are believed to have hypotensive effects. All medullary interstitial cells synthesize proteoglycans that are present in the interstitium.

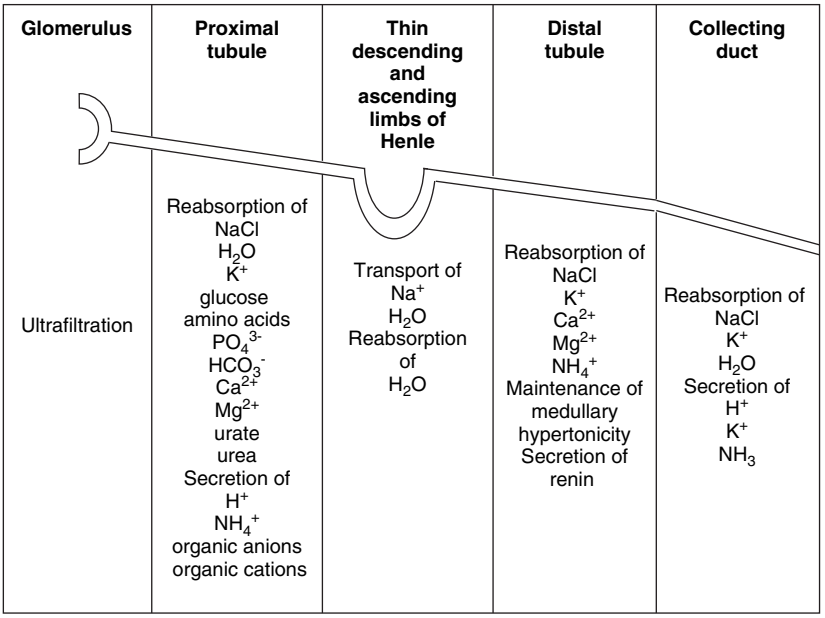

Fig. 1. Schematic representation of nephron segments showing the structural-functional relationships.

1.8. Blood Supply

Each kidney is usually supplied by one renal artery arising from the abdominal aorta. After or before entering the hilum, the renal artery divides into an anterior and a posterior branch; both of them give rise to a total of five segmental arteries. The segmental arteries are end arteries, and occlusion of a single artery results in infarction of the area supplied. These segmental branches form the interlobar arteries in the renal sinus, which follow the curvature of the kidneys to form arcuate arteries. From these arteries arise interlobular arteries that course radially through the cortex toward its surface. The interlobular arteries give rise to the afferent arterioles, which divide into five to eight lobules and form the glomerular capillaries. The loops of these capillaries reunite to form the efferent arteriole of the glomerulus. The efferent arteriole leaves the glomerulus as a short unbranched segment before it branches into capillaries. These capillaries, which supply blood to the proximal and distal tubules of the cortex, are known collectively as the peritubular capillary network. The efferent arterioles of glomeruli located in the juxtamedullary cortex and near

the medullary region not only supply blood to their own tubules but also run deep into the medulla. These long, thin vessels are called arteriolae rectae, or straight arterioles. They form a loop with straight venules or venulae rectae of the medulla to form the vasa recta of the kidney. Thus, the blood supply to the medulla is entirely derived from the efferent arterioles of the juxtamedullary glomeruli. The capillaries of the outer cortex converge to form the stellate veins which drain into the interlobular veins, then into the arcuate and interlobar veins, and finally into the renal vein.

2. CLINICAL EVALUATION OF KIDNEY FUNCTION

Currently, determination of serum creatinine and blood urea nitrogen (BUN) concentrations, and estimation of glomerular filtration rate (GFR) remain the most important tests to assess the kidney function in clinical practice. GFR can be measured directly by radioisotope methods or indirectly from serum creatinine concentration as estimated GFR (eGFR), using the Modification of Diet in Renal Disease formula. Although serum creatinine concentration of 0.8–1.2 mg/dl and a BUN concentration of 10 mg/dl are considered normal, their values vary with muscle mass and protein intake as well as the functional status of the liver. Therefore, an eGFR is recommended for evaluation of kidney function. Most clinical laboratories provide both serum creatinine and eGFR to the physician for assessment of kidney function. An eGFR of 60 ml/min/1.73 m^2 or less is considered chronic kidney disease (CKD). In addition to eGFR, urinalysis provides an assessment of glomerular, tubular, and interstitial functions of the kidney. The presence of albuminuria, hematuria, and red blood cell (RBC) casts in a well-performed urinalysis indicates significant glomerular disease. Determination of urine pH and urine osmolality is helpful in assessing the kidney's ability to acidify as well as concentrate and dilute the urine. A renal biopsy is needed to assess the pathology of the kidney in disease states.

3. KIDNEY FUNCTION IN DISEASE STATES

When GFR is decreased due to functional or structural damage to the kidney, a variety of functions and also the structure of the kidney are altered. These functional and structural disturbances are briefly discussed below.

3.1. Fluid, Electrolyte, and Acid–Base Disturbances

When GFR is below normal but not low enough, the kidneys try to maintain relatively normal fluid, electrolyte, and acid–base balance. However, when GFR is severely decreased, the kidneys retain Na^+, water, K^+, Mg^{2+}, PO^{3-} and H^+ ions, resulting in edema, either hyponatremia or hypernatremia, hyperkalemia, hypermagnesemia, hyperphosphatemia, and severe metabolic acidosis. Hypocalcemia results from decreased calcitriol production by the kidney. The patients also develop hypertension due to retention of Na^+ and water. Anemia and bone disease are commonly seen in patients with low GFR.

3.2. Acute Kidney Injury (Acute Renal Failure)

Acute kidney injury (AKI) is defined as an abrupt decrease in renal function, resulting in accumulation of nitrogenous (creatinine and BUN) and non-nitrogenous waste products. It develops over a period of hours to days. Although the clinical markers for AKI are serum creatinine and BUN concentrations, the precise increase in serum creatinine that defines AKI remains elusive. Studies have shown that even a small increase in serum creatinine levels is associated with increased morbidity and mortality. For example, it was reported that an increase in serum creatinine by $\leq$0.5 mg/dl was associated with a 6.5-fold increase in hospital mortality, while an increase in serum creatinine of 0.3–0.4 mg/dl was associated with only 70% increase in mortality risk. Even the length of the hospital stay was prolonged by AKI *(4)*.

Based on the increase in serum creatinine and urine output, the Acute Dialysis Quality Initiative group recently proposed the RIFLE system, which classifies AKI into three severity categories (R = risk; I = injury; F = failure) and two clinical categories [L = loss; E = end stage renal disease (ESRD)]. However, this classification requires further validation *(5)*.

The causes of AKI are divided into three major categories: prerenal, renal, and postrenal. Prerenal azotemia is due to decreased renal perfusion, caused by hypovolemia, decreased effective circulating volume, renal artery disease, and/or altered intrarenal hemodynamics. A variety of intrinsic renal disorders due to an acute insult to the renal vasculature, glomerulus, tubules, or interstitium can cause AKI. Acute tubular necrosis remains the major form of AKI due to intrinsic renal disease, and it is caused by renal ischemia and exposure to nephrotoxins, such as drugs or contrast material. Postrenal AKI is due to obstruction to the urinary system either by intrinsic or extrinsic masses.

Treatment of AKI includes volume repletion in hypovolemic conditions and elimination of the causative agent or disease process. Some patients may require hemodialysis or other renal replacement therapies, such as continuous venovenous hemodialysis. AKI is usually a reversible process. However, some patients progress to CKD.

3.3. Chronic Kidney Disease (Chronic Renal Failure)

CKD is defined as a gradual decrease in renal function over a period of several months to years. Diabetes, hypertension, glomerulonephritis, cystic kidney diseases, and tubulointerstitial diseases (TIDs) are the major causes of CKD. Approximately 6.2 million people are estimated to have a serum creatinine level of $\geq$1.5 mg/dl. Unlike in AKI, serum creatinine level does not represent the extent of renal disease in subjects with CKD. Therefore, either actual determination of GFR by radioisotope methods or eGFR is used to assess the severity of kidney disease in a CKD patient. Based on these methods of GFR, a staging system and action plan for CKD was developed (Table 1).

There are several risk factors for the progression of CKD, including hypertension, diabetes, hyperlipidemia, excessive protein intake, smoking, anemia, and genetic predisposition to kidney disease. CKD is one of the major risk factors for cardiovascular disease. Conservative management of CKD includes (i) control of blood pressure ($<$130/80 for patients with no proteinuria and $<$120/80 for those with proteinuria $>$1 g/day), using dietary sodium restriction $<$100 mEq/l, and antihypertensive agents such as angiotensin converting enzyme-inhibitors (ACE-Is), or angiotensin receptor-blockers (ARBs) as well as a low dose diuretic; (ii) maintenance of $HbA_{1c} < 7\%$ in diabetic patients; (iii) restriction of protein intake $<$0.8 g/kg/day; (iv) maintenance of LDL $<$100 mg/dl; (v) maintenance of hemoglobin approximately 11–12 g/dl and control of bone disease; and (vi) smoking cessation. Dialysis or kidney transplantation is required if the patient progresses to ESRD.

3.4. Nephrotic Syndrome

This syndrome is characterized by proteinuria $>$ 3.5 g/day, hypoalbuminemia, edema, hyperlipidemia, and lipiduria. The nephrotic syndrome is caused by (i) either primary (idiopathic) or secondary (known) glomerular diseases; (ii) drugs, such as nonsteroidal antiinflammatory drugs, heroin, and gold; and (iii) bacterial, viral, and parasitic infections. Among secondary glomerular diseases, diabetes is the leading cause of nephrotic syndrome in adults. The primary