Chronic Kidney Disease

Diagnosis and Treatment

Junwei Yang
Weichun He
Editors

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Preface

Chronic kidney disease (CKD) is a global health problem with an increasing morbidity and mortality. The last decade has seen significant improvement in perception of the epidemiology, etiology, pathogenesis, and complications of CKD due in major part to the development of definitions of CKD by the Kidney Disease Outcomes Quality Initiative (KDOQI) and the Kidney Disease Improving Global Outcomes (KDIGO). The increased recognition of CKD led to the awareness of the importance and urgency of familiarizing clinicians with its diagnosis and treatment which are essential to the well-being of the patients. The purpose of the work is to guide general practitioners and residents, more than just nephrologists, and to provide them with a comprehensive and systematic review of the latest available concept concerning clinical diagnosis and therapeutics over a wide spectrum of clinically important CKD.

Our goal of the work is to provide a concise, well-organized exposition of the knowledge base of CKD to the readers. Thus, the book is designed to consist of 19 chapters divided into three parts. As compared with the previous books concerning kidney diseases and CKD, the number of chapters in each part is limited, and the length of each chapter is streamlined. Chapters in Part I cover hot topics of particular concern, such as diabetic kidney disease, hypertensive kidney disease, pregnancy in CKD, CKD in the elderly, and the association between acute kidney injury and CKD. It also contains pathophysiology of CKD and advanced image techniques for diagnosis of CKD. Part II contains major complications of CKD, e.g., cardiovascular disease, anemia, mineral bone disorder, vitamin D deficiency and secondary hyperparathyroidism, immune deficiency and infection, and nervous system disorders. Part III include several crucial aspects of management of CKD, which is nutritional intervention, medication, initiation timing and modality option for renal replacement therapy, and three modalities of renal replacement therapy, i.e., hemodialysis, peritoneal dialysis, and transplantation. Based on this framework, the book is organized to be a practical guide to clinical management of great majority of CKD, and it should prove useful and valuable to clinicians. It is our hope that the reader will become acquainted with the most important topics in CKD from this book.

We wish to thank all authors of this book for taking considerable time and effort to ensure that all chapters bring state-of-the-art knowledge. In the course of compiling this book, each author has consulted the latest literatures

and textbooks with a rigorous attitude of scholarly study, thus ensuring the scientificity and referential property of the book. We hope that the readers achieve the same level of acquisition of new knowledge and enjoyment as we have attained by editing the book.

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Nanjing, China — Weichun He

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Part I

Chronic Kidney Disease

Chronic Kidney Disease: Overview

1

Yang Zhou and Junwei Yang

Abstract

Chronic kidney disease (CKD) is a condition characterized by gradual loss of kidney function over time. The major role of the kidney is excretion of water-soluble waste products. Meanwhile, the kidneys respond continually to changes in blood volume as well as osmolality, and adjust the levels of water, electrolyte, and acid-base balance by selectively excreting or reabsorbing them. In addition, the kidneys are main site of production for a number of hormones, chiefly renin and erythropoietin. Millions of adults have CKD and others who have diabetes, hypertension, and family history of renal failure are at high risk. Glomerular filtration rate is the best estimate of kidney function, combining with proteinuria is used for staging of CKD. Patients with CKD may develop complications like cardiovascular disease, anemia, mineral and bone disorders, and nervous system diseases. Those who develop kidney failure require dialysis or kidney transplantation. The cost of treatment for this growing epidemic represents an enormous burden on healthcare systems worldwide. In this chapter, we will overview definition, epidemiology, cost, and outcomes of CKD. The detailed diagnosis and treatment will be discussed in the following chapters.

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1.1 Introduction

Chronic kidney disease (CKD) has become a global public health problem with an increasing prevalence and high mortality [1]. Owing to the growing elderly population and the increasing prevalence of hypertension and diabetes as well as the improving treatment strategies, the prevalence of CKD will inevitably continue to increase in the near future. Glomerular filtration rate (GFR) and albuminuria are proposed as the best indicators of kidney function, with low GFR and increased albuminuria being associated with a high risk of kidney failure requiring renal replacement therapy and of cardiovascular disease, anemia, mineral and bone disorder, and other complications. On account of the significant development of CKD definitions by the Kidney Disease: Improving Global Outcomes (KDIGO), the recognition of CKD has greatly improved in the last few years [2]. Increased awareness of and uniform classification criteria for CKD have led to greater focus on the development of methods to slow CKD progression,

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increased emphasis on the early recognition and prevention of complications associated with CKD, and better understanding of the economic burden of CKD and accompanying illnesses. Despite the progress, therapies and clinical trials on which to base recommendations remain remarkably limited.

1.2 Definition

CKD is defined as abnormalities of kidney structure or function, present for >3 months [3]. Table 1.1 summarizes the criteria for CKD, either of which should be present for >3 months.

1.3 Staging

The KDIGO 2012 Clinical Practice Guideline suggested that CKD could be classified according to cause, GFR category, and albuminuria category (CGA) [3].

Assign causes based on observed or presumed pathological–anatomical findings within the kidney and presence or absence of systemic disease.

Assign GFR categories as shown in Table 1.2.

Assign albuminuria categories as shown in Table 1.3.

Alternatively, protein or urinary reagent strip results can be substituted (Table 1.4).

1.4 Causes and Risk Factors

Diabetes and hypertension are the leading causes of CKD in all industrialized countries and several underdeveloped countries. However, glomerulonephritis and unknown causes are more common in Asian and Sub-Saharan African countries. Table 1.5 lists the risk factors for CKD [1–3].

In China, the current leading causes of CKD are glomerular disease, diabetic kidney disease, and hypertension. IgA nephropathy is one of the most common glomerular diseases.

Table 1.1 Criteria for CKD (either of the following should be present for >3 months)

- Albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g [≥3 mg/mmol])
- Urinary sediment abnormality
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation
- GFR <60 mL/min/1.73 m^2

CKD chronic kidney disease, *AER* albumin excretion rate, *ACR* albumin-to-creatinine ratio, *GFR* glomerular filtration rate (Reproduced with permission from Elsevier [3])

Table 1.2 GFR categories in CKD

GFR category	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal/high
G2	60–89	Mildly decreased (relative to young adult level)
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

GFR glomerular filtration rate, *CKD* chronic kidney disease

Table 1.3 Albuminuria categories in CKD

Category	AER (mg/24 h)	ACR (mg/mmol)	ACR (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased (relative to young adult level)
A3	>300	>30	>300	Severely increased (including nephrotic syndrome)

AER albumin excretion rate, *ACR* albumin-to-creatinine ratio

Table 1.4 Categories of proteinuria in CKD

Category	PER (mg/24 h)	PCR (mg/mmol)	PCR (mg/g)	Protein reagent strip
A1	<150	<15	<150	Negative to trace
A2	150–500	15–50	150–500	Trace to positive
A3	>500	>50	>500	Positive or greater

CKD chronic kidney disease, *PER* protein excretion rate, *PCR* protein-to-creatinine ratio

Table 1.5 Risk factors for CKD

Clinical factors	• Diabetes • Hypertension • Autoimmune disease • Systemic infection • Urinary tract infection • Urinary stones • Lower urinary tract obstruction • Urolithiasis • Family history of CKD • Recovery from acute kidney injury • Kidney mass reduction • Exposure to certain drugs • Low birth weight
Sociodemographic factors	• Older age • Race • Exposure to certain chemical and environmental conditions • Low income/education

CKD chronic kidney disease (Reproduced with permission from Elsevier [3])

These differences among countries are primarily related to disease burden shifting from infections toward chronic lifestyle-related diseases, increased life expectancy, and decreased birth rates in industrialized countries. In contrast, infectious diseases continue to be prevalent in less developed countries secondary to poor sanitation, lack of safe water, and high concentrations of disease-transmitting vectors. Furthermore, environmental pollution, pesticides, analgesic abuse, herbal medications, and use of unregulated food additives contribute to the burden of CKD in underdeveloped countries.

Rapid urbanization and globalization have accelerated the transition and led to an overlap in disease burden in Latin American and South Asian countries, with continued high prevalence of infectious diseases and increasing prevalence and severity of lifestyle-related diseases, such as diabetes, hypertension, and obesity.

1.5 Prevalence

Approximately 10% of the population is affected by CKD worldwide, with millions annually dying because of lack of access to affordable treatment [1]. In China, the adjusted prevalence rate of estimated GFR (eGFR) <60 mL/min/1.73 m^2 and albuminuria is 1.7% and 9.4%, respectively. The overall prevalence rate of CKD is approximately 10.8%; therefore, 119.5 million patients are estimated to have CKD in China [4].

CKD can affect individuals of any race. In particular, African American, American Indians, Hispanics, and individuals of South Asian origin (Bangladesh, India, Sri Lanka, or Pakistan) have a high risk of CKD. The prevalence of CKD is high in the northern (16.9%) and southwest (18.3%) regions of China compared with that in other regions. In rural areas of China, the prevalence of albuminuria positively correlates with the level of local economic development.

Although CKD can occur at any age, it becomes more common with increasing age and in the female gender. It has been known for decades that eGFR declines in parallel with age. The mean age of 9614 patients presenting with stage 3 CKD in India and 1185 patients in China is 51.0 and 63.6 years, respectively. It is estimated that one in five males and one in four females among individuals aged 65–74 years worldwide have CKD. The prevalence rate of CKD in the Chinese females population increases from 7.4% among those aged 18–39 years to 18.0% and 24.2% among those aged 60–69 and 70 years, respectively. Relative increases in the prevalence of CKD with age are equally striking in the USA, Canadian, and European populations despite between-country differences in the absolute prevalence. Moreover, it is estimated that the number of CKD cases will disproportionately increase in China, where the elderly population is

growing. This effect will be further magnified if the trends of increasing prevalence of diabetes and hypertension persist, competing cardiovascular diseases- and stroke-caused deaths are reduced and access to treatment improves.

When CKD finally progresses to kidney failure, renal replacement therapy becomes essential for patients' survival. However, the current treatment situation is appalling. Over two million patients worldwide presently undergo dialysis or transplantation, yet this number may only represent 10% of those who actually require treatment to live. The majority of these patients receiving therapy for kidney failure reside in only five countries, namely the USA, Japan, Germany, Brazil, and Italy, which represent only 12% of the global population. More than 80% of all patients receiving therapy for kidney failure are from affluent countries, with the remaining 20% being treated in approximately 100 developing countries, which constitute over 50% of the global population. The point prevalence of patients with kidney failure on maintenance dialysis (including hemodialysis and peritoneal dialysis) in 2008 was estimated to be 71.9 per million population in mainland China, with an annual increase in the prevalence rate of 52.9%, and reached 2584, 1106, and 1870 per million population in 2010 in Taiwan, Hong Kong, and the USA, respectively. Approximately 90% of patients with kidney failure on dialysis in China underwent hemodialysis at the end of 2012, meaning that 270,000 patients underwent hemodialysis compared with just 30,000 patients on peritoneal dialysis [1, 4, 5–7].

CKD resulted in 956,000 deaths in 2013. According to the 2010 Global Burden of Disease Study, the rank of CKD in the list of causes of total number of deaths worldwide rose from 27th in 1990 to 18th in 2010, with such movement of ranking up the list being second only to that for human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). The overall increase in years of life lost due to premature mortality caused by CKD is 82%, being only behind HIV infection and AIDS (396%) and diabetes mellitus (93%). The raw annual mortality in patients on maintenance hemodialysis in Beijing, China, was 76.8 per 1000 patient-years in 2010, which was relatively low compared with 236.3 per 1000 patient-years in 2009 in the USA. The three leading causes of death in patients on hemodialysis in China are cardiovascular disease (31.0%), stroke (20.3%), and infection (19.9%).

Despite the high prevalence, screening individuals without risk factors or symptoms for CKD is not recommended. Current recommendations suggest screening those with structural diseases of the renal tract, hypertension, cardiovascular disease, diabetes, autoimmune diseases with potential for kidney involvement, family history of kidney disease, marked obesity, and age >60 years during routine primary health encounters. Despite screening for CKD in individuals with diabetes is cost-effective, it remains unclear whether screening for CKD in the general population is cost-effective.

1.6 Costs

The cost of treatment for this dramatically growing epidemic represents an enormous burden on healthcare systems worldwide. Patients with kidney failure require dialysis or transplantation, which are exceedingly costly and consume a sizeable portion of the health budget.

In low- and middle-income countries, treatment with dialysis or transplantation imposes a huge financial burden upon most patients who require it. In another 112 countries, long-term dialysis is unaffordable for many patients, resulting in death due to untreated kidney failure in over one million individuals.

CKD was defined as a major chronic disease by the Chinese government and enrolled in three basic medical insurance systems in China. The economy will lose US$558 billion over the next decade owing to effects on death and disability attributable to heart and kidney diseases [7, 8].

An extreme example is in Uruguay, the annual cost of dialysis is close to 30% of the National Resources Fund's budget for specialized therapies.

The high cost of long-term dialysis for an increasing number of patients is also a problem

even in high-income countries. Kidney failure is a major cost driver among patients and their families as well as taxpayers.

In the USA, the treatment for CKD is likely to exceed $48 billion per year. Less than 1% of the covered population consumes 6.7% of the total Medicare budget for treatment for kidney failure.

CKD costs more than breast, lung, colon, and skin cancers combined in England, recently reported by NHS Kidney Care.

Treatment for all current and new cases of kidney failure up to 2020 will cost about $12 billion in Australia.

1.7 Diagnosis

The diagnosis of CKD includes the evaluation of chronicity, causes, GFR, albuminuria, and progression [6].

1.7.1 Evaluation of Chronicity

For individuals with kidney damage or GFR <60 mL/min/1.73 m^2 (Table 1.1), reviewing their history and past measurements is necessary to determine the course of kidney disease.

CKD is confirmed if the course exceeds 3 months; otherwise, not confirmed. Tests should be accordingly repeated to differentiate CKD, acute kidney disease, or both.

1.7.2 Evaluation of Causes

Review family and personal history, environmental and social factors, and medications, and perform physical examination, lab and imaging measurements to determine the causes of CKD and establish a pathological diagnosis.

1.7.3 Evaluation of GFR

It is recommended to use serum creatinine (SCr)-based GFR-estimating equation for initial assessment.

Table 1.6 Sources of error in GFR estimation using creatinine

Source of error	Example
Non-steady state	AKI
SCr difference	
• Creatinine generation	• Race/ethnicity • Extremes of muscle mass • Extremes of body size • Diet and nutritional status High-protein diet Creatine supplements • Muscle-wasting diseases • Ingestion of cooked meat
• Tubular secretion of creatinine	• Decrease by drug-induced inhibition Trimethoprim Cimetidine Fenofibrate
• Extrarenal elimination of creatinine	• Dialysis • Inhibition of gut creatininase by antibiotics • Large volume loss of extracellular fluid
Higher GFR	Measurement error in SCr and GFR
Interference with creatinine assay	• Spectral interferences (bilirubin, some drugs) • Chemical interferences (glucose, ketones)

AKI acute kidney injury, *SCr* serum creatinine, *GFR* glomerular filtration rate

Use SCr-based GFR-estimating equation (2009 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation) instead of SCr concentration alone although $eGFR_{creat}$ might be less accurate in some clinical settings (Table 1.6).

Furthermore, the performance of additional tests (cystatin C) for confirmation is suggested when SCr-based eGFR is less accurate.

To confirm CKD, cystatin C should be measured in adults with $eGFR_{creat}$ of 45–59 mL/min/1.73 m^2 but without kidney damage markers.

CKD is confirmed if eGFRcys or eGFRcreat–cys is also <60 mL/min/1.73 m^2. Otherwise, CKD is not confirmed if eGFRcys or eGFRcreat–cys is ≥60 mL/min/1.73 m^2.

Similarly, use cystatin C-based GFR-estimating equations (2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine–cystatin C equations) rather than cystatin C concentration alone. Sometimes, eGFRcys and eGFRcreat–cys are also less accurate in clinical settings (Table 1.7).

Table 1.7 Sources of error in GFR estimation using cystatin C

Source of error	Example
Non-steady state	AKI
Serum cystatin C difference	
• Cystatin C generation	• Race/ethnicity • Thyroid function disorders • Corticosteroid administration • Other hypothesized factors (diabetes, adiposity)
• Tubular secretion of creatinine	None identified
• Extrarenal elimination of creatinine	Severe decrease in GFR
Higher GFR	• Biological variability in non-GFR determinants relative to GFR • Measurement error in serum cystatin C and GFR
Interference with cystatin C assay	Heterophilic antibodies

AKI acute kidney injury, *GFR* glomerular filtration rate

It is necessary to measure GFR using exogenous filtration markers when more accurate ascertainment of GFR will affect treatment decisions. The strengths and limitations of clearance methods and filtration markers for clearance measurements are summarized in Table 1.8.

1.7.4 Evaluation of Albuminuria

For initial proteinuria testing, the following measurements are suggested using early morning urine sample (in descending order): urinary albumin-to-creatinine ratio (ACR), urinary protein-to-creatinine ratio, reagent strip urinalysis for total protein with automated reading, and reagent strip urinalysis for total protein with manual reading.

The high biological variation and other physiological and pathological causes affect the accuracy of albuminuria (Table 1.9), repeat testing is required to confirm albuminuria. It is more accurate to measure the albumin excretion rate or total protein excretion rate in a timed urine sample.

Urinary albumin or protein may be analyzed using fresh samples, stored at 4 °C within 1 week, or stored at −70 °C for longer periods. However, freezing at −20 °C may result in the loss of measurable albumin. Stored samples should be allowed to attain room temperature and thoroughly mixed prior to analysis.

Non-albumin proteinuria could be detected using assays for specific urinary proteins, such as monoclonal heavy or light chains (known as "Bence Jones" proteins) and α1-microglobulin.

1.7.5 Evaluation of Progression

GFR and albuminuria should be assessed at least annually in individuals with CKD. Moreover, assess GFR and albuminuria more often in individuals at a higher risk of progression and/or in cases in which measurement will affect therapeutic decisions. However, GFR are commonly fluctuated slightly and not necessarily indicative of progression.

Accelerated CKD progression is defined as a drop in GFR ≥25% from baseline, a decline in GFR category, and a sustained decrease in GFR >5 mL/min/1.73 m^2 per year.

Take the following steps to determine the rate of CKD progression: perform a minimum of three GFR estimations over a period of not less than 90 days; for individuals with a new finding of reduced GFR, review the current management, repeat GFR estimation within 2 weeks to exclude causes of acute deterioration in GFR (e.g., AKI or initiation of renin–angiotensin system [RAS] antagonist therapy), and consider referral to a specialist.

CKD patients are at increased risk of progression to end-stage kidney disease if posed with either of accelerated progression conditions.

1.8 Management Principles

The management of CKD begins by providing patient education and offering information tailored to the cause, severity, and associated complications of CKD and the risk of progression [6]. Encourage patients to perform exercise, loss weight, and stop smoking. Offer dietary advice about salt intake, potassium, calorie, and phosphate appropriate to the severity of CKD (Table 1.10).

Table 1.8 Strengths and limitations of GFR measurement methods and markers

Approach	Strengths	Limitations
Methods		
Urinary clearance		
Bladder catheter and continuous intravenous infusion of marker	• Gold standard method	• Invasive
Spontaneous bladder emptying	• Patient comfort • Less invasive	• Possibility of incomplete bladder emptying • Low flow rates in individuals with low GFR levels
Bolus administration of marker	• Shorter duration	• Rapidly declining plasma levels at high GFR levels • Longer equilibration time in extracellular volume expansion
24-h urine collection		• Cumbersome • Prone to error
Plasma clearance	• No urine collection required • With potential for increased precision	• Overestimation of GFR in extracellular volume expansion • Inaccurate values with one-sample technique, particularly at lower GFR levels • Longer plasma sampling duration required at low GFR levels
Nuclear imaging	• No urine collection or repeated blood sampling required	• Less accurate
Markers		
Inulin	• Gold standard • No side effects	• Expensive • Difficult to dissolve and maintain in solution • Short supply
Creatinine	• Endogenous marker, no need for administration • Assay available in all clinical laboratories	• Section can vary among and within individuals
Iothalamate	• Inexpensive • Long half life	• Probable tubular secretion • Requirement for storage, administration, and disposal of radioactive substances when using ^{125}I as tracer • Requirement for expensive assay when using nonradioactive iothalamate • Cannot be used in patients with allergies to iodine
Iohexol	• Nonradioactive • Inexpensive • Sensitive assay allows for low dose	• Possible tubular reabsorption or protein binding • Requirement for expensive assay when using low doses • Cannot be used in patients with allergies to iodine • Nephrotoxicity and risk of allergic reactions at high doses
EDTA	• Widely available in Europe	• Probable tubular reabsorption • Requirement for storage, administration, and disposal of radioactive substances when using ^{51}Cr as tracer
DTPA	• Widely available in the USA • New, sensitive, and easy-to-use assay for gadolinium	• Requirement for storage, administration, and disposal of radioactive substances when using ^{99m}Tc as tracer • Requires standardization for ^{99m}Tc • Dissociation and protein binding of ^{99m}Tc • Concern for NSF when using gadolinium as tracer

GFR glomerular filtration rate, *EDTA* ethylenediaminetetraacetic acid, *DPTA* diethylenetriamine pentaacetic acid, *NSF* nephrogenic systemic fibrosis

For individuals with CKD, aim to maintain the blood pressure below 140 (target range, 120–139 mmHg)/90 mmHg. For those with diabetes and ACR ≥70 mg/mmol, aim to maintain the blood pressure below 130 mmHg (target range, 120–129 mmHg)/80 mmHg.

RAS antagonist should be administered to individuals with CKD under the following conditions:

Table 1.9 Factors affecting urinary albumin-to-creatinine ratio

Factors	Examples of effect
Preanalytical factors	
Transient elevation in albuminuria	• Menstrual blood contamination • Symptomatic urinary tract infection • Exercise • Upright posture (orthostatic proteinuria) • Other conditions that increase vascular permeability (e.g., septicemia)
Intraindividual variability	• Intrinsic biological variability • Genetic variability
Preanalytical storage conditions	Albumin degradation prior to analysis
Nonrenal causes of variability in creatinine excretion	• Age (lower in children and older people) • Race • Muscle mass • Gender (lower in women)
Change in creatinine excretion	Non-steady state creatinine concentration (acute kidney injury)
Analytical factors	
Antigen excess (prozone) effect	Samples with very high albumin concentrations may be falsely reported as low or normal using some assays

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(1) diabetes and an ACR ≥3 mg/mmol (ACR category A2 or A3) and (2) hypertension and an ACR ≥30 mg/mmol (ACR category A3) or ACR ≥70 mg/mmol (irrespective of hypertension or cardiovascular disease). However, the evidence supporting these criteria in individuals aged >70 years is limited. Do not administer a combination of RAS antagonists to individuals with CKD.

Serum potassium concentrations and estimate GFR should be measured before starting RAS antagonist therapy. Repeat tests between 1 and 2 weeks after starting RAS antagonist therapy and after each dose increase. Do not routinely administer RAS antagonist to individuals if pretreatment serum potassium concentration is >5.0 mmol/L. When hyperkalemia precludes the use of RAS antagonists, assessment, and treatment of factors promoting hyperkalemia should be undertaken, then recheck the serum potassium

Table 1.10 Dietary and lifestyle modification for patients with CKD

Salt intake	• Lower salt intake to <90 mmol (<2 g) of sodium per day (corresponding to 5 g of sodium chloride) in adults, unless contraindicated • Restrict sodium intake in children with CKD who have hypertension (systolic and/or diastolic blood pressure >95th percentile) or prehypertension (systolic and/or diastolic blood pressure >90th percentile and <95th percentile), following the age-based recommended daily intake • Supply free water and sodium to children with CKD and polyuria to avoid chronic intravascular depletion and to promote optimal growth
Protein intake	• Lower protein intake to 0.8 g/kg/day in adults with or without diabetes and GFR <30 mL/min/1.73 m^2 (G4–G5) • Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression
Hyperuricemia	Despite the relationship between hyperuricemia and incidence of CKD, there is insufficient evidence supporting or refuting the use of agents to lower serum uric acid concentrations in individuals with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay CKD
Lifestyle	• Encourage patients with CKD to perform physical activity compatible with their cardiovascular health and tolerance (aiming for at least 30 min five times per week) • Achieve a healthy weight (BMI 20–25, according to country-specific demographics) • Stop smoking
Additional dietary advice	Provide expert dietary advice and information in the context of an education program tailored to the severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake, when indicated

CKD chronic kidney disease, *GFR* glomerular filtration rate, *BMI* body mass index

concentration. Stop RAS antagonist therapy if the serum potassium concentration increases to ≥6.0 mmol/L and discontinue other drugs known to promote hyperkalemia.

Following the introduction of RAS antagonists or an increase in their dose, do not modify the dose if either the GFR decrease from pretreatment baseline is <25% or the SCr increase from baseline is <30%. If there is a <25% decrease in eGFR or 30% increase in SCr from baseline after starting RAS antagonist therapy or increasing the dose of RAS antagonists, repeat the test in 1–2 weeks. Do not modify the dose of RAS antagonists if the change in eGFR or SCr is <25% or <30%, respectively. If the change in eGFR or SCr is ≥25% or ≥30%, respectively, investigate other causes of deterioration in renal function, such as concurrent medication or volume depletion. If no other causes of deterioration in renal function are identified, stop the RAS antagonist therapy or reduce to previous tolerated dose and add an alternative antihypertensive medication, if required.

For CKD patients with diabetes, the target hemoglobin A1c (HbA1c) level is approximately 7.0% (53 mmol/mol) in order to prevent or delay the progression of diabetic kidney disease. This HbA1c target is not suitable for patients at risk of hypoglycemia. The target HbA1c level should be extended above 7.0% in individuals with limited life expectancy, comorbidities or at risk of hypoglycemia. For patients with CKD who have diabetes, glycemic control should be accompanied by multifactorial intervention strategies including blood pressure control and cardiovascular risk care. Use of RAS antagonists, statins, and antiplatelet therapy are recommended if clinically indicated.

For the prevention and treatment of cardiovascular diseases and several complications including anemia, bone conditions, and metabolic acidosis, see Part II.

When assessing CKD progression, extrapolate the current rate of decline in GFR, and take this into account when planning intervention strategies, particularly if it suggests that patients might require renal replacement therapy throughout their lifetime.

Patients with features summarized in Table 1.11 should normally be referred to a specialist for assessment.

Provide patients with stage 5 CKD with information on treatment options for renal replacement therapy. Treatment options include transplantation and dialysis (hemodialysis and peritoneal dialysis). Table 1.12 shows the timing for the initiation of renal replacement therapy.

Table 1.11 When to refer

GFR <30 mL/min/1.73 m^2 (GFR category G4 or G5), with or without diabetes
ACR ≥70 mg/mmol, unless known to be due to diabetes and already appropriately treated
ACR ≥30 mg/mmol (ACR category A3), together with hematuria
Sustained decrease in GFR ≥25%, and a change in GFR category or sustained decrease in GFR ≥15 mL/min/1.73 m^2 within 12 months
Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses
Known or suspected rare or genetic causes of CKD
Suspected renal artery stenosis

GFR glomerular filtration rate, *ACR* albumin-to-creatinine ratio, *CKD* chronic kidney disease (Reproduced with permission from Elsevier [3])

Table 1.12 Timing for the initiation of renal replacement therapy

Initiation of dialysis	• Symptoms or signs attributable to kidney failure (e.g., serositis, acid-base or electrolyte abnormalities, pruritus) • Inability to control volume status or blood pressure • Cognitive impairment or progressive deterioration in nutritional status refractory to dietary intervention • This often but not invariably occurs in the GFR range of 5–10 mL/min/1.73 m^2
Initiation of transplantation with living donor	GFR is <20 mL/min/1.73 m^2 with evidence of progressive and irreversible CKD over the preceding 6–12 months

GFR glomerular filtration rate, *CKD* chronic kidney disease

Key Messages

- KDIGO defined CKD as kidney abnormalities or GFR <60 mL/min/1.73 m^2 for 3 months or longer and classified CKD based on CGA.
- Lifestyle-related diseases, including diabetes, hypertension, and obesity, and glomerular disease are the major causes of and risk factors for CKD.
- The incidence and prevalence of CKD substantially differ across countries and regions. The number of patients with CKD is expected to continuously increase worldwide. Low levels of economic development have been strongly associated with reduced availability of renal replacement therapy.
- The cost of treatment with dialysis or kidney transplantation for kidney failure represents an enormous burden on healthcare systems in both developed and developing countries.
- Evaluate chronicity, causes, GFR, and albuminuria to confirm the diagnosis of CKD.
- General approaches to CKD management include patient education (e.g., lifestyle modification), treatment of primary diseases (e.g., hypertension, diabetes), prevention and treatment of complications (e.g., cardiovascular diseases, anemia), and renal replacement therapy.

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2 Pathophysiology of Chronic Kidney Disease

Jiafa Ren and Chunsun Dai

Abstract

Chronic kidney disease (CKD), a general term for heterogeneous disorders, frequently occurs in association with a variety of factors including diabetes, nephritis, hypertension, and immune system disorder. As the etiologically distinct cause progresses, a common renal pathological manifestation including glomerulosclerosis and/or interstitial fibrosis develops regardless of the cause. Over the past several years, rapid progress in deciphering the cellular and molecular mechanisms have led to better understanding of pathophysiology of CKD and would make it possible to develop clinically effective anti-CKD therapies. This chapter summarizes and updates the pathophysiological knowledge of CKD from animal models and human studies, providing new insights into the complicated process of CKD.

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2.1 Introduction

Chronic kidney disease (CKD) is defined as decreased kidney function reflected in glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2, markers of kidney damage, or both, of at least 3 months' duration, regardless of specific causes [1]. The prevalence of CKD is consistently reported to be ~10% in many countries [2], and patients with advanced CKD have a high burden of physical and psychosocial symptoms, poor outcomes, and high costs of care.

The pathological manifestation of CKD is the loss of renal cells and deposition of the extracellular matrix (ECM). Regardless of the initial insults, the progressive renal disease is characterized by morphological changes that comprise renal inflammation, glomerulosclerosis, tubular atrophy, tubulointerstitial fibrosis, and capillary rarefaction (Fig. 2.1). The pathogenesis of renal fibrosis including glomerulosclerosis and interstitial fibrosis is a progressive process that ultimately leads to end-stage renal failure, a devastating condition that requires renal replacement therapy (e.g., dialysis or transplantation). Current therapies for CKD mainly involve blockade of the renin–angiotensin–aldosterone system (RAAS) [3]. Therefore, this chapter outlines the current understanding of the cellular and molecular mechanisms of renal fibrosis including glomerulosclerosis and

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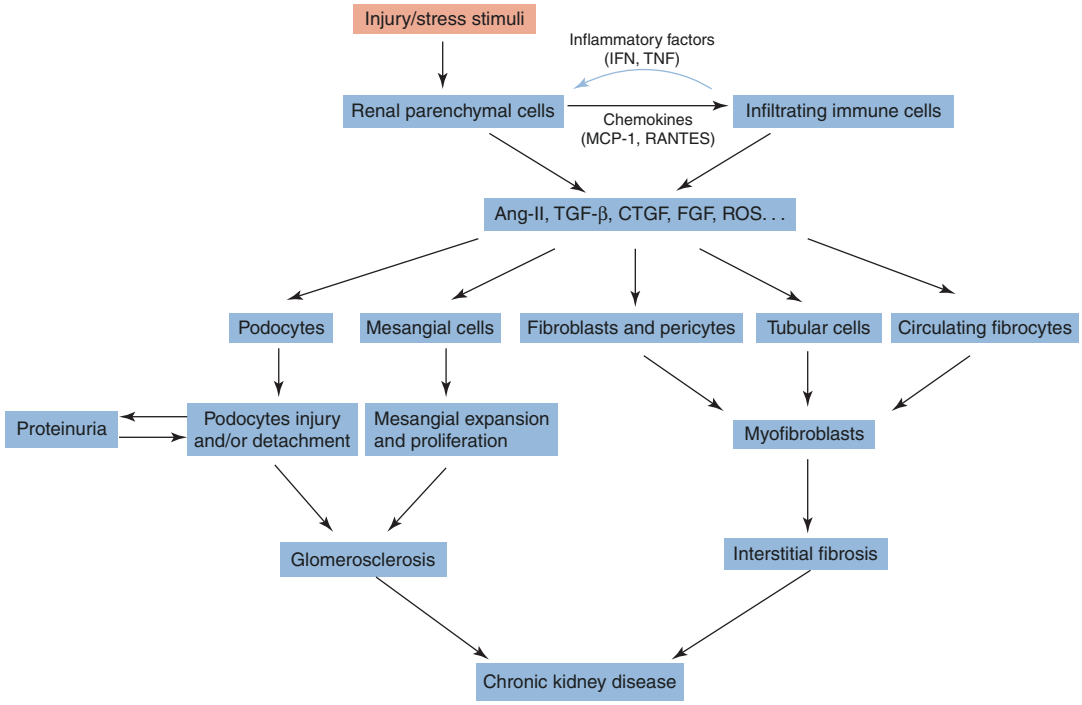

Fig. 2.1 Schematic presentation for cellular events involved in the progression of chronic kidney disease

interstitial fibrosis. Thorough knowledge of the pathophysiology of kidney fibrosis is crucial for developing newer therapeutic strategies.

2.2 Glomerulosclerosis

Each normal glomerulus is a tuft of small blood vessels called capillaries situated within Bowman's capsule with the kidney. The tufts are structurally supported by mesangial cells, which facilitate structural organization and integrity of capillaries of glomerulus. Endothelial cells lining capillaries uniquely have numerous pores also named fenestrated endothelial cells. The glomerular base membrane (GBM) separating fenestrated endothelial cells from podocytes is the basal lamina layer of the glomerulus. The podocyte foot processes, GBM and endothelial cells constitute the glomerular filtration barrier, a highly specialized blood filtration interface. Dysfunction of the glomerular filtration barrier and expansion or proliferation of mesangial cells are thought to contribute to the development of glomerulosclerosis.

Glomerulosclerosis is characterized by an increase in mesangial matrix accumulation and obliteration of glomerular capillaries. The underlying pathogenic mechanism of glomerulosclerosis is even more complicated and can be divided into several distinctive phases. First, under the influence of various risk factors such as hypertension, dyslipidemia, and/or deposition of immune complexes, glomerulus-resident cells are injured and activated, followed by a release of multiple cytokines and chemokines, which attract monocytes, lymphocytes, neutrophils, and other types of inflammatory cells to immigrate and accumulate at the injury site. Second, these infiltrating cells accompanied with intrinsic cells further produce multiple cytokines and growth factors including angiotensin, transforming growth factor β1 (TGF-β1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), tumor necrosis factor (TNF), and interferon gamma (IFN-γ) to induce the capillary collapse and obliteration, loss of podocytes, and activation of parietal epithelium cells. The final process is fibrogenesis, featuring production of new ECM components to replace damaged tissue, thereby

providing a scaffold for wound closure, remodeling, and repair. Thus, glomerulosclerosis mainly reflects podocyte injury, proliferation, and matrix production by mesangial cells as well as endothelial damage and dysfunction.

Podocyte injury is a key manifestation of proteinuric glomerulopathies, including focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranous-proliferative glomerulonephritis (MPGN), amyloid nephropathy (AN), and diabetic nephropathy (DN). Four major mechanisms cause injury to podocytes: alteration of the GBM or its interactions with the podocyte, molecular change in the slit diaphragm or interference with its structure, dysfunction of podocyte actin cytoskeleton, and changes in negative surface charge on podocytes. In response to insults, podocytes appear different adaptive changes, such as hypertrophy, transdifferentiation, dedifferentiation, detachment, and apoptosis. These adaptive responses of podocytes mainly depend on the insult severity and duration.

Mesangial cells constitute the central stalk of the glomerulus and represent continuation of the extraglomerular mesangium and the juxtaglomerular apparatus. Proliferation of mesangial cells is a prominent feature of glomerular disease including IgA nephropathy (IgAN), membranous-proliferative glomerulonephritis (MPNG) lupus nephritis (LN), and DN. Mesangial-cell proliferation and matrix accumulation promoted by many kinds of profibrotic factors including TGF-β, PDGF, and FGF2 are believed to contribute to the development of glomerulosclerosis. In response to initial injury factors, mesangial cells undergo transformation to mesangioblasts. The latter are capable of producing an excessive ECM, leading to mesangial expansion: an early sign of glomerulosclerosis. The relative contribution of podocytes, mesangial cells, and other resident glomerular cells to matrix accumulation and glomerulosclerosis may depend on the disease in question.

2.2.1 Podocyte Injury

The podocyte is one of the most important cell types for the glomerular filtration barrier. The podocyte and its slit diaphragm are the main structure of the glomerular filtration barrier. Podocytes stabilize the filtration barrier of glomerular through production of GBM molecules, maintenance of the structure of slit diaphragm, and keeping viability of endothelial cell. Podocytes injured by various risk factors undergo detachment or apoptosis, which is an irreversible loss that permanently causes inefficiency of podocytes. Because podocytes are terminally differentiated cells and can't proliferate, the area of the GBM initially covered by podocyte becomes exposed. To the areas of the exposed GBM, parietal epithelial cells may get attached. This scenario leads to form adhesions or synechiae between GBM and parietal cells, which are recognized as some of the earliest signs of segmental glomerulosclerosis. Maladaptive interactions develop between the GBM and parietal epithelial cells. Extension of the synechiae leads to the leakage of protein into Bowman's space, collapse and sclerosis of the associated capillary tuft, and the loss of endothelial cells, which is suggestive of the formation of crescents and sclerosis. Tracer studies have been performed to disclose that filtration of the tracer mainly accumulates extracellularly at the sites within tuft adhesions to Bowman's capsule and related paraglomerular spaces. The accumulation of protein debris is obligatory for capillary collapse. More than that, proteinaceous fluid derived from misdirected filtration is trapped within the space between parietal epithelium and GBM, ultimately causing the progression to global sclerosis and obsolescence.

2.2.1.1 Slit-Diaphragm Destruction

The slit diaphragm is the main barrier that limits protein leakage. The slit-diaphragm system destruction can lead to foot process effacement (FPE). The slit diaphragm can be subdivided into two parts structurally. ZO-1, α-actinin-4, podocin, and CD2AP have been recognized as intracellular parts of the slit diaphragm; NEPH family members, Nephrin, FAT, and P-cadherin are known to constitute the extracellular components of the slit diaphragm. Proteinuria is an early consequence of podocyte injury and is a typical sign of kidney disease [4]. Podocyte-specific ablation of slit-diaphragm-related proteins in mice may

result in severe proteinuria and sclerosis. Clinically, proteinuria is a strong independent risk factor of progressive CKD. Although podocyte injury directly results in proteinuria, it is possible that proteinuria further worsens podocyte injury. Electron-microscopic studies have shown that a large number of protein droplets in the podocyte may be related to proteinuria. After proteinuria develops, tubular cells also take in large amounts of albumin, which can cause interstitial inflammation and fibrosis.

In congenital nephrosis, it is known that neutralization of nephrin by a specific antibody and a podocyte-specific conditional knockout of a slit-diaphragm gene such as nephrin, CD2AP, or α-actinin-4 each results in severe proteinuria and sclerosis [5]. In response to injurious stimuli, podocytes undergo phenotypic alteration characterized by downregulation of slit-diaphragm-associated proteins including P-cadherin, ZO-1, and nephrin and their own molecular signatures such as Wilms tumor protein 1 (WT1), synaptopodin, and initiation of expression of mesenchymal markers, including desmin, fibroblast-specific protein 1 (FSP1), and matrix metallopeptidase 9 (MMP-9), producing interstitial matrix components, such as fibronectin and type I collagen. This phenotypic alteration also involves upregulation of the transcription factor Snail and integrin-linked kinase. Liu et al. have named this process "podocyte epithelial–mesenchymal transition (EMT)," which is similar to kidney tubular epithelial cells undergoing mesenchymal transition during kidney interstitial fibrosis [6, 7]. A number of important intracellular signal pathways, such as ILK, Wnt–β-catenin, Jagged-Notch, and Snail, often specially drive podocyte into "EMT" program in the pathogenesis of various proteinuric renal diseases. These data are suggestive of podocyte undergoing "EMT" program in response to various injuries. Eventually, impairment of podocyte filtration barrier is consequence for podocyte phenotype changes, leading to proteinuria and glomerulosclerosis.

Furthermore, slit diaphragm, the only structure participating in cell–cell junctions and communications, have important implications for stabilizing cellular polarity. Damaged podocytes lose their polarity, which causes proteins normally situated on the podocyte slit diaphragm to spread to abnormal locations. Arrangement of these proteins may interrupt the communications between podocytes and lead to disorganization of the architecture and to FPE shown in proteinuric renal diseases. The slit diaphragm may also have signal transduction functions. For example, tyrosine phosphorylation of nephrin correlates with the activation of signaling pathways in vivo and in vitro [8]. After nephrin phosphorylation, multiple downstream molecules perform critical functions to maintain podocyte polarity and regulate cell survival.

2.2.1.2 Changes in the Actin Cytoskeleton of Podocytes

It is known that podocytes function to support and maintain the structural of the glomerular tuft. Podocyte foot processes with highly dynamic performance partly depend on a rich actin cytoskeleton, which eventually establishes the podocyte's shape. A study conducted by Ichimura et al. [9] have shown that using electron microscopy, two populations of actin cytoskeletons are included in matured podocytes. One is actin bundle running above the level of slit diaphragms and the other is the cortical actin network situated beneath the plasmalemma. FPE often has close relations with an increase in the number of microfilaments. Meanwhile, the podocyte actin system is regulated by the Rho family of guanosine triphosphatases, whose member Cdc42 mediates filopodia formation [10]. Mice with a podocyte-specific Cdc42 knockout have severe proteinuria and extensive nephrosclerosis associated with a reduction in the expression of slit-diaphragm components. Guanosine triphosphatase dynamin plays a basic role in regulating actin cytoskeleton of podocytes [11], and interference with oligomerization of actin-dependent dynamin with inhibitor effectively attenuates proteinuria and progress of renal diseases [12]. The actin cytoskeleton system is necessary not only for supporting foot processes but also for podocytes to confront the filtrate pressure. Thus, these findings suggest that protein molecules maintaining or regulating podocyte actin cytoskeleton system

are extremely important to podocyte functions, and any changes in the actin or actin-related proteins may cause podocyte shape alterations and podocyte dysfunctions [13].

2.2.1.3 Loss of Podocytes

Podocyte Detachment

As mentioned above, podocyte detachment from the GBM resulting in the formation of adhesions or synechiae is the main pathophysiological mechanism of glomerulosclerosis. Podocytes are normally tethered to the GBM by integrins and dystroglycans. Integrins and dystroglycans expressed on the podocyte plasma membrane specifically bind to ligands in the GBM matrix to maintain tight cell attachment. Several mechanisms of podocyte detachment, including mechanical distension, shear forces, and/or impaired adhesion to the GBM, have been suggested. In response to mechanical forces, including intraglomerular hypertension, hyperfiltration, hypertrophy, and podocytes may undergo detachment from the GBM. Intraglomerular hypertension will contribute to (1) not only increased axial capillary wall and circumferential stress but also increased filtrate flow, causing (2) an increase in fluid shear stress on the podocytes. (3) In this setting of circumstances, podocytes are challenged by the hypertrophy of glomerular to obtain more motility and cover more areas of the GBM. (4) In the progressive phase of the disease, podocytes will be challenged by increased expansile forces and then undergo detachment.

Studies also show integrin outside-in signals regulate podocyte-GBM adhesion; inside-out signals from the podocyte cytoskeleton are also critical for podocyte adhesion to the GBM. Research suggests that there is decreased expression of integrin α3β1 on podocytes of humans and rats during diabetes; this phenomenon causes detachment of podocytes from the GBM [14]. Talin-1, a large cytoskeletal protein in the podocyte, favors inside-out signal transduction through the activating β1 integrin and mediating integrin–actin binding. Suppression of calpain-induced talin-1 cleavage with inhibitor compound alleviates proteinuria, and ablation of talin-1 in podocytes leads to severe nephrosis with FPE [15]. Clinically, podocytes and certain podocyte-specific protein products can be detected in the urine of patients with proteinuric renal disease, but not in healthy subjects or in nonpodocyte glomerular disease [13]. A study by Ye et al. has shown that podocyte present in urine is thought to be a more sensitive marker than proteinuria. The major underlying mechanism of podocyte loss is detachment of podocytes from the GBM, which contributes to the progression of CKD [16].

Podocyte Apoptosis

A second cause of the loss of podocytes is augmented apoptosis. Podocyte apoptosis leads to proteinuria and/or glomerulosclerosis. Bottinger is among the first to report augmented apoptosis of podocytes responding to TGF-β in a transgenic mouse model. The cytokine TGF-β and its receptors are upregulated in a variety of podocytopathic diseases, including membranous nephropathy (MN), DN, and FSGS. Proteinuria in turn accelerates podocyte loss or death. One study has revealed that upregulation of podocyte Notch1 in models of DN and FSGS is associated with proteinuria and glomerulosclerosis by Notch1-driven podocyte apoptosis via a p53-mediated pathway [17]. In vitro study, a Notch2 knockdown increases podocyte apoptosis. Inhibition of Notch2 by its specific antibody alleviates proteinuria in a FSGS mouse model [18]. Nevertheless, research indicates that podocyte apoptosis may not be the main cause of the loss of podocytes [19]. Many findings about podocyte apoptosis are obtained in in vitro studies; thus, whether these studies are reliable—from the point of view of proving that apoptosis is the common mechanism of podocyte loss in situ—needs further investigation.

2.2.2 Mesangial Expansion and/or Proliferation

The role of mesangial cells can be investigated by the injurious consequences of accumulation of mesangial immune complexes with subsequent

complement activation and production of mediators of inflammation, such as prostanoids; platelet-activating factor (PAF); reactive oxygen species (ROS); cytokines such as IL-6, TNF-α, CSF-1; and chemokines. Immune complexes such as those involving IgA get deposited in the mesangium with simultaneous complement activation. In response to these aberrant immune complexes, mesangial cells are activated and produce several mediators of inflammation, such as chemokines, cytokines, and growth factors, such as mesangial cells bFGF, PDGF, and TGF-β. These may result in mesangial-cell proliferation and matrix expansion. The production of proinflammatory mediators by mesangial cells may also cause a deleterious circle between these mediators, altering the endothelial barrier, allowing more macromolecules to enter the mesangium, and further accelerating the production of inflammatory mediators, ultimately leading to local leukocyte adhesion, activation, and extravasation. Finally, a number of inflammatory mediators produced by mesangial cells (in response to immune complex deposition) and by the infiltrating leukocytes may also change glomerular permselectivity by affecting podocyte function, eventually leading to proteinuria.

Besides being activated by the immune complex, mesangial cells can be activated by advanced glycation end products via binding to their receptor on mesangial cells in diabetes. Furthermore, production of various growth factors, matrix components, and alteration of matrix metabolism by mesangial cells can also be caused by glomerular hypertension in the early phage of diabetes, even in the absence of systemic hypertension. The resulting appearance is early mesangial-cell hypertrophy, proliferation, and deposition of mesangial matrix. The pathological manifestation of DN is characterized by the formation of nodular glomerulosclerosis first described by Kimmelstiel and Wilson. Finally, activation of mesangial cells by hyperglycemia and the sequelae mentioned above also produce chemokines that involve in the leukocytes infiltration, thereby provoking destructive proapoptotic and profibrotic responses. Consequently, mesangial cells significantly participate in the initiation and progression of diabetic glomerulopathy. Besides, changes in mesangial cell biological functions can also be noted in other glomerular diseases, such as amyloidosis and light chain deposition diseases.

2.3 Renal Interstitial Fibrosis

The process of renal interstitial fibrosis, a failure of wound healing that takes place after the initial various damages, is characterized by excessive deposition of the ECM in the interstitial compartment. Almost all cell types (either resident or nonresident kidneys cells) are in some way responsible for the pathogenesis of kidney interstitial fibrosis. Major cellular and molecular events are comprised of inflammatory cell infiltration, fibroblast activation and myofibroblast development from various cell types, generation and deposition of ECM molecules, and tubular atrophy with microvascular rarefaction. The process of renal interstitial fibrosis may be artificially subdivided into four distinguishable (but sometimes overlapping) phages:

1. After a sustained injury (e.g., proteinuria, high concentration of glucose, or hypoxemia), kidney-resident cells are damaged and release chemotactic factors providing a signal that attracts inflammatory cells to infiltrate into the injury site.
2. The infiltrating inflammatory cells producing various compounds including ROS and multiple protein factors, such as MCP-1, TNF-α, IL-1, TGF-β1, CTGF, and angiotensin II (Ang II), aggravate renal-cell injury. This series of events induces fibroblasts and other cell types, including tubular epithelial cells, pericytes, and endothelial cells, to undergo phenotypic activation or transition and to produce a great amount of ECM components.
3. Activated myofibroblasts from different sources generate ECM, as well as promoting excessive ECM deposition in renal interstitium that results in renal tubular apoptosis and atrophy.

4. Over-generation of extracellular matrix and their degradation defects are accountable for excessive matrix accumulation in the renal interstitium. In the early stage of kidney interstitial fibrosis, the fibrosis may be reversible due to the extracellular matrix prone to proteolysis. Nonetheless, as injuries are sustained and fibrosis progresses, cross-linking with tissue transglutaminase and lysyl oxidase is thought to modify matrix in late stage of renal fibrosis, eventually leading to make the matrix stiff and highly resistant to proteolysis [20]. Excessive deposition of the ECM results in the ultimate destruction of renal parenchyma, microvascular rarefaction, and loss of kidney function.

Due to the limitations of space, we are going to focus on the principal cell types that are responsible for the process of interstitial fibrosis.

2.3.1 Activation of Fibroblasts and Pericytes

In healthy adult kidneys, fibroblasts are located in the interstitial space between capillaries and epithelia, and interact with each other throughout the entire kidney, therefore stabilizing tissue architecture and matrix homeostasis via production of a basal amount of ECM molecules under physiological conditions [21]. In a resting quiescent state, interstitial fibroblasts express some relatively specific markers, including CD73 (also known as ecto-5′-nucleotidase), PDGF-β, and fibroblast-specific protein 1 (FSP1; also known as S100A4). None of these markers, however, is specific for fibroblasts. Profibrotic factors and mechanical stress trigger fibroblast differentiation into αSMA-expressing myofibroblasts. A study by LeBleu et al. shows that 50% of the total pool of myofibroblasts arises from local resident fibroblasts through proliferation during the process of unilateral ureteral obstruction (UUO) [22]. As in resident fibroblasts, there are no universal pericyte markers, whereas kidney pericytes express a number of typical pericyte markers, including PDGFR-β, PDGFR-α, CD248, CD146, desmin, and others [23].

Research suggests that vascular pericytes are also a major source of myofibroblasts in fibrotic kidneys [24, 25]. Pericytes are defined anatomically as cells of mesenchymal origin attached to capillaries that share a common basement membrane and form junctions with endothelial cells [23]. Following kidney injury, pericytes get detached from the endothelium, undergo migration and proliferation, and differentiate into myofibroblasts [26]. The detachment of pericytes and their differentiation into myofibroblasts not only lead to instability of the microvasculature, but also contribute to activation of myofibroblasts, which results in interstitial fibrosis. In addition, pericytes play pivotal roles in sensing of injury, the regulation of recruitment of leukocytes, and perpetuation of inflammation.

2.3.2 Epithelial–Mesenchymal Transition (EMT)

Another origin of cells producing matrix may be the tubular epithelium that involves in EMT: a phenotypic transformation program is that is characterized by the loss of epithelial markers and a gain of mesenchymal features. Similarly, capillary endothelium via endothelial–mesenchymal transition (EndoMT) may be another source of fibroblasts and/or myofibroblasts. EndoMT is recognized as a special form of EMT as endothelial cells are thought as a specialized type of epithelia. That tubular epithelial cells undergo EMT in vitro is not debated. Whether this transition occurs in vivo is at the center of a controversy. An early study has revealed that tubular epithelium contributes to over one-third of $FSP1^+$ interstitial fibroblasts by using bone marrow chimeras and transgenic reporter mice in a UUO model [27]. Meanwhile, two studies also have revealed that EndoMT occurring in various fibrotic kidney diseases significantly participates in the formation of fibroblast and/or myofibroblasts. Nonetheless, some studies question the above experimental results and find that no or only a small number of epithelial or endothelial cells participate in EMT [26, 28].

In 2015, however, two important studies readdressed this debate and shed light on the potential impacts of tubular EMT in the initiation and development of kidney interstitial fibrosis [29, 30]. These studies clarify the issue via several new models of genetically modified mice, in which Snail or Twist1, two key transcription factors regulating the EMT program, are specifically deleted in tubules. Consequently, the EMT program is suppressed significantly in the renal tubular cells in vivo. Both studies show that suppression of the EMT program by tubular-specific deletion of Snail or Twist1 attenuates interstitial fibrosis in several CKD models, including UUO, nephrotoxic-serum-induced nephritis, and folic-acid-induced nephropathy. Thus, the EMT program is pivotal and required for provoking tubular dysfunction and promoting fibrosis progression under pathological conditions.

2.3.3 Recruitment of Circulating Fibrocytes

Fibrocytes are recognized as bone marrow-derived cells that circulate in the peripheral blood and generate matrix components such as collagens and vimentin. Fibrocytes may be identified by dual positivity for CD34 or CD45 and type I collagen or procollagen 1. A study suggests that three markers, CD45RO, 25F9, and S100A8/A9, can distinguish monocyte-derived fibrocytes from monocytes, macrophages, and fibroblasts [31]. Nevertheless, specific markers of fibrocytes have yet to be identified. It is noteworthy that fibrocytes isolated from humans and mice also express certain chemokine receptors, such as CCR2, CCR3, CCR5, CCR7, and CXCR4, thereby regulating the recruitment to sites of fibrosis. Fibrocytes migrate, infiltrate into renal tissue, and involve in the pathogenesis of kidney fibrosis following initial renal injury. Other immune cells like CD4+ T cells can modulate the Gr1+ monocytes differentiation into fibrocytes via secretion of cytokines [32]. Profibrotic cytokines IL-4 and IL-13 promote fibrocytic differentiation, whereas antifibrotic cytokines IFN-γ and IL-12 inhibit this process, suggesting that an inflamed milieu that contains a complex mixture of cytokines is a major determinant of fibrocytic differentiation.

The relative contribution of fibrocytes to renal fibrogenesis is another field full of controversy. Studies by different labs have led to different conclusions. It is a great challenge to clearly discriminate fibrocytes from monocytes/macrophages, fibroblasts, and myofibroblasts due to the fact that there is no specific marker for fibrocytes. In addition, subpopulations of fibrocytes seem to exist [31]. Until now, results of studies on the contribution of fibrocytes in the pathogenesis of kidney interstitial fibrosis are controversial [27, 32, 33].

Over the years, board agreement has been reached that myofibroblasts in renal interstitial fibrosis have a variety of origins. They accomplish tissue repair and remodeling through synthesis and organization of the ECM that causes scarring. Myofibroblasts form from fibroblastic cells (via differentiation) that have distinct biological features, thus supporting the concept of phenotypic heterogeneity of fibroblasts. A better understanding of what cell types generate a larger amount of ECM components and how they are regulated under pathological conditions may shed new light on designing effective therapeutic strategies.

2.4 Key Molecules or Events in CKD

2.4.1 RAAS

The kidney has all the components of the RAAS, and Ang II formation in kidney does not depend on the circulating RAAS. Ang II acting through AT1 receptors activates local components of the RAAS inside the kidney. Meanwhile, Ang II acting as contracting factor mediates intraglomerular hypertension that contributes to impairment of glomerular endothelial, podocytes, and mesangial cells. Moreover, aldosterone and Ang II perform a number of nonhemodynamic functions that are critical for the pathogenesis of CKD, including effects on inflammation, ECM production, endothelial dysfunction, and ROS generation.

Ang II as a main vasoconstrictor of RAAS predominantly effects on postglomerular arterioles, which leads to intraglomerular hypertension, an increase in filtration, and impairment of the size-selective function of glomerular barrier toward macromolecules, such as plasma protein. Glomerular hypertension and outflow of plasma protein may be responsible for the initiation and progression of chronic kidney diseases. The nonhemodynamic effects of Ang II, such as upregulation of cytokines, increased generation of ROS, and cell adhesion molecules, play important roles in driving progression of kidney disease. In addition, Ang II is thought to impair the integrity of glomerular filtration barrier by decreasing negative charged proteoglycans synthesis and inhibiting nephrin expression [34]. Consequently, Ang II via hemodynamic and nonhemodynamic effects—leads to proteinuria.

The RAAS participates in interstitial fibrosis mainly by promoting the proliferation of fibroblasts, enhancing EMT, increasing production of TGF-β, and by promoting the imbalance between ECM synthesis and degradation. Studies have uncovered a close link between the RAAS and profibrotic cytokine TGF-β. Ang II not only promotes TGF-β expression through several pathways, but also stimulates expression of receptors for TGF-β. Furthermore, SMADs phosphorylation can be directly regulated by Ang II without induction of TGF-β. In addition, other molecules of the RAAS, such as renin, Ang III, and aldosterone also promote activation of TGF-β system. Given that therapeutic strategies for directly targeting TGF-β system in human diseases have not been feasible, angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers are currently the most promising drugs for interfering with this Ang-II-induced TGF-β system activation. Additionally, Ang II can induce PAI-1 and tissue inhibitor of matrix metalloproteinases 1 (TIMP-1) via AT1 receptors. Meanwhile, the RAAS participates in EMT too. Aside from the mechanism mentioned above, Ang II activates (through AT1 and AT2 receptors) the proinflammatory transcription factor NF-κB [35], enhancing an inflammatory response and contributing to renal interstitial fibrosis. In contrast, one study conducted by Zhang et al. indicates that activation of AT1 receptors on macrophages can ameliorate kidney fibrosis by inhibiting macrophage M1 polarization and by reducing the inflammatory response. This study may remind us that the RAAS acting on different cell lineages plays various roles during interstitial fibrogenesis, and angiotensin receptor blockade is related not only to previously recognized side effects but also to patently detrimental effects of blocking angiotensin receptors on hematopoietic cells [36].

Sustained activation of the intrarenal RAAS results in renal injury and plays a pivotal part in the pathogenesis of CKD. This fascinating system is found to be increasingly complex as it is characterized, and research into new members continues. Identification and characterization of the RAAS together with novel pharmacological approaches that target its components—we hope will provide methods to sufficiently retard the progression and to induce regression of kidney disease.

2.4.2 TGF-β

TGF-β is a key mediator of implicating in the regulation of fibrogenesis, cell proliferation, apoptosis, and hypertrophy, contributing to kidney fibrosis and progressive CKD. The TGF-β superfamily consists of TGF-β1, -β2, and, -β3; activins; and bone morphogenic proteins (BMPs). Canonical and noncanonical signaling cascades can be provoked by TGF-β to exert various biological functions. SMAD signaling is thought to be a major pathway among TGF-β-driven signalings in progressive renal fibrosis. TGF-β signaling is initiated when ligand-bound type II TGF-β receptor (TβRII) binds to (and phosphorylates) type I TGF-β receptor (TβRI) in the TβRI cytoplasmic glycine and serine (GS) region. Then, SMAD2 and/or -3 are highly activated along with a common SMAD: SMAD4. These SMAD proteins form an oligomeric complex and then are translocated into the nucleus to regulate the transcription of target genes in collaboration with various coactivators and corepressors. Activation of SMAD3 is associated with the downregulation

of inhibitory SMAD7 via an ubiquitin E3 ligase-dependent degradation mechanism. Additionally, TGF-β can function via SMAD-independent pathways, including p38, ERK, MAPK, Rho GTPases, Rac, Cdc42, ILK, β-catenin, and PI3K–Akt–mTOR cascades.

The cytokine TGF-β is closely associated with glomerular disease. This cytokine and its receptors are upregulated in a variety of podocyte diseases, including MN, DN, and FSGS. Increased urinary concentration of TGF-β is detected in patients with some forms of nephrotic syndrome, IgAN, and FSGS. Of note, detection of TGF-β in urine can differentiate between FSGS and the nonfibrotic process of minimal change disease (MCD). In addition to its profibrotic effects, TGF-β signaling induces apoptosis. As described above, glomerulosclerosis in animal models and humans is characterized in part by depletion of podocytes. TGF-β1 and SMAD7 synergize to induce apoptosis in podocytes in vitro. A study by Shankland's group suggests that CDK inhibitor p21 is necessary for TGF-β-induced podocyte apoptosis [37]. In a TGF-β1 transgenic model of progressive glomerulosclerosis, the time point of peak podocyte apoptosis coincides with expression of TGF-β1 and SMAD7, and with the onset of albuminuria, but precedes mesangial expansion [38]. In addition, podocyte depletion may cause decreased expression of VEGF, which acts on endothelial cells and promotes their survival [39]. These pathogenic events mediated by TGF-β signaling may represent the pathological mechanism behind podocyte depletion and progressive glomerulosclerosis.

Additionally, TGF-β signaling mediates mesangial-cell-induced glomerulosclerosis. TGF-β1 stimulates production of type I and IV collagens and fibronectin in mesangial cells, leading to glomerular-matrix accumulation in the pathogenesis of glomerulosclerosis. In addition, TGF-β1 inhibits plasminogen activator production, and this effect stimulates PAI synthesis by normal glomeruli. Moreover, TGF-β can rapidly stimulate Ca^{2+} influx, without promoting a Ca^{2+} release, thereby further promoting cytoskeletal rearrangement and increasing incorporation of αSMA into stress fibers in mesangial cells [40].

TGF-β exhibits profibrotic effects during kidney interstitial fibrosis potentially via several mechanisms below: (1) As mentioned above, kidney-resident and -nonresident cells can transdifferentiate into myofibroblasts under the action of TGF-β. TGF-β treatment drives transdifferentiation of endothelial and epithelial cells in myofibroblast-like cells, whereas inhibiting TGF-β–SMAD signaling with antagonists or blockers ameliorates or reverses the development of EndMT or EMT [6, 41]. (2) TGF-β1 directly promotes generation of the ECM, including fibronectin and type I collagen, via dependent or independent of SMAD3 pathways. (3) TGF-β1 inhibits ECM degradation via MMPs inhibition but TIMPs induction. (4) TGF-β1 directly exerts effects on various kidney-resident cells to perform different functions; for instance, it induces fibroblast proliferation to generate more matrix or may promote tubular epithelial cells apoptosis, and this effect may cause more severe renal interstitial fibrosis and incur more damage to kidney diseases.

Not surprisingly, due to the importance of TGF-β signaling, therapeutic agents that inhibit TGF-β signaling have been shown to reduce matrix accumulation in animal models of diabetes, puromycin nephropathy, and UUO. Many potential therapeutic approaches based on inhibition of TGF-β have been tested in experimental models of CKD, such as the administration of neutralizing anti-TGF-β antibodies, a soluble TGF-β receptor, or small interfering RNAs that target TGF-β type II receptor. These therapies reduce structural renal injury and decrease renal fibrosis. In 2011, the results of a phase I clinical trial of fresolimumab, an anti-TGF-β antibody, revealed that this agent is well tolerated by patients with FSGS [42]. Phase II trials of another anti-TGF-β antibody, LY2382770, have been stopped early because of futility. Although TGF-β is generally considered a central mediator of fibrotic diseases, inhibition of TGF-β and of its downstream targets has a long way to go before adoption in the clinic.

2.4.3 Wnt Signaling Pathway

Wnt signaling has been recognized for its important functions not only in carcinogenesis but also in embryonic development and in the stem cell compartment. To date, 19 Wnt ligands and 15 receptors and coreceptors have been identified. Many Wnt ligands act through the canonical Wnt pathway in which β-catenin is a key mediator. The Wnt–β-catenin cascade is silenced in healthy adult kidneys and is reactivated in adult kidneys after injury. Aberrant activation of Wnt–β-catenin signaling is associated with proteinuria, renal function decline, and kidney fibrosis in many forms of CKD, regardless of whether the injury initially occurs in the renal tubulointerstitium or glomeruli [7, 43]. Wnt expression increases in the kidneys of animal models of CKD. Noncanonical Wnt pathways include the planar cell polarity (Wnt–PCP) and Wnt–Ca^{2+} signals. Due to the importance of Wnt–β-catenin signaling, we will focus on the involvement of this signaling in kidney fibrosis.

Increased Wnt activity has been observed in glomeruli of mouse models of CKD. Wnt expression increases in the podocytes of mice treated with Adriamycin, a drug that induces podocyte injury with features similar to those of FSGS [7]. Wnt expression increases in the podocytes of mice treated with adriamycin, a drug that induces podocyte injury with features similar to those of FSGS. Tail vein injection of exogenous Wnt1 into BALB/c mice exacerbates podocyte dysfunction, as evidenced by decreased protein levels of nephrin. Blocking Wnt signaling with DKK1 in adriamycin-injected mice ameliorates albuminuria and counteracts the decrease in nephrin levels [7]. Furthermore, a podocyte-specific knockout of β-catenin protects mice from adriamycin-induced podocyte injury, including albuminuria and podocyte FPE [7]. ICG-001 also can effectively attenuate proteinuria in a model of adriamycin-induced nephropathy. Wnt signaling elicits its biological effects by promoting the expression of many different target genes. Following Wnt's binding to a cell membrane receptor and induction of a series of downstream signaling events, active β-catenin is translocated into the nucleus, binds to TCF and/or LEF transcription factors, and recruits coactivators—including CREB-binding protein (CBP) or its closely related protein p300—to form a transcriptionally active complex. The latter promotes target genes expression, such as those encoding Snail1, RAS components, MMP-7, TRPC6, FSP1, PAI-1, and fibronectin. These target genes inhibit the expression of proteins associated with the podocyte slit diaphragm, facilitate cytoskeletal organization and contraction, or promote podocyte EMT or apoptosis, thereby leading to impairment of podocyte function and perturbing slit-diaphragm integrity under pathological conditions.

The levels of many Wnt proteins and Fzd receptors are evaluated in tubular epithelium in fibrotic kidneys. In CKD, Wnt and β-catenin not only show alterations of expression, but also participate in initiation and progression of kidney fibrosis. Overexpression active form of β-catenin in tubular cells provokes dedifferentiation of tubular cells and EMT in mice. Consistent with this result, reduced Wnt/β-catenin activation closely correlates with improvement of renal fibrosis. Interventions into Wnt signaling at different levels have been studied. DKK1 is a Wnt antagonist that binds to receptor LRP5 or LRP6 and inhibits the canonical Wnt pathway. Injection of a vector encoding DKK1 into a mouse model of kidney fibrosis reduces β-catenin accumulation and fibrosis. Similarly, inhibition of Wnt–β-catenin signaling by other antagonists including sFRP4, Klotho, and the small-molecule inhibitor ICG-001 represses myofibroblast activation and reduces renal interstitial fibrosis. Emerging evidence indicates that depending on the magnitude and duration of its activation, Wnt–β-catenin signaling performs a dual function: promoting repair or regeneration or facilitating progression to CKD after acute kidney injury (AKI). Transient activation of the Wnt–β-catenin pathway is renoprotective because it promotes adaptive repair and recovery, whereas sustained activation of the same signaling cascade is detrimental and triggers maladaptive responses, leading to the onset and

progression of CKD. Feng et al. have reported that Wnt–β-catenin signaling in macrophages stimulated by Wnt3a contributes to IL-4- or TGF-β-induced macrophage M2 polarization and the phosphorylation and nuclear translocation of STAT3 in vitro; by contrast, inhibition of Wnt–β-catenin signaling prevents these IL-4- or TGF-β1-induced processes. Mice with a macrophage-specific β-catenin knockout show decreased macrophage accumulation, attenuated M2 polarization, and alleviation of kidney fibrosis after UUO [44]. This evidence suggests that Wnt–β-catenin signaling in macrophages as well as in tubular cells and fibroblasts is likely to play a key role in the pathogenesis of interstitial fibrosis.

2.4.4 mTOR Signaling

mTOR, a highly conserved serine-threonine kinase, is recognized for a critical regulator of cell proliferation, cell growth, and metabolism. Mounting evidence exhibits that mTOR performs a pivotal function in the control of kidney cell homeostasis and autophagy. mTOR kinase exists in two distinct protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 as a "nutrient sensor" is activated by amino acids and suppressed by oxidative stress and energy depletion. mTORC1 is also regulated by growth factors and cytokines via phosphoinositide 3-kinase (PI3K) signaling pathway. Phosphatidylinositol (3, 4, 5) triphosphage (PIP3) generated by PI3K stimulates 3-phosphoinositide-dependent protein kinase 1 (PDK1), which promotes Akt (protein kinase B) activity via phosphorylating of the activation loop at threonine 308. Moreover, mTORC2-mediated phosphorylation of both the turn motif in AKT (Thr^{450}) and hydrophobic motif in ATK (Ser^{473}) stabilizes and activates Akt. The activation of tuberous sclerosis complex 1 (TSC1)-TSC2 negatively regulates mTORC1 and is directly inhibited by Akt-dependent phosphorylation. TSC1-TSC2 complex therefore serve as an intermediary between PI3K-Akt signaling and mTOR. TSC1 maintains but TSC2 suppresses the activity of the guanosine triphosphatase (GTPase) RAS homolog enriched in brain (Rheb) via its GTPase-activating protein activity. Rheb provokes mTORC1 activation when they are close to each other [45]. The mTORC2 kinase mainly controls many cellular parameters and processes, including protein synthesis, cell survival, rearrangement of cell cytoskeleton, and sodium homeostasis. Akt, serum, and glucocorticoid-induced kinase 1 (SGK-1), and protein kinase Cα (PKCα) are all substrates of mTORC2 [46]. Moreover, mTOCR2 can phosphorylate and sequester forkhead box proteins O1 (FOXO1) and FOXO3 via Akt [47]. The function of mTORC2 is not as clear as that of mTORC1 due to lack of specific inhibitor of mTORC2 kinase.

Rapamycin as mTOR inhibitor induces significant ultrastructural and molecular changes in podocytes including increased foot process width, decreased Nephrin and Podocin mRNA levels, which are associated with albuminuria in BALB mice with normal renal conditions. These manifestations are finally ameliorated at week 8 after rapamycin-treated groups [48]. By contrast, mice with adriamycin-induced nephropathy have significantly reduced proteinuria and preserve renal function, with only mild histological abnormalities [49]. Gene knockout approaches provide us to well understand the functions of mTORC1 and mTORC2 in podocyte. Genetic deletion of mTOCRC1 in mouse podocytes induces proteinuria and progressive glomerulosclerosis, weight loss, and increased mortality [50]. Genetic deletion of mTORC2 in mouse podocytes does not manifest significant phenotypic differences from littermate controls. This result is suggestive of a less important role of mTORC2 in podocytes. Nevertheless, abrogation of both mTORC1 and mTORC2 in podocytes precipitates an early fulminant proteinuric phenotype. This scenario may suggest that interaction between mTORC1 and mTORC2 may regulate podocyte development and homeostasis.

Conversely, podocyte-specific deletion of Tsc1 results in excessive mTORC1 activity, which can lead to severe pathological effects. Increased activation of mTORC1 causes

increased pS6 expression, glomerular hypertrophy, GBM thickening, podocyte foot process broadening and effacement, and proteinuria, which can be ameliorated by rapamycin [50]. mTORC1 excessive activation in podocytes also leads to the progression of glomerular crescents, which is abrogated by rapamycin treatment. In cellular crescents from patients with crescentic glomerular diseases, mTORC1 signaling is remarkably activated too [51]. A publication by Canaud G et al. reveals that activation of Akt2 as downstream of mTORC2 is essential to maintain podocyte viability and function during chronic kidney disease [52].

In vitro, mTOR signaling pathway in fibroblasts is exclusively activated by TGF-β via the TSC2, and rapamycin abolishes TGF-β-induced upregulation of Rheb-mTORC1 signaling in interstitial myofibroblasts. Genetically modified mice with either ectopic expression of Rheb or fibroblast-specific deletion of TSC1 exhibit activated mTORC1 signaling in kidney interstitial fibroblasts and increased renal interstitial fibrosis, which can be abrogated by rapamycin as well [53]. Mounting evidence have revealed that treatment with rapamycin after renal damage, regardless of etiology, slows the subsequent progression of interstitial fibrosis caused by ischemic-reperfusion injury (IRI), transplantation, UUO, and/or glomerulopathy.

Li et al. have found that RICTOR–mTORC2 signaling can be activated in normal rat kidney cells (NRK-49F cell line) treated with TGF-β1 in a time-dependent manner, whereas a knockdown of RICTOR with small interfering RNA inhibits the fibroblast activation characterized by the expression of fibronectin and smooth muscle actin. In vivo, mice with a fibroblast-specific knockout of RICTOR show lower collagen content and fibrosis, apoptosis, and inflammatory cell infiltration in the UUO kidney as compared with control littermates [54]. Our group has also reported that RICTOR–mTORC2 signaling activation in macrophages drives macrophage M2 polarization, a release of multiple profibrotic factors and proliferation, which eventually induce kidney interstitial fibrosis [55].

2.4.5 MicroRNAs (miRNAs)

MiRNAs are endogenous single-stranded non-coding RNA molecule (containing about 22 nucleotides). MiRNAs have multiple key roles in regulating various biological functions such as cell differentiation, proliferation, development, and immune responses. Thus, dysregulation of miRNAs seems to result in disturbances of target gene networks and signal transduction culminating in disease onset and/or development. The biogenesis of miRNAs is detailed well in many reviews [56]. RNA polymerases II and III are responsible for miRNA transcription to generate precursors that is cleaved into mature miRNA. The regulatory functions of miRNAs are executed by the RNA-induced silencing complex (RISC). The latter is assembled from miRNA and other components and is thus activated to target messenger RNA (mRNA) specified by the miRNA.

MiRNAs are crucial modulators of nephron development. Dicer is an important RNase III family enzyme cleaving precursor miRNAs into RNA duplexes during the biogenesis of miRNAs. Specific deletion of Dicer in podocytes leads to formation of FPE, proteinuria, interstitial fibrosis, glomerulosclerosis, and eventually the animal dies several weeks later due to renal failure [57]. Several miRNAs (miR-23b, miR-24, miR-26a, and the miR-30 family) are thought to be closely related with abnormalities of podocyte phenotype. The miR-30 family has been shown to target several mRNA that mediate podocyte apoptosis and cytoskeletal arrangement. Drosha is another important enzyme accounting for miRNA synthesis, and specific deletion of Drosha in podocytes present similar phenotypes as in mice with Dicer deficiency [58]. Dicer deficiency in renin-expressing juxtaglomerular cells reduces cell number [59]. These results support the important roles of miRNA in maintaining biological functions of nephron. In addition to podocytes, mesangial cells are regulated by miRNAs too. MiR-34a and miR-335 potentially induce mesangial-cell senescence by inhibiting mitochondrial antioxidative enzymes superoxide dismutase 2 and thioredoxin

reductase 2. Akt activation through PTEN downregulation by miRNA-216a and miRNA-217, which are regulated by upstream miR-192 and TGF-β, leading to glomerular mesangial-cell hypertrophy and survival, and playing important roles in diabetic changes in kidneys. Moreover, miR-377 overexpression in mesangial cells can trigger production of fibronectin and expansion of the mesangial matrix by downregulating serine-threonine protein kinase PAK1 and superoxide dismutase.

The regulation of miRNAs is closely associated with profibrotic cytokine TGF-β in interstitial fibrosis. MiR-382 is induced in UUO-induced obstructed kidneys as well as in cultured proximal tubular cells treated with TGF-β1. MiR-382 potentially suppresses Kallikrein 5, a crucial enzyme that mediates the degradation of ECM components. Thus, blockade of miR-382 via a locked nucleic acid inhibitor apparently attenuates kidney tubulointerstitial fibrosis [60]. Furthermore, TGF-β1 acts by causing SMAD3 to positively regulate miR-21 and miR-192 expression but negatively regulate the expression of miR-29 or miR-200 families, thereby mediating renal fibrosis [61], whereas SMAD7 can antagonize the miR-21 induction [62]. MiR-21 inhibition or deletion significantly reduces interstitial fibrosis after UUO possibly by targeting the lipid metabolic pathway regulated by peroxisome proliferator-activated receptor alpha (PPAR-α) [63]. In addition, the TGF-β cascade is responsible for the inhibition of miR-29 and miR-200 and for induction of miR-192 and miR-491-5p in the UUO model; these effects in turn promote the development of renal injury [62]. Besides, miR-192 is a major contributor to the phenotype switch of tubular cells during renal tubulointerstitial fibrosis. Additionally, it has been suggested that renal miR-433 expression induced by TGF-β promotes renal interstitial fibrosis [64]. MiR-200 and miR-141 are necessary for the development and progression of TGF-β1-dependent EMT and interstitial fibrosis in vitro and in vivo [65].

Of note, miRNAs are detectable in various body fluids such as saliva, tears, serum, and urine. And they are much more stable than mRNAs [66]. Based on this fact, clinically, miRNAs are likely to be used as biomarkers for diagnosis and prognostication of human diseases.

2.4.6 Hypoxia-Induced Factor (HIF)

HIF, known as a basic heterodimeric transcription factor, is composed of two protein subunits: HIF-α and HIF-β. In normal oxygen condition, HIF-α subunit is sensitive to oxygen and regulated by O2-dependent prolyl hydroxylation, which targets the protein for ubiquitylation by von Hippel-Lindau (VHL) tumor suppressor. Ubiquitylated HIF-α is rapidly targeted for degradation. Under hypoxic conditions or loss-of-function VHL, HIF-α does not undergo degradation and subsequently translocates into nucleus, where it binds to HIF-β to form constitutively active HIF. After binding to the cis-acting hypoxia-responsive element, HIF induces a variety of target gene expression, which are adaptive response to hypoxic conditions. More than that, HIF-regulated target genes involved in angiogenesis, erythropoiesis, and energy metabolism, also favor adaptation to oxygen depletion and oxygen delivery. As a transcription factor, HIF is involved in the regulation of many biological processes that facilitate both oxygen delivery and adaptation to oxygen deprivation by regulating genes that participate in glucose uptake, energy metabolism, angiogenesis, erythropoiesis, cell proliferation, apoptosis, cell–cell and cell–matrix interactions, and barrier function.

HIFs represent a critical initial signal for the inception of glomerular capillary morphogenesis [67]. In the settings of renal glomerular diseases, podocyte-specific activation of HIF induced by a VHL knockout induces activation and proliferation of podocytes and rapidly progressive glomerulonephritis and renal failure [68]. Likewise, HIF-α hyperstabilization induces widespread podocyte foot process broadening, GBM thickening, and ectopic deposition of collagen α1α2α1 (IV) in GBM humps beneath podocytes [69]. Endothelial cells are deeply involved in CKD. Nonetheless, the functions of HIF-1 and HIF-2 in the glomerular endothelium may be dif-

ferent in the different contexts of kidney diseases. In a kidney chronically injured by Ang II-induced hypertension, elevated endothelial HIF-1α amounts contribute to the initial glomerular injury, leading to hypertension and progression of renal fibrosis. Endothelial HIF-2, but not HIF-1, regulates renal inflammation likely through suppression of VCAM1 expression and protects from hypoxia-induced renal damage [70]. Studies by Kalucka et al. indicate that specific deletion of HIF-1α in endothelial cells of glomerular induces hypoxic cell death in vitro; however, a loss of HIF-1α in endothelial cells does not significantly effect on the development profile of kidneys and does not influence renal function or the expression of adhesion proteins in the pathogenesis of fibrosis after UUO [71].

Accumulating evidence highlights chronic hypoxia in the tubulointerstitium as a final common pathway to end-stage renal disease [72]. A fibrotic kidney with advanced renal disease is devoid of peritubular capillary blood supply to (and oxygenation of) the corresponding region. In this context, of note, hypoxia per se induces a fibrogenic response which would active renal microvascular endothelial cells, tubular cells, and interstitial fibroblasts. Hypoxia is also a profibrogenic stimulation for changing the ECM homeostasis of resident cells in kidney, and then leading to peritubular capillaries rarefaction. In the setting of hypoxia, tubular cells could transdifferentiate to myofibroblasts. In addition, severe and/or prolonged hypoxia can cause kidney epithelia dysfunction that accounts for energy metabolism imbalance and subsequent cell apoptosis. The reciprocal relation between hypoxia and development of renal failure may provide us new therapeutic strategies for patients with chronic kidney diseases.

2.4.7 Defective Energy Metabolism

The kidney uses a large amount of energy, most of which is dedicated to cell structure maintenance and solute reabsorption. ATP, which is called the molecular unit of intracellular energy currency, is essential for normal cellular processes. Disturbed production of ATP during energy metabolism, e.g., mitochondrial dysfunction or dysregulation of key metabolic enzymes by various insults, will cause a cellular structural abnormality, apoptosis, or differentiation.

Mitochondria supply most of ATP to the cell via their oxidative phosphorylation (OXPHOS) system. Mitochondria are highly dynamic organelles. One of the most unique features of mitochondria is fusion and fission. Frequent cycles of fusion and fission adapt the morphology of the mitochondrial compartment to metabolic needs of the cell. Once the balance between fusion and fission is lost, the cellular functions change. Meanwhile, mitochondrial biogenesis and the regulation of OXPHOS are important for satisfying the specific energy demand of specialized cells. PGC-1α itself is a master cotranscriptional regulator that induces mitochondrial biogenesis by activating various transcription factors. Besides energy supply, mitochondria contribute to calcium signaling, ROS production, and redox homeostasis.

On the other hand, β-oxidation of free fatty acids is one of the major sources of ATP production, particularly in the proximal tubule, which has high energy demand and relatively low glycolytic capacity. Several old studies indicate that ~60% of the energy in kidneys comes from burning of fatty acids. The energy production of fatty acid β-oxidation is high: on average 106 ATP equivalents per fatty acid molecule, as opposed to 36 during oxidation of carbohydrates. The high energy consumption of the proximal tubule is due to the workings of fluid and electrolyte homeostasis, active solute secretion, and hormone production. Sometimes, glycolysis contributes to energy production too, under certain circumstances. Although this metabolic pathway is a less efficient producer of ATP as compared with mitochondria, glycolysis has several advantages. One is glycolysis that can generate additional energy when mitochondria show maximum performance. Another is generation of side products, including amino acids, nucleic acids, and lipids. Nonetheless, under stress, a switch to glycolysis may influence cellular biological functions.

The regulators of energy metabolism help to balance the energy production and consumption for energy homeostasis. AMPK has been identified as the critical molecule for the regulation of metabolism in various cells. AMPK can be activated during energy stress in response to a rise in the AMP/ATP ratio. AMPK is known to be the substrate of LKB1; the latter serves as a crucial metabolic checkpoint factor and arrests cell cycle in response to low intracellular ATP concentration, e.g., during low nutrient availability. Thus, the LKB1–AMPK axis, as the key energy metabolism regulator, plays a vital role in cellular energy homeostasis. mTOR is one of the main players that controls energy-consuming cellular processes such as cell growth and proliferation. mTOR as one of the main regulators controls energy-consuming cellular processes including cell proliferation and growth. mTOR contributes to the increase in oxygen consumption, mitochondrial membrane potential, ATP-synthetic capacity, and mitochondrial content. Thus, mTOR and AMPK coordinately regulate cellular energy homeostasis. mTOR increases mitochondrial membrane potential, oxygen consumption, ATP-synthetic capacity, and mitochondrial content. Therefore, there is a complex relation between AMPK and mTOR in terms of regulating cellular energy homeostasis.

Podocytes have many highly specialized foot processes, which require high energy consumption to maintain their structure and functions. In fact, a considerable number of mitochondrial sections are observed in the narrow peripheral foot processes. Morphological changes of mitochondria are exclusively observed in podocytes among glomerular cells in patients with mitochondrial cytopathy [73]. Mitochondrial activity loss manifesting itself as a smaller energy supply may be accompanied by increased ROS production, thus causing or accelerating podocyte injury. Furthermore, studies suggest that a reduction in the amount of mitochondrial DNA (mtDNA, which is involved in mitochondrial biogenesis and function in podocytes) is associated with the pathogenesis of podocyte injury. CoQ-deficient mice with Pdss2 conditionally knocked out only in podocytes have proteinuria and podocyte FPE [74]. In these mice, mitochondrial OXPHOS capacity is impaired. Research indicates that free-fatty acid accumulation in podocytes is toxic and induces endoplasmic-reticulum stress and podocyte death. Stimulation of fatty acid oxidation by AMPK activators can abrogate the detrimental effect of free-fatty acid accumulation. In contrast, inhibition of fatty acid oxidation by CPT-1 inhibitor etomoxir increases the toxic effect of palmitic acid on podocytes [75]. Proteins involved in the transport and oxidation of fatty acids are affected in podocytes of puromycine aminonucleoside (PAN) glomeruli [76]. It is also reported that glycolysis acts as a supplier of ATP in mouse podocytes although the main supplier is mitochondria and their OXPHOS system [77]. The podocyte's dependence on glycolysis for ATP production might change in pathological conditions.

Mitochondrial abnormality facilitates the progression of renal interstitial fibrosis, particularly due to a reduction in mtDNA copy number, a loss of mitochondrial membrane potential, and a drop of ATP production. Mitochondrial dysfunction is involved in the apoptosis and EMT of renal tubular epithelial cells and in ROS production, thereby contributing to the fibrogenic process. Stimulation of mitochondrial biogenesis by restoring cAMP levels by means of PDE4 inhibitor rolipram ameliorates UUO-induced renal fibrosis [78]. Emerging evidence suggests that defective energy metabolism—including fatty acid oxidation and glucose metabolism—is associated with CKD [79]. Impaired energy metabolism in general, and reduced fatty acid oxidation in particular, are prominent and consistent features of CKD in both human biopsy samples and several animal models. Additionally, the above study has revealed that the increased tubule-specific triglyceride concentration and higher long-chain fatty acid content after overexpression of CD36 do not induce significant renal fibrosis. These findings indicate that a defect in β-oxidation of free fatty acids is crucial for CKD development [79]. Kang et al. have reported that TGF-β1 can inhibit PPAR-α and PPARGC1A to induce EMT. In another study, the AMPK activator 5-aminoimidazole-4-carboxamide-1β riboside (AICAR) inhibited the activation of myofibroblasts both in a UUO model and in response to stimulation of NRK-49F cells by TGF-β1 [80]. Recently, Ding et al. discovered

that a switch of metabolism from OXPHOS to aerobic glycolysis (Warburg effect) in renal fibroblasts is the primary feature of fibroblast activation during UUO-induced renal interstitial fibrosis [81]. In addition, suppression of renal fibroblast aerobic glycolysis significantly reduces UUO-induced interstitial fibrosis [81].

Meanwhile, an imbalance among regulators of energy metabolism may also contribute to CKD. A loss of LKB1 in the distal tubular cells causes CKD characterized by increased matrix deposition [82]. That study has revealed that energy metabolism is diminished in LKB1 renal tubular knockout mice with CKD, and this phenomenon could be retarded by treatment with either the AMPK agonist A769662 or a PPAR-α agonist, fenofibrate. In agreement with this finding, the reduction in AMPK expression both in kidney cell lines—and in AMPK-a2-null mice subjected to UUO—increases levels of markers of EMT and fibrosis. Others have also found that after various profibrotic stimuli, including TGF-β, Ang II, aldosterone, or high glucose and albumin levels, EMT is suppressed by the AMPK activators metformin and AICAR.

2.5 Conclusion

The pathophysiology of CKD is largely dependent on the primary insult, but common pathways exist across almost all subsets of kidney disorders. The pathophysiological mechanisms of CKD mentioned above actively participate in the development and progression of CKD (Fig. 2.2); however, other cytokines or mechanisms such as CTGF, FGF, autophagy, oxidative stress, Notch signaling, and VEGF signaling (which have not been mentioned) are equally important. Our goal in the study on the pathophysiology of CKD is to find approaches to effective therapy for CKD, but no new medicines have been registered for the treatment of CKD since 2001. This situation also means (from another perspective) that the pathogenesis of CKD is intricate. It is necessary to control the prevalence of kidney disease in many ways worldwide, including prevention of CKD onset, earlier diagnosis of CKD, timely evaluation and management of patients with CKD, and prevention and management of complications. Of course, broad collaboration of academia and the industry may help to develop novel therapeutics for CKD.

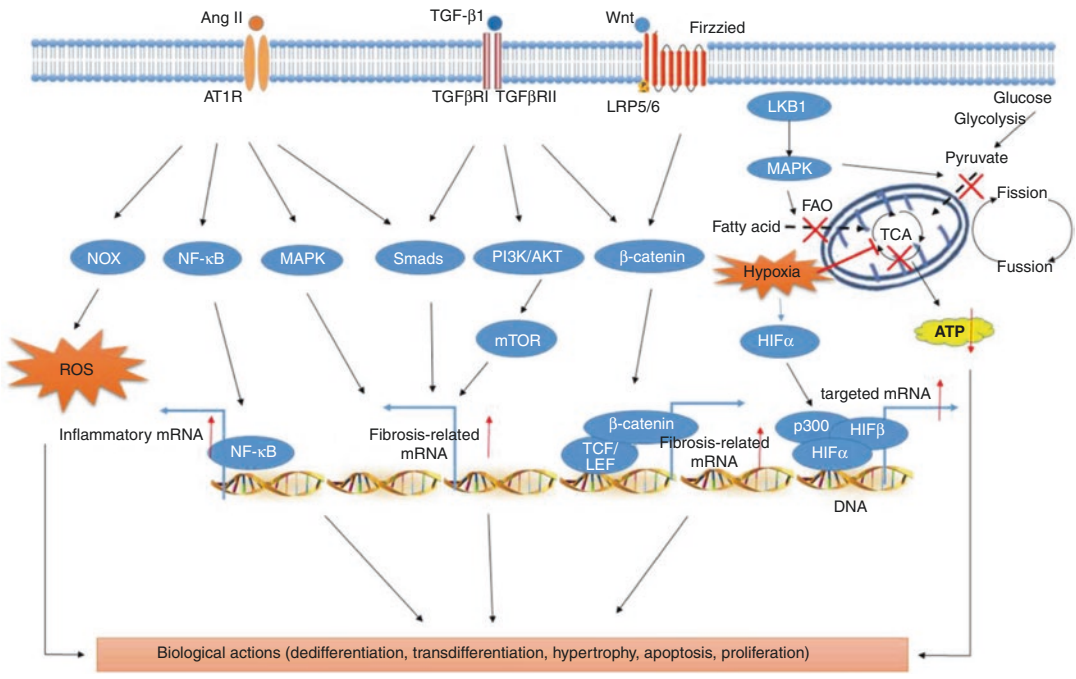

Fig. 2.2 Schematic presentation for molecular mediators or signaling pathways involved in the progression of chronic kidney disease

Key Messages

- CKD is characterized by histopathological changes that comprise renal inflammation, glomerulosclerosis, tubular atrophy, tubulointerstitial fibrosis, and capillary rarefaction.
- Podocyte injury or mesangial-cell expansion and/or proliferation are common cellular pathways for the progression of glomerulosclerosis. Infiltration by inflammatory cells and fibroblast activation and formation from various cell types contribute to tubulointerstitial fibrosis. A reciprocal relation of glomerulosclerosis and interstitial fibrosis is consistent with the above, accounting for progressive CKD.
- Many molecular mediators or signaling pathways related to CKD have been identified so far, including the RAAS, TGF-β signaling, CTGF, oxidative stress, miRNAs, HIF, Wnt–β-catenin signaling, mTOR signaling, and defective energy metabolism.

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Diabetic Kidney Disease

3

Ting Cai and Junwei Yang

Abstract

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) and is strongly associated with mortality in patients with diabetes. Persistent albuminuria is the hallmark of DKD, and some patients will finally develop ESRD with gradually decreased glomerular filtration rate (GFR) and increased serum creatinine concentration. Glomerular basement membrane thickening, mesangial expansion, mesangial matrix accumulation, Kimmelstiel–Wilson nodules, and tubulointerstitial fibrosis are typical pathological changes in DKD. Screening for DKD should begin at 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes, which should include measurement of urinary albumin-to-creatinine ratio and serum creatinine concentration, estimation of GFR, and ophthalmologic examination. The progression of DKD may be slowed by optimal therapeutic approaches, including lifestyle improvement, strict glycemic and blood pressure control, control of dyslipidemia, and renin–angiotensin–aldosterone system blockade. Patients who develop ESRD require renal replacement therapy.

3.1 Introduction

Diabetes mellitus, a disease no longer associated with affluence, is on the rise across the world. More than 425 million individuals currently have diabetes, and this number may increase to 693 million by 2045 if nothing is done [1]. The incidence of diabetic kidney disease (DKD) has more than doubled in the past decade, largely because of the increasing prevalence of type 2 diabetes. As a potential devastating complication of diabetes, DKD is currently the primary cause of end-stage renal disease (ESRD) and is the single strongest predictor of mortality in patients with diabetes that globally imposes an increased social and economic burden [2].

3.2 Natural Course of DKD

In the conventional course of DKD, pathological changes develop progressively over a long clinical silent period without evidence of proteinuria, impaired glomerular filtration rate (GFR), or hypertension. An increase in GFR, or hyperfiltration, is one of the earliest changes which is

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Table 3.1 Urinary ACR is a diagnostic test for microalbuminuria and macroalbuminuria

Condition	Urinary ACR (mg/g)	Terms
Normoalbuminuria	<30	Normally to mildly increased
Microalbuminuria	30–300	Moderately increased
Macroalbuminuria/ overt proteinuria	>300	Severely increased

ACR albumin-to-creatinine ratio

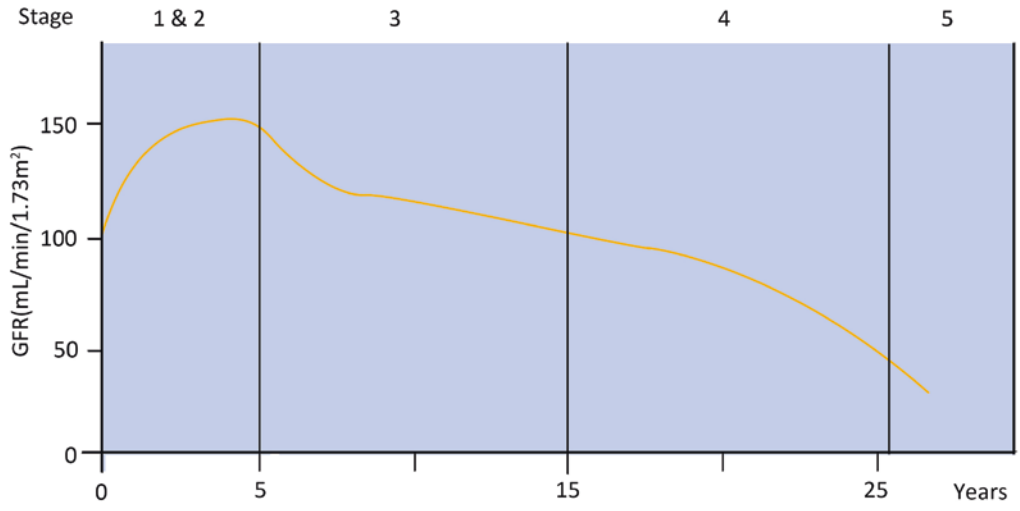
observed in most patients with type 1 diabetes and many with type 2 diabetes. Hyperfiltration is accompanied by renal hypertrophy, an increase in renal size. The next observable clinical manifestation is the development of microalbuminuria. A urinary albumin-to-creatinine ratio (ACR) between 0 and 30 mg/g and between 30 and 300 mg/g is customarily referred to as normoalbuminuria and microalbuminuria, respectively (Table 3.1). Microalbuminuria is currently accepted as a reliable marker to detect DKD at an early stage. However, not all patients with microalbuminuria will develop overt proteinuria and reduced GFR. Caramori et al. reviewed a number of clinical trials and revealed that only 30–40% of patients with microalbuminuria will develop macroalbuminuria (also called overt proteinuria, defined as urinary ACR >300 mg/g) (Table 3.1) [3]. Patients with established microalbuminuria may have different outcomes: they may improve, stay the same for a long period, or progress to macroalbuminuria and worse renal function. Perkins et al. reported as high as 50% probability for microalbuminuria to regress to normal levels in patients with type 1 diabetes [4].

Proteinuria, first characterized by Kimmelstiel and Wilson in a pathological report, results from complex damage in the glomerular filtration barrier, including the endothelial cells, basement membrane, and podocytes [5]. Proteinuria not only is a marker of glomerular injury but also implicates tubular injury. The natural course of DKD, proposed by Mogensen, including changes in proteinuria and GFR, as well as stages of preventive treatment, is shown in Fig. 3.1 [6]. In patients with type 1 diabetes, the average time from diagnosis of diabetes to onset of proteinuria is 19 years; in contrast, it is shorter and variable in patients with type 2 diabetes, as the disease may have already been present for several years prior to the establishment of diagnosis. Renal function may loss progressively over several years in patients with type 1 diabetes without intervention. Despite advances in interventions that slow down the progression of DKD, the number of patients progressing to renal failure is still increasing, making diabetes the major cause of ESRD [2].

3.3 Renal Pathology in DKD

After the onset of diabetes, kidney weight and size keep increasing until the establishment of overt nephropathy. Glomerular basement membrane (GBM) thickening is the first change that can be measured. Mesangial expansion (Fig. 3.2) develops later due to increased matrix accumulation in the mesangial region [7]. When renal dysfunction occurs, increased mesangial expansion and marked GBM thickening can be observed. Diffuse mesangial expansion can be linked with nodular lesions containing areas of marked mesangial expansion forming large round fibrillar mesangial zones with palisading of mesangial nuclei around the nodules and compression of the associated glomerular capillaries (Kimmelstiel–Wilson nodules) (Fig. 3.3). The severity of glomerular damage is associated with GFR and albuminuria.

Renal tubules and interstitium may also undergo structural changes, particularly in the later stages of DKD. The thickening of the tubular basement membrane (Fig. 3.2) closely correlates with the thickening of the GBM. Tubulointerstitial fibrosis and tubular atrophy may be the best pathologic predictors of progressive loss of GFR, which are more universal in patients with type 2 diabetes. In fact, the renal pathologic change is heterogeneous in patients with type 2 diabetes; only a subset of patients with type 2 diabetes has typical diabetic glomerulopathy, whereas a considerable proportion has



Stage	Pre (1&2)	Incipient DKD (3)	Overt DKD (4)	ESRD (5)
Structural changes	Hypertrophy GBM thickening	GBM thickening Mesangial expansion	Mesangial nodules (Kimmelstiel-Wilson nodules)	Glomerular closure Fibrosis
GFR	Increased by 20–50%	Supranormal values, predicted to decline if untreated	Decline ~10 mL/ min /1.73 m^2 / year	<10 mL/min/1.73 m^2
Urinary protein	Normal or occasional microalbuminuria	Microalbuminuria	Nephrotic proteinuria (>3.5 g /24h)	Often decline due to nephron loss
BP	Normal	Hypertension	Hypertension	Hypertension

Fig. 3.1 Nature course of diabetic kidney disease. *GFR* glomerular filtration rate; *DKD* diabetic kidney disease; *GBM* glomerular basement membrane; *BP* blood pressure

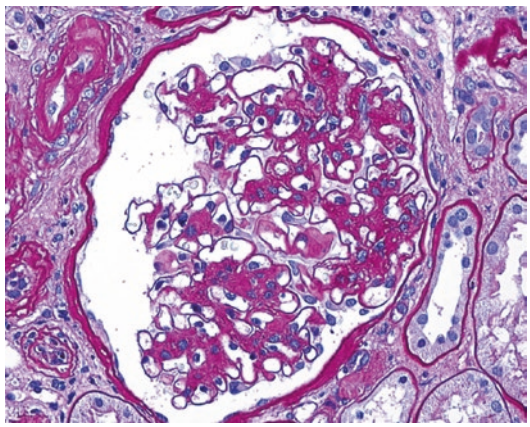


Fig. 3.2 Histopathological manifestations in diabetic kidney disease. Mesangial expansion and mesangial matrix accumulation are presented. (periodic acid-Schiff staining, ×400)

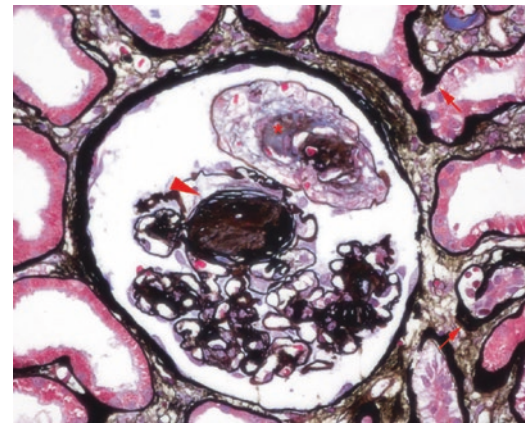


Fig. 3.3 Histopathological manifestations in diabetic kidney disease. Typical Kimmelstiel-Wilson nodule (arrowhead), dissolve of mesangium (star) and thickening of TBM (arrow) are presented. (methenamine silver staining, ×400)

more advanced tubulointerstitial and vascular damage [8]. Furthermore, the appearance of the kidney in some patients with type 2 diabetes is more suggestive of glomerular ischemia or tubulointerstitial disease.

3.4 Diagnosis of DKD

The main basis of the diagnosis of DKD is the test values of urinary protein excretion and estimated GFR (eGFR). Renal injury may be considered to be caused by diabetes in most patients with diabetes who have any of the following features [9]:

- Macroalbuminuria
- Diabetic retinopathy accompanied with microalbuminuria
- Microalbuminuria in patients diagnosed with type 1 diabetes for more than 10 years

Screening for DKD should begin at 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes. Patients with diabetes may annually undergo screening for DKD, which should include measurement of urinary ACR and serum creatinine concentration, estimation of GFR, and ophthalmologic examination (Fig. 3.4).

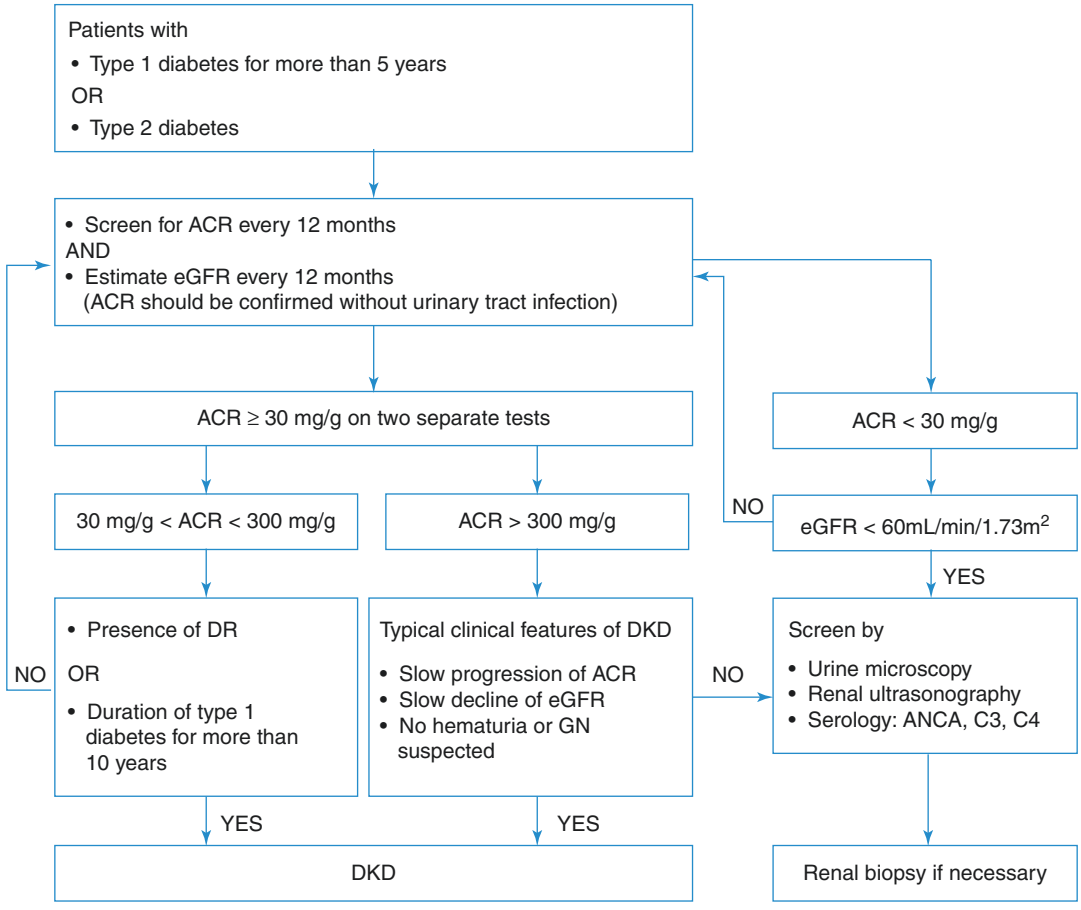


Fig. 3.4 Flowchart for the evaluation of DKD in patients with diabetes. *ACR* albumin-to-creatinine ratio; *eGFR* estimated glomerular filtration rate; *DR* diabetic retinopathy; *GN* glomerulonephritis; *DKD* diabetic kidney disease; *ANCA* anti-neutrophil cytoplasmic antibody; *C3* complement 3; *C4* complement 4

3.4.1 Measurement of Urinary ACR

Microalbuminuria is accepted as an independent risk factor associated with the progression of chronic kidney disease (CKD) and GFR loss. Measurement of microalbuminuria is currently widely available and easy to perform with relatively low cost. As the interpretation of results for albumin concentration alone may be unreliable due to variations in urinary concentration and timed collections are inconvenient, the ACR in a spot urine sample (preferably the first morning specimen) is recommended. Metabolic perturbation, hemodynamic factors, and presence of urinary tract infection may affect the appearance of albumin in the urine [10]. Hence, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that elevated ACR be confirmed in the absence of marked hypertension, urinary tract infection, and cardiac failure with two additional tests during the next 3–6 months [9].

3.4.2 Measurement of Serum Creatinine Concentration and eGFR

In clinical practice, the serum creatinine concentration is the most frequently used index to evaluate renal function. However, it is not sensitive enough and may be highly misleading when patients have low muscle mass, especially in elderly patients with diabetes. Therefore, the KDOQI guidelines recommend that the GFR be estimated with the Modification of Diet in Renal Disease Study equation; however, the evidence shows that the usefulness of eGFR alone as a regular screening test for CKD in diabetes is less secure [9].

3.4.3 Ophthalmologic Examination

A study including a cohort of patients with type 1 diabetes and with type 2 diabetes revealed that a large proportion of patients with type 1 diabetes and macroalbuminuria also showed signs of diabetic retinopathy, whereas nearly half of the patients with hypertension and type 2 diabetes who had macroalbuminuria did not have concomitant retinopathy [11]. Thus, the presence of retinopathy and macroalbuminuria in patients with type 1 diabetes strongly suggests DKD. In contrast, as for patients with type 2 diabetes, the accompanied presence of retinopathy is only partly useful in the discrimination of renal pathology, and the absence of retinopathy does not rule out the presence of DKD.

3.4.4 Indications for Renal Biopsy

Due to the variability in clinical course and complexity of clinical manifestation, renal biopsy is required for some patients with both diabetes and CKD to discriminate the potential cause of the kidney disease. Renal biopsy should be considered in the following patient situations:

1. eGFR rapidly declines, or renal dysfunction without significant proteinuria is observed.
2. The onset of proteinuria is sudden and progresses rapidly, particularly in patients with duration of type 1 diabetes <5 years. Alternatively, the evolution of proteinuria is atypical (e.g., nephrotic syndrome develops in the absence of persistent microalbuminuria).
3. The presence of macroscopic hematuria or active nephritic urinary sediment containing acanthocytes and red blood cell casts, which suggests glomerulonephritis, is detected.

3.5 Management of Patients with Diabetes and CKD

For patients with diabetes, when GFR <60 mL/min/1.73 m^2, complications of CKD should be evaluated, which commonly include electrolyte imbalance, metabolic acidosis, anemia, secondary hyperparathyroidism, and CKD–mineral bone disorder. Adjustment of drugs' dosage is necessary (Table 3.2).

Table 3.2 Management of patients with diabetes and CKD according to GFR

GFR (mL/min/1.73 m^2)	Recommendation
All patients with diabetes	Screen for serum creatinine, ACR, eGFR, and serum potassium every 12 months
45–60	Consideration of dose adjustment of drugs in use
	Screen for eGFR every 6 months
	Screen for serum electrolyte (Ca, P included), acid alkali balance, hemoglobin, and parathyroid hormone
	Evaluation of vitamin D
	Consideration of test for bone mineral density
	Nutritional consultation
	Referral to nephrologist when diabetes with non-DKD or the cause of CKD is unknown
30–44	Screen for eGFR every 3 months
	Screen for serum electrolyte (Ca, P included), acid alkali balance, hemoglobin, parathyroid hormone, albumin, and weight
	Consideration of dose adjustment of drugs in use
<30	Referral to nephrologist

GFR glomerular filtration rate; *ACR* urinary albumin-to-creatinine ratio; *eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease; *DKD* diabetic kidney disease

3.5.1 Treatment of DKD

Interventions deemed useful in preventing the progression of DKD include lifestyle improvement, strict glycemic and blood pressure (BP) control, control of dyslipidemia, and renin–angiotensin–aldosterone system (RAAS) blockade. Patients who develop ESRD may require renal replacement therapy (Fig. 3.4).

3.5.1.1 Lifestyle Improvement

The KDOQI guidelines recommend a dietary protein intake of 0.8 g/kg body weight per day for individuals with diabetes and stage 1–4 CKD [9]. For patients with diabetes on hemodialysis (HD), 1.3 g/kg weight per day is suggested. Smoking should immediately be stopped upon the diagnosis of diabetes.

3.5.1.2 Glycemic Control

Hyperglycemia is the primary cause of DKD. Strict glycemic control through insulin or islet cell transplantation improves hyperfiltration, hyperperfusion, and glomerular capillary hypertension and decreases urinary albumin excretion in experimental diabetic animals. Moreover, strict glycemic control slows the development and progression of DKD in patients with diabetes.

In the Diabetes Control and Complications Trial (DCCT), patients with type 1 diabetes who received intensive therapy (average hemoglobin A1c [HbA1c] level of 7.2%) showed a 39% lower risk of developing microalbuminuria when compared to patients who received conventional therapy (average HbA1c level of 9.1%) at 6.5-year follow-up. Furthermore, patients receiving intensive therapy showed a 54% reduction in progression from microalbuminuria to macroalbuminuria [12]. At the end of the DCCT, all patients in the previous two groups received intensive therapy, and nephropathy was evaluated based on urine specimens at 3 and 4 years after the original DCCT. The average HbA1c level was 8.2% in the previous conventional therapy group, and 7.9% in the previous intensive therapy arm. However, the intensive therapy group still has advantage over the former conventional therapy group with an 86% lower risk of new-onset albuminuria. More recently, data from the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study suggested a 50% reduction of the long-term risk of impaired GFR in patients undergoing intensive therapy as compared to their counterparts receiving conventional therapy [13].

A number of major studies have also reported a lower risk of DKD in patients with type 2 diabetes undergoing stricter glycemic control. As shown in the United Kingdom Prospective Diabetes Study (UKPDS), newly diagnosed patients with type 2 diabetes were randomly divided into intensive therapy (HbA1c level of 7.0%) treated with sulfonylurea or insulin and conventional therapy (HbA1c level of 7.9%) with diet alone [14]. The reduction in the risk of developing microalbuminuria over 9 years and of

progression from microalbuminuria to proteinuria was 24% and 42%, respectively, in the intensive therapy group. After study termination, patients were observed for another 10 years. Although the HbA1c level between the two groups was comparable within 1 year, lower risk of microvascular disease and myocardial infarction persisted. This phenomenon of prolonged beneficial effects on complications of diabetes achieved through strict glycemic control even being followed by less intensive glycemic control has been described as "metabolic memory" or "legacy effect."

Considering the impressive results from several major clinical trials, the American Diabetes Association (ADA) suggests an HbA1c level of <7% for all patients with diabetes in order to reduce their risk of developing DKD [15]. The target blood glucose level can be achieved through treatment with insulin, oral hypoglycemic drugs, or a combination of both. Insulin can be used at any stage of DKD. However, oral hypoglycemic drugs should be carefully used according to one's renal function (Table 3.3) [16]. The use of most first- and second-generation sulfonylureas should be avoided when the eGFR is ˂60 mL/min/1.73 m^2. Biguanides (metformin) should not be used if GFR is <30 mL/min/1.73 m^2 or the serum creatinine concentration is >1.5 mg/dL in men and >1.4 mg/dL in women. Thiazolidinediones can be safely used in patients with DKD.

3.5.1.3 BP Control

In patients with type 1 diabetes, microalbuminuria is typically prior to hypertension. Conversely, hypertension may have already been present in some patients with type 2 diabetes when microalbuminuria is detected [17]. The appropriate BP at which therapy should be started, and the target of BP are topics that are still under debate. Higher BP is associated with increasing albuminuria and higher risk of renal failure in diabetes. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure trial, patients with type 2 diabetes were assigned to receive either intensive treatment with a systolic BP goal of <120 mmHg or standard therapy aim-

Table 3.3 Dose adjustment of oral hypoglycemic drugs in patients with diabetes and CKD

Medication class and agents	CKD stages 3, 4, and 5
First-generation sulfonylureas	
• Acetohexamide	• Avoid using
• Tolazamide	• Avoid using
• Tolbutamide	• Avoid using
Second-generation sulfonylureas	
• Glipizide	• No dose adjustment
• Gliclazide	• No dose adjustment
• Glyburide	• Avoid using
• Glimepiride	• Start carefully with a dose of 1 mg daily
Meglitinides	
• Repaglinide • Nateglinide	• Start carefully at 0.5 mg with meals when GFR <30 mL/min/1.73 m^2 • Start carefully at 0.5 mg with meals when GFR <30 mL/min/1.73 m^2.
Biguanides	
• Metformin	• Avoid using if serum creatinine >1.5 mg/dL in men, or >1.4 mg/dL in women, suggested by the US FDA • Avoid using when GFR <30 mL/min/1.73 m^2, recommended by British National Formulary and the Japanese Society of Nephrology
Alpha-glucosidase inhibitors	
• Acarbose	• Avoid using when GFR <30 mL/min/1.73 m^2.
DPP-4 inhibitor	
• Sitagliptin	• GFR >50 mL/min/1.73 m^2: 100 mg daily
	• GFR 30–50 mL/min/1.73 m^2: 50 mg daily (1/2 of regular dose)
	• GFR <30 mL/min/1.73 m^2: 25 mg daily (1/4 of regular dose)
• Saxagliptin	• GFR >50 mL/min/1.73 m^2: 5 mg daily
	• GFR ≤50 mL/min/1.73 m^2: 2.5 mg daily
• Linagliptin	• No dose adjustment
• Vildagliptin	• GFR ≥50 mL/min/1.73 m^2: 50 mg twice daily
	• GFR <50 mL/min/1.73 m^2: 50 mg daily (1/2 of regular dose)

CKD chronic kidney disease; *FDA* Food and Drug Administration; *GFR* glomerular filtration rate; *DPP-4* dipeptidyl peptidase 4

ing for <140 mmHg [18]. However, no difference in the risk of major cardiovascular events was observed between the two groups. In a secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT), progressive systolic BP decline up to 120 mmHg was associated with increased renal survival, but with higher mortality [19]. Thus considering the detrimental effect of high BP on renal function and from a safety concern, the National Kidney Foundation (NKF) and ADA have recommended an optimal BP target of <130/80 mmHg for renal and cardiovascular benefit in patients with diabetes who have nephropathy. As for patients with diabetes and ACR <30 mg/g, a BP target of 140/90 mmHg or less is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) and Eighth Joint National Committee guidelines.

Patients with BP >120/80 mmHg should be suggested on BP reduction through lifestyle changes, which consist of weight loss, decreased sodium intake, and increased physical excise, among others. Patients with confirmed BP >140/80 mmHg should initiate pharmacological therapy promptly to reach the optimal BP. Treatment of hypertension may require selection from several different classes of antihypertensive drugs, and combination therapy is recommended with special considerations for hypertensive patients with diabetes. Pharmacological therapy should include a RAAS blocker (either an angiotensin-converting enzyme inhibitor [ACEI] or an angiotensin receptor blocker [ARB]); in addition, it is recommended to titrate up to the maximum approved dose if tolerated. Diuretics, calcium channel blockers, and β-blockers can be used as additional therapy to achieve the BP target goal in patients already treated with a RAAS blocker or as alternative therapy in individuals with poor tolerance of these drugs.

3.5.1.4 RAAS Blockade

In patients with diabetes who have established DKD, RAAS blockade using ACEIs or ARBs confers preferential renoprotection independent of BP reduction. Several clinical trials investigating a series of progressive kidney diseases have shown the value of ACEIs in slowing disease progression. In the Collaborative Study Group trial, which evaluated the renoprotective properties of captopril among patients with type 1 diabetes, captopril decreased urinary albumin excretion and delayed the progression of kidney disease compared with the placebo, although no difference of the median BP was observed between the two groups [20]. Other randomized controlled trials have reported that reduction in proteinuria appears to delay the progression of kidney disease among patients with overt nephropathy.

For patients with type 2 diabetes, results from different clinical studies are less consistent and flawed, possibly due to smaller sample sizes and the use of surrogate outcomes. Furthermore, the protective property of decreasing urinary albumin excretion seems to be less significant in patients with type 2 diabetes and DKD. Long-term benefit achieved from ACEIs was best shown in a 7-year study which compared the effects of enalapril and placebo in normotensive patients with type 2 diabetes who had microalbuminuria. The study period covered 5 years for the comparison between ACEI and placebo, followed by another 2 years, at which period patients could choose either enalapril or placebo. Initial therapy with enalapril stabilized renal function and urinary albumin excretion and reduced the risk of nephropathy by 42%. Urinary albumin excretion increased among patients initially treated with enalapril after stopping ACEI therapy but decreased among those treated with placebo who chose enalapril therapy [21].

ARBs share many effects with ACEIs and have a superior safety property, which includes lower risk of cough, angioedema, and hyperkalemia. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial (RENAAL) compared losartan with conventional antihypertensive therapy in patients with type 2 diabetes and DKD. Fewer patients treated with losartan attained the primary composite endpoint of doubling of serum creatinine concentration, ESRD, or death; moreover, proteinuria level was reduced with losartan [22]. In the IDNT, irbesartan also showed renoprotective properties as compared to the calcium channel

blocker or placebo [23]. Concerning the shared RAAS-inhibiting effects of ACEIs and ARBs, both are believed to be effective in the treatment of DKD.

3.5.1.5 Lipid-Lowering Therapy

Dyslipidemia is prevalent in patients with DKD. It can promote the development of DKD. In non-dialysis patients with type 2 diabetes and DKD, treatment with statins provides marked cardiovascular benefit. A recent meta-analysis suggested a slight positive effect of statins on albuminuria and renal function. The KDIGO Clinical Practice Guideline for Lipid Management in CKD recommends treatment with statins for adult patients with diabetes and CKD who are not treated using chronic dialysis.

3.5.1.6 Renal Replacement Therapy

Available renal replacement modalities for patients with diabetes who have GFR <15 mL/min/1.73 m^2, uncontrolled heart failure, or hyperkalemia include peritoneal dialysis (PD), HD, and renal transplantation. Patients with diabetes on HD have lower rate of hospitalization and infection but higher rate of intradialytic hypotension and cardiac death than those on PD. PD is a better option for those with sclerosed forearm vessels, which seems to have a higher survival rate than HD in patients with diabetes who have residual renal function, except for the very elderly, and facilitates BP control and prevention of heart failure owing to slow and sustained ultrafiltration [24, 25]. However, PD is less effective than HD, and patients on PD are prone to protein loss and obesity.

3.5.1.7 Emerging Therapies

Considering the complex pathophysiology of diabetes and DKD, a number of new therapeutic agents to prevent or treat DKD have been attempted.

- Sodium–Glucose Cotransporter (SGLT) 2 Inhibitor

  The kidney reabsorbs all filtered glucose through SGLT1 and SGLT2, with SGLT2 being responsible for most of this task. SGLT2 inhibitors reduce glucose reabsorption, thereby decreasing blood glucose levels, and are the only insulin-independent glucose-lowering drugs. Currently, empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin are approved by the FDA. In experimental diabetic mice, SGLT2 inhibitor was shown to decrease hyperfiltration independent of reduction in blood glucose level. In addition, SGLT2 inhibitor may reduce early kidney growth and inflammation by lowering the blood glucose level. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) study, patients with type 2 diabetes at high cardiovascular risk were assigned to receive placebo or empagliflozin at a target dose of 10 mg or 25 mg [26]. Compared with placebo, empagliflozin decreased the risk of new-onset of or worsening nephropathy by 39%. Also, patients who received empagliflozin had a lower rate of doubling of serum creatinine concentration, initiation of renal replacement therapy, and death due to kidney disease. In addition to the EMPA-REG OUTCOME study, several studies investigating the effects of SGLT2 inhibition on cardiovascular and kidney outcomes are underway, which will be issued in the next few years. The findings of these studies will complement those of the EMPA-REG OUTCOME study and help in further understanding the therapeutic potential and safety of SGLT2 inhibition.
- Bardoxolone Methyl

  Bardoxolone methyl is a synthetic compound derived from oleanolic acid, which activates the Keap1–Nrf2 pathway and regulates inflammation in the kidney. In the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) study, patients with CKD and diabetes were randomly assigned to receive either bardoxolone methyl or placebo for 52 weeks [27]. Bardoxolone methyl significantly increased the mean eGFR compared with placebo at 24 weeks. The improvement lasted for another 28 weeks. Adverse events, particularly muscle spasms, were more frequent in the bardoxo-

lone methyl group. The Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events study was designed to confirm the findings of the BEAM study. Unfortunately the study was prematurely stopped owing to unacceptable high rates of cardiovascular events in patients treated with bardoxolone methyl at a median duration of 7 months, and no benefit was observed about the risk of ESRD [28].

The beneficial effects of an Nrf2 agonist called dh404, which is a derivative of bardoxolone methyl, via reduction in inflammation and oxidative stress but only at low doses have recently been shown in mice. This finding rekindles the interests on renoprotection via activation of the Nrf2 pathway in DKD.

Key Messages

- DKD is the leading cause of ESRD and is strongly associated with mortality in patients with diabetes.
- Persistent albuminuria is the hallmark of DKD, and some patients will finally develop ESRD with gradually decreased GFR and increased serum creatinine concentration.
- GBM thickening, mesangial expansion, mesangial matrix accumulation, Kimmelstiel–Wilson nodules, and tubulointerstitial fibrosis are typical pathological changes in DKD.
- Screening for DKD should begin at 5 years after the diagnosis of type 1 diabetes and at the diagnosis of type 2 diabetes. Patients with diabetes may annually undergo screening for DKD, which should include measurement of urinary ACR and serum creatinine concentration, estimation of GFR, and ophthalmologic examination.
- The progression of DKD may be slowed by optimal therapeutic approaches, such as lifestyle improvement, strict glycemic and BP control, control of dyslipidemia, and RAAS blockade. Patients who develop ESRD require renal replacement therapy.

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Hypertensive Kidney Disease

4

Xiaobing Ji

Abstract

Hypertensive kidney disease is defined as the damage to the kidney resulted from chronic high blood pressure (BP), which is pathologically classified as benign and malignant arteriolar nephrosclerosis. Given the increasing morbidity and mortality in patients with hypertensive kidney disease, therapeutic strategies for controlling BP and maximal reducing albuminuria are needed for delaying the progression of hypertensive nephropathy to end-stage renal disease. Most individuals with hypertensive kidney disease require combined use of three or more antihypertensive medications. Weight loss, exercise, and restriction on salt and alcohol intake may aid in BP control. The early recognition and adoption of potent approach to evaluate and manage patients with resistant hypertension may be effective strategies to achieve the BP targets. The malignant hypertension is life-threatening and requires immediate BP reduction for preventing irreversible target organ damage.

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4.1 Introduction

Hypertension is currently the second leading cause of kidney failure after diabetes mellitus [1, 2]. Most hypertensive patients develop only mild to moderate hypertensive nephrosclerosis. However, the rate of renal failure due to high blood pressure (BP) is increasing because of the high prevalence of hypertension in the general population. Traditionally, hypertensive kidney disease entails nephroangiosclerosis and hyalinosis with glomerular damage. However, recent evidence suggests that high BP also results in injury to the tubular cells, inducing epithelial–mesenchymal transition and tubulointerstitial fibrosis. The consensus is that both accelerated and malignant hypertension can rapidly lead to renal failure and end-stage renal disease (ESRD); furthermore, cardiovascular outcomes of patients with chronic kidney disease (CKD) are often related to hypertension. The identification of principal determinants of hypertension is imperative to break this vicious circle. Despite improvements in hypertension awareness and treatment, 30–60% of hypertensive patients, particularly those with CKD, do not achieve the BP targets regardless of the use of three or more antihypertensive agents. The early recognition and adoption of potential approach to the evaluation and management of resistant hypertensive patients may be an effective strategy to achieve the BP targets.

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Table 4.1 BP classification in adults (age ≥18 years)

Classification	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	<120	AND	<80
Prehypertension	120–139	OR	80–89
Stage I HTN	140–159	OR	90–99
Stage II HTN	≥160	OR	≥100

BP classification was based on the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Reproduced with permission from James PA, et al. [3])
BP blood pressure; *HTN* hypertension

Table 4.2 Risk factors for the development of hypertension

Modifiable risk factors	Unmodifiable risk factors
• Being overweight or obese • Sedentary lifestyle (lack of physical activity) • Tobacco use • Unhealthy diet (high in sodium) • Excessive alcohol consumption • Stress • Sleep apnea • Diabetes	• Age • Race • Family history

Essential hypertension, otherwise called primary hypertension or idiopathic hypertension, is a form of hypertension with—by definition—no identifiable cause. BP classification in adults is shown in Table 4.1.

No acceptable unified definition of hypertensive kidney disease exists to date. Studies from the past decade showed that apolipoprotein L1 gene (*APOL1*)-associated glomerulosclerosis can occur with arteriolar nephrosclerosis, which can develop into mild to moderate systemic hypertension [4, 5], suggesting that genetic variants in glomerulosclerosis can lead to syndromes clinically indistinguishable from systemic hypertension-related renal arteriolar disease. Because genetic testing for *APOL1* variants and other glomerulosclerosis-associated genetic variants is available and can precisely define disease pathogenesis, some experts suggest the abandonment of the term "hypertensive nephrosclerosis." However, studies on the subject have only been restricted to African Americans. Furthermore, most experts agree that hypertensive kidney disease should be defined as damage to the kidney due to high BP. Hypertensive kidney disease can be classified as either benign or malignant according to the severity and rapidity of hypertension and arteriolar changes.

4.2 Benign Nephrosclerosis

4.2.1 Definition

Benign nephrosclerosis, also called hypertensive nephrosclerosis, is characterized by a very slowly progressive thickening and sclerosis of the renal resistance vessels due to long-standing poorly controlled hypertension.

4.2.2 Causes and Risk Factors

The exact causes of high BP remain unclear, although some specific genetic variants have been identified to be associated with hypertension. Several risk factors are linked to hypertension, some of which are modifiable (e.g., being overweight or obese, low physical activity, tobacco use, unhealthy diet, and excessive alcohol consumption), whereas others are unmodifiable (e.g., age, race, and family history). Risk factors for the development of hypertension are listed in Table 4.2.

Older age, long-standing poorly controlled hypertension, and intrinsic kidney diseases are the main risk factors for hypertensive kidney disease. Some degree of benign nephrosclerosis is very common among individuals aged >60 years, and African Americans have been observed to be more prone to develop hypertensive nephrosclerosis and ESRD. The Multiple Risk Factor Intervention Trial showed that hypertensive nephrosclerosis occurs earlier and is more severe in African Americans. Additionally, men are more prone to develop hypertensive nephrosclerosis than women [6].

4.2.3 Prevalence

Although benign nephrosclerosis slowly progresses to ESRD in only a small percentage of individuals, it remains one of the most common causes of ESRD owing to the high prevalence of

hypertension. In the United States, hypertensive nephropathy accounts for approximately 27.5% of incident dialysis patients according to the data from the 2016 US Renal Data System [7]. Moreover, new patients starting dialysis contributed to the continuously increasing prevalence of hypertension. The reported prevalence rate of hypertensive nephropathy greatly varies worldwide, accounting for 27% of new patients with ESRD in France, 21% in Italy, 7% in China, 6% in Japan, and approximately 12% in the European Dialysis and Transplant Association registry [8]. This variation may reflect differences in criteria for and accuracy of diagnosis of hypertensive nephropathy among various countries.

4.2.4 Clinical Manifestations

Most patients are observed to be hypertensive with nonspecific symptomatology on routine physical examination. Hypertension is usually present for many years, with persistent BP elevation and evidence of the following hypertension-related target organ damage:

- Proteinuria less than 0.5 g/day
- Hypertensive retinal changes
- Left ventricular hypertrophy
- Heart attack or heart failure
- Stroke
- Atherosclerosis
- Aneurysm

Physical examination may reveal changes in the retinal vessels, and <5% of patients with poorly controlled BP will develop renal failure during the subsequent 10–15 years.

Proteinuria develops in up to 40% of patients. Microalbuminuria has long been recognized as a major biomarker of hypertensive nephrosclerosis, and measurement of microalbuminuria level at screening and during treatment is widely recommended. However, research has consistently shown that it is clinically relevant only when increases in the macroalbuminuric range (>300 mg/day) occur in the presence of appropriate BP control. Investigators of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial reported that the histological progression of diabetic nephropathy persisted despite the maintenance of normal BP and microalbuminuria [9]. This trial illustrates the limitations of using microalbuminuria as a surrogate marker for CKD and a prognostic tool for the progression of CKD. In fact, microalbuminuria might represent vascular dysfunction and serve as a marker of cardiovascular risk instead of the progression of CKD. Conversely, macroalbuminuria may accurately represent renal parenchymal damage and should serve as a prognostic marker for the progression of CKD and a therapeutic target in the treatment of CKD.

Persistent increases in serum creatinine concentration reflect substantial renal parenchymal damage and some degree of irreversible kidney dysfunction. However, the serum creatinine concentration does not provide an accurate measure of the rate of progression of renal dysfunction. It is essential to utilize more accurate and sensitive measures for the estimation of glomerular filtration rate (GFR), which may guide targeted therapies to more effectively prevent disease progression and associated complications. The identification of an appropriate marker of early renal dysfunction remains challenging and depends on the underlying etiology of kidney disease. Hypertension-induced kidney injury can be associated with obvious markers of renal parenchymal disease, such as proteinuria. However, in the absence of overt glomerular disease such as in hypertensive nephrosclerosis or early diabetic nephropathy, evidence of early kidney injury remains elusive.

In the past decade, numerous researchers showed that serum cystatin C level could serve as an early marker of hypertension-induced kidney dysfunction and may accurately reflect the estimated GFR (eGFR) in various populations [10]. Investigators of the Heart and Soul Study evaluated the effect of baseline systolic BP by measuring the serum cystatin C level and estimating the GFR based on the serum creatinine concentration and reported that serum cystatin C level was better correlated with systolic BP than serum creatinine concentration in individuals with an eGFR >60 mL/min/1.73 m^2 [11].

4.2.5 Pathological Manifestations

Benign nephrosclerosis is histologically characterized by a series of vascular injuries, including afferent arteriolar hyalinization and interlobular thickening of the artery and arcuate artery endomysium. Renal pathology in benign nephrosclerosis is shown in Fig. 4.1. Cumulative evidence over the past years has suggested that high BP results in injury to the tubular cells, inducing epithelial–mesenchymal transition and tubulointerstitial fibrosis. Recent investigations have reported the association of podocyte effacement and loss with benign nephrosclerosis [12]. Benign nephrosclerosis-induced changes are summarized in Table 4.3.

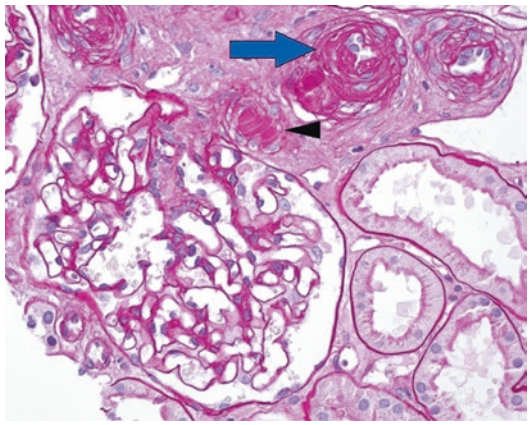

Fig. 4.1 Histopathological manifestations in benign nephrosclerosis. Hyaline degeneration (arrowhead) and intimal thickening (arrow) of renal arterioles are present (periodic acid-Schiff staining, ×400)

4.2.6 Diagnosis

The diagnosis of hypertensive kidney disease is dependent on clinical manifestations and exclusion of other primary kidney diseases. A confirmed history of hypertension and signs of target organ damage, such as left ventricular hypertrophy, hypertensive retinal changes, and proteinuria, should establish the diagnosis. However, clarifying the diagnosis is occasionally very difficult in clinical practice when hypertension and CKD coexist. A flowchart for the diagnosis of benign nephrosclerosis is shown in Fig. 4.2.

Home and ambulatory BP monitoring (ABPM) is becoming increasingly recommended for the clinical evaluation of hypertension because of its ability to identify white-coat hypertension and masked hypertension [13]. Reference values for normal ambulatory BP in nonpregnant

Table 4.3 Benign nephrosclerosis-induced changes in the vascular, glomerular, and tubulointerstitial compartments

Compartment	Changes	Effects
Vessels	• Transition from smooth muscle cells to myofibroblasts, intimal thickening of the small arterioles	• Wall stiffness, with little or no effect on the lumen caliber
	• Thinning of the media, hyalinosis of the afferent arteriole	• Reduced filtration
	• Occlusion of the intraglomerular capillaries by hyaline material	• Hypoxia
	• Breakdown of elastic fibers in the large arteries	• Laminar-to-pulsatile flow shift in the arcuate, interlobular, and afferent arterioles
Glomeruli	Not applicable	• Increased intraglomerular pressure and microalbuminuria
	• ECM accumulation	• FSGS
	• Glomerular tuft entirely replaced by collagen	• Global glomerulosclerosis
	• Capsular adhesion and segmental scars	• Reduced filtration
Tubules	• Cell dilation and flattening, cell atrophy and loss	• Proteinuria
	• EMT	• Tubulointerstitial fibrosis and CKD

ECM extracellular matrix; *FSGS* focal segmental glomerulosclerosis; *EMT* epithelial–mesenchymal transition; *CKD* chronic kidney disease

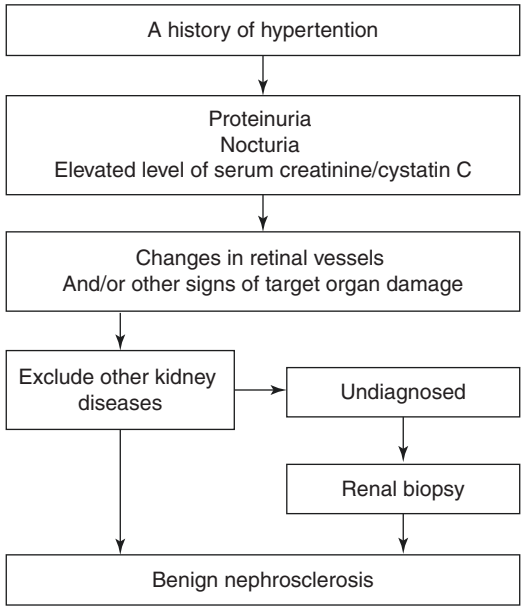

Fig. 4.2 Flowchart for diagnosis of benign nephrosclerosis

Table 4.4 Reference values for normal ambulatory blood pressure in nonpregnant adults

Time	Normal	Hypertension threshold
24-h average	<115/75 mmHg	130/80 mmHg
Daytime (awake)	<120/80 mmHg	135/85 mmHg
Nighttime (asleep)	<105/65 mmHg	120/75 mmHg

adults are summarized in Table 4.4, whereas diagnostic threshold values for ABPM (in mmHg) based on cardiovascular outcome are shown in Table 4.5.

White-coat hypertension (elevated clinical BP but normal ambulatory BP) is defined as persistently elevated BP (>140/90 mmHg) in the clinical setting but normal 24-h average BP levels (<130/80 mmHg). White-coat hypertension was previously believed to be a benign finding but is currently thought to increase the risk of cardiovascular complications similar to essential hypertension. Masked hypertension (normal clinical BP but elevated ambulatory BP), the opposite of white-coat hypertension, carries a similarly increased risk of cardiovascular complications. ABPM provides the essential time-aware and sensitive information for state-of-the-art individualized diagnostic categorization, treatment efficacy evaluation, and cardiovascular outcome prediction.

Table 4.5 Diagnostic threshold values for ABPM (in mmHg) based on cardiovascular outcome [13]

ABPM characteristic	Men	Women	High-risk patients
Awake (mean)			
SBP	135	125	120
DBP	85	80	75
Asleep (mean)			
SBP	120	110	105
DBP	70	65	60

ABPM ambulatory blood pressure monitoring; *SBP* systolic blood pressure; *DBP* diastolic blood pressure

High-risk patients include those who are diagnosed with diabetes or CKD and have experienced a previous cardiovascular event.

The differential diagnosis of hypertensive nephrosclerosis should include the following:

- Renal atherosclerotic disease
- Renal vascular hypertension
- Malignant hypertension
- Mildly active primary kidney disease
- Lead nephropathy

Hypertension is strongly associated with atheromatous renal disease (ARS), especially in the elderly. The diagnosis of ARS can be established using Doppler ultrasonography, computed tomography (CT) angiography, magnetic resonance (MR) angiography, or intra-arterial renal angiography. Comparative studies on patients indicate that both Doppler studies and CT angiography may fail to detect significant lesions. However, MR angiography can provide valuable information about the location and severity of atherosclerotic vascular lesions. Intra-arterial renal angiography should be considered when persistent and accelerated hypertension, unknown renal insufficiency, or circulatory congestion develops.

Renal biopsy findings in patients with lead nephropathy can resemble those in patients with hypertensive nephrosclerosis. Lead nephropathy should be considered as part of

differential diagnosis in patients who present with renal failure and new-onset hypertension and have past history of potential exposure, and blood lead levels should be measured. The ethylenediaminetetraacetic acid (EDTA) lead-mobilization test is used to evaluate the body's lead burden. Radiographic fluoroscopy is another test that could be used to determine skeletal lead stores.

4.2.7 Management Principles

The optimal strategy to prevent hypertensive kidney disease is the identification of patients who are predetermined to develop ESRD or are in the course of progressing to ESRD from a large number of patients with essential hypertension. A previous history of AKI, a family history of ESRD, black race, and microalbuminuria are all potential risk factors.

As noted in the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines, the success of strategies for BP management will ultimately depend on patients' self-management, their ability and willingness to adopt and maintain healthy behaviors, and their adherence to medication regimens [14].

4.2.7.1 Nonpharmacologic Approaches

Several nonpharmacologic approaches with well-established efficacy in reducing BP include lifestyle modification, weight reduction, Dietary Approaches to Stop Hypertension (DASH) diet, restriction on salt and alcohol intake, increased physical activity, increased potassium intake, and alternative approaches (Table 4.6). The DASH trial provides strong evidence on the BP-lowering effectiveness of dietary sodium restriction and weight loss in prehypertensive and hypertensive patients [15]. These approaches may control BP without the concomitant use of antihypertensive agents or with the reduction in the frequency or dosage of antihypertensive medications. Nonpharmacologic approaches to hypertension management and their effects are summarized in Table 4.6.

Table 4.6 Nonpharmacologic approaches to hypertension management and their effects

Modification	Description	Systolic BP reduction
Weight reduction	Attaining normal weight	5–20 mmHg/10-kg weight loss
DASH diet	Rich in fruits, vegetables, and low-fat dairy with reduced saturated fat, total fat, and sodium	8–14 mmHg
Reduced dietary sodium intake	Decreasing sodium intake to 65–100 mmol/day	2–8 mmHg
Increased physical activity	Regular aerobic exercise for 30 min/day during most working days	4–9 mmHg
Moderate alcohol intake	Limiting alcohol consumption to two drinks/day for men and one drink/day for women and those with lower weight	2–4 mmHg
Increased potassium intake	Increasing potassium intake to 120 mmol/L	Variable
Alternative approaches	Medication, yoga, biofeedback, device-guided breathing, acupuncture, other relaxation therapies	Variable up to 2–10 mmHg

BP blood pressure; *DASH* dietary approaches to stop hypertension

4.2.7.2 Pharmacologic Treatment

If nonpharmacologic approaches are ineffective in managing high BP, pharmacologic therapy should be initiated. First-line antihypertensive medications include thiazide diuretics, long-acting calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). The updated Eighth Joint National Committee (JNC-8) guidelines do not include beta-blockers as part of initial treatment. Combination therapy can be used as initial therapy if systolic BP is >160 mmHg and/

or diastolic BP is >100 mmHg or if systolic BP is >20 mmHg above the target and/or diastolic BP is >10 mmHg above the target. If two medications are insufficient to achieve the BP target, a third medication can be added. Alternative agents for hypertension can be administered if the BP target has not been achieved using first-line agents.

Thiazide and thiazide-like diuretics have been the mainstay of primary hypertension management for a longer period than any other antihypertensive agents. Their widespread and continued use is based on consistent evidence on their ability to reduce the risk of heart disease, stroke, heart attack, and death. Thiazide diuretics used for hypertension include indapamide, metolazone, chlorthalidone, and hydrochlorothiazide, with the latter two being the most commonly used. However, metolazone may be effective in patients with poor renal function when other thiazide diuretics prove to be ineffective.

CCBs used for hypertension include amlodipine, felodipine, isradipine, sustained-release nicardipine, long-acting nifedipine, and nisoldipine. CCBs bind to calcium channels in the blood vessels, resulting in reduced BP. Vasodilatory side effects include flushing and peripheral edema. CCB-related peripheral edema is attenuated by coadministration of an ACEI. Chest pain is one of the serious adverse events upon initiation of CCB therapy. CCBs are a useful component of multidrug regimens for patients with resistant hypertension, such as those with diabetes or CKD.

ACEIs and ARBs have been shown to prevent death in patients with congestive heart failure and in all patients at high risk of cardiac complications and to reduce the rate of progression of kidney disease in patients with diabetes. Because of their benefits, several international guidelines recommend them as first-line antihypertensive agents for patients diagnosed with diabetes. An acute increase in serum creatinine concentration and hyperkalemia are a concern in patients with CKD. One approach to initiation of ACEI/ARB therapy for hypertensive kidney disease is to start it at a low dose and then to gradually titrate the dose upward every few weeks with monitoring of creatinine and potassium concentration. However, combining an ACEI with an ARB is not recommended.

4.2.7.3 Target Goals

There has been continuing debate about the target goals. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that BP be lowered to <130/80 mmHg in patients with nephropathy (stage 3 or higher) who have proteinuric kidney disease (>300 mg/day) [14]. The BP target goals recommended in the KDIGO guidelines are shown in Table 4.7. Renin–angiotensin–aldosterone system blockers exert beneficial effects on the progression of nephropathy, especially in the subgroup of hypertensive patients with nephropathy, late-stage CKD (stage 3), and proteinuria (>300 mg/day).

Compared with previous guidelines on hypertension treatment, the JNC-8 guidelines advise higher BP goals <140/90 mmHg [3]. The BP target goals stipulated in the JNC-8 guidelines are listed in Table 4.8. Achieving target levels of <140/90 mmHg for BP control clearly slows the

Table 4.7 Blood pressure target goals recommended in the 2012 KDIGO guidelines

Patient characteristics	Goal	Evidence grade
Diabetic and nondiabetic adults with CKD and albumin excretion <30 mg/24 h	≤140/90 mmHg	1B
Diabetic and nondiabetic adults with CKD and albumin excretion ≥30 mg/24 h	≤130/80 mmHg	2D

KDIGO kidney disease: improving global outcomes; *CKD* chronic kidney disease

The strength of recommendation is indicated as levels 1 ("We recommend") and 2 ("We suggest"), whereas the quality of supporting evidence is designated as A (high), B (moderate), C (low), or D (very low)

Table 4.8 Blood pressure target goals recommended in the JNC-8 guidelines

Patient characteristics	Goal	Evidence grade
• <60 years • Diabetes • CKD	<140/90 mmHg	E
• ≥60 years	<150/90 mmHg	A

JNC-8 Eighth Joint National Committee; *CKD* chronic kidney disease
The quality of supporting evidence is indicated as A (strong recommendation), B (moderate recommendation), C (weak recommendation), D (recommendation against), or E (expert opinion)

progression of nephropathy due to hypertension regardless of the presence of albuminuria.

Although the proportion of patients achieving the recommended BP targets has improved over the past several decades, many patients do not reach these targets and are considered to have resistant hypertension (rHTN), which is particularly common among patients with CKD. Notably, patients with uncontrolled hypertension are more likely to develop target organ damage, including progressive CKD and ESRD.

In 2008, the American Heart Association issued a scientific statement that defined rHTN as BP persistently greater than >140/90 mmHg despite the concurrent use of three or more antihypertensive agents of different classes [16], one of which should be a diuretic. Patients with rHTN are more likely to develop target organ damage, including progressive CKD and ESRD. Achieving the recommended BP goals for these patients is challenging. Early recognition of rHTN using a standardized definition and adoption of a consistent approach to evaluation and management may increase the probability of success in implementing therapeutic approaches. Figure 4.3 shows a systematic approach to the evaluation of patients with suspected rHTN [17].

4.3 Malignant Nephrosclerosis

4.3.1 Definition

Malignant nephrosclerosis, also called accelerated nephrosclerosis, refers to acute kidney impairment due to severe hypertension (diastolic BP often ≥130 mmHg).

4.3.2 Causes and Risk Factors

Malignant hypertension is a multifactorial disease that may develop in patients with long-standing or secondary hypertension. Common causes of malignant hypertension are listed in Table 4.9. This section focuses on essential hypertension as cause of malignant hypertension.

4.3.3 Prevalence

Malignant hypertension is not common, occurring in approximately 1–2% of hypertensive patients, and may lead to acute impairment in one or more organ systems, including the renal system, with varying degree of severity. Malignant hypertension most likely develops in previously hypertensive patients with inadequate BP control and affects more men than women, with a higher incidence in black men and Asian patients. The age of onset ranges from 30 to 50 years, with the disease being also present in children and the elderly. The incidence of malignant hypertension has been decreasing with improvement in BP control, use of antihypertensive medications, and better understanding of the need for treatment. In Australia and New Zealand, there is a dramatic decrease in the annual incidence of malignant hypertension as a cause of ESRD over the last 25 years [18].

4.3.4 Clinical Manifestations

Patients with malignant nephrosclerosis often have a history of malignant hypertension and have experienced withdrawal from beta-blockers, alpha-blockers, or some other antihypertensive agents. Alcohol and cocaine may also lead to a hypertensive emergency.

A thorough physical examination should be performed, with BP measured in both arms. A significant difference (>20 mmHg) may suggest aortic dissection, with BP increasing in few minutes and hours (usually systolic BP >180 mmHg, diastolic BP >130 mmHg). Head and neck examination must include a complete funduscopic examination. Keith–Wagener grade III (hemorrhages and exudates) and grade IV (papilledema) retinal changes are the hallmarks of malignant

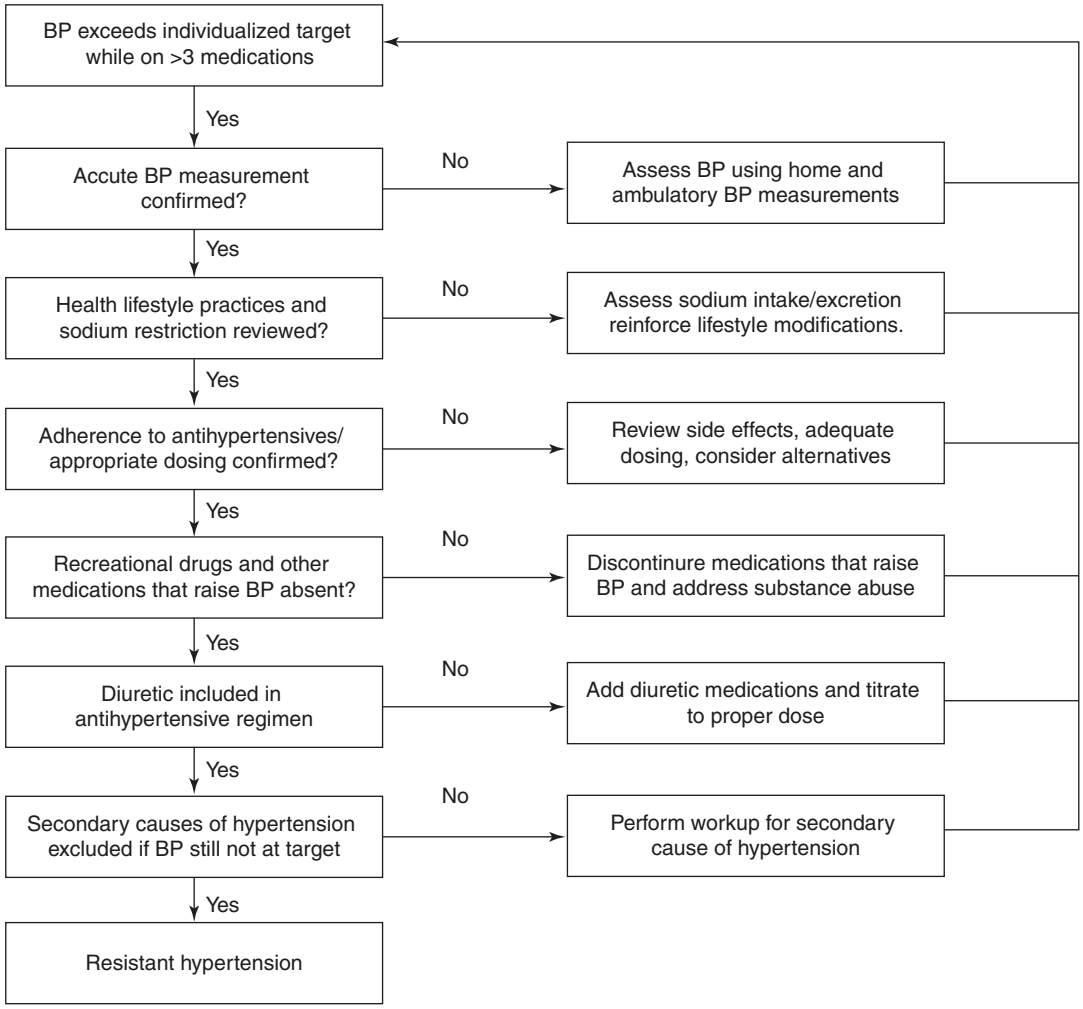

Fig. 4.3 Systematic approach to evaluate the patient with suspected resistant hypertension. (Reproduced with permission from Braam et al. [17])

hypertension. New diastolic murmurs could be detected on cardiovascular examination, supporting the diagnosis of aortic dissection.

Clinical presentation reflects the deleterious effects of high BP on target organs. Renal abnormalities include a rapid increase in serum creatinine concentration, hematuria (with 50–60% and 20% of patients having microscopic and gross hematuria, respectively), red blood cell casts, and proteinuria. Nephrotic syndrome is not often observed.

Presenting symptoms can also include the following:

- Acute heart failure
- Pulmonary edema
- Cerebrovascular event
- Hypertensive encephalopathy
- Dissecting aortic aneurysm
- Eclampsia

4.3.5 Pathological Manifestations

The classic gross pathological manifestation is a "flea-bitten" appearance of the kidney due to pinpoint petechiae on the cortical surface, whereas micropathological manifestations include fibrinoid necrosis of the arterioles and hyperplastic arteriolitis (onion skinning) due to concentric layering of collagen (Fig. 4.4). The presence of

Table 4.9 Common causes of malignant hypertension

Essential hypertension
Renal parenchymal diseases
Glomerulonephritis
Tubulointerstitial diseases
Systemic sclerosis
Diabetes
Systemic lupus erythematosus
Renal vascular diseases
Atherosclerotic renal artery stenosis
Aortitis
Fibromuscular dysplasia
Acute renal artery occlusion
Endocrine diseases
Pheochromocytoma
Primary aldosteronism
Cushing syndrome
Drugs
Cocaine
Amphetamine
Monoamine oxidase inhibitor
Erythropoietin
Ciclosporin
Tumors
Renal carcinoma
Lymphoma
Coarctation of the aorta
Obstetrics-related diseases
Preeclampsia
Eclampsia

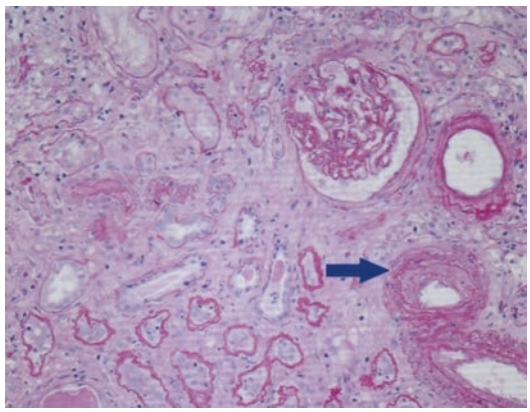

Fig. 4.4 Histopathological manifestations in malignant nephrosclerosis. Scarring concentric thickening of vessel wall by myointimal cells and deposition of basement membrane type material (onion skinning, arrow), tubular atrophy, and glomerular shrinkage are shown (periodic acid-Schiff staining, ×200)

red blood cells and red blood cell casts in the urine is sometimes a clinical manifestation. There is convincing evidence on the association of malignant hypertension with kidney injury and progressive CKD.

4.3.6 Diagnosis

A sudden BP elevation (often diastolic BP ≥130 mmHg) with acute progressive deterioration in renal function could establish the diagnosis.

It is crucial to distinguish hypertensive emergency from hypertensive urgency, with the latter involving no target organ damage. History taking and physical examination could provide clues, and some diagnostic tests such as electrocardiography and chest radiography can provide important information on end-organ damage.

4.3.7 Management Principles

Precise and rapid BP control is the principal therapeutic goal. Patients should be immediately admitted to an intensive care unit with continuous BP monitoring. BP should be reduced within minutes to an hour using a parenteral and titratable antihypertensive agent. The ideal target goal remains unknown, but reducing the mean arterial pressure by 10% during the first hour and an additional 15% during the subsequent second to third hours is recommended. Aggressive BP reduction may notably result in hypotension and worsen end-organ damage. Patients should be restricted to bed rest until severe hypertension is under control.

A number of short-acting agents of various drug classes are available for hypertension treatment. The optimal strategy is to tailor drug selection according to patients' characteristics. Both patient-specific and drug-specific factors should be carefully considered to ensure the selection of an appropriate drug. The use of ACEIs and ARBs is not recommended for malignant nephrosclerosis because of the potential risk of worsening renal function and hyperkalemia. Fenoldopam is a selective D_1 receptor partial agonist that acts as a peripheral vasodilator and a diuretic. Approved by the Food and Drug Administration

Table 4.10 Parenteral agents used in the management of hypertension in patients with malignant nephrosclerosis

Drug	Mechanism of action	Onset of action	Duration of action
Nitroglycerin	Nitrate receptors	2–5 min	5–10 min
Fenoldopam	Dopamine D_1 receptor agonist	>5 min	30 min
Nicardipine	Calcium channel blocker	5–10 min	15–30 min
Labetalol	α_1- and β-blocker	30–120 min	6–8 h

in September 1997, fenoldopam has been shown to be a rapid-acting, well-tolerated, and renoprotective intravenous agent. Other options for this patient population include nitroglycerin, nicardipine, and labetalol. Previous studies have reported that all these drugs lower BP when intravenously administered, with no evidence that one is better than the other. Parenteral agents used in the management of hypertension in patients with malignant nephrosclerosis are listed in Table 4.10.

Key Messages

- Hypertensive kidney disease should be defined as damage to the kidney due to high BP, which can be classified as either benign or malignant depending on the severity and rapidity of hypertension and arteriolar changes.
- Older age, long-standing poorly controlled hypertension, and intrinsic kidney diseases are the main risk factors for hypertensive kidney disease. African Americans have been observed to be more prone to develop hypertensive nephrosclerosis and ESRD.
- Although benign nephrosclerosis slowly progresses to ESRD in only a small percentage of individuals, it remains one of the most common causes of ESRD owing to the high prevalence of hypertension. The reported prevalence rate of hypertensive nephropathy greatly varies worldwide.
- Most patients with benign nephrosclerosis usually have a history of hypertension and present with persistent BP elevation, with evidence of hypertension-related target organ damage. The diagnosis of hypertensive kidney disease is dependent on clinical manifestations and exclusion of other primary kidney diseases.
- Most individuals with benign nephrosclerosis require the use of multiple antihypertensive medications. Weight loss, exercise, and restriction on salt and alcohol intake can also aid in BP control.
- Malignant nephrosclerosis is one of the end-organ damages of malignant hypertension. Malignant hypertension most likely develops in previously hypertensive patients with inadequate BP control and affects more men than women, with a higher incidence in black men and Asian patients. The age of onset ranges from 30 to 50 years.
- Patients with malignant nephrosclerosis often have a history of malignant hypertension and have experienced withdrawal from beta-blockers, alpha-blockers, or some other antihypertensive agents. Alcohol and cocaine may also lead to a hypertensive emergency.
- Clinical presentation reflects the deleterious effects of high BP on target organs, with systolic and diastolic BP often being >180 mmHg and >130 mmHg, respectively. Keith–Wagener grade III and grade IV retinal changes are the hallmarks of malignant hypertension.
- Patients with malignant nephrosclerosis should be immediately admitted to an intensive care unit with continuous BP monitoring. BP should be reduced within minutes to an hour using a parenteral and titratable antihypertensive agent.

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Pregnancy in Chronic Kidney Disease

5

Weichun He

Abstract

Although the pregnancy rate of women with chronic kidney disease (CKD) and the overall survival rate of their fetuses have improved, pregnancy in women with CKD still have a high risk of adverse maternal and fetal outcomes. To achieve better outcomes for this particular population, managing pregnancy in women with CKD has become a considerable challenge shared by both nephrologists and obstetricians. Strengthened management, including prepregnancy preparation, pregnancy management, peripartum management, and postpartum care, could prevent or mitigate maternal renal damage and adverse maternal and fetal outcomes. Women with CKD require risk assessment of pregnancy before conceiving, close follow-up by both nephrologists and obstetricians to monitor disease activity and detect obstetric complications during pregnancy, evaluation of indications for termination of pregnancy and selection of delivery mode, and assessment of disease activity and emotional support to prevent depression after delivery.

5.1 Introduction

With advances in medicine, the pregnancy rate of female patients with chronic kidney disease (CKD) has improved, along with an apparent increase in the overall survival rate of fetuses. However, women with CKD remain a major part of the patient population that carries the highest risk of adverse maternal and fetal outcomes. Adverse maternal outcomes include aggravated renal damage, acute kidney injury, pregnancy-associated kidney disease, increased proteinuria, hypertension, and preeclampsia (PE). Furthermore, adverse fetal outcomes include stillbirth, fetal growth restriction (FGR), and preterm delivery. Therefore, managing pregnancy in patients with CKD has become a considerable challenge shared by both nephrologists and obstetricians. To mitigate maternal renal damage and adverse maternal and fetal outcomes, both nephrologists and obstetricians need to assess the risk of pregnancy in patients with CKD in a standardized manner, determine the optimal timing of pregnancy, stabilize the condition of patients, and closely monitor any changes during pregnancy for the early detection of maternal and fetal complications.

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5.2 Risk Assessment of Pregnancy in Patients with CKD

5.2.1 Renal Physiological Alterations During Pregnancy

A series of physiological adaptations occur in the maternal kidney during pregnancy to meet the needs for fetal development and maintain maternal health. The size of the kidney increases, and the function of glomeruli and tubules changes. Renal plasma flow and glomerular filtration rate (GFR) markedly increase, reaching their peak (an increase of more than 50%) in the second trimester of pregnancy. The concentration of serum creatinine (SCr), urea nitrogen, and uric acid is slightly lower in pregnant women than in non-pregnant women because of the increased excretion of metabolites from the body during pregnancy. Although the SCr in gravid women is within the normal range, their kidney may have been damaged [1]. One study reported a U-shaped relationship between estimated GFR (eGFR) level and adverse events in the second trimester of pregnancy, suggesting that gravid women with eGFR 120–150 mL/min/1.73 m^2 had the best pregnancy outcome, whereas those with too high or too low eGFR had the worse outcome in the renal function assessment [2].

CKD is defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) as renal damage or GFR <60 mL/min/1.73 m^2 present for more than 3 months, with implications for health. Renal damage refers to structural or functional abnormalities in the kidney, including abnormal blood and urine composition, abnormal imaging findings, and pathomorphological changes in the renal tissues [3, 4]. As GFR is the best index for the evaluation of renal function, CKD staging is consequently based on the GFR level, which is typically measured using creatinine-based estimation formulas, such the Modification of Diet in Renal Disease Study equation and Chronic Kidney Disease Epidemiology Collaboration equation [5, 6]. CKD is categorized into five stages according to the GFR level: stage 1, GFR ≥90 mL/min /1.73 m^2; stage 2, GFR 60–89 mL/min/1.73 m^2; stage 3a, GFR 45–59 mL/min/1.73 m^2; stage 3b, GFR 30–44 mL/min/1.73 m^2; stage 4, GFR 15–29 mL/min/1.73m^2; and stage 5, GFR ˂15 mL/min/1.73 m^2 or maintenance dialysis [4].

In pregnancy studies, early stage CKD was defined as SCr ˂1.4 mg/dL (125 μmol/L) or creatinine clearance ≥70 mL/min. In contrast, advanced CKD was defined as SCr ˃1.4 mg/dL (125 μmol/L) and was often further subclassified into moderate (1.4–2.4 mg/dL or 125–220 μmol/L) or severe (˃2.4 mg/dL or 220 μmol/L) CKD in earlier literature. In recent years, the definition and staging of GFR have been gradually introduced to obstetric nephrology [7]. In view of renal physiological adaptations during pregnancy, CKD staging criteria can only be theoretically used to assess renal function prior to pregnancy. More recent studies have used eGFR cutoff levels endorsed by the KDIGO and KDOQI, which define moderate CKD as an eGFR between 30 and 60 mL/min/1.73 m^2 (stage 3 CKD) and severe CKD as an eGFR between 15 and 30 mL/min/1.73 m^2 (stage 4 CKD), despite the lack of validation of these formulas in pregnancy [7].

5.2.2 Assessment of Kidney Disease Conditions

It is well known that pregnancy may pose hazards to both the gravida and fetus as women progress through each stage of CKD, especially in the presence of significant proteinuria and/or hypertension as well as comorbidities such as diabetes and lupus. The more difficult blood pressure control becomes and the more advanced CKD is, the higher the risk of poor pregnancy outcome.

5.2.2.1 Stages of CKD

The degree of CKD is recognized to be an important determinant of pregnancy outcome. Women with normal kidney function or only mild CKD do not typically exhibit worsening kidney function in the absence of significant hypertension and/or proteinuria. However, women with more advanced CKD are at risk of kidney function loss during pregnancy. Pregnancy complications, including preterm delivery (˂37 weeks of gestation), small for gestational age (SGA) births, and

need for neonatal intensive care unit (NICU) admission and cesarean section, may be more common in patients with CKD than in the general population, with rates increasing with each CKD stage. Even stage 1 CKD is an independent risk factor for poor pregnancy outcomes such as preterm delivery, SGA births, and need for NICU admission [8].

5.2.2.2 Hypertension

The incidence of hypertension is higher in patients with CKD than in ordinary individuals, which further increases after pregnancy. The rate of new hypertension in pregnant women with stage 1 CKD and stage 4–5 CKD is 7.9% and 50%, respectively [9]. Poorly controlled hypertension significantly adds to the risk of pregnancy, including the risk of early pregnancy loss, superimposed placental ischemia and PE, and premature delivery and FGR [10]. The recently published Control of Hypertension in Pregnancy Study confirmed that treating hypertension in pregnancy to a lower diastolic blood pressure target is not associated with adverse neonatal events or pregnancy outcomes. A blood pressure target <140/90 mmHg has been recommended for women with CKD during pregnancy [7].

5.2.2.3 Proteinuria

Proteinuria is an independent risk factor for the progression of CKD but exerts the smallest effect on pregnancy outcome compared with CKD staging and hypertension. Gestation can aggravate proteinuria in patients with CKD. Doubling of proteinuria occurs in approximately 20% of patients with stage 1 CKD and approximately 70–80% of patients with stage 3 or higher CKD. Severe proteinuria leads to maternal hypoalbuminemia, which can result in FGR. Moreover, the decrease in plasma albumin level results in reduced uteroplacental blood flow, poor placental perfusion, insufficient supply of fetal oxygen and nutrients, and chronic fetal anoxia, which leads to FGR, neonatal asphyxia, and even intrauterine fetal death [8]. In addition, pregnancy itself is a prothrombotic state, and nephrotic syndrome with severe hypoalbuminemia (albumin level ˂25 g/L) is associated with an increased risk of venous thromboembolic disease [11].

Therefore, pregnant women with early stage CKD, mild renal damage, normal prepregnancy renal function, normal blood pressure, and normal albuminuria or microalbuminuria have lower risk of progression of renal damage, and their pregnancy outcomes are better. However, pregnancy complications remain more common in these women than in the general population. In pregnant women with advanced CKD, the risk of declining renal function and undesirable pregnancy outcomes is significantly increased.

5.2.3 Timing of Conception

In view of the above risk assessment of pregnancy in patients with CKD, patients with early stage CKD who have well-controlled blood pressure and proteinuria <1 g/24 h may consider pregnancy; however, it is recommended that the risks of pregnancy be suitably recognized.

Pregnancy is not recommended for the following patients with CKD [1, 12–14]:

- Patients with stage 3–5 CKD.
- Patients with uncontrollable hypertension are advised to postpone pregnancy until their blood pressure becomes normal.
- Patients with proteinuria are counseled to postpone pregnancy until proteinuria is managed and reduced to <1 g/24 h for at least 6 months.
- Pregnancy in women with active lupus nephritis (LN) is not recommended owing to the increased risk of flare, preterm delivery, and PE. Pregnancy should be postponed until LN has been treated with achievement of complete remission or the condition has become stable with near complete remission for at least 6 months.
- Pregnancy is not recommended for patients with diabetic nephropathy who have moderate or severe renal impairment because of higher risks of irreversible renal function decline and progression to severe proteinuria after pregnancy.
- For systemic diseases such as LN and diabetic nephropathy, refer to relevant guidelines for the assessment of extrarenal lesions not suitable for pregnancy.

If a patient with CKD mentioned above strongly desires to be pregnant, a close follow-up for high-risk pregnancy by nephrologists and obstetricians and NICU support treatment are indispensable [12, 13].

Fertility in patients on dialysis declines, and increasing the dialysis duration to >36 h/week is necessary to increase the fetal survival rate. The risk of poor pregnancy outcome remains very high despite treatment with intensive dialysis. When a dialysis patient has a pathological pregnancy, the risk of massive hemorrhage and other risks due to termination of pregnancy by medications or surgical interventions are significantly increased [15]. Therefore, pregnancy is not usually recommended for patients on hemodialysis or peritoneal dialysis.

Under the guidance of medical professionals, renal transplant recipients should select the proper time for pregnancy in accordance with their condition and treatment. In most cases, there is no significant difference in long-term graft function between pregnant and nonpregnant women; nevertheless, the risk of poor pregnancy outcome is higher in recipients than in the healthy population. The incidence of fetal loss, PE, and infection is also higher in recipients, especially in patients with SCr >150 μmol/L before pregnancy who have concomitant hypertension and diabetes [16]. The overall incidence rate of transplant rejection during pregnancy is 4.2% [17]. If renal transplant recipients desire to be pregnant, it is recommended that they wait for at least 1 year before conceiving to ensure stable graft function and enable switching of immunosuppressive drugs to nonteratogenic medications (e.g., mycophenolate mofetil replaced with azathioprine) [17]. The European Renal Best Practice guidelines recommend that women should not conceive until at least 24 months after transplantation [18]. More recent recommendations from the American Society of Transplantation advise that conception may be considered after 12 months, provided that all of the following criteria are met: no rejection in the previous year, adequate and stable renal function (i.e., SCr $^{<}$133 μmol/L) with no or minimal proteinuria, no acute fetotoxic infections (e.g., cytomegalovirus infection), and stable kidney function with nonteratogenic maintenance immunosuppression [19].

5.3 Pregnancy Management in Patients with CKD

To achieve better outcomes for pregnant women with CKD, multidisciplinary support is required to strengthen management, including prepregnancy preparation, pregnancy management, peripartum management, and postpartum care. In particular, treatment of primary kidney diseases, hypertension, and related complications should be emphasized [1, 13].

5.3.1 Prepregnancy Preparation

The use of an immunosuppressant considered safe in pregnancy for 3–6 months before conception is recommended for women with CKD to achieve disease remission. Strict contraception is required prior to disease remission, and progesterone-only preparations are recommended. For women of childbearing age, try to avoid the use of drugs with effects on their fertility.

5.3.1.1 Contraception

Strict contraception should be implemented prior to disease remission, with progesterone-only contraceptive methods, including tablets, intramuscular injections, and intrauterine birth control devices, being recommended. As estrogen may increase the risk of thrombosis and worsen hypertension, women with hypertension, vascular disease, or heavy proteinuria or those who smoke should avoid being prescribed with preparations containing estrogen. The use of an estrogenic drug is particularly prohibited in patients with vascular disease [20]. Contraception using birth control devices is not reliable and is not recommended as the only contraceptive method.

5.3.1.2 Fertility

Both primary diseases and therapeutic drugs may affect patients' fertility. Aggravation of renal dysfunction and abnormal hormone levels can increase the rate of infertility. Adverse drug reactions, fatigue, depression, and use of immunosuppressive agents can all lead to sexual dysfunction and fertility decline [21]. Cyclophosphamide can directly cause ovarian damage, with its oral administration

having more lasting effect on amenorrhea than intravenous administration. Intravenous administration with careful selection of treatment dosage and course is recommended. Try to avoid prescribing cyclophosphamide to women of childbearing age [22]. Other immunosuppressants such as mycophenolate mofetil, calcineurin inhibitor, azathioprine, and rituximab are appropriate for the treatment of immune glomerular diseases such as LN, nephrotic syndrome, and vasculitis. Assisted reproductive technology can possibly facilitate conception in women with CKD, but there is no study to guide clinical practice.

5.3.1.3 Optimized Management of CKD

Any active kidney disease may lead to adverse pregnancy outcome. It is recommended that disease remission be achieved using an immunosuppressant considered safe in pregnancy for at least 3–6 months before attempting to conceive. Renin–angiotensin system (RAS) inhibitors are the main drugs used to reduce proteinuria in patients without administering an immunosuppressant. The use of RAS inhibitors could be continued until conception is attempted [23].

5.3.2 Pregnancy Management

Gestational management in patients with CKD includes medication adjustment, blood pressure control, laboratory examination, fetal monitoring, and matters requiring attention during delivery (Table 5.1). Nephrologists should focus on drug management during pregnancy (Table 5.2),

Table 5.1 Aspects of pregnancy management in patients with CKD

Classification of aspects	Aspects of management
Medications	• Selection and adjustment of immunosuppressant and other medications for CKD (Table 5.2)
	• Low-molecular-weight heparin, which is recommended to prevent thrombosis in patients with nephrotic syndrome and high risk of thrombus formation
	• Low-dose aspirin (50–100 mg/day) until 28 weeks of gestation
	• Calcium monitoring and supplementation
	• Folic acid (5 mg/day)
Blood pressure	• Use of antihypertensive drugs considered safe in pregnancy to enhance blood pressure control (Table 5.2)
	• Blood pressure target of 130–140/80–90 mmHg
	• Use of family self-test sphygmomanometer and recording of daily blood pressure at home
	• Recording of blood pressure at each follow-up
Laboratory examination	• Renal function (including SCr and serum urea levels, CCr rate, and proteinuria) should be examined at least once a month, depending on the severity and progression of kidney disease
	• Recording of baseline serum uric acid and liver enzyme levels, platelet count, and proteinuria, which is useful for the differential diagnosis of suspected PE after pregnancy
	• Glucose tolerance test, especially for pregnant women treated with glucocorticoid or calcineurin inhibitors
Fetal monitoring	• Biophysical profile
	• Assessment of fetal growth and development
	• Evaluation of placental function once a month in the first trimester of pregnancy, once every 2 weeks in the second trimester of pregnancy, and once a week in the third trimester of pregnancy
Delivery	• If the condition is stable and no obstetric-related indication for cesarean section exists, vaginal delivery is performed as much as possible
	• Termination of pregnancy if the condition is aggravated, endangering the lives of both the fetus and pregnant woman
	• If delivery is expected to be less than 34 weeks, glucocorticoid is administered prior to delivery to promote fetal lung maturation
	• Intermittent oxygen therapy, if necessary
	• Stress dose of hydrocortisone may be administered, if necessary

CKD chronic kidney disease; *SCr* serum creatinine; *CCr* creatinine clearance; *PE* preeclampsia
(Adapted from Guidelines for pregnancy management in patients with chronic kidney disease. Natl J Med China. 2017;97(12):3604–11 [40])

Table 5.2 Drug management during pregnancy in patients with CKD [40]

Drugs	Permeability of the placenta	Teratogenic effects	Effects on the fetus and newborn	Safety in pregnancy	Safety in lactation
Immunosuppressant					
Prednisone	Limited	The incidence of cleft palate may be increased	Infrequent; large dosage can lead to cataract, infection, and adrenal insufficiency	Maternal side effects include bone loss and osteonecrosis, gestational diabetes, hypertension, cataract, and adrenal insufficiency	Yes; breastfeeding is not recommended at doses greater than 60 mg/day
Azathioprine	Yes	No	Transient immune changes in newborns	Yes	Yes
Tacrolimus/ Cyclosporine A	Yes	No	Hypokalemia and renal insufficiency	Yes; increasing the dose is often required	Yes; 0.23–0.50% of dose adjusted for maternal body weight is secreted into breast milk
Mycophenolate mofetil	Yes	The incidence rate of congenital malformations is 22.9%, which include cleft lip and palate; absence of the ear canal; considerable distance between organs; small ear, fifth finger, and limb deformities; and toe hypoplasia	No	No; should be stopped before conception	No
Cyclophosphamide	Yes	Yes	Chromosomal abnormalities and leukopenia	No; should be stopped before conception	No
Antihypertensive agents					
Methyldopa	Yes	No	No	Top choice; restrict use when adverse events such as lethargy occur	Yes
Beta blocker	Yes	No	Some studies indicate limited fetal growth; the use of atenolol in the first trimester of pregnancy leads to bradycardia	Labetalol is preferred	It can be secreted to breast milk, but no adverse reactions have been reported

Table 5.2 (continued)

Drugs	Permeability of the placenta	Teratogenic effects	Effects on the fetus and newborn	Safety in pregnancy	Safety in lactation
Calcium channel blocker (nifedipine, amlodipine)	Yes	No	No	Second-line drugs commonly used in combination with methyldopa and labetalol	It can be secreted to breast milk (<5% therapeutic dose), but no adverse reactions have been reported
Diuretic (furosemide, hydrochlorothiazide)	Yes	No	Can cause fetal diuresis	In theory, it can reduce intravascular volume and placental perfusion. It can be carefully used in patients with excess fluid or refractory hypertension	Mother will exhibit polydipsia, and large doses can inhibit lactation
Hydralazine hydrochloride	Yes	No	No	Often combined with sympathetic nerve blockers to prevent reflex tachycardia	It can be secreted to breast milk, but no adverse reactions have been reported
ACEI/ARB	Yes	Teratogenic effects include neonatal anuria and renal insufficiency, limb contracture, craniofacial deformity, pulmonary dysplasia, and patent ductus arteriosus	Owing to renal papillary atrophy and disorders that prevent the establishment of renal medullary concentration gradients, long-term application can lead to renal insufficiency and impaired kidney function with regard to the concentration of urine	No; should be stopped before conception	A small amount of enalapril, captopril, and quinapril is secreted to breast milk, and no adverse reactions have been reported
Other drugs					
Recombinant EPO	No	No reports	No reports	Yes; increase the dose according to the need, which may cause hypertension	May be safe; protein may be damaged in the gastrointestinal tract of the infant
Intravenous iron	Yes	No reports	No reports	Yes	May be safe
Calcium-containing phosphate binder (calcium carbonate)	Yes	No reports	No reports	Yes	May be safe

(continued)

Table 5.2 (continued)

Drugs	Permeability of the placenta	Teratogenic effects	Effects on the fetus and newborn	Safety in pregnancy	Safety in lactation
Calcium-free phosphate binder (sevelamer, lanthanum carbonate)	NA	Animal studies show reduction in osteogenesis or osteogenic irregularity	NA	No; should be stopped before conception	No
Calcimimetics (cinacalcet)	NA	Animal studies show low risk	NA	Its use in patients with hypercalcemia can be continued	No
Sodium hydrogen carbonate	Yes	No reports	No reports	Yes	May be safe

CKD chronic kidney disease; *ACEI/ARB* angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; *EPO* erythropoietin; *NA* not applicable
(Adapted from Guidelines for pregnancy management in patients with chronic kidney disease. Natl J Med China. 2017;97(12):3604–11 [40])

especially the use of immunosuppressive and antihypertensive agents.

5.3.2.1 Immunosuppressants

Immunosuppressive agents deemed safe in pregnancy include corticosteroids, hydroxychloroquine, azathioprine, and calcineurin inhibitors. The use of rituximab is the last treatment option in the first trimester of pregnancy and should be considered only if its potential benefit outweighs the potential fetal risk. Cyclophosphamide, mycophenolate mofetil, leflunomide, and methotrexate should be contraindicated in pregnant women because of their teratogenic effect, and their use should be discontinued at least 3–6 months prior to conception (Table 5.2).

- **Corticosteroids**
  Corticosteroid dosage should be minimized during pregnancy based on the status of kidney disease. Methylprednisolone at high dosage may be used when disease activity becomes severe. Prednisone or prednisolone is appropriate, but it is not recommended to use fluorinated glucocorticoids, such as dexamethasone and betamethasone, which are only used in the third trimester of pregnancy to promote fetal lung maturation. Approximately 10% of maternal prednisone dosage can enter into the fetus through the placenta. Hence, prednisone is generally safe for the fetus, but its high dosage may be associated with premature rupture of membranes [24]. Other side effects of corticosteroids are similar to those in nonpregnant patients, including increased risk of diabetes, hypertension, osteoporosis, weight gain, infection, cataract, and mood changes during pregnancy.
- **Hydroxychloroquine**
  Hydroxychloroquine has no teratogenic effect. During pregnancy, hydroxychloroquine should be continued or started to maintain kidney disease remission or control lupus activity outside the kidney. Stopping hydroxychloroquine will increase the risk of relapse during pregnancy [25].
- **Azathioprine**
  Azathioprine is usually used during pregnancy to maintain disease remission. Animal studies have reported the teratogenicity of azathioprine. However, azathioprine exerts no teratogenic effect on the human fetus because the liver of the human fetus lacks hypoxanthine nucleotide pyrophosphorylase, which can metabolize azathioprine into 6-mercaptopurine. After administration of azathioprine in renal transplant recipients during pregnancy, the incidence of congenital malformation in

newborns was not different from that in the general population, indicating that azathioprine had no teratogenic effect [26].

- **Calcineurin inhibitors**
  Studies on renal transplant recipients have shown that calcineurin inhibitors such as cyclosporine A and tacrolimus do not increase the risk of teratogenicity and, thus, can be safely used during pregnancy. Considering the change in the distribution volume of cyclosporine A and tacrolimus and the increase in liver metabolism during pregnancy, the dosage should be gradually increased by 20–25% of the dosage before gestation starting from the second trimester of pregnancy [27]. Furthermore, individual differences should be considered to reduce the side effects of drugs, and the effective minimum dosage should be selected to reduce potential drug toxicity. The drug concentration needs to be carefully titrated, maintaining the effective concentration within the lower treatment window. Postpartum dosage should be quickly reduced to the prepregnancy level [28].
- **Mycophenolate mofetil and cyclophosphamide**
  The use of mycophenolate mofetil and cyclophosphamide is avoided during pregnancy owing to their teratogenicity. The use of mycophenolate mofetil in the first trimester of pregnancy may result in a high abortion rate and severe congenital defects in the fetus, including cleft lip and palate, microtia, and external auditory canal atresia. A prescription of cyclophosphamide in the first trimester of pregnancy may lead to abnormal fetal skull, ear, and head, as well as abnormal and delayed development of the limbs and internal organs. In addition, its prescription in the third trimester of pregnancy can lead to FGR, hematopoietic suppression, and nerve injury [29].
- **Rituximab**
  Rituximab can pass through the placenta and cause neonatal B-cell depletion, the incidence and severity of which increase from midterm to full-term pregnancy. Therefore, rituximab is recommended as the last treatment option in the first trimester of pregnancy [30]. However, the effect of intrauterine exposure to rituximab on fetal immune system development remains uncertain. B cells in newborns whose mothers were treated with rituximab should be monitored before routine vaccination; if necessary, vaccination should be delayed.

5.3.2.2 Hypertension Management

The blood pressure target during pregnancy is 130–140/80–90 mmHg. Avoid excessive hypotension, which could result in insufficient placental perfusion that affects fetal growth and development. Antihypertensive agents considered safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine (Table 5.2).

- **Blood pressure target**
  The blood pressure during pregnancy has been suggested to be maintained at 130–140/80–90 mmHg. It should be noted that the blood pressure should be steadily decreased. The amplitude of blood pressure reduction should not be too large. The appropriate amplitude is 10–25% of the mean arterial pressure and should be achieved within 24–28 h, avoiding excessive hypotension that may lead to insufficient placental perfusion, which affects fetal growth and development. The Control of Hypertension in Pregnancy Study confirmed that treating hypertension in pregnancy to a lower diastolic blood pressure target is not associated with adverse neonatal events or pregnancy outcomes. Furthermore, women with less tight control more frequently developed a blood pressure ≥160/110 mmHg, which may aggravate potential kidney diseases; hence, a blood pressure target <140/90 mmHg has been recommended for women with CKD during pregnancy [31].
- **Antihypertensive drugs**
  Antihypertensive drugs considered safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine. Studies have reported that adverse outcomes in perinatal and pregnant women, including SGA births, preterm delivery, severe hypertension and PE, infant respiratory distress syndrome, sepsis, and epilepsy, were fewer in the methyldopa group

than in the labetalol group, suggesting that methyldopa is more beneficial in hypertensive pregnant women than labetalol [32, 33]. Long-acting nifedipine and amlodipine are second-line drugs, often with methyldopa and labetalol. Other beta blockers (such as metoprolol) and calcium channel blockers (such as nimodipine and nicardipine) are substituted only when pregnant women cannot tolerate these recommended safer antihypertensive drugs. As diuretic can lead to increased plasma concentration, effective reduction in the circulating blood volume, and hypercoagulability, loop diuretics such as furosemide can only be used when pregnant women have systemic, pulmonary, or cerebral edema, renal insufficiency, and acute cardiac failure. Antisterone can pass through the placenta to produce an antiandrogenic effect on the fetus and, thus, should be avoided during pregnancy. The use of RAS inhibitors can lead to fetal heart and kidney defects, including atrial septal defect, ventricular septal defect, pulmonary stenosis, patent ductus arteriosus, renal hypoplasia, oligohydramnios, and complications such as limb contracture, pulmonary hypoplasia, and craniofacial malformation, and is therefore absolutely prohibited during pregnancy [34].

5.3.2.3 Other Drugs Commonly Used in Patients with CKD

Pregnant women with advanced CKD may have several complications, including anemia, acidosis, hyperphosphatemia, and bone disease.

Owing to the relative lack of erythropoietin (EPO) in pregnancy and EPO resistance due to pregnancy-related inflammatory factors, severe anemia, which affects placental and fetal growth, may occur in pregnant women with CKD. It is recommended that the hemoglobin level be maintained at 100 g/L in pregnant women with CKD [9]. The use of EPO and oral iron to correct anemia is safe, and the dosage usually needs to be increased; nevertheless, there are no adequate and well-controlled studies for intravenous iron in pregnant women. The blood pH in pregnant women is alkalescent, and no bicarbonate supplementation is required for them unless severe acidosis occurs. Studies on the safety of drugs commonly used as treatment for calcium and phosphorus metabolic disorders and secondary hyperparathyroidism during pregnancy are limited. Calcium carbonate can be used during pregnancy, although there exists no study reporting the safety of calcium carbonate, lanthanum carbonate, and calcimimetics during pregnancy. Thrombosis in patients with severe proteinuria and serum albumin <20 g/L should be prevented throughout the entire pregnancy period, whereas anticoagulation therapy for patients without severe nephrotic syndrome but with other high-risk factors, such as obesity, lack of ambulatory capacity, membranous nephropathy, or vasculitis, should also be considered. Low-molecular-weight heparin for anticoagulation can be subcutaneously injected. Thrombosis prevention is usually stopped during delivery. However, the risk of postpartum thrombosis is particularly high, and anticoagulation therapy should continue as long as possible until at least 6 weeks postpartum. See the American College of Chest Physicians guidelines [35] and the American Diabetes Association guidelines on the use of glucose-lowering agents during pregnancy [36].

5.3.2.4 Diet Management

For pregnant women with CKD at any stage or renal transplant recipients, the energy intake is 35 kcal/kg/day in the first trimester of pregnancy; however, this energy intake should be increased by an additional 300 kcal/day from the baseline during the second and third trimesters of pregnancy. For pregnant women with stage 1–3 CKD, with stage 4–5 CKD, and on dialysis, the protein intake is 0.8, 0.6, and 1.2–1.3 g/kg/day, respectively, and a daily increase of 10 g protein should be added on this basis [37]. Daily supplementation with 0.63 g/8–10 kg keto acid based on the ideal body weight may reduce SGA births [38].

5.3.3 Follow-Up During Pregnancy

During pregnancy, women with CKD require close follow-up by both nephrologists and obstetricians to monitor disease activity and detect

obstetric complications (Table 5.1) and follow-up at least once per 4–6 weeks in the nephrology department. The monitoring frequency can be increased according to the severity and progression of kidney disease. Patients are followed up to monitor blood pressure (measurement and recording at home are recommended), renal function (including SCr and serum urea levels and creatinine clearance rate), serum uric acid level, 24-h urinary protein quantitative analysis, urine red blood cell count, midstream urine culture (especially in patients with pyelonephritis), and blood glucose level (glucose tolerance tests, if necessary, especially for pregnant women taking hormone or calcineurin inhibitors). Recording the platelet count and levels of basal uric acid, liver enzymes, and urinary proteins is helpful for the differential diagnosis of suspected PE after pregnancy. For systemic diseases such as LN and vasculitis, related immunological parameters need to be monitored at each follow-up visit. At baseline and every 10–12 weeks, nutritional parameters should be monitored, including iron, folic acid, vitamin D, vitamin B_{12}, albumin, and total protein. While following the instructions from nephrologists, pregnant women with CKD should simultaneously follow the instructions of obstetricians during regular follow-up.

5.3.4 Peripartum Management

5.3.4.1 Indication for Termination of Pregnancy

The pregnancy should be terminated if the condition of the gravida or fetus severely deteriorates before 32 weeks of gestation or does not deteriorate too seriously after 32 weeks of gestation. In addition, when typical PE or HELLP syndrome occurs, the condition of pregnant women gradually deteriorates, showing severe and uncontrollable hypertension and nephrotic syndrome accompanied by a rapid increase in proteinuria and/or SCr. The condition of the fetus also gradually deteriorates, presenting abnormal fetal heart rate at any gestational week, umbilical artery diastolic blood flow deficiency at ≥32 weeks on Doppler ultrasonography, and no fetal growth in the third trimester of pregnancy during the period of >2 weeks. In case of the above situation, a full course of dexamethasone to promote lung maturation should be routinely administered. Cesarean section should be performed to end the labor if the fetus is abnormal before parturition or during labor, adverse conditions occur during induced labor, or induced labor fails. All newborns with birth weight <1500 g, gestational age <34 weeks, and Apgar score <7 at 5 min and those in need of intubation should be transferred to the NICU [39].

5.3.4.2 Delivery Mode

If the condition is stable and no obstetric-related indication for cesarean section exists, an attempted vaginal delivery may be considered. Otherwise, if the condition is aggravated and it is estimated that vaginal delivery within a short period of time is impossible, cesarean section should be performed.

5.3.5 Postpartum Management

Postpartum management of patients with CKD includes monitoring kidney disease activity, blood pressure, and GFR; performing urine analysis; paying attention to plasma concentration assessment in patients treated with calcineurin inhibitors; continuously preventing thrombosis until 6 weeks after delivery in patients at high risk of thrombosis, if necessary; encouraging patients to breastfeed their infants; and providing emotional support to prevent postpartum depression.

Patients with CKD are encouraged to use the minimum dose of drugs safely used during pregnancy and breastfeeding. Only a small amount of prednisone, azathioprine, and tacrolimus can be secreted into breast milk, with cyclosporine A being almost undetectable in breast milk; therefore, the use of these drugs can be continued during lactation. Because of the change in postpartum maternal physiology, the plasma concentration of calcineurin inhibitors will increase. It is necessary to reassess and adjust the dose as soon as possible to avoid nephrotoxicity to the mother

and possibly to the infant. Do not breastfeed when patients require treatment with mycophenolate mofetil or cyclophosphamide for obvious disease activity. As macromolecules, particularly monoclonal antibodies, are not secreted into breast milk, active postpartum nephritis can be treated using rituximab. With respect to antihypertensive therapy, methyldopa, labetalol, and long-acting nifedipine are the most commonly used drugs. Diuretic-induced dehydration may impede milk secretion; thus, the use of diuretics is usually avoided. Several RAS inhibitors, including enalapril, captopril, and quinapril, are not detected in breast milk and should be used as early as possible to reduce proteinuria. Considering patients' experience of a very risky pregnancy, attention should be paid to their mood changes to prevent postpartum depression.

Key Messages

- Women with CKD remain a part of the patient population that carries the highest risk of adverse maternal and fetal outcomes; therefore, managing pregnancy in patients with CKD has become a considerable challenge shared by both nephrologists and obstetricians.
- To achieve better outcomes for pregnant women with CKD, strengthened management is required, including prepregnancy preparation, pregnancy management, peripartum management, and postpartum care.
- The more difficult blood pressure control becomes and the more advanced CKD is, the higher the risk of poor pregnancy outcome. Hence, patients with early-stage CKD who have well-controlled blood pressure and proteinuria <1 g/24 h may consider pregnancy, but the risks of pregnancy should be well recognized.
- The use of an immunosuppressant considered safe in pregnancy for 3–6 months before conception is recommended for women with CKD to achieve disease remission. Strict contraception is required prior to disease remission.
- Gestational management in patients with CKD includes blood pressure control, medication adjustment, laboratory examination, fetal monitoring, and matters requiring attention during delivery. Nephrologists should focus on drug management, especially the use of immunosuppressive and antihypertensive agents.
- During pregnancy, women with CKD require close follow-up to monitor blood pressure, renal function, serum uric acid level, 24-h urinary protein quantitative analysis, urine red blood cell count, midstream urine culture, and blood glucose level.
- If the condition of the patient is stable and no obstetric-related indication for cesarean section exists, vaginal delivery is performed as much as possible; otherwise, if the condition is aggravated, endangering the lives of both the fetus and pregnant woman, the pregnancy needs to be immediately terminated.
- Postpartum management of patients with CKD includes monitoring kidney disease activity, blood pressure, and GFR, performing urine analysis, encouraging patients to breastfeed their infants, and providing emotional support to prevent postpartum depression.

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Aging and Chronic Kidney Disease

6

Tao Zhang

Abstract

With renal aging, a complex interplay of genetics, environmental changes, and cellular dysfunction leads to the histological and functional changes. The faster expanding population of elderly is more likely to experience chronic kidney disease (CKD) and progress to end-stage kidney disease (ESRD). Glomerular filtration rate (GFR) is the most important indicator commonly used for the diagnosis and grading of CKD. The MDRD and CG formulas are the most widely applied, and the CKD-EPI$_{SCr–cys}$ formula is an acceptable choice for the elderly. The treatment of CKD in older patients requires overall consideration because the risk of cardiovascular disease mortality is greater than the risk of developing ESRD at the same GFR level. An individualized patient-centered approach may offer more benefits than a traditional disease-oriented approach in old patients. There are few clinical practice guidelines on the management of the elderly with CKD. The European guideline recommends the use of four variables (age, sex, eGFR, and albuminuria) to predict the risk of ESRD and of the REIN score to predict the risk of mortality in older patients with stage 5 CKD. Further studies are required for solving the controversy concerning CKD in the elderly.

6.1 Introduction

Aging is a natural process in all species that results in degenerative changes in many organs and is determined by genetic, environmental, and stochastic factors [1]. Age-related changes in the structure of the kidney usually begin at the age of 40 years and accelerate at approximately 50 years. These changes include gradual nephron loss, glomerulosclerosis, tubular atrophy, and interstitial fibrosis, resulting in renal function decline and hemodynamic and water electrolyte disturbance [2]. Kidney aging poses a serious health risk in the elderly.

The proportion of the elderly population is steadily increasing worldwide, especially in lower- and middle-income countries [3]. This demographic change is related to social and economic development and prolongation of life [4]. As chronic kidney disease (CKD) can impose serious disease burden and consume huge amounts of health resources and the prevalence rate of CKD is higher in the elderly population than in the general population, more attention should be paid to research on

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CKD and aging. CKD is one of the multiple risk factors for death in elderly patients. Other risk factors include diabetes, hypertension, heart disease, and stroke [5–7]. Therefore, in 2014, the International Society of Nephrology and the International Federation of Kidney Foundations established "chronic kidney disease in the elderly" as the theme of the World Kidney Day to raise awareness about and enhance the recognition of CKD in the elderly [8]. This chapter mainly describes the diagnosis, management, and treatment of CKD in elderly patients and also discusses some related controversial issues pertaining to CKD in the elderly.

6.2 Epidemiology of CKD in the Elderly

Few studies have investigated the prevalence of CKD in the elderly population aged >65 years to date. Although the prevalence of CKD increases with age, data on this quite vary. The National Health and Nutrition Examination Survey (NHANES) is the most consummate epidemiologic study on US civilian residents with CKD in the United States. Serial analyses of the NHANES data indicate that the prevalence of CKD significantly increased in the aging US population. Coresh et al. compared the prevalence of CKD in the 1988–1994 NHANES with that in the 1999–2004 NHANES and determined that the prevalence rate of stage 1–4 CKD in the adult population increased from 10 to 13.1%, whereas the prevalence rate of CKD in the elderly (aged >70 years) increased from 36.8 to 47.8%. Further adjustment for the higher prevalence of diagnosed diabetes and hypertension and higher body mass index (BMI) practically explained all of the difference in addition to older age. In fully adjusted models, the prevalence of albuminuria was strongly associated with diagnosed diabetes (odds ratio [OR], 3.58; 95% confidence interval [CI], 3.12–4.12) and hypertension (OR, 1.70; 95% CI, 1.10–1.92), as well as older age and all race groups ($P < 0.001$), but not with higher BMI ($P = 0.12$). Of individuals aged >65 years with CKD (higher than stage 3), 11% developed uremia (Fig. 6.1) [9]. Murphy et al. examined the 1988–1994 and 1999–2012 NHANES data and reported that the prevalence of stage 3–4 CKD adjusted for sex, race/ethnicity, and diabetes status was higher in older individuals (estimated glomerular filtration rate [eGFR] calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula: 15–59 mL/min/1.73 m^2). However, in all age groups, the prevalence of stage 3–4 CKD had largely stabilized since 2003–2004 (Fig. 6.2) [10, 11]. A 2015 study reported that the prevalence rate of CKD was 11.5%, 16.3%, and 64.1% in Chinese people aged >45 years, 60–79 years, and >80 years, respectively [12]. The prevalence of CKD increases with aging but has been differently reported in various studies owing to the lack of adjustment for age, sex, race/ethnicity, and diabetes status.

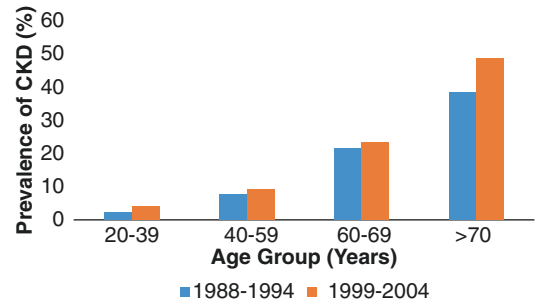

Fig. 6.1 Prevalence of chronic kidney disease by age group in the National Health and Nutrition Examination Survey (NHANES) for 1988–1994 and 1999–2004. (Reproduced with permission from Coresh et al. [9])

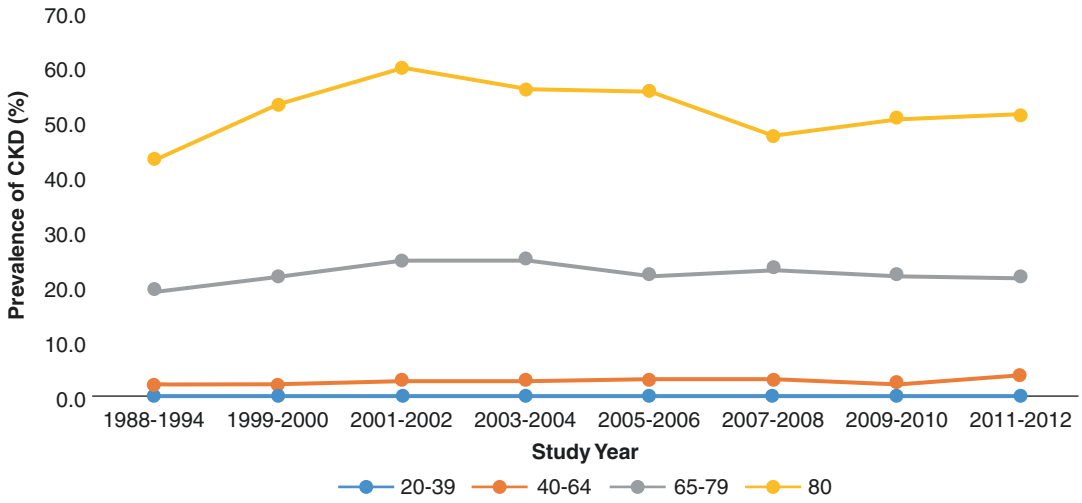

Fig. 6.2 Prevalence of chronic kidney disease by age group in the National Health and Nutrition Examination Survey (NHANES) for 1988–1994 and every 2 years from 1999 to 2012 [10])

6.3 Diagnosis of and Controversy Concerning CKD in the Elderly

Beginning at the age of 40 years, the glomerular filtration rate (GFR) declines by approximately 8 mL/min/1.73 m^2 per decade in a healthy individual although the rate of decline is highly variable. After approximately 75 years of age, the rate of GFR decline may accelerate; however, such progressive GFR decline is not fast enough to cause kidney failure throughout the human life span [13, 14]. According to contemporary diagnostic criteria for CKD, any subject, regardless of age, with a measured or estimated GFR <60 mL/min/1.73 m^2 present for at least 3 months is considered to have CKD (stages 3–5) irrespective of the presence or absence of other signs of kidney injury, as recommended in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline [15, 16]. Consequently, a great majority of the elderly can be "diagnosed" with CKD although this can and does occur in healthy aging [9]. Therefore, considerable controversy exists as to whether the GFR decline in the elderly indicates disease status or occurs with natural aging. This has been suggested as an example of "overdiagnosis" of CKD in the elderly, which leads to unnecessary medical expenses due to the inappropriate use of CKD definition based on measured GFR or eGFR [17, 18]. It is debatable whether the diagnosis of stage 1–2 CKD in the elderly should be cut off. Although the 2012 KDIGO clinical practice guideline proposed a "special concern" for the diagnosis of CKD in the elderly, no special recommendation concerning the diagnostic criteria for CKD in the elderly has been put forward. In a meta-analysis that included 46 cohort studies and approximately two million patients, Hallan et al. discussed in 2012 the correlation between progression to end-stage renal disease (ESRD), mortality, age, proteinuria, and GFR level. Furthermore, their analysis showed that eGFR decline and urinary protein level were independent risk factors and were associated with the relative risk of all-cause mortality and ESRD in the general population, supporting the current KDIGO guideline on the analysis of GFR and proteinuria level [19, 20]. It is also based on these findings that the 2012 KDIGO clinical practice guideline does not have specific diagnostic criteria for CKD in the elderly. Findings from the study of Dousdampanis et al. also supported the diagnostic criteria for CKD without the boundary value for age [18, 21, 22]. However, the lack of evidence from studies on CKD in the elderly

underlines the need for a large number of prospective studies on the diagnostic criteria for CKD in elderly patients.

6.4 Renal Function Evaluation Formula for the Elderly

GFR is the most important indicator for the diagnosis and staging of CKD. Inulin clearance is the gold standard for GFR determination, but its high price and complex operation limit its clinical use. Thus far, a total of more than 25 GFR estimation formulas based on serum creatinine (SCr) exist, with the simplified version of the Modification of Diet in Renal Disease (MDRD) Study formula and Cockcroft–Gault (CG) formula being the most widely applied [23, 24].

The MDRD formula was designed based on patients with CKD, and its applicability has been widely validated in patients with CKD. With respect to its application in healthy individuals with normal renal function and patients with CKD who have mild renal insufficiency (GFR >60 mL/min/1.73 m^2), the equation appears to provide a low estimate of the true value, resulting in error in estimating the clinical renal function. Owing to the limitation of the MDRD formula, the CKD-EPI research group in 2009 proposed the CKD-EPI formula and performed a larger investigation [25]. This study included healthy individuals and patients with CKD as subjects, and the MDRD formula was subsequently further modified. The CKD-EPI formula is better than the MDRD formula with respect to accuracy and relevance, especially in population with high GFR [26–28]. Recent studies have shown that cystatin C is an ideal endogenous marker of glomerular function that cannot be affected by inflammation, tumor, age, sex, muscle mass, stress, immunity, and endocrine diseases. Cystatin C can be used for the early detection of CKD, as its concentration sensitively reflects impaired renal function [29]. With the widespread use of cystatin C, some GFR estimation formulas have been based on cystatin C measurement [30, 31]. In 2012, the CKD-EPI research group also advanced two improvements: CKD-EPI_{cys} formula, which is based on cystatin C, and CKD-$EPI_{SCr–cys}$ formula, which is based on the combination of SCr and cystatin C. However, there were considerable controversies as to which GFR estimation formula might be more suitable for the elderly. Studies using GFR estimation formulas were not specifically designed for the elderly, and there was no medical evidence supporting the evaluation of these formulas in older patient populations.

Drenth-van Maanen et al., Péquignot et al., and Helou considered the CG formula to be the most accurate in older patients, especially those with malnutrition and chronic inflammatory disease, because values corrected by the ideal body mass are used in the CG formula [32–34]. However, Flamant et al. recommended the use of MDRD and CKD-EPI formulas for the elderly, as the CG formula underestimated the renal function in older individuals [35]. In the study of Nyman et al., which had a small European elderly sample, the deviation and accuracy of the CKD-EPI formula were better than those of the improved simplified version of the MDRD formula [36]. Dowling et al. believed that the CG formula should be used when the drug dosage is adjusted according to the renal function of older patients [37]. Many studies examined the bias in different GFR estimation formulas in relation to measured GFR [37–39]. SCr-based renal function evaluation often showed deviation due to reduced physical function and chronic diseases in older patients [40]. Owing to the overestimation of the prevalence rate of stage 3a CKD (GFR, 45–59 mL/min/1.73 m^2) by the SCr-based GFR equation, the 2012 KDIGO clinical practice guideline further recommended the use of GFR estimation formulas based on cystatin C to validate whether patients were diagnosed with stage 3a CKD in the absence of evidence of renal injury in order to reduce excessive diagnosis of stage 3a CKD. According to the guideline, GFR estimation formulas based on cystatin C had less bias than other formulas used to calculate GFR in the elderly [16, 41]. In 2016, the European clinical practice guideline on the management of older patients with stage 3b or higher CKD (GFR

<45 mL/min/1.73 m^2) advised the use of estimation formulas instead of SCr measurements to assess renal function in older patients. No equation was preferred, and the CKD-$EPI_{SCr–cys}$ formula was considered an acceptable choice [42, 43]. In view of current controversies, epidemiologic studies on the elderly are required to develop a more suitable GFR estimation formula for this particular group.

6.5 Treatment and Intervention for Older Patients with CKD

The elderly, particularly those with comorbidities, are not enrolled in most reported studies, and clinical guidelines for them are lacking [44–46]. Some treatments proposed by clinical guidelines for older patients with CKD, including the use of renin–angiotensin system blockers, are controversial [47]. Treatment for adults with CKD is different from that of older patients with CKD, as the clinical manifestations of the latter mainly include eGFR reduction and unapparent proteinuria or albuminuria. For the elderly without albuminuria, the benefit of renoprotection therapy is very limited [48]. Clinicians could not mechanically apply CKD guidelines in the elderly and should pay attention to delaying the progression of CKD. It is more important to reduce renal damage under stress and preserve renal function because older individuals could have more serious injury and more difficult recovery than younger individuals under the same stress [49]. Many risk factors could be avoided, including the use of nephrotoxic drugs, cardiac surgery, interventional therapy, ischemia, and inflammation [50]. At the same GFR level, the risk of death, myocardial infarction, and stroke in older patients with CKD is greater than the risk of developing ESRD [51]. A high risk of all-cause and cardiovascular disease mortality in community-dwelling elderly individuals with CKD has been reported [52]. These patients could benefit from slowing down renal impairment and improving metabolic acidosis, anemia, and hyperphosphatemia, and the risk of cardiovascular events could be reduced. Sufficient evidence on the use of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) to delay the progression of CKD in most older patients with CKD remains lacking. There is an increasing risk of renal injury under the circumstances of hypovolemia, excessive diuresis, renal artery stenosis, severe left heart failure, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

No randomized controlled trials have compared dialysis and nondialysis treatment in older patients diagnosed with ESRD [53]. In a retrospective analysis of patient survival among those older than 75 years with CKD stage 5, the first- and second-year survival rates of the dialysis group were superior to those of the conservative group. However, this survival advantage was lost in patients with multiple comorbidities [54]. Decisions about whether to receive dialysis or not are difficult before dialysis, and the choice between hemodialysis and peritoneal dialysis should remain individualized in the elderly [55–57]. Age alone does not necessarily preclude candidacy for renal transplantation. In 2011, 60% of renal transplant recipients were older than 50 years, of whom 18% were older than 65 years [58]. Improvement in the quality of life is the most important goal and should be evaluated from various aspects such as organ function, prognosis, cognitive status, social support, treatment burden, and nutritional status. Renal replacement therapy (RRT) is an appropriate option for older individuals with good baseline quality of life.

6.5.1 Changes in the Management of the Elderly with CKD

Well-defined disease-oriented models (Table 6.1) for different conditions exist. These models show the relationship between signs and symptoms and the pathophysiology of underlying diseases. Treatment plans target pathophysiological mechanisms, with improvement in disease-related outcomes as their goal [59]. Furthermore, these models have the advantage of providing a systematic framework

for guidance, diagnosis, evaluation, and measurement in patients. This disease-oriented method provides a simple and clear framework that is easy to be applied to a defined population [60].

Because GFR can be affected by the aging process, the prevalence of CKD increases with advancing age [61, 62]. However, several features of aging may limit the utility of disease-oriented models of care. In older individuals, complex comorbidities and geriatric syndromes are common, and signs and symptoms often do not reflect a single underlying pathophysiological process. Information on the safety and efficacy of recommended interventions is often lacking [63, 64]. For all these reasons, an individualized patient-centered model of care tends to be applied to the elderly over more traditional disease-oriented approaches (Table 6.1). An individualized patient-centered approach prioritizes patient preferences and embraces the notion that observed signs and symptoms often do not reflect a single unifying disease process but instead reveal the complex interplay among several different factors, including aging, social, pathological, and psychological factors [65]. This model focuses on alterable outcomes that matter to the patient. Prognostic information related to these and other outcomes is generally used to shape rather than dictate treatment decisions. For older populations with CKD, an individualized patient-centered approach to care may offer more than a traditional disease-oriented approach [64, 66].

6.5.2 Clinical Practice Guideline on the Management of Older Patients with CKD

Considering that the proportion of older patients with severe CKD increased at the end of 2016 based on the increasing number of older patients with infirmity although evidence from existing studies remains limited, the European Renal Best Practice released the clinical practice guideline on the management of older patients with CKD stage 3b–5 [43]. The new guideline is based on the old CKD-related research data, and its main contents include renal function evaluation in elderly patients with CKD and assessment of the benefits of diagnosing CKD during follow-up.

Renal function evaluation is recommended in the selection section of the renal function formula. The guideline recommends the four-variable Kidney Failure Risk Equation (KFRE), as it performs sufficiently well for use in older patients with advanced CKD and eGFR <45 mL/min/1.73 m^2 [67, 68]. The four-variable KFRE (age, sex, eGFR, and albuminuria) predicted the risk of ESRD at 2 and 5 years and achieved excellent discrimination (pooled c-statistic 0.91 and 0.88 at 2 and 5 years, respectively) in further validation cohorts that included 721,357 individuals with CKD stage 3–5 in North America, Asia, Europe, and Australasia [19, 69]. This guideline suggests the use of the Bansal score to predict the individual 5-year risk of mortality before ESRD in non-frail older patients with CKD stage 3–5 and recommends that an assess-

Table 6.1 Changes in the decision-making model for the treatment of chronic kidney disease in the elderly

Model	Disease-oriented model	Patient-centered model
Primary concern	• Diagnosis, prevention, and treatment of the disease	• Particularity and priority of patients
Treatment target	• Pathophysiology of the disease	• Variable factors affecting the health of patients
Clinical outcome	• Determined by the disease	• Determined by the specific priority of patients
Survival	• The first goal of treatment and prevention	• One of the goals
Pathogeny	• Pathological causes of the disease (mental, environmental, social, and other secondary factors) are not the main determinants of the disease	• The state of health is due to the interaction of complex factors, such as hereditary, religious, environmental, and social factors

ment of frailty be performed for patients at low risk based on the Bansal score [70, 71]. The final risk prediction model includes nine readily available demographic, clinical, and biochemical predictors: age, sex, ethnicity, eGFR, urinary albumin-to-creatinine ratio, diabetes, smoking status, history of heart failure, and stroke. It is recommended that patients at low risk based on the Bansal score be evaluated for physical weakness [72–74]. High-risk management should be implemented for patients with physical weakness who require dialysis. The guideline also recommends that the Renal Epidemiology and Information Network (REIN) score be used to predict the risk of mortality in older patients with CKD stage 5 [75]. The risk prediction model developed from 12,500 French incident dialysis patients and validated in 11,848 different dialysis patients, includes nine predictors: age, sex, history of congestive heart failure, peripheral vascular disease, dysrhythmia, cancer, severe behavioral disorder, mobility, and baseline serum albumin concentration [69, 76, 77].

The guideline recommends that a simple score be regularly used to assess functional status in older patients with CKD stage 3b–5d in order to identify those who would benefit from a more in-depth geriatric assessment and rehabilitation [78–80]. Furthermore, according to this guideline, most simple scores, including self-report scales and field tests (sit-to-stand, gait speed, and 6-min walk tests), have comparable and sufficient discriminating power to identify patients with decreased functional status [81–83]. As exercise has a positive effect on the functional status of older patients with CKD stage 3b or higher, the guideline recommends that exercise training be offered in a structured and individualized manner to avoid adverse events. The formulation of sports training programs should be systematized and individualized to avoid the occurrence of adverse events [84–86]. Exercise training under supervision at 2 hours before dialysis and regular follow-up are very important for patients on dialysis [87–89]. The guideline proposes subjective global assessment as the gold standard for assessing the nutritional status of older patients with CKD stage 3b or higher and suggests that a score including serum albumin concentration, BMI, SCr normalized to body surface area, and normalized protein nitrogen appearance may be used to assess the nutritional status of older patients on hemodialysis [90, 91]. The elderly are mostly in a high-energy consumption risk state, and nutritional assessment can predict the survival rate of patients on dialysis, which has important clinical implication [92, 93].

6.5.3 RRT vs. Conservative Treatment

Some scholars believe that the survival benefit from RRT is not obvious in elderly patients with CKD [94, 95]. Taking into account the reduced organ functional status and poor quality of life in patients with CKD, complicated treatment processes, and increased medical expenses, conservative treatment is considered appropriate [96, 97]. The European guideline recommends a comprehensive assessment of renal function and survival risk and selection of appropriate RRT method. With respect to the choice of management methods for ESRD, conservative treatment is recommended in the shared decision-making [98, 99]. The REIN score is recommended to predict short-term (6-month) prognosis in RRT patients [100]. At the same GFR level, the risk of death, myocardial infarction, and stroke in older patients with CKD is greater than the risk of developing ESRD. Slowing down renal damage and improving metabolic acidosis, anemia, and hyperphosphatemia can reduce the risk of cardiovascular events and benefit elderly patients with CKD [95, 99].

For most elderly patients with CKD, evidence on the use of ACEIs/ARBs to delay the progression of the disease, especially in combination with insufficient blood volume or excessive diuretic use, remains lacking [101]. Renal artery stenosis, obvious left-sided heart failure, and NSAID use also increase the risk of kidney injury. There is no unified answer as to whether elderly patients with end-stage CKD require dial-

ysis or conservative treatment [102, 103]. In developed countries, older patients with end-stage CKD have gradually switched from conservative treatment to dialysis. Under suitable conditions, age is not a contraindication for renal transplantation [104, 105]. Improvement in the quality of life is the most important goal and should be evaluated from various aspects such as organ function, prognosis, cognitive status, social support, treatment burden, vision or hearing, and nutritional status [106, 107]. RRT is a suitable option for the elderly with good baseline quality of life.

6.6 Conclusions

Many problems concerning the diagnosis and treatment of CKD in the elderly still exist, such as the suitable diagnostic criteria, causes of CKD, therapeutic targets, and related complications. The treatment for these patients requires a comprehensive balance, and management using a patient-centered approach rather than a disease-oriented approach should be established.

Key Messages

- The prevalence of CKD is higher in the elderly than in the younger population. Various renal functions are affected by the complex process of aging. The GFR in older patients with CKD declines with normal aging and disease progression.
- There is currently no special recommendation with respect to the diagnostic criteria for CKD in the elderly. The criteria proposed by the 2012 KDIGO clinical practice guideline could overestimate the prevalence of CKD in the elderly.
- No equation for renal function evaluation in the elderly is preferred. The MDRD and CG formulas are the most widely applied, and the CKD-EPI$_{SCr–cys}$ formula is an acceptable choice in the elderly.
- For the management of CKD in older populations, an individualized patient-centered approach may offer more benefits than a traditional disease-oriented approach.
- The treatment of CKD in older patients requires overall consideration because the risk of cardiovascular disease mortality is greater than the risk of developing ESRD at the same GFR level.
- In 2016, the European Renal Best Practice released the clinical practice guideline on the management of the elderly with CKD stage 3b–5. This guideline recommends the use of four-variable KFRE (age, sex, eGFR, and albuminuria) to predict the risk of ESRD and of the REIN score to predict the risk of mortality in older patients with CKD stage 5.

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Acute Kidney Injury and Chronic Kidney Disease

7

Yu Chen and Weichun He

Abstract

Chronic kidney disease (CKD) is a potent risk factor for acute kidney injury (AKI) and a modifier for the relationship between AKI and adverse outcome, while AKI increases the risk of de novo CKD and is an accelerator for the progression of underlying CKD. When patients with CKD develop dialysis-requiring AKI, available data suggest that the recovery of kidney function is less likely than in patients without CKD. Patients with AKI were more likely to develop CKD compared with matched control patients without AKI. For CKD patients at high risk for developing AKI, preventive measures for AKI include adequate fluid repletion in those with hypovolemia, avoidance of hypotension by providing inotropic support as needed, and readjustment of nephrotoxic medications based on close monitoring of renal function and drug levels, if available. For CKD patients developing AKI, the basic principles of general management include specific treatment of the underlying cause, fluid management, electrolyte management, adjustment of drug dosing, nutritional support, renal replacement therapy, and specific pharmacologic therapies.

7.1 Introduction

Recent epidemiological studies have shown complex interactions between acute renal injury (AKI) and chronic renal disease (CKD). An increasing body of evidence supports bidirectional relationships between these two clinical events, that is, the existence of CKD increases the risk of AKI, while AKI causes CKD or worsens prior CKD. Given that the presence of potential CKD may change the correlation of AKI with adverse outcomes, CKD not only remains one of the most powerful predictors of AKI, but also acts as an effective modifier for AKI and its associated outcomes [1]. In this chapter, we will review the evidence that CKD predisposes to AKI, which in turn contribute to aggravate the preexisting CKD and the evidence that recovery after AKI to baseline renal function relates to an increase in the risk of de novo CKD. In addition, we will focus on the diagnostic criteria for AKI in patients with CKD, and the strategy for preventing and managing AKI on CKD.

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7.2 Acute Kidney Injury

7.2.1 Definition and Criteria

AKI, formerly known as acute renal failure, is characterized by abrupt deterioration of renal function [2]. A sudden decline in renal function causes the accumulation of nitrogen-containing wastes such as urea in the body as well as the disturbance in extracellular fluid volume, electrolyte, and acid-base. The replacement of the term AKI for acute renal failure to a large extent reflects the realization that even a smaller decline in renal function that does not result in obvious organ failure has important clinical significance and is related to an increase in morbidity and mortality. The definition of AKI used in clinical and epidemiologic studies is based on specific criteria that have been sequentially developed, with the Kidney Disease: Improving Global Outcomes (KDIGO) definition being the most recent and preferred [3]. Other criteria include the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [4] and its subsequent modification proposed by the Acute Kidney Injury Network (AKIN) [5] and others.

7.2.1.1 KDIGO's Definition for AKI

The KDIGO guidelines define AKI as follows [3]:

1. An increase in serum creatinine (SCr) concentration by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or
2. A ≥1.5-fold increase in SCr concentration from baseline, which is known or presumed to have occurred within the prior 7 days or
3. Urine output <0.5 mL/kg/h for 6 h

The KDIGO criteria allow for correction of volume status and obstructive causes of AKI prior to classification. Before diagnosing and classifying AKI, one should assess and optimize volume status and exclude obstruction. The timeframe for the absolute increase in SCr concentration ≥0.3 mg/dL is retained from the AKIN definition (i.e., 48 h), whereas the timeframe for a ≥50% increase in SCr concentration is reverted to 7 days originally included in the Acute Dialysis Quality Initiative's RIFLE criteria.

7.2.1.2 KDIGO's Staging Criteria for AKI

Using the KDIGO's criteria, AKI is staged as follows [2]:

- **Stage 1**—A 1.5–1.9-fold increase in SCr concentration from baseline, an increase in SCr concentration by ≥0.3 mg/dL (≥26.5 μmol/L), or a reduction in urine output to <0.5 mL/kg/h for 6–12 h.
- **Stage 2**—A 2.0–2.9-fold increase in SCr concentration from baseline or a reduction in urine output to <0.5 mL/kg/h for ≥12 h.
- **Stage 3**—A 3.0-fold increase in SCr concentration from baseline, an increase in SCr concentration to ≥4.0 mg/dL (≥353.6 μmol/L), a reduction in urine output to <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h, the initiation of renal replacement therapy (RRT), or in patients aged <18 years, a decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m^2.

The KDIGO criteria differ from the RIFLE criteria in that, instead of changes in glomerular filtration rate (GFR), the KDIGO criteria only utilize changes in SCr concentration and urine output for staging, except for children aged <18 years for whom an acute decrease in eGFR to <35 mL/min/1.73 m^2 is included in the criteria for stage 3 AKI. As with the RIFLE and AKIN staging systems, the KDIGO suggested that patients be classified according to criteria that result in the highest (i.e., most severe) stage of injury.

7.2.2 Epidemiology

AKI is an important complication of inpatients, accounting for 15% of all hospitalized patients according to previous studies. Among more than 3.5 million hospitalized patients in a meta-analysis that included 143 studies, the global incidence rate of AKI, as defined in accordance with KDIGO guidelines, was estimated to be 22%, the

equivalent of one in five hospitalized patients [6]. However, a more recent cross-sectional study performed in 97 intensive care units (ICUs) from 33 countries and based on data from 1802 patients during their first week of ICU admission reported a much higher AKI burden. Of enrolled patients, 57% fulfilled the KDIGO criteria for AKI [7].

AKI is responsible for approximately two million deaths worldwide every year [8–10], and it is becoming more and more common in critically ill patients. The mortality rate of the most severe AKI patients in need of RRT is 50–80% [10].

7.2.3 Etiology

The etiology of AKI is not involved in its definition, so the diagnosis of AKI is based on its clinical syndrome without considering its pathogenesis. Nevertheless, determining the cause of AKI is important for identifying appropriate treatment strategies to improve the prognosis of patients. In general, the causes of AKI can be classified into three categories, i.e., prerenal AKI, renal AKI, and postrenal AKI [11–13].

7.2.3.1 Causes of Prerenal AKI

Prerenal AKI may result from the following causes:

- True volume depletion—Volume depletion may be due to gastrointestinal disease (vomiting, diarrhea, bleeding); renal losses (diuretics, glucose-induced osmotic diuresis); cutaneous or respiratory losses (insensible losses, sweat, burns); and third space sequestration (crush injury or skeletal fracture).
- Hypotension—Severely reduced blood pressure may result from shock (hypovolemic, myocardial, or septic) and posttreatment of severe hypertension.
- Edematous states—Heart failure and cirrhosis may result in marked reductions in kidney perfusion that parallel the severity of the underlying disease. The respective mechanisms are decreased cardiac output in heart failure and splanchnic venous pooling and systemic vasodilation in cirrhosis.
- Selective renal ischemia—Bilateral or unilateral renal artery stenosis in a solitary functioning kidney is frequently worsened by treatment with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB).
- Drugs affecting glomerular hemodynamics—Drugs that affect glomerular hemodynamics can reduce GFR by lowering the intraglomerular pressure that drives this process. This can occur by decreasing either afferent arteriolar dilatation (e.g., with nonsteroidal anti-inflammatory drug [NSAID] or calcineurin inhibitor) or efferent arteriolar constriction (e.g., with ACEI or ARB).
- Nephrotic syndrome—Mostly in adults with minimal change disease, nephrotic syndrome can lead to AKI. Decreased renal perfusion, reduced glomerular permeability, and excessive diuresis are among the mechanisms that may contribute to AKI.

Hypovolemia is the commonest cause of prerenal AKI, followed by impairment of intrarenal autoregulation which is usually due to NSAIDs or reduction of cardiac output. When kidney filtration capacity cannot be maintained owing to reduced renal plasma flow and concomitant decrease in intraglomerular pressure, the occurrence of prerenal AKI is inevitable. Although prerenal AKI often appears to be recoverable with returning of SCr to baseline level, it may cause a permanent renal tissue damage.

7.2.3.2 Causes of Postrenal AKI

Postrenal AKI is caused by obstruction of the urinary tract, and the obstruction may occur anywhere in the urinary tract. Causes include abdominal or pelvic cancer, ureteral obstruction owing to kidney stones, or surgical or post-traumatic ureteral injury, neurogenic bladder owing to diabetes, spinal cord injury or multiple sclerosis, benign prostatic hyperplasia, and urethral stricture.

One of the initial actions for patients with AKI is to exclude urinary outflow obstruction which may possibly be relieved by appropriate measures. If left untreated, obstructive nephropathy may lead to irreversible tubulointerstitial fibrosis.

7.2.3.3 Causes of Renal AKI

Renal AKI may be associated with nephrotoxic drugs (e.g., aminoglycoside antibiotic), other nephrotoxins (e.g., contrast, myoglobin, hemoglobin, light chain), sepsis, local infections, renal ischemia, inflammation (e.g., glomerulonephritis, vasculitis, allergic reactions), or malignant hypertension. The causes leading to renal AKI can usually be classified into three categories according to the anatomical site involved (Table 7.1) [13].

Acute tubular necrosis (ATN) is the most common histopathological change among various pathogenesis of renal AKI. Nephrotoxins, renal ischemia, and sepsis are three major causes of ATN [14–16]. A number of drugs and exogenous and endogenous toxins can cause ATN. These include aminoglycosides, heme pigments, cisplatin, radiocontrast media, pentamidine, foscarnet, cidofovir, tenofovir, intravenous immunoglobulin, mannitol, hydroxyethyl starch, and synthetic cannabinoids. All causes of severe prerenal AKI, particularly if accompanied by hypotension, surgery, and/or sepsis, can lead to ischemic ATN. Sepsis-induced ATN is often associated with prerenal factors such as reduced renal perfusion and systemic hypotension, and other factors, including cytokine release and neutrophil activation by cytokines, can also contribute.

Table 7.1 Causes of renal AKI

Tubuli and interstitium	Nephrotoxins • Contrast • Medications • Hemolysis • Rhabdomyolysis • Myeloma Allergic reaction • NSAID • Antibiotics • Proton pump inhibitors • 5-ASA Ischemia Sepsis Local infection Tumor lysis syndrome
Glomerulus	Inflammatory systemic disease involving kidney • Systemic lupus erythematosis • Systemic vasculitis Primary glomerulonephritis Infections with secondary glomerulonephritis • Hepatitis B • Hepatitis C • HIV
Vessel	Atheroembolic renal disease Renal vein thrombosis Thrombotic microangiopathy Antiphospholipid syndrome

NSAID nonsteroidal anti-inflammatory drug; *5-ASA* 5-aminosalicylic acid; *HIV* human immunodeficiency virus

Among all causes of renal AKI, drugs, contrast, cardiac surgery, and sepsis are relatively common. AKI-related drugs include NSAIDs, several antimicrobial agents, and several chemotherapeutic drugs [17]. The incidence of contrast-induced AKI following coronary angiography is about 2.6–13% [18]. Although noncardiac surgery is deemed to be related to AKI at a lower risk than cardiac surgery [19], one study showed that 7% developed AKI which was defined as a >50% increase in SCr levels after noncardiac surgery [20]. The incidence of AKI in patients undergoing cardiac surgery ranged from 1 to 50%, relying on the classification of AKI and the type of surgery [21]. AKI is common in patients with sepsis, while hospital mortality in septic shock patients with AKI has almost doubled [22].

7.2.4 Risk Factors for AKI

Some patient-specific factors, including old age, diabetes, left ventricular systolic dysfunction, dehydration, and CKD, may predispose the patient to develop AKI when exposed to the etiology of AKI [2, 23]. Besides these high risk factors, several conditions that may occur during some particular operations are related to the development of AKI. For patients who need intra-aortic balloon counterpulsation, who need to use cardiopulmonary machines for too long, or who need blood transfusion to supplement blood volume, the risk of developing AKI is significantly increased [24]. When patients with CKD encounter with any cause of AKI, they are prone to progress to a more serious AKI requiring RRT, and they are also more likely to deteriorate to end-stage renal disease (ESRD) [25].

For preventing the development of AKI, especially in patients with CKD, estimating and identifying patients who may be at high risk before exposure to potential nephrotoxic drugs or other nephrotoxins or before surgery is of great importance.

7.3 Bidirectional Relationship Between AKI and CKD

7.3.1 Effect of CKD on Development or Outcome of AKI

7.3.1.1 CKD Is a Potent Risk Factor for AKI

It can be predicted that the decrease of renal mass and nephron number, vascular insufficiency, and reduced tissue repair ability in patients with CKD may decrease the renal homeostasis under the action of acute stressor, thus making this population more vulnerable to the influence of AKI. Almost all AKI risk prediction scores have confirmed that CKD is one of the strongest risk factors for AKI, which has been proved in many large retrospective cohort studies.

The proportion of preexisting CKD has been 30–35% in most studies on AKI in hospitalized patients [10, 26–29] but as high as 75% in one large series [15]. An analysis showed that the risk of developing dialysis-requiring AKI increased from twofold in patients with CKD whose baseline estimated GFR (eGFR) was in stage 3a to 40-fold in those with CKD whose baseline eGFR was in stage 5 when compared with the risk in control patients with baseline eGFR ≥60 mL/min/1.73 m^2, which suggested that CKD is a potent predictor of dialysis-requiring AKI in hospitalized patients [15]. This study was also the first to report that proteinuria is a strong risk factor for AKI [15]. Another analysis of data from a CKD cohort with an eGFR <30 mL/min/1.73m^2 showed that, within a median 19-month follow-up, 44.9% of patients had, at least once, an episode of AKI which is defined as a 25% decrease in eGFR over a period of 25 days [30]. The relationship between baseline renal function and the occurrence of AKI was assessed in one study and the findings displayed that patients with eGFR <30 mL/min/1.73m^2 were 18 times more likely to develop AKI than those with eGFR >60 mL/min/1.73 m^2, which suggested that the incidence of AKI evidently increased following the decline of baseline eGFR [31].

7.3.1.2 CKD Worsens Renal Outcome After AKI

Some studies have shown that AKI-related attributional mortality is higher in patients with CKD than in those with normal renal function. Actually, not only does the risk of AKI increase significantly in patients with CKD, but the existence of CKD does alter or, rather, increase the correlation between AKI and its adverse outcomes. Observational studies have also found that renal function in patients with CKD after an episode of dialysis-requiring AKI is less likely to return to baseline levels than that in those without CKD [1].

A study enrolled 48 patients initiating dialysis for AKI showed that the survivors with preexisting CKD were more likely to be dialysis-dependent at 90 days (50% vs. 11% of those without preexisting CKD) [16]. Similar findings were noted in a review of 299 critically ill patients with dialysis-requiring AKI, 102 of whom had underlying CKD. Among survivors, the rate of dialysis dependence at hospital discharge was higher in those with underlying CKD (34%) than in those without CKD (5%) [29]. A stratified analysis of postdischarge outcomes of inpatients with medical insurance showed that AKI patients with prior CKD had a 41-fold increased risk of developing ESRD, while patients with AKI alone had a 13-fold increased risk of progression to ESRD [32]. Another analysis displayed that individuals with a baseline eGFR <30 mL/min/1.73 m^2 and severe AKI had a 4.71-fold increase in the risk of long-term outcome of ESRD or death, which suggested that there is a consistent and graded relationship between both baseline eGFR and severity of AKI and long-term adverse outcomes [31].

7.3.2 Effect of AKI on Onset or Progression of CKD

Numerous studies have linked AKI to occurrence and progression of CKD. Indeed, in AKI survivors, the duration, severity, and recovery of AKI are related to the subsequent development of de novo CKD or deterioration of underlying CKD, and a growing body of evidence have confirmed the influence of AKI on CKD. Furthermore, patients with CKD who develop AKI are more likely to progress to ESRD than those who never have an AKI episode. The KDIGO clinical practice guideline on AKI recommended the evaluation of patients by clinicians at 3 months after AKI for resolution, new onset, or worsening of preexisting CKD [3].

7.3.2.1 AKI Increases the Risk of Both De Novo CKD and Deterioration of Underlying CKD

A population-based matched cohort study that included 3769 patients with dialysis-requiring AKI who survived free of dialysis for at least 30 days after discharge reported a 3.2-fold increase in the risk of incidence of chronic dialysis [33]. An analysis of matched data obtained from US Medicare beneficiary claims and the US Renal Data System showed that patients aged 67 years or older who developed AKI were 6.7 times more likely to develop ESRD at 2 years after discharge than those without AKI. Patients with a history of CKD who developed AKI had a 41-fold increase in the risk of ESRD [32]. In an analysis that compared 36,980 patients admitted to a US Department of Veterans Affairs facility between 1999 and 2005 with patients admitted with myocardial infarction (MI) alone, those admitted with AKI or AKI plus MI had a 2.07-fold or 2.30-fold increase in the risk of having an adverse kidney outcome (defined as a >25% decline in eGFR, need for long-term dialysis, or death) at a maximum of 6 years of follow-up, respectively [34]. A meta-analysis that included 13 cohort studies showed an 8.8-fold and 3.1-fold increase in the risk of developing CKD and ESRD in patients who developed AKI than in those who did not, respectively [35].

Several reports suggest that an episode of AKI is related to an elevated hazard for CKD even among patients without any detectable kidney disease. For example, 1610 patients enrolled in a cohort study developed AKI during hospitalization and their kidney functions were normal before AKI. Their kidney functions recovered to at least 90% of the baseline levels within 3 months after the onset of AKI, and in 81% of these patients, the kidney function recovered to pre-AKI levels within 4 days. However, compared with matched control patients who didn't develop AKI, patients were more prone to develop CKD at 3.3 years after the episode of AKI [36]. In another cohort study, 3809 patients with AKI and normal pre-AKI kidney function were observed, and it was found that AKI had a correlation with a high risk of CKD at 2.5 years in these patients [37].

7.3.2.2 Factors Affecting Effect of AKI on Onset or Progression of CKD

- **Effect of AKI severity on onset or progression of CKD**
- In a population-based cohort study, patients who developed reversible AKI, i.e., whose renal function recovered to more than 75% of baseline, had better clinical outcomes than those with irreversible AKI. Compared to patients with reversible AKI, the irreversible group had a 1.26-fold increase in the risk of death and a 4.13-fold increase in the risk of composite renal outcomes which included doubling of SCr level and ESRD [38].
- Several studies linked dialysis-requiring AKI to progression of CKD. Dialysis-requiring AKI means that AKI is so severe that RRT is indispensable, and the "dialysis" in this phrase refers to various acute RRT modalities, e.g., continuous RRT, peritoneal dialysis, or intermittent hemodialysis. In an analysis of information from a large integrated healthcare delivery system concerning patients with baseline eGFR ≥45 mL/min/1.73 m^2 who underwent an episode of dialysis-requiring AKI and recovered to be released from RRT at one month after hospital discharge, an association between a 28-fold higher risk of deterio-

rating stage 4 or 5 CKD and the previous dialysis-requiring AKI was observed [14]. Another analysis of data from the same system showed a 47% higher risk of ESRD in the following 30 days after discharge in patients with underlying CKD (baseline eGFR <45 mL/min/1.73 m^2) who went through dialysis-requiring AKI, comparing to CKD patients with same level of baseline eGFR who did not have AKI [41].

- In one study enrolled in children with AKI in ICU who developed subsequent CKD that was defined as albuminuria or eGFR <60 mL/min/1.73 m^2, incidence of CKD elevated from 5% in patients with AKIN stage 1 AKI (defined as an increase in SCr concentration by ≥50% or by ≥0.3 mg/dL from baseline) to 17% in patients with stage 3 AKI (defined as a ≥3-fold increase in SCr concentration from baseline, an increase in SCr concentration to ≥4 mg/dL with an absolute increase by 0.5 mg/dL, or requirement for RRT) in the following 1–3 years after AKI. It suggested that an increase of CKD incidence was closely related to the grading of previous AKI [49].
- An analysis of data from the Department of Veterans Affairs healthcare system presented that the increase in the severity of AKI at each stage (based on the RIFLE criteria) was associated with a 4.4-fold increase in odds ratio of progressing stage 4 or 5 CKD. In addition, dialysis-requiring AKI alone was related to a 53-fold increase in odds ratio of progressing stage 4 or 5 CKD. These results demonstrated that the severity of AKI could be used as a risk stratification factor for CKD progression [50].
- **Cumulative effect of repeated AKI episodes on progression of CKD**
- According to a study focusing on recurrent AKI which was defined as one episode of AKI happened again in the following 12 months after a previous AKI, the prevalence rate of recurrent AKI was 25% [44]. Although most studies paid more attention to the consequence of one episode of AKI for the risk of CKD, the effects of multiple episodes of AKI on the progression of CKD were analyzed in patients with diabetes mellitus from the US Department of Veterans Affairs healthcare system. The findings showed a 3.6-fold increase in the risk of stage 4 CKD in patients with one episode of AKI, compared to patients without AKI. In addition, for every additional episode of AKI, this risk increased by an extra double [43]. These observations further increase the likelihood of the phenomenon observed in other studies, that is, repeated episodes of AKI promote the progression of CKD, which is characterized by a no-linear decline in kidney function [45–48]. Nowadays, it has been generally accepted that the progression of CKD isn't at a constant rate with a nonlinear trajectory of decline in eGFR.
- **Reversible AKI is associated with a risk of developing CKD**
- An analysis of data from a large integrated healthcare delivery system in Central Pennsylvania suggested that an increase in the risk of subsequent CKD development was even correlation with reversible AKI, which was defined as that the increase in SCr levels fall back to within no more than 10% of baseline values in the following 3 months after AKI in patients without CKD at baseline. The incidence of CKD in the patients who suffered from reversible AKI was 1.9-fold higher than that in matched controls who did not experience AKI [51]. In another study, data from a large integrated healthcare delivery system in Utah was analyzed and it was found that AKI with almost complete renal function recovery which was defined as that the return of SCr values is less than 1.1 times of the baseline values was significantly related to the incident of stage 3 CKD. At a median follow-up of 30 months, the incidence of CKD was 15% in individuals with recovery AKI, showing a 3.8-fold increase in the risk of CKD development compared to the risk in individuals who did not experience AKI [37]. The analysis of Veterans Health Administration data revealed that even the individual experienced stage 1 AKI according to KDIGO criteria with quick recovery which was defined as the return of SCr levels from peak to no more than 0.3 mg/dL above baseline values within 48 h had a 1.4-fold increase in the risk of CKD development [52].

- **CKD is one of possible factors leading to irreversible AKI**
- Several studies suggested that the decline of renal function owing to AKI was more possible to be irreversible in patients with lower baseline GFR, old age, heart failure, hypertension, or hypoalbuminemia [36, 39]. An analysis of data from 281 patients who developed in-hospital dialysis-requiring AKI and continued outpatient dialysis after discharge showed that renal function returned at a median of 8 months in 52 (19%) patients, in which most (94%) exhibited recovery within 6 months. The findings suggested that ATN secondary to surgery or sepsis and higher level of baseline eGFR were two independent factors for predicting recovery of renal function while heart failure independently predicted no recovery within 6 months after AKI. The first RRT in ICU and catheter access for dialysis were not independent predictors. Even with a higher level of baseline eGFR, the decline of renal function in patients with heart failure who developed AKI was more prone to be irreversible [40].
- **Proteinuria aggravates the effect of AKI on the progression of CKD**
- In addition to eGFR, proteinuria is also an important parameter reflecting the severity of CKD. The relationship between baseline eGFR, proteinuria, and AKI was studied in a large database of nearly one million adults in Alberta, Canada. The results of observation showed that a higher risk of AKI was correlated with the lower levels of baseline eGFR and the higher levels of urinary protein excretion, and the further analysis revealed that massive proteinuria could serve as a predictor for long-term prognosis of kidney, e.g., doubling of SCr levels or ESRD, after an AKI episode. These studies confirmed that the effects of an AKI episode on the long-term decline in kidney function at all levels of baseline eGFR can be aggravated by proteinuria [42].

7.4 AKI on CKD (Also Applicable to AKI Alone)

7.4.1 Diagnosis

As mentioned above, AKI is a powerful accelerator to push forward the progression of CKD. For patients with CKD, it is important to make a diagnosis in time when AKI occurs. When AKI occurs, however, patients rarely develop symptoms and signs owing to AKI, and symptoms and signs are more likely to be related to underlying causes than AKI itself. Therefore, examination and treatment should depend on the clinical background and underlying causes (see "common causes of AKI" in this chapter). In addition to the condition of CKD, other medical histories, including exposure to nephrotoxic drugs and other nephrotoxins, should be reviewed in detail. Obstruction of any part of the urinary tract should be excluded initially. Ultrasound should be performed to examine the size of bilateral kidneys, and the length of kidneys <8 cm may indicate CKD rather than AKI, but does not rule out AKI-on-CKD [11].

Blood samples should be collected for analyzing SCr, electrolytes, standard bicarbonate, blood cell count, and serum albumin. Dipstick urine analysis and analysis of urine sediment should be used routinely to investigate the AKI causes. Urine volume should be regularly measured as oliguria and anuria is common in patients with AKI, and urine volume is an earlier marker of the progression in AKI than level of SCr [2]. For patients with CKD, the diagnosis of AKI complies with the KDIGO criteria. Meanwhile, determination of the cause of AKI is essential. The activity or rapid progression of the primary cause of CKD should also be taken into account.

7.4.1.1 Differential Diagnosis Between Prerenal and Renal AKI

In some patients, prerenal and renal AKI need be distinguished. There are three major diagnostic approaches that, in the appropriate clinical setting, are used to distinguish prerenal disease from ATN and other causes of renal AKI:

1. Urinalysis.
2. Fractional excretion of sodium and, to a lesser degree, urinary sodium concentration. The fractional excretion of urea may be helpful in patients being treated with diuretics.
3. Response to fluid repletion in patients with evidence of volume depletion, which is the gold standard for the diagnosis of prerenal disease. This does not apply to prerenal disease due to heart failure (cardiorenal syndrome) or cirrhosis (hepatorenal syndrome).

Other parameters that may be helpful in selected patients include the following: blood urea nitrogen/SCr ratio, rate of increase in SCr concentration, urine osmolality, and urine volume.

In patients with prerenal AKI due to cardiorenal syndrome or abdominal compartment syndrome, definitive diagnosis should be established through cardiac functional evaluation (e.g., echocardiography, invasive hemodynamic monitoring) or bladder pressure transduction, respectively.

7.4.1.2 Concurrent of Prerenal and Renal AKI

Prerenal and renal AKI often overlap in many patients. Concomitant prerenal and renal AKI may occur in patients with rhabdomyolysis, hypercalcemia, or sepsis, and may also be observed in patients after cardiac surgery. Rhabdomyolysis is usually related to hypovolemia which may result in prerenal AKI, meanwhile, myoglobin and heme proteins may induce intraluminal cast formation and tubular obstruction, which is the direct toxic effects on the kidney. Hypercalcemia is also a disorder which may cause both prerenal and renal AKI owing to the severe hypovolemia and the simultaneously nephrotoxicity of calcium [53]. The causes of AKI in sepsis are multifactorial, which include hypotension, activation of sympathetic nerves system, and mediating effects of hormones and inflammatory factors [54]. The causes of AKI after cardiac surgery are usually ischemia, hypotension, embolism, inflammation, and free hemoglobin in blood transfusions.

7.4.2 Biomarkers of Kidney Injury

It is assumed that delayed detection of AKI is one of the reasons for the failure of intervention trials designed to treat AKI. Hence, kidney injury biomarkers for early detection of the clinical process of AKI and for predicting the need of dialysis or other complications before the changes of the functional biomarkers (i.e., SCr) have been searching by a lot of efforts. These biomarkers including kidney injury molecule 1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), liver-type fatty acid-binding protein (L-FABP), interleukin 18 (IL-18), insulin-like growth factor binding protein 7 (IGFBP-7), and tissue inhibitor of metalloproteinase-2 (TIMP-2) can provide information about tubular damage, usually before renal function declines.

The well-studied biomarkers are listed as below:

- L-FABP—After ischemic injury, the expression of L-FABP was induced in renal proximal tubules. One hour after injury, the amount of this protein in urine increases to detectable levels, reaching a peak 6 h after AKI [55].
- NGAL—An enzyme that can activate protective enzymes and prevent production of oxygen-free radicals is released from damaged proximal and distal tubular cells after kidney injury. The neutrophils and liver cells in septic patients also release this enzyme. It can be detected in urine and serum 3 h after AKI, reaching a peak 6 h after AKI [56].
- IL-18—A pro-inflammatory cytokine that is upregulated in proximal tubule after ischemic AKI. It is detectable in urine and serum 6 h after AKI and peaks 12–18 h after AKI [57].
- IGFBP-7 and TIMP-2—Both proteins can induce G1 cell cycle arrest in G1 phase, thus preventing endothelial cells proliferation. They are detectable in urine 12 h after AKI [58].
- KIM-1—A protein produced by proximal tubular cells after injury can activate immune cells resulting in elimination and reconstruct-

ing of damaged tubule. It is detectable in urine 12–24 h after AKI and peaks 48–72 h after AKI [59].

7.4.3 Prevention

For patients with CKD, measures for the prevention of AKI are similar to that for general population or patients with non-CKD. Nonetheless, patients with CKD are susceptible to the damage which may lead to AKI, preventive measures should be particularly emphasized. General preventive measures are as follows:

1. Fluid administration in some situations, such as hypovolemia, tumor lysis syndrome, or hemoglobinuria.
2. Prevention of hypotension by providing inotropic support following adequate volume repletion.
3. Readjustment of nephrotoxic medications based on close monitoring of renal function and drug levels.

Fluid administration in the following situations may effectively prevent renal AKI:

- Prerenal AKI due to hypovolemia—For patients with a history and physical findings consistent with hypovolemia, administration of an intravenous (IV) fluid bolus with normal saline (10–20 mL/kg over 30 min) may prevent more severe renal AKI and can be repeated twice, if necessary, until urine output is re-established. Fluid challenge is contraindicated for patients with obvious volume overload or heart failure.
- Patients at risk of AKI—Volume expansion with IV normal saline is effective in preventing AKI in patients at risk of AKI with the following conditions: hemoglobinuria and myoglobinuria; administration of potential nephrotoxins including aminoglycosides, amphotericin B, radiocontrast media, cisplatin, and IV acyclovir; tumor lysis syndrome; surgical procedures in which the intravascular volume is reduced during either the intraoperative or postoperative period.

Because nephrotoxic drugs is an important risk factor for AKI, monitoring the SCr concentration (i.e., renal function evaluation) and drug level (if possible) is important, as it enables appropriate adjustment of drug dosing based on the knowledge of altered pharmacokinetics in early AKI. In addition, clinicians should monitor drug efficacy and toxicity.

7.4.4 Treatment and Management

7.4.4.1 General Principles

The main purpose of treatment for AKI is to limit the continuous damage and block the further decline in renal function. For patients who develop AKI on the basis of CKD, the strategy of treatment complies with the general principles for patients with AKI and includes the following:

- Specific treatment of the underlying cause.
- Fluid management.
- Electrolyte management.
- Acid-base balance adjustment.
- Drug dosing adjustment.
- RRT.
- Nutritional support.
- Specific pharmacologic therapies.

These are several key principles that should be followed, the most important of which is etiological treatment and maintenance of normal blood volume and stability of hemodynamics. Furthermore, it is necessary to correct the electrolyte disorders, to stop the use of nephrotoxic drugs or to adjust the dosage, and to adjust the dosage of the drugs excreted through the kidney accordingly. In order to prevent the deterioration of AKI and the occurrence of hyperkalemia, the use of potassium-sparing diuretics and ACEIs or ARBs need to be stopped. In addition, acid-base imbalances need to be corrected. The main type of acid-base imbalances is metabolic acidosis, which is more common in patients with stage 2 and stage 3 AKI. For all patients with AKI, monitoring urine volume and SCr several times per day is the essential measure of management [11].

7.4.4.2 Hemodynamic Optimization

1. **Fluid management**
   For all patients who suspect that hypovolemia is the main etiology of AKI, the most urgent task is to regain fluid balance for increasing cardiac output, stabilizing hemodynamics, and maintaining adequate renal blood flow without causing fluid overload. In clinical practice, the evaluation of patients' hydration status is difficult. Recently, several methods such as measuring bioimpedance and assessing the size of vena cava and left ventricle by ultrasound have been utilized. Rehydration rate should be evaluated individually [60, 61].
2. **Types of rehydration liquid**
   It is considered that high concentration of chloride at macula densa increases the tubuloglomerular feedback, resulting in the constriction of afferent glomerular anteriole and the decrease of renal perfusion. One study found that high chloride crystal solutions may damage the kidneys and worsen renal function [62]. A meta-analysis displayed a link between resuscitation and liquids containing high chloride, with an increase in the risk of AKI, metabolic acidosis, and time on mechanical ventilation [63]. Conversely, a randomized trial in an intensive care environment showed that there was no difference in the risk of AKI or dialysis in patients between treated with balanced crystal solutions and saline [64]. In spite of this controversy, the use of balanced crystal solutions as a rehydration liquid for patients with AKI is still recommended.
3. **Prevent fluid overload**
   Fluid overload may cause increased intra-abdominal pressure and kidney edema, while the kidney is surrounded by a nonexpansive fibrous capsule, which may reduce renal perfusion pressure. For preventing fluid overload, the Acute Dialysis Quality Initiative proposed a new fluid resuscitation strategy, which consists of four phases: rescue, optimization, stabilization, and de-escalation phases [65].
   - Rescue—A large amount of fluid is given under life-threatening hemodynamic instability.
   - Optimization—When the patient's hemodynamics is stable, the fluid is carefully given to maintain hemodynamic stability.
   - Stabilization—When the patient is in a stable state, the goal is zero or negative fluid balance.
   - De-escalation—In the de-escalation phase, the excess fluid should be removed.
4. **Vasoactive drugs**
   Vasoactive drugs can cause systemic vasoconstriction and elevated blood pressure, which may lead to increased renal perfusion. Proper dose of norepinephrine can reduce the risk of AKI in patients with vasodilation shock. In patients with vasogenic shock after cardiac surgery, increased mean arterial pressure (MAP) by norepinephrine led to elevation of GFR and increased renal oxygen delivery [66]. A higher MAP with norepinephrine has also been shown to reduce the requirement for dialysis in septic patients [67]. As a drug that can also increase blood pressure, vasopressin is usually used as a second-line drug in combination with noradrenaline for stabilizing hemodynamics [68]. As a calcium sensitizer, levosimendan can improve right ventricular function, reduce central venous pressure, and decrease renal venous congestion. In addition, levosimendan can dilate afferent glomerular arterioles and improve renal circulation [69]. The current recommendation is not to use dopamine in patients with AKI.

7.4.4.3 Drug Treatment for AKI

Several drugs such as acetylcysteine, diuretics, sodium bicarbonate, and statins have been tested for treatment of AKI; however, none of them has been determined as standard treatment in clinical practice because the results from different studies have been inconsistent. Among these drugs, although it is difficult to reach a clear consensus due to the heterogeneity of study results, the KDIGO group has recommended that oral acetylcysteine combining with intravenous isotonic crystalloid solutions should be used in patients at high risk of contrast-induced AKI [70].

7.4.4.4 Indications for RRT

With regard to the timing of the start of RRT, current recommendations include life-threatening fluid imbalances, electrolyte and acid-base disorders, or uremic complications [2]. Generally, RRT is required when patients with AKI develop the following indications:

- Fluid overload refractory to diuretics.
- Hyperkalemia (serum potassium level >6.5 mEq/L) or rapid increase in potassium levels refractory to medical therapy.
- Metabolic acidosis (pH <7.1) in patients with contraindications for bicarbonate administration, such as those with volume overload (who would not tolerate the required sodium load) or those with lactic acidosis or ketoacidosis, in whom bicarbonate administration has not been shown to be effective.
- Signs of uremia, including pericarditis, neuropathy, or an otherwise unexplained decline in mental status.

It should be pointed out that the benefits of early compared with late initiation of RRT have still been controversial, in which early initiation of RRT means that treatment of RRT is started before life-threatening complications occur. Although the best initiation time for RRT has not been obtained from the data accumulated from different observational studies and clinical trials, the results from several recent randomized clinical trials have displayed that the mortality, length of hospitalization and duration of RRT were reduced in critically ill patients with AKI performed early starting continuous RRT compared to those in patients with late initiation of RRT [11].

7.5 Summary

Over the past decade, we have made great progress in comprehending the relationship between AKI and CKD, but there is still a lot of work to be done. It has been believed that AKI is a trigger of development and progression of CKD, while CKD is a potent risk factor for AKI. Observations focusing on the correlation between these two clinical events have explored that AKI and CKD contributes to each other. For improving the outcomes of patients, identification of potential best opportunities for intervention is essential, which requires rigorous epidemiological studies to discern the weights of these interrelated components.

Key Messages

- The proposed criteria for AKI include an increase in SCr level by ≥0.3 mg/dL (26.5 μmol/L) within 48 h; a ≥1.5-fold increase in SCr level from baseline, which is known or presumed to have occurred within the prior 7 days; or a decrease in urine volume to <0.5 mL/kg/h over 6 h.
- Many observations have indicated that CKD is a potent risk factor for AKI and a modifier for outcome of AKI, whereas AKI is a trigger of development and progression of CKD. Patients should be evaluated at 3 months after AKI for resolution, new onset, or worsening of preexisting CKD.
- For CKD patients at high risk for developing AKI, preventive measures for AKI include adequate fluid repletion in those with hypovolemia, avoidance of hypotension by providing inotropic support as needed, and readjustment of nephrotoxic medications based on close monitoring of renal function and drug levels, if available.
- For patients with CKD, it is important to make a diagnosis in time when AKI occurs. In addition to the condition of CKD, other medical histories, including exposure to nephrotoxic drugs and other nephrotoxins, should be reviewed in detail.
- For CKD patients developing AKI, the basic principles of general management include specific treatment of the underlying cause, fluid management, electrolyte management, adjustment of drug dosing, nutritional support, renal replacement therapy, and specific pharmacologic therapies.

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8 Advanced Image Techniques in Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. How to accurate assessment this irreversible disease process is a key point for the secondary treatment. Over the past decade, applications of novel image methods provide noninvasive, reliable, quantitative data of renal perfusion, glomerular filtration, interstitial diffusion, and the degree of renal fibrosis. Moreover, these techniques also offer pathophysiologic data such as energy dysmetabolism in the initial disease stage. This chapter reviews advanced applications of the image techniques including ultrasound-based techniques, multi-detector computed tomography, magnetic resonance imaging, and nuclear-based techniques in CKD. The knowledge of the applications, advantages, and disadvantages of these techniques could open a framework for nephrologists to make informed decisions in clinical practice. However, there remains a gap between theoretical studies and clinical applications. Standard protocol and generic analysis model are needed for large-scale clinical application in the future.

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8.1 Introduction

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem, and affects more than 10% of the population worldwide [1]. CKD progression to end-stage renal disease (ESRD), which requires dialysis, is still considered irreversible, although many antifibrotic agents are in various stages of clinical trials [2]. Thus, detection, monitoring, and prediction of the disease process are key points for early intervention and prevention of subsequent development of renal dysfunction.

In progressive CKD, common pathological changes include parenchyma capillary rarefaction, reduction of microvascular blood flow, reduction of glomerular filtration rate (GFR), and tubulointerstitial injury. Renal fibrosis is the common pathway for progression of CKD, which leads to increased tissue stiffness and eventually reduction in size. Tissue hypoxia is an additional characteristic of CKD, which can initiate and promote kidney injury.

Percutaneous renal biopsy and radionuclide imaging are the gold standards for assessment of renal morphology and function. However, the biopsy is an invasive examination with significant clinical risks, such as bleeding [3]; thus, it cannot be used repeatedly. Additionally, kidney lesions are often heterogeneously distributed, whereas tissues for renal biopsy analysis are approximately 2 mm in diameter (<1% of one kidney); this approach is inherently subject to

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sampling bias. Nuclear medicine-based techniques are further limited by the radioisotope exposure of the contrast agents injected, and time is required for the excretion of radioisotopes from the body.

Recently, new imaging technologies that can provide noninvasive, reliable, quantitative data regarding morphologic structural information and signal-kidney function to quantify the progression of CKD are expanding in terms of applications, both in research and in clinical contexts; thus far, most approaches remain experimental.

8.2 Ultrasound (US)-Based Techniques

US-based techniques play a key role in the diagnosis of CKD. A complete ultrasonic examination involves assessing structure, vascularization (both extrarenal and intrarenal), and functional changes in kidneys. These techniques are convenient, uniquely real-time in nature, and exhibit good repeatability; thus, they remain first-line techniques to assess and monitor progressive kidney injuries.

8.2.1 B-Mode Ultrasound

Until recently, B-mode US has been the most widely used approach to clinically evaluate the morphological changes of CKD. In this technique, maximum renal diameter and cortical thickness are the most valuable parameters. Many studies have shown relationships between these parameters and deterioration of renal function (reduction of GFR) [4]. Recently, renal volume was measured in vivo by three-dimensional (3D)-ultrasound, and direct correlations were found between this volume and both functional nephrons and GFR [5]. Moreover, the volume measured by US is similar to the actual size measured intraoperatively. However, ultrasound-detected morphological changes are often visible in late stages of disease, so this approach is limited in its ability to monitor and predict CKD in early stages.

8.2.2 Color-Doppler Ultrasound

Renal resistive index (RRI) is measured by the Doppler spectrum of intrarenal vessels (typically segmental or interlobar arteries), defined as the peak systolic (PS) and end-diastolic (ED) blood velocities divided by the peak systolic velocity (PSV). In adults, RRI typically ranges from 0.47 to 0.70.

Initially, RRI was used to assess intrarenal vascular resistance; accumulating evidence has shown that RRI >0.75 is an indicator for both the onset and progress of renal damage. Notably, a value >0.8 indicates irreversible damage in CKD. The causative mechanism for increased RRI remains unknown; however, it is generally accepted that the interaction of interstitial fibrosis with post-glomerular vessels could increase resistance to renal cortical blood flow and reduce glomerular perfusion [6, 7].

Recently, it has been suggested that systemic (e.g., pulse pressure) influences the predictive role of RRI. In younger hypertensive people with normal renal function and no sign of albuminuria, RRI is an early marker of renal damage. Conversely, in older subjects, the predictive ability of RRI is weak, as it is influenced by systemic vascular stiffness [8]. However, the importance of RRI requires a long-term clinical follow-up study [9].

8.2.3 Contrast-Enhanced Ultrasound (CEUS)

In CEUS, by using contrast agents as red blood cell tracers, continuous imaging of the vasculature and blood flow can be achieved; a time-dependent intensity curve is generated with respect to selected regions of interest (ROI) in the renal cortex and medulla, in order to calculate several perfusion parameters, including peak intensity (PI), rise time (RT), time to peak (TTP), mean transit time (MTT), and area under the curve (AUC).

Conventional applications of CEUS for diagnosis are limited to parenchymal masses, especially to differential diagnosis of benign and

malignant diseases [10]. Due to the excellent spatial resolution that enables it to detect slower flow in smaller blood vessels, CUES recently began to be used in studies of renal microvascular perfusion and renal blood flow (RBF) in healthy individuals, as well as in patients with various kidney diseases, including CKD (especially in patients with diabetes) [11].

In normal kidneys, CEUS-derived RBF parameters have been reported to exhibit a good correlation with those obtained by para-aminohippurate, which is a gold standard for RBF [12]. Notably, CEUS can correctly validate renal perfusion following pharmacologic intervention, such as with angiotensin II, captopril, noradrenaline, and dopamine [13, 14].

In CKD, perfusion parameters obtained by CEUS (e.g., PI, RT, and AUC) have shown differences with respect to measurements in healthy controls; of note, this change exists in early disease stages (CKD stages 1–2). Another exciting finding involves DKD cases without reductions in GFR (CKD stage 1): CEUS-derived parameters change with respect to urinary microalbumin/creatinine, which is an early biomarker for DKD, indicating that CEUS offers great potential for both monitoring and prediction of disease processes [15].

Compared with other imaging techniques for hemodynamic abnormalities, the greatest advantages of CEUS are its high degree of safety, renal tolerance, and lack of radiation. The fundamental compositions of contrast agents used in this approach are microbubbles comprising gases embedded within a shell; because these exhibit no known nephrotoxicity, CEUS is safe for regular use in patients with CKD at any stages. Although it lacks systematic evaluation and multicenter, large-scale clinical trials involving diffuse renal lesions, CEUS has a great advantage in its ability to assess renal perfusion, as well as to monitor and assess the progression of CKD.

8.2.4 Ultrasound Elastography

The intrarenal shear-wave velocity varies with external mechanical wave pressure. In theory, qualitative tissue stiffness might be obtained by comparing two US acquisitions before and after compression. It is broadly accepted that cortical elasticity values are higher than medullary values in healthy kidney, and that these values vary with age. However, no reference values for normal renal elasticity have been reported thus far [16]. US elastography has been demonstrated in liver fibrosis; in kidney diseases, this approach has found value primarily in differential diagnosis of renal masses. In transplanted kidneys, several limited studies have shown a moderate correlation between renal stiffness, quantified by US, and the degree of interstitial fibrosis [17, 18].

However, data regarding this novel US technique in CKD are rare and preclinical. Kidney stiffness is not solely related to fibrosis. The filling pressure of the renal collecting system, the ratio of arterial to venous blood flow, and other mechanical and functional parameters can also influence the degree of stiffness, making data analysis quite complex. In addition, a variety of technical factors (e.g., operator experience; patient state, such as obesity; direction of the sound wave with respect to the kidney; and depth that the US wave can reach, typically <5 cm) affect the elasticity values and increase the difficulty in obtaining stable and reproducible data.

8.3 Multi-Detector Computed Tomography (MDCT)

The utility of CT in CKD is limited and controversial. Recently, some small, single-center studies showed that unenhanced MDCT could estimate renal volume (both cortical and medullary) in CKD cases, and found a moderately positive correlation between renal volume and GFR as measured by the serum creatinine level; this suggests that MDCT can serve as a surrogate marker for the assessment and monitoring of renal function.

Contrast-enhanced MDCT can provide noninvasive, standardized, quantitative measurements of single-kidney or global hemodynamics data (e.g., regional renal perfusion, RBF, and GFR). In this technique, by administering exogenous

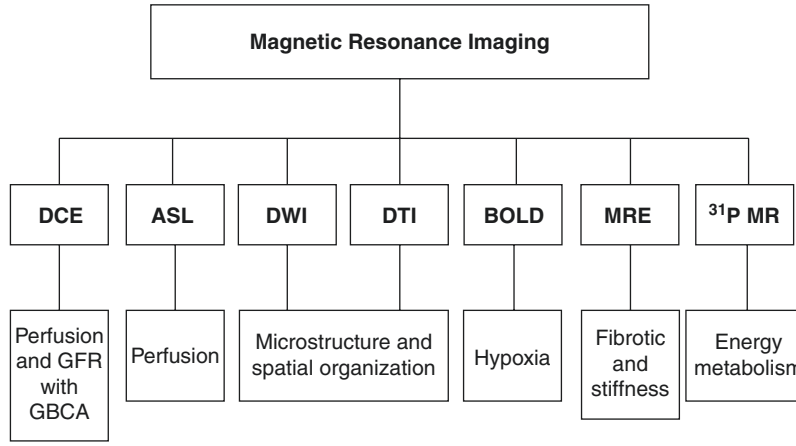

Fig. 8.1 Clinical usage of magnetic resonance imaging. *DCE* dynamic contrast-enhanced; *ASL* arterial spin labeling; *DWI* diffusion-weighted imaging; *DTI* diffusion tensor imaging; *BOLD* blood oxygen level-dependent; *MRE* magnetic resonance elastography; *P MR* P magnetic resonance spectroscopy; *GBCA* gadolinium-based contrast agents

iodine contrast agents, the density kinetics (which are linear with the concentration of contrast agents) passing though vascular space and tissues are measured sequentially, and a time-density curve is obtained to calculate renal hemodynamics parameters by mathematical modeling. Today, two primary types of analysis modeling are used: the gamma variate and Patlak methods. Contrast-enhanced MDCT plays a role in noninvasive, longitudinal monitoring of the reduction of blood perfusion related to renal injury, in both animal models and clinical cases [19–21].

However, the clinical application of this technique remains limited. This technique is based on a bolus injection of iodine contrast agents (2 × 0.5 mL/kg for gamma variate modeling; 100–150 mL for the Patlak method), and nephrotoxicity must be considered for patients with impaired renal function. Moreover, bolus injection increases preloading of the heart, so greater attentions should be given to patients with serious cardiac problems and pulmonary disease. Finally, the risk of exposure to X-rays should be considered, especially in patients who undergo repeated tests.

8.4 Magnetic Resonance Imaging (MRI)

With the development of higher magnetic field strengths, sophisticated pulse sequences, and mathematics modeling (particularly in research applications), MRI with or without exogenous contact agents has begun to assess the pathological processes of CKD [22]; however, this research has solely been performed as a signal-center, experimental study, without a standard protocol, and remains controversial. This is considered a novel approach to assess renal function and structure noninvasively (Fig. 8.1).

8.4.1 Dynamic Contrast-Enhanced (DCE)

Gadolinium-based contrast agents (GBCA) are used worldwide for DCE-MRI examinations. The tissue containing GBCA exhibits shortened tissue T1 and T2∗ values, through the so-called relaxation effect. By acquiring a series of dynamic tissue T2∗ data, an MR signal-time curve is depicted, which is typically used to describe the exchange rates between compartments (e.g., GFR) and hemodynamic parameters such as RBF, renal blood volume, MTT, and regional filtration fraction, within more sophisticated models that involve two or more compartments. Therefore, DCE-MRI could be useful for the assessment of parenchymal perfusion, including dysregulation, atherosclerosis, and microvascular rarefaction. Another application of DCE-MRI images is noninvasive estimation of GFR. Contrast media in the blood rapidly circulates through the parenchymal vasculature, but slowly accumulates in the tubule, which is similar

to the behavior of other body fluids; thus, it can be used to calculate the single-kidney GFR by mathematical modeling. A correlation has been reported between standard radioisotope measures and the DCE-MRI approach [23].

However, the limitations of this technique are obvious. (1) Nephrotoxicity of the contrast agent: GBCAs have been reported to cause nephrogenic systemic fibrosis and gadolinium body storage [24, 25], and they are primarily excreted from the body by the kidneys; thus, safety should be thoroughly considered in cases with severe renal dysfunction. (2) DCE-MRI requires an extensive duration (3–10 min), such that it is clearly impacted by respiratory motion [26]. (3) Lacking standard mathematics models and internal controls, the sensitivity and specificity of this technique must be considered. It has been reported that DCE-MRI is reliable in cases with severe renal injury (e.g., artery stenosis >80%) [27]. There remains a gap between DCE-MRI results and "real" renal perfusion and function.

8.4.2 Arterial Spin Labeling (ASL)

ASL-MRI is an imaging technique to obtain a series of perfusion-weighted images by using inflowing blood as an endogenous contrast agent, which temporarily alters blood flow magnetization. ASL is primarily used for measurement of cortex perfusion, but rarely for such measurement of the medulla. Recently, ASL was applied to assess renal perfusion in patients with metabolic syndrome, and to detect hemodynamic responses to pharmacologic interventions [28]. However, because of its low signal-to-noise ratio (SNR), and because it requires complex imaging sequences and mathematical modeling to analyze the resulting data, ASL-MRI remains largely used for research.

8.4.3 Diffusion-Weighted Imaging (DWI)

DWI-MRI is a powerful imaging technique to provide diffusivity information by detecting random Brownian motion of water molecules in the kidneys. In DWI-MRI, water molecules accumulate in a strong magnetic gradient field (positive diffusion gradient), and un-accumulate in a second gradient field (negative diffusion gradient). When moving between these two fields, water molecules in motion exhibit an MR signal loss; when water molecules exhibit greater freedom of movement, a greater signal loss occurs. By adjusting the applied gradient pulse with respect to different diffusion sensitivities (b-values, where a higher b-value requires stronger diffusion weighting), the signal intensity-time curve is fitted to calculate the apparent diffusion constant (ADC), a quantitative measure of MR signal loss. Lower ADC values indicate slower free water movement, which is more common in pathological conditions.

DWI-MRI has shown high potential for use in a variety of acute and chronic kidney diseases. In CKD, the ADC value is reduced in both cortex and medulla, compared with healthy kidneys; it correlates with kidney injury in histological analysis of core biopsy specimens [29–31]. There is a statistically significant association between reduced ADC values and deterioration of renal function [32]. Paired comparisons show that ADC values exhibit statistically significant differences among CKD stages; the sensitivity and specificity were 75.44% and 69.81% to detect CKD stages 3–5 [33]. Several factors might lead to alterations of ADC value, such as the reduction of glomerular filtration and tubular reabsorption functions, and the accumulation of cellularity and extracellular matrixes.

The advantages of this technique are obvious: it does not require exogenous contrast agents and it acquires images in a short time (<1 min), within a few breath-hold intervals, such that it is minimally affected by breath movement. However, DWI-MRI remains limited in research use, and the "true" meaning of ADC values is controversial. Thus far, research involving DWI-MRI comprises small, single-center studies; larger, multicenter studies must be performed to ascertain the power of ADC to diagnose CKD. Moreover, ADC values vary along with *b* values, such that a standard protocol and generic analysis model are needed for large-scale clinical application.

8.4.4 Diffusion Tensor Imaging (DTI)

Compared with DWI-MRI, the DTI technique provides more information regarding the diffusion direction of free water in tissues. This information can be provided by markers such as fractional anisotropy (FA), a measure of directional diffusivity within a range of 0–1. When FA = 0, water molecule diffusion occurs in all directions, whereas FA = 1 reflects restricted diffusion along a single orientation. In healthy kidney, both cortex and medulla are highly organized and exhibit high integrity, so water may theoretically diffuse preferentially along a fixed orientation (e.g., the direction of the tubules). Recently, several small clinical studies have shown that FA is more reflective of microstructure and spatial organization related to CKD, compared with ADC [34–36]. However, like other novel functional MRI techniques, DTI-MRI is limited in clinical application by the required sophisticated analysis model and time-intensive data acquisition processing.

8.4.5 Blood Oxygen Level-Dependent (BOLD)

Tissue hypoxia is a distinctive characteristic of CKD; in some degree, hypoxia is consistent with the morphometric and functional changes that contribute to the progression to ESRD. BOLD-MRI was initially developed for neuroimaging; in the kidney, it has attracted much attention because it can provide information regarding blood oxygenation and tissue hypoxia in vivo. Deoxyhemoglobin is a paramagnetic molecule that can act as an endogenous T2∗ contrast agent. With increasing concentration of deoxyhemoglobin, the MR signal decay becomes more rapid (shorter T2∗). Tissue parameter R2∗ (1/T2∗) has been considered to be associated with renal oxygen levels.

In healthy kidney, PO_2 in the medulla is approximately 10–20 mmHg, which is much lower than that in cortex (50 mmHg). Active reabsorption by the Na/K/Cl cotransporter in the thick ascending limb is a process of high energy consumption. Thus, the renal medulla is more sensitive to hypoxia. In healthy tissue, the demarcation of cortex and medulla is sharp in MR R2∗ images, and R2∗ gradually increases from the cortex to the medulla near the renal hilus. This effect is validated by administering furosemide, an inhibitor of the Na/K/Cl cotransporter. There is no difference in R2∗ value between the left and right kidney; this value is positively related to age, but not to gender. The acquisition time of BOLD-MRI is relatively short (1–5 min) and is collected over several breath-hold intervals, which is also an advantage in clinical applications.

It has been reported that renal R2∗ (especially in the medulla) is suitable for the assessment of different pathologic conditions in kidney, including CKD [37, 38]. Recent studies in an animal model of diabetic nephropathy have shown that R2∗ values increase in the outer medulla, suggesting lower tissue oxygenation [31, 39]. However, this change only occurs in advanced stages of disease. Some studies have also shown differences in baseline T2∗ in diabetic kidneys in humans. However, other research showed that medullary BOLD signals were nonspecific and did not reflect renal function in diverse chronic renal diseases [40]. Thus, the correlation between measured T2∗ and disease stage remains controversial.

However, the sensitivity and specificity of this technique must be considered. Firstly, CKD is a sophisticated pathologic condition. Its hemodynamics, such as microvascular density and regional renal blood flow, can influence the MRI signal, as indicated by the R2∗. Secondly, with the assumption that the blood and tissue are in strict accordance with tissue oxygenation, some pathological conditions, such as fibrosis, may restrict oxygen diffusion across the microvascular lumen, and may cause heterogeneity between the vascular and renal parenchyma. Finally, kidneys are retroperitoneum organs, so intestine gas might increase $R*$ values of a specific area of kidney leading to misdiagnosis as a region of hypoxia or kidney scars. Nevertheless, BOLD-MRI remains the most popular and effective technique to invasively measure tissue oxygenation in vivo.

8.4.6 Magnetic Resonance Elastography (MRE)

Based on the assumption that excessive extracellular matrix deposition in fibrotic tissues increases the stiffness of the kidneys, MRE-MRI is used to estimate tissue stiffness, as an index of fibrosis, by using translocation of mechanical shear waves. Some studies have shown the utility of this technique in patients with transplant and renal artery stenosis [41–43]. However, similar to US elastography, the results are influenced by anisotropy, vascularization, hydronephrosis, and external pressure. Therefore, advanced development of appropriate models is likely to increase the use of this novel technique.

8.4.7 Molecular Imaging

Energy dys-metabolism with a loss of ATP is an important early functional change in renal failure. ^{31}P MR spectroscopy, which can detect the ratio of phosphomonoesters to inorganic phosphorus, is able to evaluate renal metabolism in vivo. This technique was initially used to evaluate posttransplant graft function, and is now used to assess CKD progression [44]. However, this technique remains limited by low SNR and the advanced data acquisition approach.

8.5 Nuclear-Based Technique

Radionuclide imaging, which is a functional imaging technique that uses different types of radioisotopes bound to non-metabolized molecules with known pharmacokinetics (tracers), is considered to show glomerular filtration (^{99m}Tc-DTPA and ^{99m}Tc-MDP), tubular function (^{99m}Tc-DMSA), and effective renal plasma flow (^{99m}Tc-MAG3M and ^{131}I-OIH) [45, 46]. Both noninvasive and non-nephrotoxic, it is widely used in the clinic to evaluate total and partial divide kidney functions in CKD patients. Importantly, its disadvantage is obvious, such as relatively high radiation exposure, as well as low quantitation and spatial resolution with respect to morphological abnormities.

The development of scintigraphic methods, such as positron emission tomography (PET) and combined PET/CT imaging, enhanced the value in acquisition of reliable renal blood flow (using ^{82}Rb or ^{64}Cu-PTSM as a tracer) and GFR (using ^{68}Ga-EDTA or ^{55}Co-EDTA as a tracer) information because of good correlation with gold standard determination by radioactive microspheres [47]; moreover, this information is more valuable when fused with anatomic information. However, the clinical usage remains limited because of its high cost and complicated process.

Another attractive but limited aspect, predominately used in experimental studies, is that nuclear-based technique can directly assess molecular targets, such as membrane transporters, receptors, signal transduction, and gene expression; this makes it quantitative and suitable for in vivo assessment of tissue hypoxia, apoptosis, and endothelial dysfunction in pathological conditions. It has been reported in studies of other organs that hypoxia could by visualized by PET with ^{18}F-fluoroazoycinarabinofuranoside or ^{18}F-fluoromisonidazole [48]; the expression of some molecules, such as integrin, could be monitored in vivo by ^{18}F-labeled integrin antagonists [49]. However, the usage of this approach in CKD is likely in the distant future.

8.6 Conclusion

Image techniques in the kidney have become an indispensable research tool (Fig. 8.2). Some tools, such as DCE-MRI and Doppler US, have been extensively investigated in the clinic. However, there remains a gap between theoretical studies and clinical applications. More sophisticated analysis models and the combined utilization of these novel tools are needed to maximize clinical values in the future.

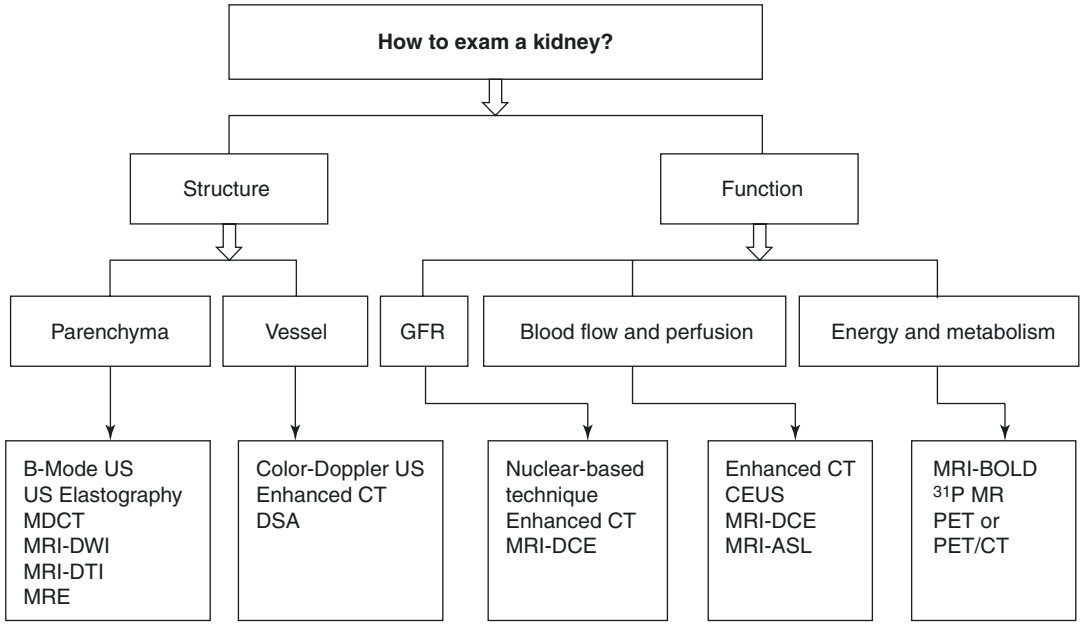

Fig. 8.2 Clinical application of image techniques in kidney disease. *GFR* glomerular filtration rate; *US* ultrasonic; *MDCT* multi-detector computed tomography; *MRI* magnetic resonance imaging; *MRE* magnetic resonance elastography; *CT* computed tomography; *DSA* digital subtraction angiography; *DCE* dynamic contrast-enhanced; *CEUS* contrast-enhanced ultrasound; *ASL* arterial spin labeling; *BOLD* blood oxygen level-dependent; *P MR* P magnetic resonance spectroscopy; *PET* positron emission tomography

Key Messages

- US remain a first-line and indispensable tool for acquiring qualitative and quantitative information regarding morphology and vasculature in CKD patients. This technique provides a large advantage for real-time imaging analysis, high safety and renal tolerance, and radiationless; however, it is limited by operator experience, patient state, and poor space resolution.
- Nuclear-based technique remains the gold standard for evaluating GFR, while MDCT and MRI are becoming widely applied in the clinic.
- BOLD-MRI is the most effective technique to invasively measure tissue oxygenation in vivo, while DWI-MRI and DTI-MRI provide the microstructure and spatial organization of fibrotic kidney by detecting the movement of free water molecules.
- Recent developments in imaging provide unique insights into metabolism and fibrosis that surpass simple anatomy. However, most techniques require sophisticated analysis models and time-sensitive data acquisition processing, which limit their use in research. A standard protocol and generic analysis model is needed for large-scale clinical applications.

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Part II

Complications of Chronic Kidney Disease

9 Cardiovascular Disease in Chronic Kidney Disease

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Abstract

Cardiovascular disease (CVD) is a leading cause of death among patients with chronic kidney disease (CKD). In addition to the traditional risk factors associated with the condition, uremic toxins may contribute directly to the pathogenesis of CVD in patients with CKD. Because of the multifactorial pathogenesis, treating patients with CKD and concomitant CVD is challenging. Treatable factors such as anemia, hyperphosphatemia, hypercalcemia, and hyperparathyroidism cannot completely explain the broad spectrum of CVD observed in this patient population. To date, no study has identified effective drug therapy to control cardiovascular outcomes in patients with CKD.

9.1 Introduction

Cardiovascular diseases (CVD) including coronary artery disease (CAD), congestive heart failure (CHF), arrhythmias, and sudden cardiac death are the primary contributors to morbidity and mortality in patients with chronic kidney disease (CKD). Arteriosclerosis and disorders of left ventricular (LV) structure and function are common in patients with CKD. In addition to the traditional risk factors observed in the general population, numerous CVD-related risk factors are specifically relevant in patients with CKD and are related to the development of CVD. Patients with CKD demonstrate a very high prevalence of traditional risk factors for CVD such as diabetes and hypertension. However, they are also exposed to other nontraditional uremia-related cardiovascular risk factors including abnormal calcium-phosphorus metabolism and inflammation. In this chapter, we will discuss the epidemiology and pathophysiology of CVD in patients with CKD. We shall also discuss the primary diagnostic and therapeutic principles and pathophysiology of different types of CVD in patients with CKD.

9.2 Epidemiology

CVD is the leading cause of death in patients with CKD and end-stage renal disease (ESRD), accounting for approximately 50% of all CKD-related mortality [1]. The latest data obtained from the 2015 United States Renal Data System Annual Data Report show that to date, CVD remains the primary cause of death in patients with ESRD. CVD in patients with CKD primarily manifests as myocardial and arterial vascular

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diseases [2]. Left ventricular hypertrophy (LVH) and myocardial fibrosis constitute the common myocardial pathologies in patients with CKD, whereas arteriosclerosis and atherosclerosis constitute the primary arterial vascular diseases in this patient population. These etiological contributors to CVD can lead to clinical manifestations of ischemic heart disease (IHD), CHF, cerebrovascular, and peripheral vascular disease. The prevalence of CVD even in patients with CKD stage 1 and 2 (indicating milder disease) is significantly higher than that in the general population. Proteinuria, which manifests as either micro- or macroalbuminuria, is an independent risk factor for a higher prevalence of CVD and CVD outcomes.

The incidence and mortality rates associated with CVD tend to increase following a decline in renal function. This high burden of CVD mortality is well illustrated by comparing between the CVD-related mortality in patients with ESRD and that in the general population. It has been shown that approximately 75% of patients with ESRD present with LVH. Moreover, the prevalence of hypertension increases progressively with the decline in renal function in patients with CKD, and 75–85% of patients undergoing dialysis demonstrate hypertension. In addition to hypertension, anemia, vascular noncompliance, and volume overload are all known contributors to LVH. Based on echocardiographic studies, 85–90% of patients with ESRD show LV ejection fraction (LVEF) ≥50%; however, CHF is common in these patients.

9.3 Risk Factors for CVD in Patients with CKD

The risk factors associated with CVD in patients with CKD can be categorized as traditional and nontraditional risk factors. Traditional risk factors refer to the usual/universal risk factors for CVD that are observed in the general population including smoking habits, and history of hypertension and diabetes, among others. Nontraditional risk factors primarily refer to the risk factors for CVD related to CKD, such as proteinuria, oxidative stress, and disorders of calcium and phosphorus metabolism. Traditional and nontraditional risk factors for CVD are summarized in Table 9.1.

Table 9.1 Traditional and nontraditional cardiovascular risk factors

Traditional risk factors	Nontraditional risk factors	
	Hemodynamic factors	Metabolic factors
Old age	Volume overload	Proteinuria
Male sex	Anemia	Chronic inflammatory state
Menopause	Arteriovenous fistula	Malnutrition
Smoking habit	Arteriosclerosis	Disorders of lipid metabolism
Diabetes		Oxidative stress
Hypertension		CKD–MBD
Dyslipidemia		Thrombogenic factors
Physical inactivity		
Family history of CVD		

CKD–MBD chronic kidney disease-mineral bone disorders; *CVD* cardiovascular disease

Progressive kidney damage leads to cardiac damage through a variety of mechanisms and factors, culminating in the unique risks that ESRD patients experience secondary to the dialysis procedure itself. Volume overload occurring in patients with ESRD may be attributable to diastolic dysfunction or circulatory congestion. As mentioned earlier, in terms of IHD and CAD, the relationship between CKD and CVD may involve shared risk factors, a reflection of widespread vascular disease and endothelial dysfunction, and/or the toxicity caused by the uremic milieu. Furthermore, IHD itself can contribute to CAD and predispose to arrhythmia. LVH and cardiac failure are the most common complications observed in patients with CKD, which are primarily attributable to fluid overload and, usually, hypertension. Myocardial fibrosis occurs secondary to impaired angio-adaptation, reduced capillary angiogenesis, myocyte-capillary mismatch, and micro-arteriopathy. The vascular tree is affected by both arteriosclerosis and

atherosclerosis with widespread arterial media calcification and the deposition of lipid-rich plaques [3].

9.4 Clinical Manifestations of CVD in Patients with CKD

9.4.1 Cardiomyopathy

LVH is the most important cardiovascular structural change in patients with CKD, particularly in those with ESRD. LVH in patients with CKD is not only related to hypertension and volume load, but is also associated with activation of the local renin-angiotensin-aldosterone system and increased aortic wall stiffness. LVH is associated with diastolic dysfunction, which suggests an unfavorable prognosis in patients with CKD.

9.4.2 Coronary Atherosclerotic Heart Disease

Secondary to the occurrence of autonomic neuropathy in patients with CKD and the volume overload, myocardial ischemia may atypically present as asymptomatic acute myocardial infarction (AMI), which may be misdiagnosed, and thus patients may not receive prompt treatment.

9.4.3 Congestive Heart Failure

Patients with CKD, particularly those with ESRD undergoing dialysis, demonstrate the hypervolemia that can lead to LVH, LV enlargement, edema, and acute pulmonary edema.

9.4.4 Arrhythmia and Sudden Cardiac Death

Arrhythmia is a common clinical complication in patients with ESRD, particularly during the course of hemodialysis (HD). Sudden death is known to occur in patients with ESRD, primarily related to ventricular fibrillation, and approximately 20% of these cases are secondary to cardiac arrest. Cardiac arrhythmia is usually associated with hyperkalemia in patients with CKD.

9.4.5 Pericarditis

Untreated uremic pericarditis is rare, although dialysis-related pericarditis is common in patients with ESRD and usually occurs in those with insufficient dialysis. Echocardiography should be performed in patients presenting with pericardial pain and fever or when auscultation reveals pericardial friction sounds.

9.4.6 Heart Valve Disease

Disorders of calcium and phosphorus metabolism, long dialysis vintage, hypoalbuminemia, and old age are significant risk factors in patients with CKD complicated with valvular disease and calcification. Valvular calcification with regurgitation can cause stenosis and hemodynamic instability, as well as conduction disorders in patients with CKD.

9.4.7 Peripheral Vascular Diseases

Diabetic patients and those with atherosclerosis undergoing dialysis are at a high risk of peripheral vascular disease. The occurrence of peripheral vascular diseases in patients undergoing HD is related to dialysis vintage and hypoalbuminemia. Peripheral arterial calcification does not always lead to occlusive disease; however, occlusive small vessel disease causes gangrene.

9.5 Diagnosis of CVD in Patients with CKD

Although CVD is highly prevalent in patients with CKD, its clinical diagnosis remains challenging because of atypical signs and symptoms observed in patients. The diagnostic criteria used

in the general population are not always applicable to patients with CKD owing to the decline in renal function in this patient population. For example, symptoms of heart failure (e.g., dyspnea, fatigue) and physical signs of volume overload are highly prevalent in patients with CKD even in the absence of cardiac dysfunction. It has also been reported that patients with ESRD with AMI may not always present with chest pain.

9.5.1 Serological Tests

9.5.1.1 Cardiac Troponins

Although the estimation of single myocardial enzymes does not show high diagnostic specificity, the dynamic changes in levels of enzymes such as creatine kinase-MB and lactate dehydrogenase can effectively diagnose AMI. Positive serum cardiac troponin T (cTnT) and troponin I (cTnI) indicate acute ischemia, and the sensitivity of these tests in assessing the extent of myocardial infarction is greater than that of myocardial enzymes. High-sensitivity-cardiac troponin (hs-cTn) is the preferred cardiac marker to diagnose acute coronary syndrome (ACS). However, the upper reference limits for cTnT and cTnI were originally established in patients without CKD, and these biomarkers are elevated in approximately 80% of patients with asymptomatic CKD and ESRD. Notably, cTn elevation does not necessarily indicate acute ischemia secondary to coronary atherosclerosis. Elevated cTn levels may be secondary to decreased renal clearance or chronic myocardial injury. Multifactorial pathomechanisms are involved including myocardial strain from hemodynamic alterations, inflammation, endothelial dysfunction, and subendocardial ischemia. In contrast to cTnI, cTnT assays are standardized. In asymptomatic patients with CKD, cTn levels are associated with various surrogate markers such as LVH, doubling of serum creatinine levels, and CKD progression, as well as serious clinical outcomes such as death and cardiovascular events. Patients with ESRD presenting with an initial cTnT concentration >0.35 ng/mL demonstrate an unfavorable prognosis; therefore, a higher cutoff value is recommended for cTnT for prompt diagnosis and treatment in patients with ACS undergoing dialysis. Regular and close monitoring of hs-cTn is important in patients with CKD for clinical management rather than using a single value that is higher than the upper limit of normal [4].

9.5.1.2 Estimation of Brain Natriuretic Peptide and N-Terminal-pro-BNP

Brain natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-pro-BNP) levels are commonly tested in symptomatic patients with suspected acute CHF exacerbation. Previous reports have shown elevated levels in 56% of asymptomatic patients with CKD. LV myocytes release BNP and NT-pro-BNP from precursors in response to increased stretch or tension. BNP is an active molecule with a short plasma half-life and is metabolized in the circulation by enzymatic action. NT-pro-BNP is the inactive form of BNP, with a longer half-life and primarily undergoes renal clearance. A reduced estimated glomerular filtration rate (eGFR) correlates with elevated plasma NT-pro-BNP levels to a greater extent than with elevated BNP levels. An increased NT-pro-BNP/BNP ratio shows a significant correlation with progression of CKD, particularly with eGFR <30 mL/min/1.73 m^2. However, both BNP and NT-pro-BNP are associated with surrogate markers and serious clinical outcomes in asymptomatic patients with CKD [4]. A previous study involving 150 asymptomatic patients undergoing HD with a mean follow-up of 24 months showed that the correlation between NT-pro-BNP and all-cause and cardiovascular mortality was significantly stronger than that with cTnT. A recent cross-sectional study has shown that NT-pro-BNP levels of 6000 and 10,000 pg/mL are the optimal cutoff values to diagnose CAD and LV systolic dysfunction, respectively. Therefore, estimation of the NT-pro-BNP level prior to the initiation of dialysis is an important screening tool for cardiac abnormalities. A recent prospective cohort study involving 3483 patients with CKD without heart failure showed that the potential rate of heart failure was

higher in patients with the highest levels of NT-pro-BNP (>433 pg/mL) with a risk ratio of 9.57. Therefore, NT-pro-BNP and BNP are useful biomarkers for LV dilatation, and systolic and diastolic dysfunction in patients undergoing dialysis. Notably, they serve as biomarkers for the prediction of cardiovascular mortality in patients with CKD not undergoing dialysis [5].

9.5.1.3 Serum Mineral and Bone Biomarkers

Patients with CKD-MBD demonstrate increased serum intact parathyroid hormone (iPTH) levels, vitamin D deficiency, and hyperphosphatemia, which serve as independent risk factors of CVD. The fibroblast growth factor 23 (FGF23) regulates phosphorus and vitamin D metabolism and its levels increase progressively in early CKD, partially as an adaptation to the uremic environment and also as a primary pathophysiological event that may account for several clinical manifestations including bone and cardiovascular complications. Increased plasma FGF23 levels are associated with LVH, vascular calcification, cardiovascular dysfunction, and increased mortality in patients with CKD.

9.5.1.4 Other Serum Biomarkers

In addition to cTnT and BNP, C-reactive protein, asymmetric dimethylarginine (ADMA), N-monomethyl-L-arginine (L-NMMA), plasminogen-activator inhibitor type I, homocysteine, serum amyloid A protein, ischemia modified albumin, and several others serve as biomarkers that progressively increase with a decline in the eGFR. Many of these are independently associated with CVD in patients with CKD. C-reactive protein is a well-known inflammatory biomarker that is strongly associated with vascular disease. In addition to being a biomarker, it is considered potentially causally related to vascular disease. ADMA and L-NMMA are endogenous inhibitors of nitric oxide synthases that attenuate nitricoxide production and enhance the generation of reactive oxidative species. Increased plasma levels of ADMA and/or L-NMMA are strong and independent risk factors for CKD and various types of CVD. The increased cardiovascular morbidity associated with CKD may be attributed to significantly increased levels of systemic ADMA and L-NMMA [6].

9.5.2 Instrumental Examinations

9.5.2.1 Electrocardiography and 24-H Dynamic Electrocardiography

Static electrocardiography (ECG) performed in patients undergoing HD show prolonged PR and QRS intervals and nonspecific ST-T segment changes. These changes are more pronounced during intra- and extracellular fluid shifts during dialysis. Typical ECG changes can be observed in patients with acute coronary ischemia. Monitoring with 24-h dynamic ECG is helpful to diagnose premature beats and other arrhythmias in patients with CKD.

9.5.2.2 Echocardiography and Doppler Ultrasonography

Echocardiography is the primary tool used to evaluate ventricular and valvular structures and cardiac function. This noninvasive diagnostic modality used in clinical practice performs real-time qualitative and quantitative evaluation. Echocardiography demonstrates signs of volume overload, particularly left and right ventricular dysfunction in patients with ESRD and those undergoing HD. Volume overload is indicated by increased atrial volumes or areas, pleural or pericardial effusion, and lung comets. Valvular calcification (related to secondary hyperparathyroidism) and features of right-sided cardiac dysfunction such as high pulmonary artery pressures or right chamber dilatation are commonly observed. Echocardiography and Doppler ultrasonography can also diagnose complications of uremic cardiomyopathy such as coronary and peripheral artery disease, LVH, vascular and valvular calcifications, and myocardial fibrosis. LVH is usually assessed by performing standard two-dimensional (2-D) echocardiography, which though not very accurate, is cost-effective. The accuracy of echocardiography depends upon the technique used, the timing of the test relative to the dialysis session,

and the index used for "normalization" of the data generated. Estimation of the LV mass in patients with CKD and ESRD can be performed using 2-D and 3-D echocardiography techniques. Assessment of LV mass, volume, and EF using real-time 3-D echocardiography shows higher accuracy than that with 2-D echocardiography. The accuracy of this modality is close to that of cardiac magnetic resonance imaging (CMRI). Tissue Doppler imaging scores over conventional Doppler echocardiography in evaluating CKD-related cardiac complications and early diastolic dysfunction based on its ability to accurately record local and global myocardial velocity changes. With the development of advances in ultrasonographic technology might provide better and a greater number of radiological techniques to evaluate cardiac abnormalities in patients with CKD.

9.5.2.3 Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging

Cardiac computed tomography (CT) and cardiac magnetic resonance imaging (CMRI) are useful to evaluate complications of uremic cardiomyopathy. Cardiac CT detects coronary artery calcifications and can diagnose coronary atherosclerosis in patients with CKD. CMRI is considered the gold standard for the accurate evaluation of the LV mass, to define the volume and pattern of LVH (eccentric, concentric or asymmetric), and to assess the magnitude of fibrosis. Compared with CMRI, classical echocardiography often overestimates the LV mass in patients undergoing dialysis; however, CMRI is not a practical option for widespread use owing to the higher costs. Therefore, echocardiography remains the primary tool to evaluate LV mass in clinical practice. CMRI allows complete assessment of arterial function through measurement of aortic distensibility (AD); a reduction in the AD is observed in the early stages of the evolution of CKD-related cardiomyopathy.

9.5.2.4 Coronary Angiography

Coronary angiography is the gold standard to diagnose CAD. Patients with CKD in the pre-dialysis stage are at a high risk of developing contrast nephropathy and deterioration of renal function following the administration of contrast agents. All patients with CKD are also at risk for cholesterol embolism. Therefore, coronary angiography should be cautiously performed in patients with CKD. Coronary angiography is warranted in patients with unstable angina or myocardial infarction prior to undergoing coronary angioplasty.

9.5.2.5 Doppler Angiography and Intravascular Ultrasound Imaging

The development of ultrasound imaging technology has enabled the real-time analysis of blood vessels and vascular blood flow. Waveforms typically vary across vascular beds, and abnormal waveforms indicate arteriopathy. The lesions and plaques in surrounding vessels and the coronary arteries, as well as changes in the endovascular cavity, can be identified using high-frequency probes and intravascular imaging.

9.5.2.6 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) is essential for the accurate determination of BP levels, particularly in patients with CKD [7]. ABPM scores over traditional office BP measurements in that it can avoid the white coat effect and provide additional information regarding a patient's BP including short-term BP variability and circadian rhythm (i.e., "dipping" or "non-dipping" status). It is also essential to diagnose "white coat hypertension" and "masked hypertension." In our previous study, we observed that approximately 50% of the patients undergoing dialysis who were considered to show controlled BP actually demonstrated "masked uncontrolled hypertension" and that this condition is associated with hypertensive end-organ damage [7]. Therefore, physicians should routinely use ABPM in these patients.

9.5.2.7 Measures of Arterial Elasticity, Endothelial Function, and Pulse Wave Velocity

Previous studies have shown that a few noninvasive modalities that are not widely adopted in

clinical practice are useful to assess cardiovascular health and for risk prediction in patients with CKD. Assessment of vascular function including the estimation of arterial elasticity and endothelial function serves as a potentially valuable indicator of cardiovascular health and should be considered in the care of patients with CKD [8, 9]. Measurement of pulse wave velocity is a standard measure of arterial stiffness and can be performed with several commercially available devices [10]. The "flow-mediated dilation" test is the traditional method to assess endothelial function; however, it requires a highly experienced operator, and its reproducibility is usually unsatisfactory. A device based on peripheral arterial tonometry has recently been developed for automatic measurement of peripheral endothelial function. We adopted this measurement method in a dialysis cohort to test if it could overcome the challenge of the fistula and predict cardiovascular outcomes in patients undergoing maintenance HD [11].

9.6 Treatment of CVD in Patients with CKD

9.6.1 Risk Factor Intervention

9.6.1.1 Intervention for the Management of Traditional Risk Factors

- **Antihypertensive treatment**
- Hypertension is highly prevalent among patients with CKD and contributes to the high burden of CVD-related morbidity and mortality. Strict volume control via sodium restriction constitutes the first-line approach for the treatment of hypertension in this patient population; however, antihypertensive drug therapy is often needed to control BP. Selection of an optimal antihypertensive regimen should be individualized. The latest 2018 European Society of Cardiology/European Society of Hypertension guidelines for the management of hypertension recommend initial combination therapy with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) or diuretics in patients with CKD. ACEIs/ARBs are more effective than other antihypertensive drugs in reducing proteinuria in patients with CKD. Serum potassium and creatinine levels should be closely monitored in patients with CKD who receive ACEIs or ARBs. Thiazide diuretics are contraindicated and loop diuretics can be used in patients with CKD demonstrating eGFR <30 mL/min/1.73m^2. Probing dry weight can improve BP among hypertensive patients undergoing HD. Intra- and interdialytic pharmacokinetics, effect on cardiovascular reflexes, treatment of comorbidities, and the adverse effect profile are important factors that determine individualization of therapy. Beta-blockers and dihydropyridine CCBs constitute the first- and second-line antihypertensives, respectively, that are commonly prescribed. ACEIs and ARBs are third-line choices because there is limited evidence supporting their use in patients undergoing dialysis. Diuretics have little to no role in patients with ESRD [12].
- **Correction of abnormal lipid metabolism**
- The short-term efficacy and safety of statins have been confirmed in patients with CKD, and statins are the most effective drugs to reduce low-density lipoprotein (LDL)-cholesterol in these patients. The long-term effects of statins on cardiovascular outcomes in patients with CKD have also been well documented, and they are known to reduce proteinuria. Statins are recommended in patients presenting in the early stages of CKD because their use during this period significantly reduces the relative risk of CVD. The continued role of statins in patients who require dialysis is controversial because previous trials that investigated statin use in patients undergoing dialysis have shown negative results. All patients with CKD are considered to be at a high risk, and lipid-lowering therapy is indicated in patients with LDL-cholesterol >100 mg/dL except in patients undergoing dialysis.

9.6.1.2 Intervention for the Management of Nontraditional Risk Factors

- **Correction of anemia**
- Anemia is an important risk factor associated with the prognosis of CVD in patients with CKD. However, in patients with CVD undergoing HD, normalizing the hemoglobin may not reduce mortality. In contrast, higher target hemoglobin values are associated with higher mortality in patients with CKD. Therefore, patients with CKD require close and regular monitoring of hemoglobin levels and indicators of iron metabolism. The target hemoglobin value should be set at 110–120 g/L.
- **Control of inflammation**
- CKD is characterized by a state of chronic inflammation, which serves as a strong predictor of morbidity and mortality in this population. Chronic inflammation plays an important role in the pathogenesis of CVD in patients with CKD. Increased levels of specific cytokines (interleukin 6 and tumor necrosis factor α) or acute phase proteins (C-reactive protein) are associated with CVD in patients undergoing HD. To date, no specific intervention strategy is known to treat chronic inflammation in patients with CKD. Aspirin and statins can be used in the general population as well as in patients with CKD to control inflammation. Advanced blood purification technology such as improvements in the biocompatibility of dialysis membranes and the popularization of a high-throughput dialyzer could control chronic inflammation in patients undergoing dialysis.
- **Management of disorders of calcium and phosphorus metabolism**
- Judicious use of active vitamin D and phosphorus binders is recommended to correct disorders of calcium and phosphorus metabolism and to maintain optimal blood levels of calcium, phosphorus, and PTH within the recommended range. The target range for serum calcium levels is 2.2–2.4mmoL/L, for serum phosphorus levels is 0.81–1.78mmoL/L, and for PTH levels is 150–300 pg/mL. Severe vascular calcification is closely associated with mortality in patients with CKD. In patients with severe secondary hyperparathyroidism undergoing dialysis, parathyroidectomy should be performed to correct the deranged calcium and phosphorus metabolism.
- **Correction of coagulation disorders**
- Aspirin is widely accepted as an effective agent for the primary prevention of CAD in patients without CKD. However, aspirin may aggravate platelet dysfunction in patients with CKD, particularly those undergoing HD and may increase the risk of bleeding. Routine use of aspirin is not recommended in patients with CKD without clinically proven CVD. However, low-dose aspirin therapy may reduce cardiovascular events in patients with CKD concomitant with significant CVD.

Intervention measures for reducing the risk of cardiovascular disease in patients with CKD are summarized in Table 9.2.

Table 9.2 Intervention measures to reduce the risk of cardiovascular disease in patients with chronic kidney disease

Intervention for traditional risk factors
• Smoking cessation • An appropriate increase in exercise • Controlling blood glucose levels • Controlling BP • Dietary restrictions/modifications
Intervention for nontraditional risk factors
• Reduction in the volume overload and determining an appropriate dry weight • Correction of anemia • Prevention of inflammation and correction of hypoalbuminemia • Statin therapy for correction of deranged lipid metabolism • Administration of active vitamin D and phosphorus binders to correct CKD-MBD • Judicious administration of ACEIs/ARBs to reduce proteinuria • Judicious administration of aspirin

ACEIs/ARBs angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; *BP* blood pressure; *CKD–MBD* chronic kidney disease–mineral bone disorders

9.6.2 Treatment of CKD Concomitant with Various Types of CVDs

9.6.2.1 Left Ventricular Hypertrophy

LVH represents a challenging therapeutic target. Modifying the risk factors for LVH (and subsequent heart failure) such as anemia, hypertension, extracellular volume overload, abnormalities of mineral metabolism, and arteriovenous fistulae may reduce the incidence of LVH. However, few clinical trials performed in this context have included patients with CKD. Data from several small observational studies and non-randomized trials have suggested that LVH can be treated by modifying risk factors including anemia and hypertension and performing daily dialysis for strict management of fluid volume. However, multiple randomized trials, including studies involving both patients undergoing dialysis and those with CKD stages 3 and 4, have not demonstrated a significant relationship between regression of LVH or a decrease in LV mass and near-normalized hemoglobin levels. Current treatment for LVH focuses on afterload reduction and the management of fluid volume through the administration of ACEIs or ARBs, often in combination with diuretics.

9.6.2.2 Ischemic Heart Disease

An elevation in cardiac biomarkers may indicate IHD and chronic injury even in the absence of ECG-documented changes. Diagnosis of AMI is primarily based on the dynamic changes in levels of troponins and other cardiac injury biomarkers. A sequential rise and fall in blood levels of these markers is consistent with acute cardiac damage. The principles of treatment for both acute and non-acute CAD in patients with CKD are similar to those applicable to the general population. However, the incidence of asymptomatic ischemia is relatively higher in patients with CKD secondary to the autonomic neuropathy caused by uremia and diabetes.

The recommended targets for optimal management of risk factors are as follows:

1. Predialysis BP goal of >140/90 mmHg while avoiding intradialytic hypotension.
2. Serum LDL-cholesterol level <100 mg/dL in patients with known atherogenic disease.
3. Strict control of diabetes guided by frequent blood glucose assessments.

Optimal control of BP may be accomplished by maintaining an appropriate dry weight and the administration of antihypertensive drugs. Coronary angiography should be performed followed by immediate revascularization if the procedure reveals significant CAD. However, patients with CKD demonstrate a higher risk of complications after myocardial vascularization and an unfavorable long-term prognosis. Data from a Danish nationwide cohort study have shown that the administration of clopidogrel was associated with improved outcomes in patients with non-end-stage CKD during a 1-year follow-up after MI. Moreover, ticagrelor significantly reduced ischemic endpoint events and mortality, with no significant increase in major bleeding in patients with CKD and concomitant ACS [13].

9.6.2.3 Congestive Heart Failure

Treatment of acute heart failure differs between patients based on the stages of CKD. Diuretics are commonly used in patients during the predialysis stage, whereas ultrafiltration effectively reduces acute fluid overload in patients undergoing dialysis. Several patients undergoing dialysis benefit from the use of longer treatments or more frequent short treatments. Two randomized placebo-controlled trials have established the efficacy of ARBs in reducing the risk of heart failure. Theoretically, further benefits may be achieved by aldosterone blockade. However, combination therapy using ACEIs and ARBs precipitates hyperkalemia, which therefore limits its use in clinical settings. Beta-blockers, another mainstay of heart failure therapy in the general population, are beneficial in patients with CKD. Cardiac glycosides (e.g., digoxin) decrease morbidity but not mortality in the general population with heart failure. However, no specific study has investigated their efficacy in patients with CKD. It is recommended that they should be

used cautiously, with particular attention to appropriate dosages and monitoring of serum potassium levels. Reportedly, angiotensin receptor neprilysin inhibitors (ARNIs) are superior to enalapril in reducing the mortality risk and rate of hospitalization for heart failure [14]. In July 2015, the United States approved ARNIs for the treatment of CHF, which is expected to serve as the basis of future treatment in patients with heart failure. However, further data are needed to support the use of ARNIs in patients with CKD.

9.6.2.4 Pericardial Disease

Treatment of pericardial diseases is dependent upon symptoms and effusion size. Small, asymptomatic pericardial effusions are relatively common in patients undergoing dialysis and require no acute intervention. Heparin is avoided during dialysis to avoid hemorrhagic tamponade. Adjuvant medical therapies including the oral and intravenous administration of glucocorticoids and nonsteroidal anti-inflammatory medications are ineffective. Patients with hemodynamic instability require emergency drainage of the pericardial effusion.

9.6.2.5 Endocarditis

Endocarditis should be treated with appropriate antibiotics; however, the survival rate is often poor. Surgical intervention may be an alternative, and indications for surgery are similar to those applicable to the general population including progressive valvular destruction and heart failure, recurrent systemic emboli, and failure to respond to antibiotic treatment.

9.6.2.6 Aortic Calcification and Stenosis

Treatment of aortic stenosis requires a multipronged approach including the prevention of progression and the development of endocarditis and eventually valve repair. Management of mineral metabolism disorders theoretically inhibits the progression of aortic stenosis. Valve replacement can be considered in patients with critical aortic stenosis. The timing of surgery is dependent on the patient's condition.

9.6.2.7 Atrial Fibrillation

Optimal management of atrial fibrillation involves control of the heart rate with or without restoration of sinus rhythm. Beta-blockers and CCBs are useful for rate control, and amiodarone is effective for chemical cardioversion. The risk-benefit ratio of anticoagulation in patients undergoing dialysis should be judiciously assessed and individualized.

9.6.2.8 Ventricular Arrhythmias and Sudden Death

Potential strategies to reduce the risk of fatal cardiac arrhythmias include close surveillance of the dynamic changes in fluid volume and serum electrolyte levels. HD units equipped with automated external defibrillators and well-trained staff may effectively prevent arrhythmia-induced deaths. Potential medical interventions include the routine administration of beta-blockers.

Key Messages

- CVD is the leading cause of death in patients with CKD and ESRD, accounting for approximately 50% of all CKD-related mortality.
- Progressive kidney damage leads to cardiac damage through a variety of pathomechanisms and factors, both traditional and nontraditional.
- The diagnostic criteria used in the general population are not always applicable to patients with CKD owing to the decline in renal function in this patient population.
- Despite the known and currently used strategy of managing traditional and nontraditional risk factors, treating patients with CKD and concomitant CVD is challenging.

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Anemia in Chronic Kidney Disease

10

Yi Fang and Weichun He

Abstract

Anemia is an important and frequent complication in patients with chronic kidney disease (CKD), and its prevalence increases as renal function declines. The etiology of anemia in CKD is multifactorial, including absolute or relative lack of erythropoietin, iron deficiency, blood loss, shortened red blood cell survival, and other factors. Anemia in CKD is associated with impaired quality of life and elevated morbidity and mortality of cardiovascular diseases. Patients with CKD should monitor hemoglobin levels regularly. If the degree of anemia is not consistent with that of renal dysfunction in patients with CKD, it is necessary to rule out the existence of other diseases that can cause anemia. Erythropoiesis-stimulating agent (ESA) and iron supplementation are the primary treatment for anemia in CKD. Hemoglobin levels and iron status should be monitored regularly during treatment. It is generally recommended that hemoglobin concentration not exceed 115 g/L in patients undergoing ESA maintenance; the monthly hemoglobin growth rate should be limited in ≥10 g/L, but <20 g/L. Transfusions should be avoided as much as possible. Inhibitors of hypoxia-inducible factor prolyl hydroxylase is a kind of new promising therapeutic drugs.

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10.1 Introduction

Anemia, an important clinical manifestation of the complications of chronic kidney disease (CKD), may occur in patients with stage 1 CKD and becomes more prevalent with progression of the disease [1]. The anemia induced by CKD is primarily due to reduced production of erythropoietin (EPO) by the kidneys, as well as iron deficiency, which results in a hypoproliferative state of erythropoiesis. Anemia leads to higher rates of morbidity and mortality [2], thus diminishing quality of life in patients with CKD. Since the late 1980s, the use of exogenous erythropoiesis-stimulating agent (ESA) has greatly advanced the management of renal anemia, significantly reducing the need for blood transfusion and improving quality of life for many patients with CKD. The most common therapeutic options for correction of anemia include ESA administration, iron supplementation, and transfusion of red blood cells. However, the optimum target hemoglobin concentration and anemia management practices in patients with CKD remain controversial.

10.2 Definition

Anemia is a state of reduction in blood hemoglobin concentration or hematocrit, which can lead to insufficient oxygen delivery to tissues and organs. The normal ranges for hemoglobin and hematocrit depend on gender, race, age, and other

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factors. According to the 2012 Kidney Disease Improving Global Outcome (KDIGO) guidelines, the definition of anemia in adults and children >15 years of age with CKD is hemoglobin concentration <130 g/L in males and <120 g/L in females; the definition of anemia in children under 15 years of age with CKD is hemoglobin concentration <110 g/L in children 0.5–5 years, <115 g/L in children 5–12 years, and <120 g/L in children 12–15 years [3].

10.3 Prevalence

The prevalence of anemia in patients with CKD has been widely studied. Notably, the reported prevalence depends upon how GFR is estimated, how anemia is defined, and the characteristics of the study population. Community-based analyses are most useful for avoiding the inherent biases in studies of clinic-based populations. In general, the prevalence of anemia in patients with CKD increases with deteriorating renal function. It begins to increase significantly when GFR is <60 mL/min/1.73 m^2, and becomes more frequent or severe when GFR is <30 mL/min/1.73 m^2. Stauffer and co-workers reported their studies of 12,077 adults from the National Health and Nutrition Examination Survey in 2007–2010. They found that the prevalence of anemia in people with CKD (15.4%) was twofold greater than that in the general population (7.6%); moreover, the prevalence of anemia increased with stage of CKD: 8.4% at stage 1, 12.2% at stage 2, 17.4% at stage 3, 50.3% at stage 4, and 53.4% at stage 5 [1]. This trend has been reported by several other authors [4, 5]. In China, recent studies found that the prevalence of anemia in patients with CKD not undergoing dialysis was 51.5%, and that it increased with advancing CKD stage; stage 1: 22.4%, stage 2: 30.0%, stage 3: 51.1%, stage 4: 79.2%, and stage 5: 90.2% [6]. These data suggest that the reduced production of endogenous EPO may be attributed to reductions in estimated GFR.

Patients with diabetic kidney disease (DKD) tend to have a higher incidence of anemia, which typically occurs at earlier stages of CKD and is more severe among patients with DKD, relative to patients with non-DKD [6–8]. Elderly patients with CKD exhibit a high incidence of anemia. Particularly, the incidence of anemia gradually increases with increasing age among male patients with CKD. However, the incidence of anemia among young women is higher than among elderly women [9], which may be related to the loss of iron due to menses. In comparison, the incidence of anemia also shows a gradually increasing trend with age in elderly female patients [10]. Calcium-phosphorus metabolic disorder is also correlated with the high incidence of anemia. In particular, CKD patients with hypocalcemia or hyperphosphatemia, with or without elevated serum parathyroid hormone (PTH) level, also exhibit a high incidence of anemia [11, 12]. Additionally, the incidence of anemia in patients who are current smokers is lower than that in never smoking patients, which may be related to smoking-induced hypoxia [11]. Because of the high prevalence of anemia in CKD patients with GFR <60 mL/min/1.73 m^2, it is recommended that these populations should be screened for anemia, especially among individuals with diabetes or in elderly adults.

10.4 Pathogenesis

Although its etiology is multifactorial, abundant evidence indicates that the anemia associated with CKD arises primarily from inadequate EPO produced by the kidneys [13]; thus, anemia in CKD is often characterized by a normochromic and normocytic appearance of peripheral circulating erythrocytes. Other contributors include impairment of the erythropoietic response to endogenous or exogenous EPO, iron deficiency, blood loss, hemolysis, and other factors [14].

10.4.1 Absolute or Relative Lack of EPO

Absolute or relative EPO deficiency is the primary factor that leads to anemia among patients with CKD. Endogenous EPO is a circulating

glycoprotein of 165 amino acids with one O-linked and three N-linked carbohydrate chains. Its molecular weight is 30,400 Da, and its half-life is 5 h. EPO is synthesized primarily by peritubular type I interstitial cells located in the cortex or outer layer of the renal medulla between the basolateral membrane of the proximal tubules and peritubular capillaries [15]. The gene that encodes EPO is located on chromosome 7 (q11-q22) [16], and its gene transcription is activated by hypoxia-inducible factor (HIF) [17], which is a transcription factor that responds to hypoxia and activates the transcription of all hypoxia-induced genes, including EPO, vascular endothelial growth factor, platelet-derived growth factor, and glycolytic enzymes. In response to hypoxia and anemia, the concentration of EPO in the circulation can vary up to 1000-fold, compared with its concentration under basal conditions [18].

Indeed, compared with normal persons who do not exhibit anemia, CKD patients with mild or moderate renal hypofunction have normal or higher serum EPO levels, and their hemoglobin levels negatively correlate with EPO levels. Thus, lower hemoglobin levels may result in higher EPO levels in these patients [19]. However, the EPO levels in CKD patients with anemia are lower than those in non-kidney disease patients with different degrees of anemia; this is also referred to as relative EPO deficiency.

When renal tissue is increasingly destroyed with the progression of kidney disease, the diseased kidney cells reduce their response to anemia and hypoxia, causing reduced EPO synthesis and secretion. Under inflammatory conditions, excessive PTH level and elevated levels of inflammatory factors, such as interleukin (IL)-1α, IL-1β, and tumor necrosis factor (TNF)-α, also inhibit EPO synthesis. In patients with severe renal insufficiency, when the creatinine clearance rate (CCR) declines to <40 mL/min/1.73 m^2, the serum EPO level begins to decrease greatly, in a manner that is not regulated by the current severity of anemia; this is known as absolute EPO deficiency [19, 20]. The clinical manifestations of anemia become more obvious at this time. The serum EPO concentration in these patients is positively correlated with CCR, indicating parallel decline in renal excretory and endocrine functions [19, 20]. A prior study showed that the serum EPO level can partially increase or decrease in the presence of aggravated anemia, or because of an increase in hemoglobin due to blood transfusion [20].

10.4.2 Iron Deficiency

Iron deficiency is an important factor that leads to anemia development and progression in patients with CKD. The total iron amount in healthy adults is approximately 4000 mg. Iron is actively recycled in the body, and the daily circulating level of iron can approach approximately 20 mg during the destruction and production of erythrocytes. However, the iron absorption and secretion pathways are extremely limited and comprise approximately 1–2 mg daily. The small intestine is the sole site of iron absorption, and Fe^{3+} in food can be reduced to Fe^{2+}, then transported through intestinal epithelial cells. Additionally, heme can be absorbed and degraded by intestinal epithelial cells to release Fe^{2+}. Importantly, Fe^{2+} absorbed through the above pathways can be stored in the liver, small intestine, and macrophages in the form of ferritin for the use by body when necessary. Further, Fe^{2+} can penetrate the intestinal epithelial basilar membrane under the joint action of ferroportin 1 (FPN1) and hephaestin (Hp) and be released into the blood, where it is oxidized to Fe^{3+} and can bind with transferrin. Hepatocytes can internalize the bound iron by using transferrin receptor (TfR) 2. A proportion of the absorbed iron reaches the bone marrow through blood and is then used in hemoglobin synthesis and erythrocyte production. Alternatively, it may bind with TfR1 on normoblasts and enter reticulocytes for hemoglobin synthesis during the erythrocyte differentiation process.

Patients with stage 3–5 CKD may exhibit reduced appetite or food restriction, which causes reduced iron uptake from the digested food. Additionally, antacid/acid-inhibitory drugs and calcium carbonate, as well as phosphate and carbonate in food, may suppress iron absorption. Long-term blood loss in small vol-

umes, such as residual blood in the dialyzer and pipeline after each episode of hemodialysis (iron loss of approximately 1–2 g/year), regular blood extraction examination, blood loss during vascular access surgery, and intestinal blood loss in some patients, may ultimately result in body iron consumption. The application of ESAs can stimulate erythrocyte synthesis, which also leads to increased iron depletion. Insufficient iron uptake and increased iron depletion may lead to insufficient iron reserve (absolute deficiency). The micro-inflammatory status in patients with CKD can lead to impaired iron utilization (functional deficiency) [21, 22].

Hepcidin is a cysteine-enriching antibacterial polypeptide that is synthesized and secreted by the liver. It plays a crucial role in regulating iron metabolism by binding with FPN1 to promote its degradation. In patients with iron overload or inflammatory status, hepcidin gene expression can be upregulated, and its synthesis and secretion by the liver can be increased, thus accelerating FPN1 degradation and reducing iron transportation from intestinal epithelial cells and macrophages to blood. However, hepcidin gene expression and its synthesis can be downregulated by iron deficiency, increased erythrocyte production, or hypoxia. In addition, micro-inflammatory status in patients with CKD can induce elevations in circulatory cytokines and pro-inflammatory factors, particularly IL-6, which may lead to elevated synthesis of hepcidin [23, 24]. Concurrently, in patients with CKD, the excretion of hepcidin from kidney is reduced, which causes elevations in circulatory hepcidin levels, thus resulting in reduced intestinal iron absorption and iron retention in macrophages. Ultimately, the available iron cannot satisfy the requirement of erythrocyte production. Iron deficiency gives rise to slow synthesis of hemoglobin, which affects erythrocyte production, leading to anemia and ESA resistance in patients with CKD. In addition, iron deficiency also results in neurotransmitter dys-synthesis and affects myelinogenesis, which can lead to central nervous system disorder, maldevelopment, and restless leg syndrome.

10.4.3 Inhibitors of Erythropoiesis

Certain substances in plasma inhibit erythrocyte production in patients with CKD, which play a crucial role in the pathogenesis of renal anemia. However, the precise mechanism of their action remains unclear at present. Currently, inhibitors of erythropoiesis have been suggested to mainly include polyamines, PTH, and cytokines. Polyamines are the metabolites of amino acids, which include spermine, spermidine, putrescine, and cadaverine. Due to the reduced scavenging capacity of polyamines by the kidney, polyamines accumulate in the plasma of patients with renal insufficiency, which can inhibit the production of colony-forming unit-erythrocytes (CFU-E) [25]. In CKD patients with secondary hyperparathyroidism, the high PTH level can downregulate the erythrogenin receptor located at the CFU-E membrane, thus reducing its sensitivity to EPO [26]. In addition, PTH can also inhibit the calcitriol receptor on the CFU-E membrane surface, inhibit CFU-E proliferation and differentiation, directly suppress bone marrow hematopoiesis, and cause reduced erythropoiesis [27]. Furthermore, PTH can also induce renal osteopathia and myelofibrosis, which results in reduced CFU-E numbers, thereby leading to anemia [27]. In patients with CKD, multiple cytokines produced under micro-inflammatory conditions, such as TNF-α, IFN-1, and IL-1, can directly suppress or indirectly inhibit CFU-E formation through IFN-β. In addition, IL-1β and TNF-α can also reduce the responsiveness of bone marrow to EPO, resulting in anemia [28].

Other factors can also inhibit erythropoiesis in patients with CKD. For example, ribonuclease activity in the plasma of uremia patients is remarkably enhanced, which can inhibit the formation of CFU-E in a dose-dependent manner [29]. N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) can inhibit erythropoiesis by suppressing hematopoietic stem cells. Notably, the plasma AcSDKP level in uremia patients is higher than in normal persons; this is more obvious in patients using ACEI [30]. Quinolinic acid [31], an oxidation product of tryptophan, as well as uremia toxins, such as 3-carboxyl-4-methyl-5-propyl furan

levulinic acid, can also induce renal anemia by inhibiting the production of CFU-E [32].

10.4.4 Malnutrition

Some patients with CKD suffer from malnutrition. Low serum albumin can result in hemoglobin synthetic disorder and malnutrition-inflammation complex syndrome (MICS), thus inducing anemia. CKD patients with renal insufficiency, also known as chronic renal failure (CRF), especially patients undergoing hemodialysis, frequently experience nutrient deficiencies, such as folic acid and L-carnitine, due to insufficient intake and dialysis removal. Folic acid is an essential material for hematopoiesis and its deficiency can deteriorate renal anemia. In addition, L-carnitine deficiency may accelerate erythrocyte osmotic fragility [33]; it may also reduce the deformability [34] and membrane stability of RBCs [35] and is associated with renal anemia.

10.4.5 Aluminum Poisoning

Aluminum poisoning may occur in the presence of excessive aluminum content in water for hemodialysis or the application of aluminum-containing drugs [36], although this is currently rare. Aluminum can bind with transferrin and block the binding of iron with hemoglobin, thus affecting the synthesis of erythrocytes. In addition, aluminum can suppress the activities of some enzymes for synthesizing hemoglobin (such as ferrochelatase, uroporphyrinogen decarboxylase, and delta-aminolevulinic acid dehydratase), thus resulting in anemia. Moreover, aluminum poisoning can cause reduced EPO responsiveness, further aggravating anemia.

10.4.6 Shortened Life Span of Erythrocytes and Hemodialysis

The erythrocyte membrane function in patients with CKD may change under uremic conditions, due to inflammation and oxidative stress, which cause erythrocyte damage. Hemodialysis can also induce hemolysis through a variety of factors. The average life span of erythrocytes in normal persons is approximately 120 days, while it is approximately 40–60 days in patients with CRF.

Multiple uremia toxins in the plasma of CRF patients under uremic conditions can lead to chronic hemolysis. For instance, an elevated PTH level may activate the erythrocyte membrane calcium pump activity and induce influx of calcium ions into erythrocytes, thus increasing the osmotic fragility of the erythrocytes, such that they are easily destroyed [37]. Additionally, PTH may suppress Na-K-ATPase activity in erythrocytes, blocking energy metabolism and shortening their lifespans.

A large quantity of free radicals is produced under an oxidative stress state in CRF patients. High concentrations of free radicals may induce lipid peroxidation of erythrocyte membranes, reduce the deformability of erythrocytes, and increase their fragility. Therefore, they may be eliminated by the reticuloendothelial system before the end of their lifespans, which constitutes hemolysis.

Generally, macrophages can remove aging erythrocytes in blood circulation. However, in an inflammatory status in patients with CKD, because erythrocytes are enveloped by immunoglobulin or immune complexes, macrophages may accelerate the removal of erythrocytes after activation by inflammatory signals, thus shortening the erythrocyte lifespan [38].

Hemodialysis may be related to hemolysis. If impure water for dialysis contains oxidizing agents, such as chloramines, copper, and nitrate, erythrocyte fragility may be increased, leading to hemolysis. In addition, disinfecting formalin residue in the dialyzer or dialysis channel may suppress glycolysis and ATP formation in erythrocytes, which may cause acute hemolysis. Moreover, extreme dialysate temperature (>45 °C) or the application of hypotonic dialysate may induce acute hemolysis. Blood pump rotation may induce hemolysis through mechanical injury.

Hypophosphatemia, which may be induced by large doses of phosphate binder or malnutrition, is a factor for hemolysis in patients with CKD. When the serum phosphorus concentration is lower than 0.32 mmol/L, erythrocyte fragility may increase due to reduced ATP production, thus causing hemolysis [34]. In addition, other factors that complicate CKD, such as hypersplenism, incompatible transfusion, microvascular lesion, or excessive zinc concentration in the blood, may result in hemolysis.

10.4.7 Certain Drugs Affecting Erythrocyte Production

ACEI could block the generation of angiotensin II (Ang II), which acts as a growth factor for erythroid progenitors and an erythropoietin secretion agonist; notably, Ang II is an important physiological regulator of erythropoiesis, which can increase red blood cell numbers. Some clinical studies have reported that the administration of ACEI or ARB may reduce serum EPO levels [39], which may subsequently reduce hematocrit or cause anemia in patients with renal insufficiency or renal transplantation who use these medicines. The reduction of EPO by ACEI or ARB is dose-dependent.

In patients with CKD with diabetes, the use of thiazolidinediones may reduce hemoglobin levels by downregulating the erythroid lineage transcription factor GATA-1 [40], inducing reductions in testosterone levels [41] and increasing fluid retention [42].

Diuretic drugs reduce tubular oxygen consumption by inhibiting active sodium reabsorption. Acetazolamide, acting at proximal tubular sites, can significantly reduce EPO formation in response to normobaric hypoxia, in a dose-dependent manner [43].

Theophylline is a nonselective antagonist of adenosine that has been shown to increase the secretion of EPO. The administration of theophylline has been reported to attenuate the production of EPO through modulation of adenosine [44].

10.5 Clinical Symptoms of Anemia

Anemia can result in reduced tissue oxygen supply and oxygen consumption in patients with CKD, thus resulting in a series of clinical symptoms.

10.5.1 Reduction in Quality of Life

In patients with CKD, some non-specific symptoms induced by anemia may reduce their quality of life, including fatigue, weakness, fear of cold, anorexia, tachypnea, dyspnea, impaired exercise tolerance, difficulty in focusing attention, headache, dizziness, insomnia, depression, and sexual dysfunction.

10.5.2 Cognitive Impairment

Reduced oxygen supply in the central nervous system may reduce the intelligence quotient, attention, memory, and speed of information processing in patients with CKD.

10.5.3 Increased Morbidity and Mortality in Cardiovascular Diseases

The blood oxygen-carrying capacity is reduced accordingly in anemic conditions; as a result, cardiac output increases through enhanced heart rate and stroke volume, in order to maintain tissue oxygen supply. Moreover, the left ventricular end-diastolic volume and left ventricular wall thickness may be increased in a compensatory manner. In patients with CKD, the severity of anemia is closely related to the morbidity of left ventricle hypertrophy [2, 45], which is also associated with increased risks of myocardial infarction, stroke, and death. Additionally, anemia may lead to increased susceptibility to infection and may accelerate the progression of kidney lesions in patients with CKD.

10.6 Diagnosis of Renal Anemia

The diagnosis of anemia primarily depends on hemoglobin detection. To avoid the impact of long dialysis interval on blood volume and the effect of blood concentration after dialysis, the blood sample for hemoglobin in hemodialysis patients should be collected in the middle of the week (Wednesday or Thursday, in accordance with the hemodialysis schedule), before or at the beginning of a hemodialysis session. The timing of blood testing for hemoglobin is not important in patients with non-dialysis CKD.

In the 2012 KDIGO guidelines, the diagnosis of CKD-induced anemia is defined in adults and children >15 years of age with CKD as hemoglobin concentration of <130 g/L in males and <120 g/L in females; in children with CKD, the diagnosis of CKD-induced anemia is defined as hemoglobin concentration of <110 g/L in children 0.5–5 years, <11.5 g/dL in children 5–12 years, and <12.0 g/dL in children 12–15 years [3].

10.6.1 Assessment Frequency of Anemia

Hemoglobin levels should be monitored regularly in patients with CKD [3].

1. For patients without anemia, the frequency of hemoglobin monitoring is as follows:
   - Upon occurrence of clinical symptoms in patients with CKD stage 1–2.
   - At least once per year in patients with CKD stage 3.
   - At least twice per year in non-dialysis patients with CKD stage 4–5.
   - At least every 3 months in patients undergoing hemodialysis and peritoneal dialysis.
2. For CKD patients with anemia that is not treated with ESA, the frequency of hemoglobin monitoring is as follows [3]:
   - At least every 3 months in non-dialysis patients with CKD stage 3–5 and in CKD stage 5 patients undergoing peritoneal dialysis.
   - At least once per month in CKD stage 5 patients undergoing hemodialysis.
3. For CKD patients with anemia receiving ESA therapy, the frequency of hemoglobin monitoring is as follows:
   - At least once per month at the initiation of ESA therapy.
   - At least every 3 months in non-dialysis patients and at least once per month in dialysis patients during the maintenance of ESA therapy.

10.6.2 Differential Diagnosis of Anemia

CKD patients that meet the above criteria can be diagnosed with renal anemia if there are no other causes of anemia. If the degree of anemia is not consistent with that of renal dysfunction in patients with CKD (i.e., early renal dysfunction is accompanied by moderate to severe anemia), it is necessary to rule out the existence of other diseases that can cause anemia. The following examination should be performed for differential diagnosis with anemia caused by other diseases.

1. Complete Blood Cell Count
   Complete blood cell count includes hematocrit/hemoglobin; red blood cell-related indicators, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration; white blood cell count and classification; and platelet count.
   - Microcytic anemia is associated with iron deficiency, aluminum toxicity, or hemoglobinopathy.
   - Macrocytic anemia is associated with deficiency of vitamin B_{12} or folic acid, and may also be due to the entry of immature reticulocytes into the circulation, promoted by iron overload and/or EPO treatment.
   - In cases of abnormal counts of white blood cells and platelets, aplastic anemia, leukemia, tumors, hypersplenism, and vasculitis should be excluded.

2. Reticulocyte Count
   - Increased reticulocyte counts indicate the possibility of hemolytic anemia; sickle cell anemia, sepsis, and thrombotic thrombocytopenic purpura should be considered. Iron deficiency anemia and megaloblastic anemia may also be accompanied by slightly increased reticulocyte counts.
   - Reduced reticulocyte counts suggest reduced hematopoietic function of bone marrow, such as aplastic anemia.
3. Iron Store and Iron Utilization Indicators
   Iron is necessary for hemoglobin synthesis. Detection of serum iron and total iron-binding capacity can determine iron availability in patients. Serum iron and transferrin saturation (TSAT) reflects the iron that can be readily used for hemoglobin synthesis, while ferritin represents the total iron store in the body. A reduction in any of the above indicators indicates a lack of iron in the body, and its cause must be clarified.
   - **Acute or chronic blood loss**
     Chronic blood loss is the most common cause, commonly observed in gastrointestinal bleeding, including peptic ulcers and polyps, which can be assessed by fecal occult blood examination. Patients undergoing ESRD may also lose blood during the vascular access procedure; blood loss can occur after hemodialysis, where blood is left in the dialyzer and tubing; coagulation might exacerbate blood loss during dialysis. In addition, hemoptysis and female menorrhagia can lead to blood loss.
   - **Iron absorption disorders**
     Iron absorption disorders are observed after subtotal gastrectomy, in gastric cancer, and in malabsorption syndrome.
   - **Reduced iron intake**
     Iron intake is reduced in certain CKD patients because of limited protein intake or loss of appetite.
4. Serum Folate and Vitamin B_{12} Levels
   Deficiency of vitamin B_{12} or folic acid is found in cases of malnutrition or upon administration of antiretroviral drugs.
5. Other Indicators Related to CKD Status
   Even if anemia caused by other diseases is excluded, hyperparathyroidism, inflammation, malnutrition, and insufficient dialysis, all of which might aggravate anemia, should be considered in patients with CKD. It is clinically and economically significant to correct reversible causes of anemia.

10.7 Therapy of Renal Anemia in CKD

10.7.1 The Therapeutic Target Value of Renal Anemia

Studies have demonstrated that the incidences of all-cause mortality, fistula thrombosis, refractory hypertension, and myocardial infarction in patients with a high-level target of hemoglobin (135 g/L) are significantly higher than those in patients with a low-level target of hemoglobin (115 g/L), whereas a lower target of hemoglobin (90 g/L) also negatively affects the end point. Therefore, the 2012 KDIGO guidelines for clinical practice suggest that the hemoglobin concentration generally should not exceed 115 g/L in patients undergoing ESA maintenance; for all patients, it is not recommended to increase the hemoglobin concentration by more than 130 g/L by ESA [3].

10.7.2 Treatment with ESAs

ESAs are a group of drugs that mimic the effects of EPO; they promote erythropoiesis, cell proliferation, and differentiation, and can also inhibit cell apoptosis, primarily by binding to receptors on CFU-E. Prescription of ESAs is the primary therapeutic approach for renal anemia. Presently, ESAs can be classified into the following groups:

1. Recombinant human erythropoietin (rHuEPO), the ESA most commonly applied in clinic, is a sialic acid protein hormone with immunological and biological properties that closely resemble human EPO, primarily comprising rHuEPO-α and rHuEPO-β. The half-

life of rHuEPO is short, such that it should be administered one to three times per week to ensure sustained stimulation of RBC production.

2. Long-acting ESA preparations, including darbepoetin alfa and continuous erythropoietin receptor activator (CERA). Darbepoetin alfa is an improved version of rHuEPO, whose half-life is twofold longer than that of rHuEPO-α, either by intravenous or subcutaneous injection; it can be administered every 2–3 weeks. CERA is the only agent capable of maintaining ESA by monthly administration, with a half-life of 134–139 h. CERA can be administered once every 2 weeks or once every 4 weeks to effectively correct renal anemia and maintain hemoglobin levels [46, 47].
3. Novel ESA agents, including HIF stabilizers, activin traps, EPO mimetic peptides, EPO fusion proteins, antibody agonists to EPO receptors, and EPO gene therapy, are all in clinical research stages and are not available for treatment.

10.7.2.1 Initiation and Timing of the Use of ESAs

Before the initiation of ESA therapy, all other potential causes of anemia should be addressed, including iron deficiency inflammatory conditions, and so on. The pros and cons of ESA treatment should be weighed at the time of initiation, and maintenance therapy with ESA should be assessed. The benefits of ESA treatment include reduction of blood transfusions and alleviation of anemia-related symptoms; however, the potential therapeutic risks, such as stroke, loss of vascular access, and hypertension, should be carefully evaluated.

In patients with non-dialysis CKD, ESA therapy is unnecessary in patients with hemoglobin >100 g/L. In patients with hemoglobin <100 g/L, personalized decisions regarding ESA therapy should be made by considering the rate of hemoglobin decline, previous responses to iron therapy, the risk of transfusion, the risks associated with ESA treatment, and the presence or absence of symptoms due to anemia. For patients with CKD stage 5 who are undergoing maintenance dialysis, ESA therapy is recommended when hemoglobin level is within the range of 90–100 g/L. Because quality of life is improved in some patients at higher hemoglobin concentrations, individualized ESA may be given at hemoglobin >100 g/L. ESA treatment should be cautiously managed for patients with a history of stroke or malignancy, and those who harbor tumors that are expected to be curable.

10.7.2.2 ESA Access

Intravenous and subcutaneous routes of ESA administration are both effective to treat renal anemia. Subcutaneous injection exhibits better pharmacodynamics than intravenous injection and can extend the maintenance time of effective drug concentration in the body; however, it is accompanied by increased pain compared with intravenous injection. For CKD hemodialysis patients, although intravenous administration can reduce pain, either intravenous or subcutaneous administration of ESA is recommended. For patients with non-dialysis or peritoneal dialysis CKD, subcutaneous injection of ESA is recommended.

10.7.2.3 ESA Dose

- **Initial dose**

  The initial dose of ESA is determined on the basis of the level of hemoglobin, body weight, clinical status, and type of ESA used for the patient, as well as the access of administration. The initial dose of rHuEPO is recommended as 80–120 U/(kg·w), 2–3 times per week by subcutaneous injection, or 120–150 U/(kg·w), three times per week by intravenous injection. The initial dose of darbepoetin is recommended as 0.45 μg/kg once per week, or 0.75 μg/kg every 2 weeks. The degree of anemia should be considered when selecting the initial dose. For patients with hemoglobin <70 g/L, the initial dose should be appropriately increased. For non-dialysis patients or dialysis patients with better residual renal function, the initial dose may be appropriately reduced. For patients with a history of hypertension, diabetes, cardiovascular disease, vascular embolism, or epilepsy, ESA should initially be administered at a low dose.

- **Adjustment of dose**
  Hemoglobin levels should be regularly monitored during ESA treatment. If the monthly growth rate of hemoglobin is under 10 g/L, after ruling out other causes of anemia, the dose of ESA should be increased by 25%. In contrast, a sharp increase in hemoglobin levels may cause an increased incidence of cardiovascular adverse events. In patients whose hemoglobin growth rate within 2 weeks is >10 g/L, the dose of ESA should be reduced by 25%, but not immediately discontinued. Cessation of ESA, especially prolonged withdrawal, may lead to sustained reduction in hemoglobin, such that it declines below the target range.

10.7.2.4 Frequency of ESA Administration

The administration frequency should be based on the CKD stage, degree of anemia, therapeutic strategy, efficacy, patient tolerance and preference, and type of ESA. It is not recommended to administer high-dose ESA therapy once per week, either via subcutaneous or intravenous administration of rHuEPO. Instead, multiple injections at lower doses are recommended to minimize fluctuations in the serum concentration of rHuEPO, in order to optimize the effect of rHuEPO.

10.7.2.5 Side Effects of ESA Therapy

- **Hypertension**
- Hypertension is the most common side effect of ESA. ESA causes a direct increase in the level of endothelin-1 [48, 49], which constricts blood vessels and subsequently leads to hypertension. In addition, ESA increases calcium influx in vascular smooth muscle cells in a dose-dependent manner, thereby reducing the response of vascular smooth muscle cells to NO and increasing vascular resistance, ultimately increasing blood pressure [50, 51]. ESA also upregulates the expression levels of renin, angiotensinogen, and angiotensin receptor in vascular smooth muscle cells [52], thereby inducing hypertension. Thus, during ESA therapy, blood pressure should be monitored and doses of antihypertensive drugs should be adjusted accordingly.
- **Thrombosis of dialysis access**
  Studies have shown that the risk of thrombosis in hemodialysis access increases in response to increased levels of hemoglobin, which may be related to improved platelet function and stimulation of proliferation of vascular endothelial cells and vascular smooth muscle cells by EPO treatment; this may lead to stenosis of vascular access [53]. Vascular access of hemodialysis patients should be assessed during EPO treatment. However, there is insufficient evidence that the current target of hemoglobin will increase the incidence of thrombosis of hemodialysis access.
- **Tumor progression**
  ESA treatment may promote tumor progression and increase mortality among tumor patients [54]. Some scholars have shown that the activation of EPO receptors (EPORs) on the surface of tumor cells can promote tumor cell proliferation and inhibit apoptosis, subsequently reducing the sensitivity of anti-tumor therapy [54]. However, recent studies have found that many tumor cell lines express very low levels of EPORs, and that many of these EPORs are nonfunctional [55]. Despite the unclear mechanism, based on previous results of clinical studies, ESA therapy should be cautiously administered in CKD patients with tumors [3]. Closer monitoring is necessary after treatment with ESA.
- **EPO antibody-mediated pure red cell aplasia (PRCA)**
  The appearance of EPO antibodies after EPO treatment is rare, but is often very serious. If, after EPO treatment for >4 weeks, the hemoglobin level declines rapidly at a rate of 5–10 g/(L·w) and the number of reticulocytes is <1% or $<10 \times 10^9$/L, while the numbers of white blood cells and platelets are normal, PRCA should be suspected. The diagnosis of PRCA should be based on the presence of EPO antibodies and support from bone marrow findings. The occurrence of PRCA may be associated with increased antigenicity with subcutaneous injection of EPO, as well as

adjuvant components in some products. Confirmed patients should discontinue EPO treatment, and blood transfusion and immunosuppressive therapy may be effective [56].

- **ESA hyporesponsiveness**
  ESA hyporesponsiveness occurs in 5–10% of ESRD patients who are prescribed ESA. The definition of ESA hyporesponsiveness is an ESA requirement of >300 IU/kg per week of subcutaneous epoetin, 400–450 IU/kg per week of intravenous epoetin, or 1.5 μg/kg per week of darbepoetin [57, 58]. ESA hyporesponsiveness may be associated with increased morbidity and mortality in chronic hemodialysis patients [59]. Pre-transplantation ESA hyporesponsiveness in renal transplantation recipients may be related to increased kidney allograft failure [60]. Iron deficiency, infection, and other pro-inflammatory conditions are important causes of ESA hyporesponsiveness. Other causes of ESA hyporesponsiveness include secondary hyperparathyroidism, inadequate dialytic clearance, active blood loss, deficiency in vitamin B_{12} and folic acid, malnutrition, aluminum overload, multiple myeloma, hemolysis, hemoglobinopathy, administration of ACE inhibitors and ARBs, and erythropoietin-associated PRCA. For patients with ESA hyporesponsiveness, the dose of ESA should not be increased indefinitely; instead, appropriate treatment should be performed by identifying relevant causes.

10.7.3 Iron Therapy

Iron deficiency is an important cause of renal anemia and poor response to ESA therapy. Iron supplementation can significantly improve the efficacy of ESA and can reduce the amount of ESA required for a desired outcome.

10.7.3.1 Assessment of Iron Status

The body's iron status should be monitored in CKD patients with anemia. During ESA treatment, iron status should be assessed at least once every 3 months, including at the time of the decision to initiate or continue iron treatment. Iron status should be assessed more frequently when ESA treatment is initiated or the dose is increased, if blood loss occurs, or in other conditions associated with depletion of iron stores. Furthermore, the efficacy after one intravenous iron therapy cycle should be monitored [3]. The indicators of assessment of iron deficiency include:

- **Bone marrow iron staining**
  Bone marrow iron staining is the gold standard for diagnosis of iron deficiency, but its application is limited due to the inherent trauma required to obtain usable specimen.
- **Serum ferritin (SF) and TSAT**
  A combination of SF and TSAT is currently used to diagnose iron deficiency. If the TSAT is <20% and SF is <100 μg/L in non-dialysis and peritoneal dialysis patients, or if TSAT is <20% and SF is <200 μg/L in hemodialysis patients, the body iron store is judged to be deficient, a state known as absolute iron deficiency. If TSAT is <20% and SF is >100 μg/L in non-dialysis and peritoneal dialysis patients, or if TSAT is <20% and SF is >200 μg/L in hemodialysis patients, deficiency of available iron is suggested, a state known as relative iron deficiency. However, patients with CKD often exhibit a co-existing inflammatory state, and acute phase reactions can lead to increased SF [61].
- **Reticulocyte hemoglobin content (CHr)**
  CHr represents early changes in iron deficiency, which are not affected by the acute phase response; these can more accurately reflect the status of body iron deficiency [62]. In patients receiving ESA therapy, the diagnostic threshold for functional iron deficiency is 29 pg [63].
- **Red blood cell distribution width (RDW), MCH, MCV**
  An increase in RDW, accompanied by reductions in MCH and MCV, indicates iron deficiency.
- **Liver iron content (LIC)**
  LIC is a primary indicator of iron overload in the body. Liver biopsy is the "gold standard" for measuring liver iron content, but has been gradually replaced by noninvasive technology

due to its invasiveness. Noninvasive methods for measuring LIC include magnetic resonance imaging and super-conducting quantum interference device biomagnetic liver susceptometry.

- **Other new parameters**
  Soluble TfR is not affected by inflammation, and can be used to distinguish absolute iron deficiency from functional iron deficiency [24]. However, its clinical diagnostic efficacy requires further investigation. Other parameters include hepcidin, non-transferrin-bound iron, and labile plasma iron.

10.7.3.2 The Timing of Iron Therapy

The benefits and risks should be weighed before initiating iron therapy by assessing potential benefits and therapeutic risks to reduce blood transfusions and alleviate anemia-related symptoms (e.g., allergic reactions and other acute reactions, or unknown long-term risks). Patients with active infection should avoid the administration of iron.

In adult CKD patients with SF ≤500 μg/L and TSAT ≤30%, iron therapy should be administered on the basis of criteria for anemia in CKD, not on the basis of criteria for iron or ESA therapy, in order to increase hemoglobin levels. In patients who have received ESA therapy but not iron therapy, iron therapy should be administered if increased hemoglobin levels or reduced ESA doses are desired [3]. Iron therapy is not routinely administered in patients with SF >500 μg/L; however, iron therapy can be attempted if high-dose ESA fails to alleviate anemia; in these patients, acute inflammation, iron overload, and other conditions should be ruled out [64]. Pediatric CKD patients with anemia should be administered iron therapy when SF is ≤100 μg/L and TSAT is ≤20% [3].

10.7.3.3 Categories of Iron Therapy

- **Oral iron**
  Oral iron formulations include ferrous sulfate, ferrous succinate, ferrous gluconate, and ferrous fumarate. Oral iron is less expensive, but is poorly absorbed. A subset of patients (approximately 30%) may experience gastrointestinal side effects. New formulations of liposomal iron exhibit a high absorption rate in the gastrointestinal tract with high bioactivity, but the gastrointestinal side effects remain [65].
- **Intravenous iron**
  Intravenous iron includes iron sucrose, ferumoxytol, ferric carboxymaltose, ferric gluconate, and iron dextran. Intravenous iron has the advantages of high bioavailability, low incidence of gastrointestinal reactions, and lack of susceptibility to effects from other drugs; moreover, it can improve the efficacy of ESA, thus reducing the ESA dose required to achieve and maintain the target value of hemoglobin [66, 67]. However, intravenous iron is associated with hypersensitivity [68]; in this regard, iron sucrose, ferumoxytol, and ferric carboxymaltose are safer, whereas iron dextran may cause serious allergic reactions and is generally not recommended. Intravenous iron may increase the risk of infection [69, 70]; furthermore, free iron from circulation or iron overload can lead to oxidative damage of blood vessels and other tissues [71, 72].

10.7.3.4 Medication with Iron

Non-dialysis patients and peritoneal dialysis patients may initially attempt oral iron therapy or intravenous iron therapy, on the basis of the status of iron deficiency. Intravenous iron therapy is given priority in hemodialysis patients. Iron status should be assessed after 1–3 months of oral iron therapy; modification of intravenous iron therapy is recommended in cases where the target values of iron status and hemoglobin could not be reached, or in cases of intolerance of oral iron therapy [3].

Dose of oral iron: Daily supplementation of elemental iron is recommended at 200 mg and 2–3 mg/kg (body weight) in adult and children, respectively; this should be orally administered 2–3 times per day.

Dose of intravenous iron:

- Loading dose: In non-dialysis and peritoneal dialysis patients, 750–1000 mg of elemental iron should be supplemented within 1–2 weeks by 2–3 intravenous injections each week. In

maintenance hemodialysis patients, 100–125 mg iron should be injected intravenously each week; the cumulative dose of one course of iron is 1000 mg. If iron status fails to reach standard levels, injection can be repeated as necessary.

- Maintenance dose: A low dose of iron (for example, 50–60 mg per week in adult hemodialysis patients and 1 mg/kg/week in pediatric patients) is provided to maintain iron stores after the iron status has been met [73].
- The dose and time interval of intravenous iron therapy should be adjusted based on the response to iron, iron status, hemoglobin levels, ESA dose, ESA response, and recent complications of patients.

10.7.3.5 Precautions of Iron Therapy

- Avoid intravenous iron in patients with active systemic infections.
- For first-time intravenous administration of iron dextran, or for first-time intravenous non-dextran administration, patients should be monitored for 1 h after infusion; resuscitation equipment (including medication) and training should be provided to react to possible serious adverse reactions.
- During the application of intravenous iron, iron indicators should be regularly monitored to prevent iron overload.

10.7.4 Transfusion Therapy

Transfusions should be avoided as much as possible to reduce the risks associated with transfusions and with allogeneic sensitization in patients eligible for organ transplantation. In patients with chronic anemia, simple hemoglobin levels should not be used as a threshold for transfusions. Red blood cell transfusion can be performed in case where the benefits outweigh the risks from ESA in patients with cardiovascular and neurological symptoms, patients for whom ESA therapy has been ineffective, or patients with a history of malignancy and stroke. In acute clinical conditions, red blood cell transfusion can be conducted as necessary for rapid correction of anemia to stabilize the patient (for example, in cases of acute bleeding or unstable coronary heart disease).

10.7.5 Other Adjuvant Therapy

Consideration should be given to the existence of folic acid and vitamin B_{12} deficiency in patients with renal anemia. Hemodialysis can remove folic acid and vitamin B_{12}; thus, patients undergoing maintenance hemodialysis should be supplemented with appropriate doses of folic acid and vitamin B_{12}. In addition, for hemodialysis patients, the application of L-carnitine may be beneficial, but is not recommended as a routine treatment; it should be handled accordingly in clinical practice.

10.7.6 Emerging Therapy

It has been demonstrated that HIF prolyl hydroxylase inhibitors, a kind of new promising therapeutic drugs for treatment anemia in patients with CKD, can take effects through multiple pathways. In addition to increasing EPO levels, they also play a role in iron handling and inflammation. Recent reports from two phase 3 clinical trials performed in China have showed that HIF prolyl hydroxylase inhibitor was superior to placebo in increasing hemoglobin levels in anemia patients with non-dialyzed CKD and was noninferior to EPO in increasing hemoglobin levels in anemia patients with maintenance hemodialysis [74, 75].

10.8 Summary

High prevalence of anemia is seen in patients with CKD, and the shortage of EPO and iron is the main cause of anemia in this population. Since anemia contributes to increased morbidity and mortality of cardiovascular diseases, it is important to evaluate the state of anemia regularly in patients with each stage of CKD. A schematic presentation of evaluation for anemia in CKD adults is shown in Fig. 10.1.

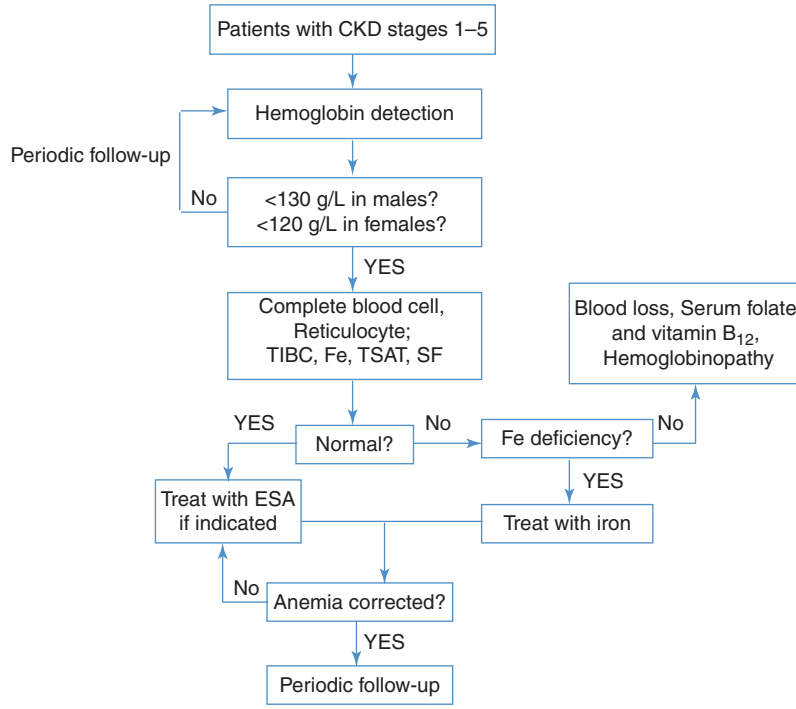

Fig. 10.1 Flowchart for the evaluation of anemia in patients with chronic kidney disease. *TIBC* total iron-binding capacity; *TSAT* transferrin saturation; *SF* serum ferritin; *ESA* erythropoiesis-stimulating agent

Key Messages

- KDIGO defines anemia in patients with CKD as hemoglobin <130 g/L in adult males and <120 g/L in adult females, <110 g/L in children 0.5–5 years, <115 g/L in children 5–12 years, and <120 g/L in children 12–15 years.
- Anemia is a frequent complication in patients with CKD, and its prevalence increases as renal function declines. Hemoglobin levels should be regularly monitored in patients with CKD.
- The etiology of anemia in CKD is multifactorial; it includes absolute or relative lack of EPO, iron deficiency, blood loss, shortened red blood cell survival, and other factors.
- Anemia in CKD is associated with impaired quality of life, as well as elevated morbidity and mortality of cardiovascular diseases.
- ESAs and iron supplementation are the primary treatment for anemia in CKD. Hemoglobin levels and iron status should be monitored regularly during treatment. It is generally recommended that hemoglobin concentration not exceed 115 g/L in patients undergoing ESA maintenance; the monthly hemoglobin growth rate should be ≥10 g/L, but <20 g/L. Transfusions should be avoided as much as possible. HIF prolyl hydroxylase inhibitors is a kind of new promising therapeutic drugs.

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11 Chronic Kidney Disease-Mineral and Bone Disorder, Vitamin D Deficiency, and Secondary Hyperparathyroidism

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Abstract

Chronic kidney disease-mineral and bone disorder (CKD-MBD) encompasses laboratory and bone abnormalities and vascular or other soft tissue calcification and has adverse effects on clinical prognosis. The 2017 KDIGO clinical practice guideline recommends monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a. Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together. In patients with CKD G3a–G5D with severe hyperparathyroidism who fail to respond to pharmacological therapy, we suggest parathyroidectomy. The ambiguity and lack of unequivocally actionable recommendations highlight potential challenges for implementation and underscore the need for future research in this important area.

11.1 Introduction

Disorders in calcium, phosphorus, and parathyroid hormone (PTH) are common in chronic kidney disease (CKD). In 2006, Kidney Disease: Improving Global Outcomes (KDIGO) published a position statement proposing a new approach to classification of bone and mineral disorders, termed as "chronic kidney disease-mineral and bone disorder" (CKD-MBD) [1]. KDIGO views CKD-MBD as a systemic disorder manifested by one or more of the following: (1) abnormalities of calcium, phosphorous, parathyroid hormone (PTH), or vitamin D metabolism, (2) abnormalities in bone pathology and histomorphometry marked by changes in bone turnover, mineralization, volume, linear growth, or strength (TMV system), and (3) the presence of vascular or other soft tissue calcification [1].

11.2 Pathophysiology

There exists evidence on bone remodeling that progresses with advanced kidney disease to stage 3 CKD, which is referred to as renal osteodystrophy. Interestingly, these changes may occur earlier [2, 3]. In a large cross-sectional study on MBD biochemical markers, serum PTH elevated in 12% of patients with an estimated glomerular filtration rate (eGFR) >80 mL/min/1.73 m^2, whereas other biochemical parameters, serum phosphorous (Pi) and calcium (Ca) levels, remained within the normal range until eGFR <40 mL/min/1.73 m^2 [3]. These bone changes are responsible for fractures, bone pain, immobility, and weakness [2, 4, 5], and the associated MBD biochemical disorders were associated with an

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increase in cardiovascular events and all-cause mortality [6–11]. Observational studies that included hemodialysis patients have reported the correlation of cardiovascular events with serum Pi, serum Ca and Pi product, and PTH levels, whereas a few observational studies that included predialysis patients showed that cardiovascular events have a similar correlation with elevated serum Pi and PTH levels [11, 12]. Elevation in PTH level in CKD patients is an adaptive response to an increase in serum Pi level from reduction of eGFR, a low serum Ca^{2+} level from a decrease in 1,25-dihydroxy vitamin D_3 ($1,25[OH]_2D_3$, calcitriol) level, an increase in fibroblast growth factor (FGF)-23 level, and a decrease in calcitriol level from a reduction in 1-α-hydroxylase production, which is correlated with both renal osteodystrophy and the adverse clinical outcomes.

The term "renal osteodystrophy" was previously used to describe both bone histology and biochemistry findings and is currently defined based on only by histology and histomorphometric findings obtained by bone biopsy at an ideal site such as the iliac crest [2, 4]. Bone biopsy should be considered in advanced CKD patients with unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates [4]. There are four types of renal osteodystrophy: (1) osteitis fibrosis (high turnover) related to an elevated serum PTH level, (2) adynamic bone disease (low turnover), (3) osteomalacia (low turnover), and (4) mixed uremic osteodystrophy [2, 4, 12–14]. The 2017 KDIGO guideline states: "in patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions" [15].

The prevalence of CKD and osteoporosis is particularly increased in the elderly population in whom they commonly coexist, which may further complicate MBD [16, 17]. Osteoporosis is an absorptive process, whereas CKD-MBD is an imbalance of bone formation, mineralization, and volume, and both can result in fractures. Therapy differs for these two disorders; hence, differential diagnosis is very important to avoid inappropriate treatment. The dual-energy X-ray absorptiometry (DEXA), a two-dimensional bone density scan used to diagnose osteoporosis, may not be useful in differentiating these two disorders and, in fact, may sometimes overestimate bone mineral density (BMD) in moderate CKD [16]. Quantitative computerized tomography (qCT) and micromagnetic resonance imaging (mMRI) better discriminate changes in the cortical and trabecular bone and changes in bone volume [16] and might aid in the differential diagnosis. However, the gold standard for differentiating these two disorders is the two-phase tetracycline labeling bone biopsy [16, 17].

11.3 Biochemistry in CKD-MBD

Hyperphosphatemia, hypocalcemia, low calcitriol level, elevated FGF-23 level, and elevated serum PTH level, all play important roles in the development and progression of CKD-MBD at different periods. As renal function declines, serum Pi level increases, which can stimulate the secretion of FGF-23 from osteocytes. There is a decline in the production of the 1-α-hydroxylase in the proximal convoluting tubule (PCT). The inactivity of the Na-Pi transporter can result in phosphaturia. Low calcitriol levels commonly seen in renal failure may be secondary to inhibition by FGF-23 rather than by a decrease of 1-α-hydroxylase in renal parenchymal [18–20]. More recently, FGF-23 and klotho also have been identified as important regulators of mineral metabolism. Klotho deficiency and high circulating FGF-23 levels precede secondary hyperparathyroidism in CKD patients. Levels of FGF-23 and PTH increase with the progression of CKD to overcome end-organ resistance and to maintain mineral homeostasis [21–23]. It is difficult to define when the increase of both hormones becomes maladaptive. The components of the mineral bone abnormalities and their contribution to MBD will be discussed individually. The 2017 KDIGO clinical practice guideline recommends monitoring the serum levels of calcium, phosphate, PTH levels, and alkaline phosphatase activity beginning in stage G3a CKD [15].

11.3.1 Calcium

Calcium is one of the main cations in the human body, which can maintain the structure of bone and regulate cell function. Furthermore, 99% of the body's calcium is contained in skeletal and the intracellular compartment, and only 1% is available for calcium homeostasis [24, 25]. The normal serum calcium range in adults is 8.4–10.4 mg/dL, and 50% of serum calcium circulates freely, whereas the remainder is bound to albumin or anions. Serum calcium is maintained by various hormones such as PTH, calcitonin, and calcitriol, which in turn regulate the intestine, kidney, and bone to maintain serum calcium level [24].

In advanced CKD, calcium absorption in the small intestine is reduced secondary to a decrease of calcitriol and dietary intake. Elevation in Pi and a low serum Ca^{2+} level result in an increase of PTH secretion via the Ca^{2+} sensing receptor (CaSR) [24, 25]. This increase in serum PTH level can stimulate renal distal tubules to reabsorb more Ca^{2+} and an increase of bone resorption for attempting to maintain normal serum Ca^{2+} level.

11.3.2 Phosphate

Phosphorus (Pi) is an abundant element in the body and is essential for a wide variety of key biological processes. It plays an important role in cellular energy metabolism and cell signaling, e.g., adenosine and guanosine triphosphates (ATP, GTP), and in the composition of phospholipid membranes and bone, and is an integral part of DNA and RNA [24, 26]. In the body, 80–85% of Pi is in the skeleton [24], 1% is in the serum in an inorganic form [26], whereas the remainder is in other intracellular and extracellular compartments.

Pi homoeostasis is maintained by a balance between dietary Pi absorption by the gut, mobilization from bone, and renal excretion. The serum Pi is largely unbound [24], ranging from 2.5 to 4.5 mg/dL. Pi is absorbed in the small bowel under the influence of calcitriol. In the kidney, unbound Pi is filtrated by the glomerulus freely, of which 80–90% is reabsorbed in the PCTs (60–70%) and distal nephron (20–30%) [24]. In early CKD, the serum Pi level is maintained by reduced absorption in the GI tract due to decreased calcitriol level [24] and increased Pi excretion through decreased expression of the Na-Pi 2a cotransporter in the PCTs via the action of PTH [24, 26] and FGF-23 [22, 27].

Hyperphosphatemia is associated with a higher prevalence of soft tissue calcification, such as coronary arteries, descending aorta, aortic valve, and mitral valve [7]. Besides extraskeletal calcification, hyperphosphatemia is also responsible for other adverse outcomes in CKD patients. A study reported that rats with CKD fed with high phosphate diet had higher heart weights than corresponding control rats [28].

11.3.3 Parathyroid Hormone

PTH is the major modulator of bone and mineral metabolism through its regulation of calcium and Pi homeostasis. Synthesis and cleavage of PTH occur within the parathyroid gland. PTH is a polypeptide synthesized in the endoplasmic reticulum following two successive cleavages: 115 amino acid pre-pro-PTH cleaved to 90 amino acid pro-PTH. Pro-PTH is then cleaved again to form an active mature full-length 84 amino acid PTH, with the first 6 amino acids accounting for its activity, while the 7–84 amino acids fragment protein is inactive [4]. The whole process of PTH synthesis, its cleavage and storage, is fast and has been estimated to take less than an hour. After release, PTH is rapidly removed from the serum by the kidney and the liver.

PTH has a major biological function in maintaining ionized calcium and phosphate within the reference range by stimulating specific receptor-mediated responses in cells throughout the body. If a decrease in circulating ionized calcium occurs, PTH increases and has three major functions that help to restore a normal circulating concentration: receptor-mediated tubular reabsorption of calcium (kidney); stimulation of osteoclast resorption to release skeletal calcium

(bone); and increasing activity of renal 1-α-hydroxylase, resulting in production of $1,25[OH]_2D_3$ and increasing calcium absorption (bowel). The increase in calcium in response to these effects mediated by PTH acts via a classic endocrine feedback loop on the CaSR, decreasing secretion of PTH [29–33]. PTH is a major regulator of bone turnover and acts directly on osteoblasts and indirectly on osteoclasts [24].

Increased serum PTH levels are prone in African Americans, the obese, and nondiabetic patients with CKD [11]. Although initial evaluation of MBD is recommended for patients with stage 3 CKD, some observational studies suggest that SHPT might occur earlier [3, 11]. In one study, elevated PTH levels were detected in 50.1% of participants with stage 3 CKD, which appeared to increase the risk for cardiovascular disease. Li et al. evaluated the association of iPTH with all-cause mortality in a cohort, comprising 8530 maintain hemodialysis patients who underwent 6–70 months follow-up (with a median of 40 months). Multivariate Cox regression analysis showed that patients with a low iPTH level (<75 pg/mL) at baseline had greater risk of mortality (HR = 1.36, 95% CI 1.16–1.60) than those with an iPTH level within 150–300 pg/mL at baseline [34]. Therefore, close surveillance for hyperparathyroidism should be recommended in patients with CKD.

11.3.4 Fibroblast Growth Factor 23

FGF23 is mainly produced in the bone and, upon secretion, forms a complex with a FGF receptor and coreceptor αKlotho [19, 33], induces renal phosphaturia by decrease $1,25[OH]_2D_3$ synthesis, through enhanced expression of 24-hydroxylase, whereas $1,25[OH]_2D_3$ itself increases FGF-23 transcription. An increase in PTH follows [18, 19, 34]. Healthy medical students on a high Pi diet showed an increase in serum FGF-23 levels at 16 h [33]. Their serum $1,25[OH]_2D_3$ levels declined, and urinary Pi excretion increased. These parameters remained unchanged in the group on a normal Pi diet [33]. An elevated level of FGF-23 may be a mechanism to maintain Pi homeostasis in early CKD [32, 33].

The FGF-23 receptor complex, Klotho–FGFR1, is expressed in the parathyroid cells, and a challenge with recombinant FGF-23 activates the mitogen-activated protein kinase (MAPK) 1 pathway to decrease PTH mRNA levels and PTH secretion both in vivo and in vitro [35, 36]. In both experimental CKD and in parathyroid tissue from patients with CKD, serum PTH and FGF-23 levels are markedly increased, suggesting a resistance of the parathyroid gland to FGF-23. This resistance is caused by a decreased expression of the Klotho–FGFR1 complex in the parathyroid gland in stage 5 CKD and prolonged experimental renal failure but not in short-term experimental renal failure [37, 38].

11.3.5 Vitamin D

Vitamin D3 (cholecalciferol), the natural form of vitamin D, is a steroid hormone that can be synthesized endogenously or taken in from the diet. In the skin, irradiation of 7-dehydrocholesterol produces pre-vitamin D3 that is immediately converted to cholecalciferol. The production of vitamin D in the skin is the most important source of vitamin D and depends on the intensity of UV exposure. Vitamin D can also be provided to a small extent in the diet, being mainly present in fish oils and fortified dairy products [39]. Vitamin D3 is transported to the liver by vitamin D-binding protein (VDBP), which is subsequently converted to calcidiol by 25-hydroxylase (CYP2R1). Serum calcidiol reflects total body vitamin D from dietary intake, skin, and liver stores [39]. Circulating calcidiol bound to VDBP is taken up by megalin-mediated endocytosis in the PCTs and converted to calcitriol, the active form, by 1-α-hydroxylase (CYP2B1) [40]. Serum calcitriol level is under the control of phosphorous, FGF-23, PTH, and calcitriol (negative feedback) [18, 19, 39, 40].

Vitamin D deficiency (<20 ng/mL) and insufficiency (20–29 ng/mL) are common among patients with CKD, particularly the elderly and advanced CKD [39, 40]. In addition to nutritional and sunlight exposure deficits, factors that affect vitamin D deficiency include race, gender, age,

obesity, dietary intake and impaired vitamin D synthesis and metabolism [39]. With the deterioration of renal function, serum 1,25$[OH]_2D_3$ levels also decrease progressively because of vitamin D3 deficiency, together with impaired availability of CYP2B1 by renal PCTs, high FGF-23.

Vitamin D is involved in the regulation of bone metabolism, skeletal muscle strength and mobility, and in the maintenance of calcium and phosphate homeostasis [39, 40]. Observational studies showed that vitamin D has some beneficial extraosseous functions involving cardiac and immune system. Insufficient vitamin D is related to high-renin hypertension and diabetes [39, 40], whereas sufficient vitamin D is associated with improved outcomes in these diseases [41]. Together with the progressive decline of serum calcitriol, vitamin D deficiency leads to SHPT and its complications, tertiary hyperparathyroidism and hypercalcemia, which require surgical parathyroidectomy or calcimimetics. As in the general population, this condition is associated with increased morbidity and poor outcomes.

11.3.6 Bone

Owing to the lack of evidence showing that BMD measured by DEXA predicts fractures in patients with CKD as it does in the general population, and to the inability of DEXA to indicate the histological type of bone disease, the 2009 guideline recommended that BMD measurement be not routinely performed in patients with stage CKD G3a–G5D and CKD-MBD [4]. An evidence-based review of the 2017 KDIGO CKD-MBD guideline update identified four prospective cohort studies on adults [15], showing that BMD measured by DEXA predicted fractures in the entire spectrum from stage CKD G3a–G5D [42–45]. These studies represent a significant progress since the publication of the original 2009 guideline. Based on these insights, the KDIGO work group concluded that BMD assessment by DEXA is recommended if low or declining BMD will lead to additional interventions for the reduction in falls or the use of medications for osteoporosis.

The term renal osteodystrophy (ROD) is defined as alterations in bone physiology that can be detected histologically and includes CKD-mediated changes in bone turnover, mineralization, and volume (TMV). Double tetracycline labeled bone biopsy is thus far the gold standard for the diagnosis and classification of ROD. Over the past few years, bone biopsy studies have yielded several clinically important insights into CKD-related bone dysfunction and have defined a critical role for bone as an endocrine organ, responsible for many of the complications that accompany CKD-MBD. The 2009 guideline recommended a bone biopsy prior to anti-resorptive therapy in patients with stage G4–G5D CKD and evidence of biochemical abnormalities in CKD-MBD, low BMD, and/or fragility fractures [4]. However, the KDIGO work group understands clinical experience concerning the performance and evaluation of bone biopsies may be limited. There is growing evidence that anti-resorptive therapies are effective in patients with stage G3a–G4 CKD; however, no robust evidence suggests that anti-resorptive medications induce adynamic bone disease. Therefore, the 2017 guideline update no longer suggests performing bone biopsy be performed prior to initiation of these medications [15].

11.3.7 Vascular Calcification

Cardiovascular complications are the main clinical problems in patients with CKD, and the main cause of death in patients with end-stage renal disease [46, 47]. The combination of vascular calcification and disturbed bone metabolism in CKD has been termed as CKD-MBD by the KDIGO in 2009 [4]. Increased vascular calcification in CKD patients is an important risk factor for poor prognosis in overall survival, cardiovascular morbidity and mortality [47–49]. Vascular calcification, previously considered as a passive deposition of calcium and phosphate hydroxyapatite, is now considered as a cellular regulatory process in which vascular smooth muscle cells (VSMCs) undergo molecular and phenotypic changes similar to bone formation

during embryogenesis. Paradoxically, in both patients with CKD and animal models of CKD, bone loss occurs simultaneously with increased vascular calcification [50], suggesting that different intrinsic signals in tissue-specific microenvironments may dominate bone and vascular mineralization. The exact mechanism of vascular calcification in CKD and the contribution of impaired bone metabolism to vascular calcification have not been fully elucidated. Systemic uremic factors and bone metabolic disorders play an important role in the pathogenesis of vascular calcification in CKD. The regulation of Runt-related transcription factor 2 (Runx2), a key transcription factor for bone formation, and the emerging role of Runx2-dependent receptor activator of nuclear factor kappa-B ligand (RANKL) in vascular calcification of CKD were emphasized.

For patients with CKD G3a–G5D, we recommend that abdominal lateral radiographs be used to detect the presence or absence of vascular calcification, and echocardiography be used to detect the presence or absence of valvular calcification, as a reasonable alternative to CT-based imaging. We recommend that patients with CKD G3a–G5D with known vascular or valvular calcification be considered to have highest cardiovascular risk. It is reasonable to use this information to guide the management of CKD-MBD.

11.4 Treatment of CKD-MBD

Management of CKD-MBD requires understanding of the complex interactions between ions, hormones and their target organs. Since the release of KDIGO CKD-MBD guidelines in 2009, our understanding of the pathophysiology has improved. However, there is still a lack of high-quality clinical evidence to support specific interventions. Using available data, KDIGO has now updated diagnosis and treatment recommendations for patients with CKD-MBD. In patients with CKD G3a–G5D, the therapy of CKD-MBD should be based on a series of measurements of phosphate, calcium, and PTH levels.

11.4.1 Treatment Targeted at Lowering High Serum Phosphate Level and Maintaining Serum Calcium Level

With the deterioration of renal function, the iPTH level increases earlier than Pi as a response to maintain serum Pi, the later does not increase until the eGFR falls below 40 mL/min/1.73 m^2 [3], and FGF-23 acts similarly to iPTH. In an animal study performed in dogs, when the dietary Pi intake was titrated to renal function decline, serum iPTH and Pi levels, and excretion of Pi remained unchanged [51]. This study highlights the importance of dietary Pi restriction in patients with CKD. When kidney disease progresses, for PTH and FGF-23, it is harder to maintain serum Pi in normal range without damaging other organs. The serum Pi level target for the patient with stage G3a–G5D CKD is toward the normal range, and phosphate binders will be prescribed if this target is not achieved by diet Pi restriction alone. The available Pi binders are classified as either calcium based or non-calcium based [52–54]. The former includes calcium carbonate and calcium acetate, whereas the latter includes sevelamer carbonate or hydrochloride (an anion exchange resin), lanthanum carbonate, and aluminum hydroxide. Aluminum hydroxide is now restricted in patients with advanced CKD [55, 56] because of the extrarenal side effects which include low turnover bone decrease, skeleton fractures, encephalopathy, skeletal muscle weakness, and microcytic anemia without iron shortage [19, 57, 58]. Chertow GM et al. compared calcium acetate with sevelamer with respect to the development and progression of calcification in coronary artery and aorta using electron beam technique (EBT) in dialysis patients [60]. At baseline, both groups had severe extensive vascular calcifications. At the end of the 2-year follow-up, there was no further progression of calcification in the sevelamer group, but a significant increase in calcification in the coronary artery and aorta was observed in the calcium acetate group [60]. A systematic review [63] of 60 trials found that although sevelamer hydrochloride significantly reduced serum Pi and PTH levels compared

with calcium-based binders, the use of sevelamer was associated with a higher risk of gastrointestinal side-effects but lower risk of hypercalcaemia. There was no significant reduction in all-cause mortality with sevelamer hydrochloride compared with calcium-based phosphate binders.

In adult patients with stage G3a–G5D CKD, we suggest that hypercalcemia be avoided. In children with stage G3a–G5D CKD, we suggest that the serum calcium level be maintained in the age-appropriate normal range. In patients on maintain hemodialysis, we suggest the use of a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L). The association between calcium-based Pi binders and extraskeletal calcifications has led to the prescription of non-calcium-based Pi binders. If calcium-based Pi binders are prescribed, the dose should be limited to 1.5 g of elemental calcium per day [14, 59–62]. In adult patients with stage G3a–G5D CKD receiving phosphate-lowering treatment, we suggest that the dose of calcium-based phosphate binders should be restricted. In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels.

11.4.2 Treatment of Abnormal PTH Levels in CKD-MBD

In patients with stage G3a–G5 CKD not on dialysis, the appropriate PTH level is yet not known until now. Even so, we recommend that patients with iPTH levels gradually increasing or continually exceeding the upper normal limit should be assessed for modifiable factors, such as hyperphosphatemia, hypocalcemia, hyperphosphate diet, and vitamin D deficiency.

The updating of the KDIGO guidelines in 2017 gives the following reasons for its emphasis on not starting treatment for a single elevated PTH value: (1) the optimal PTH level is still unclear; (2) a moderate increase in PTH level is an appropriate adaptive response that contributes to phosphaturia in CKD and may therefore be conducive to maintain normal serum phosphate levels as GFR decreases; and (3) high PTH level does not predict high turnover osteopathy, so it is not necessary to correct the slightly elevated PTH levels to normal levels in CKD. The KDOQI work group agreed with the update and its reasons, particularly in view of the high variability of PTH levels within and between individuals [64–67].

We recommend unconventional prescriptions of calcitriol and vitamin D analogues in adult patients with stage G3a–G5 CKD not on dialysis. It is reasonable to retain the use of calcitriol and vitamin D analogues for patients with stage G4–G5 CKD with severe or progressive hyperparathyroidism. In children, calcitriol and vitamin D analogues can be used to maintain serum calcium levels within normal age-appropriate ranges. The PRIMO and OPERA studies demonstrated that in patients with non-dialysis-dependent CKD, the use of vitamin D analogues may be associated with significant reductions in PTH levels, no change in cardiovascular end points, and significant increases in risk for hypercalcemia [68, 69].

For patients with stage G5D CKD, we recommend that iPTH levels be maintained within about 2–9 times the normal upper limit of the test. We suggest that significant changes in iPTH levels beyond this range should be avoided, either in therapy or not. For patients with stage G5D CKD requiring PTH reduction therapy, we recommend the use of calcimimetics, calcitriol, vitamin D analogues, or a combination of calcimimetics with calcitriol or vitamin D analogues. Calcimimetics, calcitriol, and vitamin D analogues have shown efficacy in lowering the PTH level in the patients with stage G5D CKD in the United States [70–72]. Although pre-specified secondary analysis and post hoc analysis of the EVOLVE data noted improvement in some outcomes in a subgroup of patients (e.g., a reduction in fracture incidence when treated with cinacalcet vs placebo in patients aged >65 years) [73], the results of preliminary analysis were not positive. Since the advantage of cinacalcet over other drugs has not been established, the selection of PTH reduction treatment in patients with stage G5D CKD may be based on cost, adverse events, and presence of other mineral metabolism abnormalities.

11.4.3 Parathyroidectomy

For patients with stage G3a–G5D CKD with severe hyperparathyroidism who fail to respond to medical or pharmacological treatment, we recommend parathyroidectomy. In tertiary hyperparathyroidism, the parathyroid gland becomes autonomous, nodular in composition, and unresponsive to feedback inhibition by vitamin D analogues or cinacalcet owing to a reduction in VRD and CaSR. For more than six decades, many patients with advanced CKD have undergone surgical parathyroidectomy (PTX) for severe SHPT mainly according to historical clinical practice patterns. Mugurel Apetrii et al. conducted a meta-analysis to evaluate the benefits and hazards of PTX in patients with SHPT [74]. The final analysis included 15 cohort studies, comprising 24,048 participants. Compared with standard therapy, PTX significantly reduced all-cause mortality (RR 0.74 [95% CI, 0.66 to 0.83]) in patients with end-stage renal disease who had biochemical and/or clinical evidence of SHPT. In six observational studies involving nearly 10,000 patients, PTX was also associated with reduced cardiovascular mortality (RR 0.59 [95% CI, 0.46 to 0.76]). In conclusion, the results of this meta-analysis suggest that PTX has a significant clinical benefit in all-cause and cardiovascular mortality in CKD patients with SHPT. Our study showed that total parathyroidectomy without autotransplantation could improve BMD at the L1–L4 level and the hip in SHPT patients [75]. However, in view of the observational nature of the studies included, there is a strong demand for appropriately performed, independent randomized controlled trials to compare surgery with medical treatment and featuring many different outcomes from mortality to quality of life.

Due to the complexity of basic pathophysiology, the lack of evidence certainty, and multiple morbidities in the patient population, clinical providers in the kidney care setting often encounter patients with CKD-MBD and strive to find treatment methods. The ambiguity and lack of clear and actionable recommendations highlight potential challenges in implementation, remind us that clinical practice guidelines should be used in conjunction with clinical judgments, and emphasize the need for future research in this vital area.

Key Messages

- CKD-MBD is a systemic disorder manifested by one or more of the following: (1) abnormalities of calcium, phosphorous, PTH, or vitamin D metabolism, (2) abnormalities in bone pathology and histomorphometry marked by changes in bone turnover, mineralization, volume, linear growth, or strength (TMV system), and (3) the presence of vascular or other soft tissue calcification.
- The 2017 KDIGO clinical practice guideline recommends monitoring the serum calcium, phosphate, and PTH levels and alkaline phosphatase activity beginning in stage G3a CKD.
- Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered altogether.
- In patients with stage G3a–G5D CKD with severe hyperparathyroidism who fail to respond to medical or pharmacological therapy, we suggest parathyroidectomy.

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Immune Deficiency and Infection in Chronic Kidney Disease

12

Lei Jiang and Ping Wen

Abstract

Chronic kidney disease (CKD) has long been recognized to be associated with immune deficiency. CKD-associated immune deficiency is orchestrated by the innate immune system and adaptive immune system. Immune deficiency could lead to graft dysfunction and impaired response to vaccination. Owing to the immune deficiency of CKD patients, opportunistic infections such as fungal, *Pneumocystis jiroveci,* and virus are more common in patients with CKD than in the general population. The high mortality risk of patients with CKD has been partly attributed to the infected diseases. Interventions targeting the immune dysfunction and infection can improve the outcomes of CKD.

12.1 Introduction

Chronic kidney disease (CKD) has long been recognized to be associated with immune deficiency, and the CKD-associated immune dysfunction is orchestrated by the innate immune system and adaptive immune system. The deficiency of the immune system may induce an increased incidence of infections among patients with CKD, which could increase the morbidity and mortality in this population [1].

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12.2 CKD-Associated Immune Deficiency

The development of CKD is associated with a significant increase in the risk of morbidity and mortality, which is linked to aberrant immune responses. Recent research has revealed that uremic toxins (Table 12.1), malnutrition, immunosuppressive and cytotoxic drugs, increased oxidative stress, priming of immune cells, aberrant apoptosis, and metabolic kidney activities [such as hormone erythropoietin (EPO), vitamin D, parathyroid hormone, and renin] lead to the immune dysfunction in CKD [2–4].

12.2.1 Immune Deficiency Caused by Immunosuppressive Agents

Immunosuppressive drugs have become some of the most successful treatments for some glomerular-nephritis patients and transplant patients, but these patients also appear to show increased susceptibility to infections because of immune deficiency (Table 12.2) [5–9].

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Table 12.1 Functional disturbances of immune cells caused by uremic toxins

Uremic toxins	Effects on immune cells
Low molecular weight (LMW) toxins	
Phenylacetic acid (PAA)	Macrophages: inducible nitric oxide synthase PMNLs: oxidative burst, phagocytosis, increased integrin expression, and decreased apoptosis
Dinucleoside polyphosphates	Leukocytes: oxidative burst
Guanidino compounds	Monocytes/macrophages: pro- and anti-inflammatory
Indoxyl sulfate	Endothelial cells: upregulation of E-selectin
P-cresyl sulfate	Leukocytes: oxidative burst
Homocysteine (Hcy)	Increased ICAM-1 expression, damage of DNA and proteins
Methylglyoxal (MGO)	PMNLs: increased apoptosis and oxidative burst Monocytes: increased apoptosis
Middle molecular weight (MMW) proteins	
Immunoglobulin light chains (IgLCs)	PMNLs: chemotaxis and decreased apoptosis
Retinol-binding protein (RBP)	PMNLs: chemotaxis, oxidative burst, and decreased apoptosis
Leptin	PMNLs: chemotaxis and decreased apoptosis
Resistin	PMNLs: chemotaxis and decreased apoptosis
Tamm–Horsfall protein (THP)	PMNLs: decreased chemotaxis and apoptosis, increased phagocytosis
High-density lipoprotein (HDL)	Loss of anti-inflammatory properties

PMNLs polymorphonuclear leukocytes (Adapted from Cohen G, Horl WH. Toxins. 2012;4:926–90 [3])

Table 12.2 The mechanism of action of immunosuppressive agents

Drug	Mechanism
Steroids	Reductions in leukocyte migration, in neutrophilic and monocytic phagocytosis, and in T-cell function
Azathioprine 6-Mercaptopurine methotrexate	Proapoptotic effects on T lymphocytes
Cyclosporine Tacrolimus (FK506)	Induction of antibody, leukocyte, and lymphocyte formation and of differentiation into proinflammatory Th17 cells
Mycophenolate mofetil (MMF)	Inhibition of both T-lymphocyte and B-lymphocyte activities

12.2.2 CKD-Associated Innate Immune Deficiency

The innate immune system consists of monocytes, macrophages, polymorphonuclear leukocytes (PMNLs), neutrophils, eosinophils, basophils, dendritic cells, and natural killer cells. The effects of CKD on the innate immune system may be due to the accumulation of uremic toxins, increased levels of proinflammatory molecules, alterations of TLRs, increased oxidative stress, decreased erythropoietin production, and increased parathyroid hormone concentration. The disturbances of innate immune cells associated with CKD are summarized in Table 12.3 [10].

Table 12.3 The dysfunction of innate immune cells associated with CKD

Innate-immune-cell type	CKD-associated changes	Altered functions
Monocytes and macrophages	$CD14^+CD16^+$ subset expansion	Production of cytokines Decreased phagocytic capacity ROS Production of osteoactivin
PMNLs	Increased apoptosis of PMNLs	Decreased phagocytic capacity
Dendritic cells	Reduction in numbers of DCs Functional anomalies of DCs	Impaired defense against microbial infection and a poor response to vaccination
Neutrophils	Reduction in the killing capability of neutrophils Unchanged number of neutrophils capable of phagocytosis and producing ROS	Reduced ability to kill microorganisms and increased susceptibility to infection
Eosinophils	Increased number	Associated with vascular disease in CKD patients
Natural killer cells	Decreased number of NKG2D-positive NK cells	Associated with high levels of the circulating HLA-related molecule MICA

PMNLs polymorphonuclear leukocytes; *DCs* dendritic cells; *ROS* reactive oxygen species

12.2.3 CKD-Associated Adaptive Immunity Deficiency

Patients with CKD exhibit T-cell lymphopenia, which is primary due to loss of naïve $CD4^+$ and $CD8^+$ T cells and central memory $CD4^+$ T cells; aberrant activation of terminally differentiated memory cells; and an imbalance between suppressive regulatory T cells (Treg cells) and T helper 17 cells (T_H17 cells). The aberrations of T cells are related to uremic toxins, oxidative stress, secondary hyperparathyroidism, an iron overload, and inflammation.

Significant B-cell deficiency and dysfunction have been demonstrated in CKD, which are mediated by increased apoptosis and impairment of maturation. Uremia toxin-induced B-cell lymphopenia may increase the frequency of infections and cause a defective response to vaccination in patients with CKD. The T-cell and B-cell anomalies associated with CKD are summarized in Table 12.4 [11–13].

12.2.4 Conclusions

The CKD-associated immune dysfunction is orchestrated by the innate immune system and adaptive immune system. The deficiency of the immune system may induce an increased incidence of infections among patients with CKD.

12.3 Immune Deficiency-Associated Infection in CKD

Owing to the immune deficiency in patients with CKD, the incidence of infection is higher than in the general population, and the high mortality risk among patients with CKD has been partly attributed to infectious diseases. The spectrum of infections among immunocompromised patients is quite broad. Among such patients, opportunistic pathogens should not be ignored. Given the toxicity of antimicrobial agents and the need for rapid remission of infection, early specific diagnosis is essential in this population.

12.3.1 Etiology

Immune deficiency in patients with CKD patients due to the immune dysfunction is induced by uremic toxins, nutrient deficiencies, kidney transplant, use of drugs, obesity, and so on (see upper section).

Table 12.4 The T-cell and B-cell anomalies associated with CKD

Type of adaptive immune cells	CKD-associated changes	Mechanism and altered function
Naïve T cells	Loss of circulating naïve $CD4^+$ and $CD8^+$ T cells, central memory $CD4^+$ T cells Remaining naïve T cells show aberrant activation and higher expression of CD24, CD69, CXCR3, and CXCR5	Increased apoptosis Reduced IL-17 homeostatic signals Impaired thymic output
Effector memory T cells	Increased number of $CD8^+$ T_{EMRA} cells	Transplant rejection
Treg and Th17 cells	Decreased number of Treg cells Increased number of Th17 cells	Increased apoptosis Increased angiogenin Increased production of 2,3-dioxygenase and arginase Decreased production of interleukin 2
B cells	Decreased numbers of $CD5^+$ innate B cells and $CD27^+$ memory B cells	Increased apoptosis BAFF downregulation Reduced antibody production Increased production of proinflammatory cytokines

12.3.2 Immunosuppressive Agents-Induced Infection

12.3.2.1 Fungal Infection

1. **Pathogens**
   The incidence of infection increases significantly among patients using immunosuppressive drugs. CKD patients with immunodeficiency are at a risk of opportunistic infection with a variety of fungal pathogens, the most important of which are *Candida* species (53%), *Aspergillus* spp. (19%), *C. neoformans* (8%), *non-Aspergillus spp*. (8%), *endemic fungi* (5%), *and zygomycete* (2%) [14].
   - *Candida*
     - *Candida spp.* is the most frequent agent of fungal pathogen. Candia infections manifest as mucocutaneous candidal infection, pneumonia, peritonitis, urinary tract infection, empyema, candidemia, surgical anastomosis infection, or oesophagitis. The mortality of invasive candidiasis is 34% at 12 months [15].
   - *Aspergillus* Species
     - Invasive aspergillosis (IA) is the most deadly infection in solid organ transplantation [16]. Aspergillosis mainly causes tracheobronchitis or invasive pulmonary disease (the most common clinical form with about 67–82% of high mortality). Corticosteroid usage, long time renal replacement therapy, and leukopenia are the major risk factors for IA.
   - *C. neoformans*
     - The incidence of cryptococcosis is higher in patients with kidney transplantation, high doses usage of corticosteroids, alemtuzumab or infliximab.

2. **Diagnosis**
   The methods utilized to detect fungal infection are as follows:
   - Positive blood culture, sputum culture, skin culture, or urine culture.
   - Combined detection of mannan and antimannan antibodies (specific for *Candida spp.*).
   - Detection of galactomannan (GM) in bronchoalveolar lavage (BAL) or cerebrospinal fluid (CSF) (specific for IA).
   - Quantification of the 1,3-β-D glucan (BDG) (panfungal diagnostic method) (cutoff value: 80 pg/mL; sensitivity: >65%, specificity rates: >80%).
   - Detection of cryptococcal antigen in serum or CSF.
   - Polymerase chain reaction (PCR)-based methods (sensitivity: 80%, specificity rates: 70%).
   - Other molecular based diagnostic methods such as sequence, hybridization and mass spectroscopy.
   - High-resolution chest CT is recommended for detecting pulmonary aspergillosis, cranial fungal infection, sinonasal fungal infection, liver microabscess, or fungal abscesses in kidney, liver or spleen.
   - Magnetic resonance imaging (MRI) is recommended for detecting cranial fungal infection, cryptococcosis, sinonasal fungal infection, skin and soft tissue fungal infection, or fungal abscesses in kidney, liver or spleen.
   - Ultrasound is the recommended method for detecting fungal abscesses in kidney, liver, or spleen [17, 18].

3. **Treatment**
   - Fluconazole (400–800 mg/day, adjustment for renal dysfunction) is usually used as initial therapy, unless the patient is critically ill or with fluconazole-resistant species infection (e.g., *Candida glabrata* or *C. krusei*). In fluconazole-resistant species infection, echinocandin or amphotericin B in lipid preparation is recommended to use. Flucytosine is an adjunctive therapy in resistant infections, which must be guided by drug levels with attention to hematopoietic toxicity.
   - Voriconazole is recommended for IA (4 mg/kg twice daily for 2 weeks). Plasma levels is recommended to maintain the range between 2 and 4 mg/L. Liposomal amphotericin B is recommended in

patients who are resistant, hepatotoxic, intolerant, or allergic to voriconazole. Nephrotoxicity must be considered. In severe disease, a combination of antifungals treatment with voriconazole plus caspofungin or anidulafungin is recommended.

- For cryptococcosis, combination of liposomal amphotericin B (3–4 mg/kg/day) plus flucytosine (25 mg/kg/6 h) is recommended as induction therapy. Next, fluconazole is used at 400–800 mg/day for 8 weeks and at 200 mg/day for 6–12 mouth as maintenance [17, 18].

12.3.2.2 *Pneumocystis jirovecii* Pneumonia (PCP)

P.jirovecii is a common cause of community-derived opportunistic fungal infections, and PCP is commonly associated with the use of immunosuppressive drugs such as corticosteroids or cyclosporine, or is a coinfection with CMV.

1. **Diagnosis**
   The diagnostic basis for PCP infection includes clinical manifestations, laboratory tests, and auxiliary examinations as follows:
   - Typical clinical symptoms are typically pneumonia, fever, non-productive cough, worsening chest pain, shortness of breath, and low arterial-oxygen tension.
   - Elevated serum lactic dehydrogenase (LDH) (>300 international units per milliliter) while the C-reactive protein (CRP) is not elevated.
   - Elevated levels of 1,3-β-D-glucan in serum.
   - Chest CT: bilateral peripheral interstitial infiltrates, ground glass opacities in early PCP; predominant consolidation in the latter stages of PCP.
   - Microbiological diagnosis includes positive pathogen staining from sputum, BALF, oral wash, or lung tissue.
   - Genetic testing includes PCR or loop-mediated isothermal amplification (LAMP) from sputum, BALF, or oral wash.
2. **Therapy**
   - Antipneumocystis treatment: TMP (15–20 mg/kg/day)-SMX (75–100 mg/kg/day) is the first-line therapy for PCP.
   - Glucocorticoids: glucocorticoids are recommended to administer in patients with hypoxia (PaO_2 <70 mmHg); adjunctive glucocorticoids are recommended in HIV patients with PJP [19, 20].

12.3.2.3 CMV-Induced Pneumonia (CMP)

Diagnosis involves detection of a CMV pathogen and of a specific antibody to a CMV antigen in respiratory secretions, saliva, or lung biopsy samples. CMV PCR detection or anti-CMV-IgM positivity or an increase in the anti-CMV IgG level more than fourfold is helpful for the diagnosis of CMP. In the treatment of CMP, nucleoside drugs such as ganciclovir and phosphonic acid are commonly used.

12.3.2.4 *Legionella* Pneumonia

Detection of a *Legionella* antigen in urine is useful for early diagnosis. Macrolides are the first choice, whereas quinolones, tetracycline, and rifampicin are effective too. Erythromycin is the most effective treatment. New macrolide antibiotics, such as clarithromycin, azithromycin, and roxithromycin, are expected to replace erythromycin. In severe cases, rifampicin or fluoroquinolones can be added.

12.3.3 Vascular-Access-Associated Infections

These diseases are the most common infections among hemodialysis patients and account for 28–60% of septicemia cases among these patients. The most common risk factors for infection in hemodialysis patients include the type, site, and duration of access; the puncture technique of nurses; and the immune state of the patients. Epidemiological studies have revealed that the infection prevalence rate for an arterial venous graft is higher than that for arterial venous fistula

and lower than the infection prevalence rate for a central venous catheter. The spectrum of pathogens is presented in Chap. 17 "Hemodialysis."

12.3.3.1 Treatment of Infection-Associated HD Access (KDOQI Guideline)

1. **An infected HD catheter or port**
   Treatment of an infected HD catheter or port should be based on the type and extent of infection.
   - The catheter exit site or port cannulation site should be examined for roper position of the catheter or port catheter system and the absence of infection by experienced personnel during each HD session before opening and accessing the catheter/port catheter system. (B)
   - The dressing of a catheter exit site should be changed during each HD treatment, to either a transparent dressing or gauze and tape. (A)
   - The aseptic technique should be used to prevent contamination of the catheter or port catheter system, including the use of a surgical mask for the staff and patient and clean gloves for all catheter or port catheter system connection, disconnection, and dressing procedures. (A)
2. **Fistula infection**
   Infections of primary arteriovenous fistulas are rare and should be treated (as subacute bacterial endocarditis) with 6 weeks of antibiotic therapy. Surgical excision of the fistula should be performed in cases of septic emboli. (B)
3. **AVG infection**
   - Initial antibiotic treatment should cover both gram-negative and gram-positive microorganisms. (B)
     – Subsequent antibiotic therapy should be based upon culture results.
     – Incision and drainage may be beneficial.
   - Extensive infection of an AVG should be treated with an appropriate antibiotic and resection of the infected graft material. (B)

∗According to evidence-based levels (A, B, C, and D), the guidelines can be divided into two categories: recommendations and suggestions. Recommendations can be applied to the majority of patients, and the evidence-based level is higher than A and B. Suggestions can be applied to some patients, and a physician needs to consider the patients' individual differences, and the evidence-based level is mostly C and D [21–23].

12.3.4 Peritoneal-Dialysis-Associated Infections

For details, see Chap. 18 "Peritoneal dialysis."

Key Messages

- Chronic kidney disease (CKD) has long been recognized to be associated with immune deficiency and infectious diseases.
- Recent research indicates that uremic toxins, immunosuppressive and cytotoxic drugs, increased oxidative stress, priming of immune cells, aberrant apoptosis, and metabolic kidney activities [such as hormone erythropoietin (EPO), vitamin D, PTH, and renin] lead to the immune dysfunction in CKD.
- Due to immunodeficiency of patients with CKD, opportunistic infections with such pathogens as fungi, *Pneumocystis jiroveci,* and/or viruses are more common among patients with CKD than in the general population.

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13 Nervous System Disorders in Chronic Kidney Disease: Neurocognitive Dysfunction, Depression, and Sleep Disorder

Wenjin Liu

Abstract

Nervous system disorders, including cognitive impairment, depression, and sleep disorder, are highly prevalent in patients with chronic kidney disease (CKD). The mechanisms leading to the increased prevalence are usually multifaceted. These complications can pose great threat to patients' health and quality of life, but sometimes could be neglected or unrealized in clinical practice. Therefore, physicians should be aware of the features of these conditions in CKD patients and need to consider performing routine screening tests, especially in those with advanced renal dysfunction. Management of these complications usually requires identification and targeted treatment of reversible underlying causes, general supporting management of CKD, and consultation with specialist in relevant areas.

13.1 Introduction

Chronic kidney disease (CKD) is associated with an accelerated process of aging that involves several organs and systems of the human body. Brain injury is a remarkable example of the systemic nature of CKD. Various nervous system disorders, including cerebrovascular diseases, cognitive impairment, depression, and sleep disorder, are found at a higher prevalence in individuals with renal dysfunction than in the general population. The reasons for CKD-related nervous system disorders are multifaceted and include the direct neurotoxic effects of accumulated uremic toxins as well as contributions from other risk factors secondary to CKD (e.g., hypertension, fluid overload, and inflammation). Although such complications can pose a significant threat to patients' health and quality of life, they are sometimes neglected or unrealized in clinical practice. Therefore, there is a need for physicians to better understand the disorders that can arise in individuals with kidney diseases and improve the comprehensive management of CKD, as doing so would be beneficial for improving patients' quality of life and prognosis.

In this chapter, we focus on three key components of nervous system disorders: neurocognitive dysfunction, depression, and sleep disorder. Considering that the development of cerebrovascular disease in the context of renal dysfunction is mainly due to increased cardiovascular injury stimuli, we do not discuss it here. Readers interested in cerebrovascular complications can refer to Chap. 9 for a detailed discussion.

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13.2 Neurocognitive Dysfunction

13.2.1 Prevalence

Cognitive impairment has long been a neglected problem in patients with CKD. Only in the past decade has this issue drawn increasing attention. Kidney disease has been shown to be an independent risk factor for cognitive impairment and dementia [1, 2]. In a recent study that administered cognitive tests over a number of years, patients with impaired renal function (defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) had fewer cognitive impairment-free life-years than those with an eGFR ≥ 90 mL/min/1.73 m^2 [3].

Given the significant link between CKD and the development of cognitive dysfunction, a number of studies have reported the prevalence of cognitive impairment in various CKD stages. It is established that cognitive impairment becomes more prevalent as renal function decreases. In patients with end-stage renal disease (ESRD) receiving renal replacement therapy, the estimated prevalence of cognitive impairment ranges from 30% to 87%. In the study by Murray et al., the prevalence of mild, moderate, and severe cognitive impairment was 13.9%, 36.1%, and 37.3%, respectively, in a group of 338 hemodialysis patients. It should be noted that the choice of cognitive evaluation test, cut-off value for defining cognitive impairment, variation in patient characteristics, and possible temporal changes due to the improvement of disease management over time might all contribute to the varied prevalence found in different studies [4]. There is also evidence implying that peritoneal dialysis is associated with better cognitive outcome than hemodialysis [5, 6]. However, this discrepancy in dialysis modality needs to be evaluated more carefully due to the possibility of selection bias.

In addition to the data from patients with ESRD, some studies have also noted the development of cognitive dysfunction in earlier stages of CKD. In the National Health and Nutrition Examination Survey (NHANES) III study, Hailpern et al. found that in nearly 5000 subjects aged 20–59 years, moderate CKD (eGFR 30–59 mL/min/1.73 m^2) was associated with poorer performance in visual attention and learning/concentration tests [7]. This finding is supported by data from a longitudinal study in which the authors found that moderate CKD, defined as serum creatinine ≥1.3 mg/dL for women and 1.5 mg/dL for men, was associated with a 37% increase in the risk of incident dementia [8]. The association has also been validated in patients with preserved renal function [9]. Moreover, the association between cognitive impairment and renal dysfunction seems to be "dose-dependent," as the risk of cognitive impairment was more pronounced in patients with more severe renal dysfunction [10].

However, despite a great number of studies supporting the link between cognitive impairment and renal dysfunction, there are also lines of evidence indicating that such an association does not exist. In the study by Freedman et al., the authors found no association between eGFR and cognitive test performance despite finding an association between the urine albumin–creatinine ratio and digit symbol coding performance [11]. A possible explanation for the lack of association between eGFR and cognitive performance may be that the Mini-Mental State Examination test that was used for global cognitive evaluation in the study is not sensitive to mild cognitive impairment, which is the predominant type of cognitive dysfunction found in CKD patients.

13.2.2 Awareness

In addition to the high prevalence of cognitive impairment in CKD patients, cognitive impairment is often poorly recognized by physicians and patients. In the DOPPS (Dialysis Outcomes and Practice Patterns Study) study, a previous record of a diagnosis of dementia was only found in 4% of patients on maintenance hemodialysis [12]. The low prevalence of dementia found in this study was an underestimation given the aforementioned epidemiologic data. Poor recognition leads directly to insufficient or even a lack of intervention and can be associated with

treatment noncompliance by patients. Therefore, it is of great importance to increase the awareness of the importance of periodic cognitive assessment for both physicians and patients.

13.2.3 Impact on Quality of Life and Outcome

It is apparent that cognitive impairment, either dementia or mild cognitive impairment, poses a significant detriment to patients' quality of life. Impairment of certain cognitive domains, including executive function, orientation, working memory, language, and attention, is a major complaint from patients (especially those with ESRD) and their family members, as well as caregivers. Cognitive impairment can also affect patients' adherence to treatment regimens and impair decision-making.

Multiple lines of evidence have demonstrated that dementia in dialysis patients is associated with mortality [12–14]. The association between mild cognitive impairment and a hard outcome has not been fully elucidated. Griva et al. defined cognitive impairment as performance one standard deviation less than normative values on two or more cognitive tests in a group of 145 dialysis patients and found that it was an independent risk factor for mortality in these patents [15]. In a more recent study, Drew et al. found that worse executive function and memory deficit were independently associated with a risk of mortality in 292 hemodialysis patients (excluding those with dementia) [16]. However, the associations became nonsignificant after further extensive adjustment.

13.2.4 Pathophysiology

The exact mechanisms underlying cognitive impairment and dementia in the context of CKD remains to be fully elucidated. Cardiovascular risk factors and diseases emerging with renal function decline are considered the predominant contributing factors to impaired cognition in CKD patients. Cerebral circulation and the renal vascular bed share several features, which has led to the speculation that cognitive impairment in CKD is a manifestation of systemic vascular injury. Hypertension, chronic inflammation, and oxidative stress, as well as many other cardiovascular risk factors, are more prevalent and severe in CKD patients than in the general population. In addition to the increased prevalence of stroke in CKD patients, silent cerebrovascular disease, of which the severity increases as renal function declines, is also highly prevalent in these patients. However, although data from previous studies suggest a link between these subclinical cerebrovascular changes in cognitive impairment in the general population, there are few data regarding CKD patients that have confirmed these associations.

Previous studies have shown that CKD is a risk factor for cognitive decline and dementia independent of cardiovascular risk factors, including age, hypertension, and diabetes, which suggests that factors other than those of cardiovascular origin contribute to cognitive impairment in kidney disease. It has been speculated that the neurologic toxicity of uremic toxins also contributes to CKD-associated cognitive impairment. Various uremic toxins, from small molecules (e.g., creatinine) to large molecules (e.g., protein-bound uremic toxin), have been implicated as being involved in the pathogenesis of cognitive impairment. For example, cystatin-C, which is an inhibitor of cysteine proteases that co-localize with b-amyloid in the brain of patients with Alzheimer's disease, was found to be associated with lower cognitive test scores and predictive of future cognitive decline in a community-dwelling population [17]. In the study by Yeh et al., the authors explored the cross-sectional association of two protein-bound uremic toxins with cognition in a group of CKD patients and found that indoxyl sulfate, but not *p*-cresyl sulfate, was associated with cognitive impairment [18].

In addition to cardiovascular and uremic factors, there are reports indicating that other factors are involved in the development of cognitive impairment in CKD. These factors include sleep disturbance, depression, anemia, and hyperparathyroidism.

Table 13.1 Common instruments for the assessment of cognitive function

Domains	Tests
Global cognition	Mini-Mental State Exam (MMSE)
	The Modified Mini-Mental State (3MS)
	Montreal Cognitive Assessment (MoCA)
	The Kidney Disease Quality of Life (KDQOL) cognitive function subscale (KDOQL-SF)
	Mini-cog
Memory	Wechsler Memory Scale-Third Edition (WMS-III)
	Auditory Verbal Learning Test (AVLT)
	Delayed Story Recall Test
Attention	Trail Making Test
	Paced Auditory Serial Addition Test (PASAT)
	Digit Span tests from the Wechsler Adult Intelligence Scale-III (WAIS III)
Executive function	Tower of London Test (TLT)
	The Picture Arrangement sub-test of the Wechsler Adult Intelligence Scales (WAIS-R)
	Wisconsin Card Sorting Test (WCST)
Verbal skill	Boston Naming Test
	Sentence Repetition

13.2.5 Diagnosis

A variety of tools are available for the assessment of cognitive function, some of which were specifically designed for the CKD population. Table 13.1 lists some of the most common tests used in research and clinical practice.

For global cognition, the two most widely used and studied tests are the Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA). Both tests have a maximum score of 30 and can be administered in 10 min. MMSE has some limitations in its application to the CKD population. First, it is most useful for diagnosing dementia and less sensitive for mild cognitive impairment, which the major form of cognitive deficit found in CKD patients. Second, there is a lack of evaluation of executive function in the MMSE, and executive deficit is a prominent feature of cognitive impairment from vascular causes that is common among CKD patients.

The MoCA overcomes the above limitations and therefore may be more suitable for screening cognitive impairment in the context of CKD. However, one should bear in mind that these screening tests are generally influenced by education level and language fluency. Hence, it is very important to consider these factors when interpreting the scores. Specific cut-off values are needed for varying education levels as well as for application in different language areas.

The Kidney Disease Quality of Life (KDQOL) cognitive function subscale is specifically designed for the CKD population and has the advantage of being self-reported. However, despite its validation against the Modified Mini-Mental State (3MS), its value has been questioned due to its low sensitivity.

It is natural to perform these tests when there is a clinical need to do so (e.g., when a patient's family member complains about the patient's symptoms). However, no general recommendations or guidelines exist regarding the frequency of performing the tests in CKD patients. In light of the high prevalence of cognitive impairment in CKD patients, we recommend performing a screening test (e.g., MoCA) at least once every 2 years in patients with an eGFR $\leq$ 60 mL/min/1.73 m^2 who are not on dialysis and annually in ESRD patients on dialysis. If the test results indicate the existence of cognitive impairment, referral to a neurologist is recommended for more thorough neuropsychological evaluation and management.

13.2.6 Management

The general management strategy for dementia in patients with CKD should follow the same criteria used for the treatment of Alzheimer's disease and should involve consultation from a specialist in neurology. Cholinesterase inhibitors and *N*-methyl D-aspartate receptor antagonists could be beneficial in slowing cognitive functional decline, but their effect on long-term outcome is uncertain. Additionally, there are limited data on the use of these drugs in CKD patients. For a detailed description of their use in

the CKD population, please refer to the review by Kurella et al. [19].

The management of mild cognitive impairment in CKD is an area of uncertainty. Although vascular injury is considered to be the most important contributor to cognitive impairment in CKD, it is unknown whether cardiovascular risk factor modification will prevent cognitive impairment/dementia. Even in the general population, there is conflicting evidence regarding the role of antihypertensive therapy in cognitive decline.

Erythropoietin has been suggested to exhibit a protective effect on cognitive function [20, 21]. However, such evidence has generally come from observational studies and needs to be confirmed in randomized clinical trials.

Transplantation has been shown to be consistently beneficial for cognitive function in various studies, whereas increasing the frequency and intensity of hemodialysis is not [22–24].

13.3 Depression

13.3.1 Prevalence

Depression is not uncommon in the CKD population. However, the exact estimate of its prevalence in patients with CKD is unknown and varies widely in the existing literature. Palmer et al. performed a systematic review of previous observational studies and found that the prevalence of interview-based depression in the dialysis population was 22.8% [25]. For patients with non-dialysis-dependent CKD, a study by Tsai et al. demonstrated that self-reported depressive symptoms are found in 37% patients [26]. It should be noted that self-report scales may overestimate the presence of depression [25].

13.3.2 Impact on Quality of Life and Outcome

The high burden of depressive symptoms in CKD can lead to significant impairment of a patient's quality of life. In a multicenter cross-sectional study involving 194 dialysis patients, depressive symptoms were strongly associated with the Kidney Disease Quality of Life Short-Form, a measure of health-related quality of life [27]. The link between depression and impaired quality of life among patients with renal dysfunction has also been confirmed in several other studies [28, 29].

There is a lack of significant evidence of an association between depression and mortality in CKD patients in previous studies. For example, in the study by Kimmel et al., the authors found that depression (as assessed by the Beck Depression Inventory) was not a predictor of mortality in 295 dialysis patients [30]. Similar results were also noted by Devins et al. [31]. However, these studies are limited by their relatively small sample size. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), self-reported depression was associated with an increased risk of mortality and hospitalization in over 5000 patients on hemodialysis [32].

13.3.3 Risk Factors

Various factors could contribute to depressive symptoms in the context of CKD. The possible pathophysiological factors include chronic inflammation, oxidative stress, and activation of the hypothalamus-pituitary-adrenal (HPA) axis. Psychological factors could also play a critical role in inducing depression in the CKD population. The anxiety induced by suffering from a chronic disease, lifestyle disruption caused by hemodialysis or peritoneal dialysis, disease-related financial challenges, and impatience of being on a transplantation waiting list are considered to be contributing factors of depression in CKD [33].

13.3.4 Diagnosis

Major depressive episodes are defined as the presence of five or more of the following symptoms

during the same 2-week period that represent a change from previous functioning (either depressed mood or loss of interest or pleasure is essential): (1) depressed mood; (2) markedly diminished interest or pleasure in (almost) all activities; (3) significant weight loss when not dieting, weight gain, or decrease or increase in appetite; (4) insomnia or hypersomnia; (5) psychomotor agitation or retardation; (6) fatigue or loss of energy; (7) feelings of worthlessness or excessive or inappropriate guilt; (8) diminished ability to think or concentrate, or indecisiveness; and (9) recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt.

While a psychologist should make the formal diagnosis of depression, screening could be performed by a nephrologist or trained staff using a variety of tools as part of routine clinical practice or in the dialysis unit. A summary of the most widely used assessment tools is presented in Table 13.2.

Table 13.2 Instruments for the screening of depression

Tests	Number of items	Notes
Beck Depression Inventory	21	Three versions available: BDI-I, BDI-IA, BDI-II
Patient Health Questionnaire-9	9	
Patient Health Questionnaire-2	2	PHQ-2 serves as a "first-step" approach in screening for depression. It consists of the first two items of the PHQ-9
Hamilton Rating Scale for Depression	17	The original HRSD consisted of 17 items. Other versions include more (up to 29)
Zung Self-Rating Depression Scale	30	
Geriatric Depression Scale	30	For use in the elderly
Major Depression Inventory	10	Can be used to generate a diagnosis
Center for Epidemiologic Studies Depression Scale	20	A modified version for use in children is available

13.3.5 Management

It is of critical importance to initiate intervention for those with depression as early as possible since depression is usually a recurrent disorder and complete remission is associated with a lower risk of relapse. Psychotherapy and pharmacotherapy are both essential for the management of depression.

The most widely used type of psychotherapy for depression is cognitive behavioral therapy (CBT). This evidence-based therapy is generally short-term and aims to teach people to understand the thoughts and feelings that influence their behavior, thereby allowing them to alter their disturbing thoughts. Some previous studies have suggested that CBT is helpful for alleviating depressive symptoms in both CKD and ESRD patients, though these studies were limited in sample size.

Very few studies have assessed the effectiveness of pharmacotherapy for depression in the CKD population. From the pharmacokinetic point of view, the classical antidepressants fluoxetine and sertraline do not need dosage adjustment in patients with reduced eGFR. However, caution should be taken with transplant recipients since fluoxetine and sertraline may increase the serum level of calcineurin inhibitors.

More data regarding the efficacy and safety of antidepressants are needed, especially from randomized clinical trials. However, even with limited available evidence, intervention, either psychotherapy or pharmacotherapy, should be implemented as soon as possible once depression is diagnosed. Cooperation between nephrologists and psychologists is encouraged.

13.4 Sleep Disorder

13.4.1 Prevalence

Sleep disorder refers to a group of conditions that affect the normal sleep pattern. There are multiple types of sleep disorder, including insomnia, sleep apnea, restless legs syndrome, periodic leg movement, excessive daytime sleepiness, and

nightmares, among others. While some types of sleep disorder can be occasional and have a minor impact on an individual's overall emotional state and health, others can be persistent and significantly affect physical, social, emotional, and mental functioning.

Sleep disorders are becoming increasingly prevalent in the general population and the CKD population. Among 883 patients on maintenance dialysis, the prevalence of insomnia, restless legs syndrome, obstructive sleep apnea syndrome, and excessive daytime sleepiness was 69.1%, 18.4%, 23.6%, and 11.8%, respectively. Eighty percent of the patients had at least one type of sleep disorder [34]. In a study involving 52 patients with early-stage CKD, the author found that sleep disorders were present in 80.7% of the patients [35].

Despite the high prevalence of sleep disorders in patients with CKD, there is evidence suggesting that these disorders are largely underrecognized by healthcare providers [36].

13.4.2 Pathophysiology

The exact pathophysiological mechanism underlying sleep disorders in the context of CKD is unknown. Given the systemic nature of CKD and the varied manifestation of sleep disorder, multiple contributing factors may be involved. The possible factors contributing to sleep disorders in CKD are:

- Anemia
- Presence of uremic toxins
- Volume overload
- Iron deficiency
- Chronic inflammation
- Depression
- CKD-related chronic pain
- Stress and anxiety

13.4.3 Diagnosis

Patients with sleep disorder usually present with typical symptoms. A detailed sleep history and a sleep diary are generally sufficient for screening. Sometimes physicians may use questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI), to evaluate sleep quality and sleep pattern. However, the value of these questionnaires is limited since they are subjective. Objective validated measures are available in some sleep laboratories. Polysomnography is used to record the biophysiological changes (e.g., brain activity, eye movement, muscle activity, and heart rate) during sleep. The Multiple Sleep Latency Test (MSLT) measures the time elapsed from the start of a daytime nap period to the first signs of sleep (sleep latency) and is especially useful for the diagnosis of narcolepsy (excessive daytime sleepiness).

13.4.4 Management

Determination of the exact type of sleep disorder is the first step toward treatment. Exploring the possible underlying cause of a sleep disorder is of critical importance. For example, depression is a common cause of sleep disorder in CKD patients, especially in those on maintenance dialysis. In this situation, treating depression should be the key component of the management strategy.

Sleep apnea: When symptoms (fragmented sleep or daytime sleepiness) are present, or the apnea-hypopnea index exceeds 30, sleep apnea should be treated. Treatment options include weight loss, avoidance of the supine position during sleep, and the use of a dental appliance, continuous positive airway pressure, or surgical correction of the upper airway.

Insomnia: cognitive behavioral therapy and medication therapy can be considered.

Excessive daytime sleepiness: If the underlying cause cannot be determined and the symptoms are severe enough to affect the patient's daily activities, stimulant medications (e.g., modafinil or methylphenidate) may be considered.

Key Messages

- Brain injury is a remarkable aspect of the systemic nature of CKD. In the context of renal dysfunction, a variety of nervous system disorders, including cerebrovascular diseases, cognitive impairment, depression, and sleep disorder, have a higher prevalence than in the general population.
- Kidney disease has been shown to be an independent risk factor for cognitive impairment and dementia.
- In patients with end-stage renal disease (ESRD) receiving renal replacement therapy, the estimated prevalence of cognitive impairment ranges from 30 to 87%. Despite an increased prevalence, this condition is often poorly recognized by physicians and patients.
- Cardiovascular risk factors and diseases that emerge as renal function declines have been considered the predominant contributing factor to impaired cognition in CKD patients.
- Depression is not uncommon in the CKD population. The high burden of depressive symptoms in CKD patients leads to significant impairment of a patient's quality of life.
- Sleep disorders are becoming increasingly prevalent in the general population and in the CKD population. Despite the high prevalence of sleep disorders in patients with CKD, there is evidence suggesting that these disorders are largely under-recognized by healthcare providers.

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Part III

Management of Chronic Kidney Disease

14 Nutritional Management of Chronic Kidney Disease

Li Fang

Abstract

Since chronic kidney disease (CKD) may lead to a unique constellation of nutritional and metabolic abnormalities, a suboptimal nutritional status among the population with CKD is common, and this poses a direct risk for protein-energy wasting, disease progression, and increased mortality. Therefore, given the high incidence and prevalence of CKD and the urgent need for alternative disease management strategies, the patient-centered and cost-effective nutritional management with disease-specific dietary ranges may be a cornerstone required not only to simply adjust suboptimal nutritional status but also to help manage uremia and other complications. Moreover, it may help increase longevity and prolong the dialysis-free interval for millions of people worldwide. Nutritional interventions may be increasingly chosen as an effective management strategy for CKD.

14.1 Introduction

With an occurrence rate of approximately 10–15%, chronic kidney disease (CKD) has become a major noncommunicable disease with increasing epidemic proportion worldwide. Moreover, the increasing incidence of diabetes suggests that the frequency of CKD will continue to grow in the near future. With a gradual loss in kidney function, CKD might lead to a unique constellation of nutritional and metabolic abnormalities. Altered protein and energy homeostasis, abnormal protein catabolism, acid–base derangements, bowel flora alteration, and hormonal dysfunction usually ensue. Hence, a suboptimal nutritional status among the population with CKD is common, and this poses a direct risk for protein-energy wasting (PEW), disease progression, and increased mortality [1–3]. Therefore, nutritional intervention is a cornerstone required not only to simply adjust suboptimal nutritional status but also to help manage uremia and other complications such as electrolyte and acid–base imbalances, water and salt retention, mineral and bone disorders, and failure to thrive [1, 2, 4]. In this chapter, we mainly focus on nutritional interventions as an important management strategy for CKD.

14.2 Nutritional Assessment

As renal failure advances in patients with CKD, nitrogen-containing products accumulated from dietary and intrinsic protein catabolism might distort taste and blunt appetite. Additionally, since uremia status might affect the gut microbiome and disrupt the intestinal barrier function,

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gastrointestinal nutrient absorption may also become abnormal. Hence, poor nutritional status, defined as PEW and manifested as decreased body storage of protein and energy fuels, is common in patients with renal insufficiency.

Although a consensus on the importance of identifying and treating malnutrition in patients with CKD existed for decades until now, a well-established assessment system to accurately reflect the nutritional status remains unclear and not well-used in the clinical setting [1–3]. Several biochemicals, clinical, anthropometric, and nutritional parameters are associated with and frequently indicative of PEW in patients with CKD. However, the National Kidney Foundation K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure recommends that nutritional status should not be evaluated with only a single parameter alone but instead using a combination of valid and complementary parameters. According to an expert panel directed by the International Society of Renal Nutrition and Metabolism, the current procedure for the diagnosis of PEW recommends the analysis of serum chemistry (s-albumin, s-prealbumin, and s-cholesterol), body mass (body mass index, body weight variation, and percent of body fat), signs of muscle wasting over time (reduced mid-arm muscle circumference and creatinine appearance), as well as unintentional low dietary intake for at least 2 months [5–8]. Overall, the data for nutritional evaluation could be classified into four categories four categories—biochemical, anthropometric, clinical, and dietary—discussed in detail as follows:

14.2.1 Biomarkers of Nutritional Status

14.2.1.1 Serum Albumin

Serum albumin is an important nutrient manufactured by the liver that helps support muscle growth, repair damaged tissue, and defense against pathogen infection. Its concentration is influenced by many factors, such as rates of synthesis and breakdown, volume of distribution, exchange between intra- and extravascular spaces, as well as losses and wasting from the body. In patients with CKD, hypoalbuminemia can be the result of factors such as fluid overload, proteinuria, and losses to the dialysate. Counter-regulatory mechanisms may also influence the serum albumin concentration. In the short term, protein deficiency might reduce the hepatic albumin-synthesizing activity; however, in the long term, compensation might occur through a decreased albumin breakdown and a shift of albumin from the extravascular to the intravascular space. Furthermore, because albumin has an extraordinarily long circulatory half-life of about 20 days and is present in large quantities, the impact of reduced dietary protein intake on serum albumin levels is limited. Hence, even in extreme cases of malnutrition, such as marasmus and anorexia nervosa, serum albumin concentrations could remain normal or only slightly reduced. Numerous studies have shown that serum albumin levels in CKD patients and dialysis patients are usually low. However, it is important to consider that patients with CKD commonly have comorbid conditions, such as insufficient food intake, fluid overload, and chronic inflammation, all of which are known to affect serum albumin levels. Hypoalbuminemia in patients with CKD seems to be associated with a chronic inflammation rather than with malnutrition. Despite the wide use of albumin as a nutritional status biomarker in CKD in many researches, serum albumin levels might actually be a marker of disease severity rather than nutrition and may be a poor parameter of nutritional status in patients with CKD [9, 10].

14.2.1.2 Prealbumin

Prealbumin, which is also primarily synthesized by the liver, is a 55-kD homotetrameric protein in blood that plays a role in carrying thyroxine and retinol throughout the body. Prealbumin has a half-life in plasma of ~2 days, much shorter than that of albumin. It is catabolized partly in the kidneys, and consequently any renal dysfunction causes an increase in its serum levels. Generally, prealbumin correlates with the level of nutrition support, increasing with sufficient dietary intake and decreasing when dietary intake is declining.

In patients with CKD, the levels of prealbumin show a linear relationship to the degree of protein-energy malnutrition in patients with CKD, which are restored by refeeding. However, as with serum albumin, prealbumin decline sensitively in response not only to inadequate protein intake but also to acute or chronic inflammation (i.e., "acute-phase reactant"), limiting its specificity as a marker of nutritional status. Therefore, although prealbumin is more sensitive in assessing changes of nutritional status than serum albumin, however, since it could be influenced by many non-nutritional factors, serum prealbumin is not considered to be a valid indicator of nutritional status in patients with CKD.

14.2.1.3 Creatinine Height Index

Creatinine is a waste product that comes from continuous creatine phosphate breakdown in muscle. Since almost all creatinine is filtered from the blood into the urine by kidneys, serum creatinine level is usually a good indicator of kidney functions. Under normal renal function, creatinine is typically produced by the body at a relatively constant rate at a level proportional to total muscle mass. Urinary creatinine excretion rate is generally related to muscle mass [11]. Normalized for height, the measurement of 24-h creatinine excretion is an indicator of muscle mass, particularly in young males. However, it is dependent on complete 24-h urine collections and urinary excretion; low excretions of urinary creatinine may result in an inappropriate diagnosis of malnutrition. Therefore, the creatinine height index might be an inaccurate indicator of malnutrition in patients with CKD.

14.2.1.4 C-Reactive Protein (CRP)

C-reactive protein is an inflammation marker and not a direct nutritional marker. However, it also plays an important role in the overall assessment of nutritional status in patients with CKD because it is an acute-phase reactant that is inversely correlated with the concentrations of visceral proteins. In clinical practice, one should remember that very low levels of visceral proteins, for instance, serum albumin, are often due to the presence of inflammation rather than the low protein intake or protein depletion [9]. Thus, both in the clinical and research settings, it is recommended to check CRP levels in conjunction with other nutritional markers and when deciding possible nutritional intervention as well as interventions against factors causing increased CRP levels.

14.2.1.5 Cholesterol

Cholesterol is a lipoprotein that functions as a precursor for the synthesis of steroid hormones, bile acids, and vitamin D. Serum cholesterol and several other blood lipids and lipoproteins such as total cholesterol, triglycerides, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and non-HDL cholesterol are indicators of patients' nutritional status. Indeed, s-cholesterol has been proposed as an assessment criterion for malnutrition and PEW. Contrary to the general population, a high s-cholesterol level in the CKD and dialysis population is associated with improved survival [1, 2]. However, this association seems to only be true in patients with inflammation and/or malnourishment, which suggest that low levels of s-cholesterol may be a surrogate marker of inflammation and/or malnutrition.

14.2.2 Clinical and Anthropometric Markers of Nutritional Status

14.2.2.1 Subjective Global Assessment (SGA)

Subjective Global Assessment (SGA) is a simple and reliable nutritional assessment tool. It is composed of five components of a medical history (recent dietary intake, gastrointestinal symptoms, weight change, functional capacity, disease, and its relationship to nutritional requirements) and three components of a physical examination (signs of fat and muscle wasting, nutrition-associated alternations in fluid balance) to predict nutrition-associated complications. Since SGA evaluations could effectively demonstrate the changes of nutritional status occurring throughout the course of the disease, it was found to be highly predictive of malnutrition and outcome in those who are nutritionally compromised

in any stage of CKD or in danger of becoming malnourished [12]. Using the SGA, many studies reported that patients with CKD, whether or not on dialysis, met only 50–70% of their energy needs and only about 50% of their protein needs. The SGA has been used as a surrogate for PEW in many studies [13–15]. The Academy recommends that SGA be performed in patients with CKD at the initial visit and quarterly to determine the patients' nutrition status. These numbers and SGA scores improve if the dietitians followed their patients monthly.

Although SGA has recently been recommended by the National Kidney Foundation (NKF) Kidney Disease/Dialysis Outcomes and Quality Initiative (K/DOQI) for assessing the nutritional status in the adult dialysis population, it is a subjective score that may be biased by inter- and intrapersonal differences. Therefore, a longitudinal research study conducted by the well-trained investigator following patients over time might be necessary.

14.2.2.2 Malnutrition Inflammation Score (MIS)

Stemming from the original SGA, a new comprehensive nutritional assessment tool called the MIS which involves seven components from the SGA questionnaire (weight change, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat, and signs of muscle wasting) and the three additional biochemical parameters influenced by inflammation status (body mass index, serum albumin, and total iron-binding capacity (TIBC)) was proposed by Kalantar-Zadeh et al. [16]. In total, MIS system comprises ten parameters, each including four degrees of severity (where 0 = normal and 3 = severely abnormal) and summing each component to produce a final score (0 = normal nutritional status and 30 = severely malnourished). Numerous studies have demonstrated that higher MIS scores were associated with worse nutritional status, poorer health-related quality of life, as well as higher hospitalization and mortality rates in maintenance hemodialysis patients [17].

14.2.2.3 Other Nutritional Scoring Systems

In addition to the SGA and MIS, alternative scoring systems have also been developed to assess nutritional status. Among those, Mini Nutritional Assessment (MNA) has been originally developed as nutritional assessment tools for the geriatric population [18]. It is made up of a screening section (six questions), known as Mini Nutritional Assessment-Short Form (MNA-SF), which can be further complemented by 11 questions in order to gain a malnutrition indicator score scale (full-MNA form). In addition, these tools have also been used in CKD and dialysis patients; however, the usefulness of the MNA-SF remains questionable.

14.2.2.4 Body Mass Index (BMI)

Body mass index (BMI), which is calculated as body weight in kilograms divided by the square of height in meters, is an indicator of body fat. According to the World Health Organization (WHO) guidelines, the healthy range for BMI is between 18.5 and 24.9 kg/m^2 for adults. Obesity is defined as a BMI $\geq$30.0 kg/m^2, overweight as a BMI of $\geq$25.0 kg/m^2, and underweight as a BMI <18.5 kg/m^2. In patients with CKD, the BMI may not reflect the real nutritional status, as a gross imbalance in fluid status in these patients may cloud the results. Furthermore, loss of muscle mass is characteristic of PEW; however, a relatively well-preserved fat mass usually remains, resulting in small changes in BMI that can be disguised by imbalances in fluid homeostasis. Finally, overweight patients with end-stage renal disease (ESRD) may also suffer from PEW. For these reasons, BMI alone does not accurately reflect the nutritional or PEW status in patients with CKD.

14.2.2.5 Hand Grip Strength (HGS)

Muscle strength in patients with CKD is often evaluated by muscle dynamometry such as hand grip strength (HGS) [19], which associates with lean body mass as assessed by anthropometry, dual-energy X-ray absorptiometry (DEXA, see below), and creatinine kinetics and with nutritional

status as assessed by SGA score. In addition, the combined assessment of body composition (lean body mass) and muscle function has become more prevalent as a composite marker of nutritional status. Indeed, a dynamometric HGS measurement standardized to age and gender has emerged as an easily performed bedside test that is considered to be a reliable and available marker of both nutritional status and future mortality risk.

14.2.3 Dietary Intake Information

There are many methods to estimate dietary intake; however, the accuracy of document is frequently fluctuating. In general, during a nutrition interview, the clinical dietitian may ask what the individual ate during the previous 24 h, beginning with the last item eaten prior to the interview. Alternatively, practitioners can also train individuals on completing a food record typically obtained for 3–7 days. The documentation should include portion sizes and how the food was prepared. However, documenting portion sizes is usually difficult, and requesting that every food be measured or weighed is usually very difficult to implement and time-consuming. Therefore, nutrition interviews are not commonly used in practice.

14.2.4 Other Methods to Assess Nutritional Status

14.2.4.1 Bioelectrical Impedance and Conductance

Bioelectrical impedance analysis (BIA) has been proposed as a noninvasive and simple technique to measure body hydration status of patients, especially with regard to the determination of "dry" body weight in hemodialysis patients [20, 21]. BIA has also been suggested as a valuable tool in subjects undergoing peritoneal dialysis. BIA assumes that the human body may be viewed as a number of parallel connected resistors. By connecting electrodes to various body parts (typically the arms and legs) with a conductive gel, an electric current passes through the body at various frequencies and the conductance is measured. The current standard BIA models used in CKD view the body as five interconnecting cylinders: two each for the arms and legs and one for the trunk, instead of the more common previous assumption that the whole body can be visualized as a single cylinder. BIA models are prone to errors of simplification which depend on body size, shape, and regional fluid accumulation.

14.2.4.2 Dual-Energy X-Ray Absorptiometry

Dual energy X-ray absorptiometry (DEXA), which was primarily used for assessing bone mineral density, has become another more reliable tool to estimate body composition [20]. When DEXA passes low-energy X-rays through the body, a low-resolution image could be generated to measure fat distribution throughout the body [22]. However, although DEXA could accurately measure fat mass with high-precision, low X-ray exposure, and short scanning time, it is hardly feasible in routine clinical practice due to its high cost and its inaccuracy in severely overhydrated patients. Furthermore, the amount of radiation used during repeated DEXA scans, although small, may be of concern in patients.

14.2.4.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is a noninvasive medical imaging technique measuring nuclear relaxation times from nuclei of atoms with magnetic moments that are aligned within a powerful magnetic field. Magnetic resonance imaging can be used to quantify components at the tissue-system levels of body composition, including skeletal muscle, adipose tissue, visceral organs, and the brain. Clinical systems are based on hydrogen, although it is possible to create images and spectrographs from phosphorus, sodium, and carbon. The collected data are transformed into high-resolution images, which allow the quantification of whole-body or regional-body compositions. However, to our knowledge, no high-quality clinical studies have assessed imaging methods in relation to outcome.

14.3 Nutritional Management

14.3.1 Energy Intake

Designing a diet for the patients with CKD to receive enough calories is of most importance. However, in clinical practice, it is really a challenge to estimate accurate energy requirements in patients with CKD, since the daily energy requirements are influenced by many variable factors, such as resting energy expenditure, thermic effect of meals, physical activity level, and so on. Many previous studies have shown that the energy requirements of patients with CKD were similar to those of normal adults. Therefore, in CKD stages 1–3, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that energy intake levels support a balanced diet and maintain desirable body weight but does not recommend specific energy intake amounts. However, in CKD stages 4 through 5 (GFR <30 mL/min/1.73 m^2), specific energy intake amounts are recommended: 35 kcal/kg/day for those younger than 60 years and 30–35 kcal/kg/day for those older than 60 years. If the patients were overweight and obese, calories should be restricted because calories intake in excess of requirements might cause obesity, and obesity might in turn engender insulin resistance and impaired glucose disposal [1, 2, 4].

14.3.2 Protein Intake

Whether the quantity or quality of ingested protein is a risk factor for chronic kidney disease progression has been debated for nearly a century. Now, there are mounting evidences that the western-type diet, which contains exceeding 1.5 g per kilogram of ideal body weight per day, may cause glomerular hyperfiltration and proinflammatory gene expression, which are known risk factors for CKD progression. Experimental evidence in animal models has also shown that a high-protein diet dilates the glomerular afferent arterioles and increases glomerular filtration, whereas low protein intake constricts the afferent arterioles and lowers intraglomerular pressure. The current evidence has suggested that reducing protein intake could decrease proteinuria as efficiently as angiotensin-converting enzyme inhibitors, mainly because that a low-protein diet has a preglomerular effect that may enhance the postglomerular effect of angiotensin pathway modulators that dilate the efferent arterioles and consequently lower the intraglomerular pressure [1, 2, 4].

Besides, limiting protein intake also results in an instant reduction in urea generation. After protein breakdown, individual amino acids are deaminated by the removal of an α-amino group, leaving a carbon skeleton of ketoacids, which can be recycled to form other amino acids and proteins or can be used for energy generation through the tricarboxylic acid cycle, while urea is generated through the urea cycle. A persistently high blood urea level, termed azotemia, which is a commonly used marker for uremia, may enhance protein carbamylation and generate reactive oxygen species, leading to oxidative stress, inflammation, endothelial dysfunction, and ultimately, cardiovascular disease. Reducing protein intake could effectively decrease the production of wasted products and uremic toxins which in turn diminishes the uremic symptoms. Metabolic consequences of low protein diet have also been extensively researched in recent years: reduced oxidative stress, improved insulin sensitivity, better control of metabolic bone disorders in response to a reduced phosphate load, and improved anemia management.

For healthy persons, the recommended dietary allowance for protein is 0.8 g per kilogram per day, whereas the estimated average requirement for adults with CKD who are otherwise healthy is 0.66 g per kilogram per day. Hence, of the various ranges of low protein intakes, 0.6–0.8 g per kilogram of body weight per day is the most frequently recommended target for adults with moderate-to-advanced kidney disease (estimated GFR <45 mL/min/1.73 m^2) and for the management of substantial proteinuria (urinary protein excretion, >0.3 g per day), especially if half of the protein is of "high biologic value" (e.g., dairy products). However, the so-called very-low-protein diet (<0.6 g of protein per kilogram per

day), supplemented with essential amino acids or their ketoacids, is also used. People at increased risk for kidney disease, such as those who have undergone nephrectomy for kidney donation or for cancer treatment or who have diabetes mellitus, hypertension, or polycystic kidneys, may benefit from a modest protein intake (<1 g per kilogram per day) in order to maintain a moderately low intraglomerular pressure [1, 2, 4, 23, 24].

As mentioned previously, protein-energy wasting (PEW) is commonly seen in patients with chronic kidney disease (CKD); the safety and feasibility of long-term dietary modification are among the main concerns. From a basic point of view, the direct relationship between low protein intake and muscle wasting should be discovered. Unfortunately, this approach is not clinically relevant: muscle wasting in chronic kidney diseases seems to be caused by the imbalance toward a catabolic state (more protein degradation than synthesis) and is further deteriorated by the lack of physical activity. Additionally, metabolic acidosis closely related to inflammation and insulin resistance is also an important reason. Restrained protein intake has been proven to improve all these catabolic conditions. Therefore, the safety of and adherence to a low-protein diet might be improved by providing adequate energy (30–35 kcal per kilogram per day), ongoing nutritional education, and surveillance.

14.3.3 Sodium Intake

Patients with hypertension and CKD are usually salt-sensitive. The available evidence, detected as an increase in blood pressure of more than 10% when a low salt diet is switched to a high salt intake, demonstrated that a high-sodium diet (>4 g of sodium per day) in CKD has an influence on hypertension, cardiovascular risk factors, and outcomes. In patients with established CKD, dietary sodium restriction is invariably recommended to control fluid retention and hypertension and to improve the cardiovascular risk profile. However, the association between salt intake and renal outcome in subjects with preserved kidney function remains less well investigated and confounding. Several studies have demonstrated that a reduced sodium intake could enhance the effects of a low-protein diet and angiotensin-modulation therapy in decreasing intraglomerular pressure and might also decrease proteinuria and slow the progression of kidney disease. However, some other studies reported that strict sodium restriction might also activate the renin-angiotensin-aldosterone system, sympathetic nervous system, and insulin resistance.

As ingested sodium is primarily excreted via the kidneys, a 24-h urinary sodium excretion is a good indicator of sodium intake. Observational studies using urinary sodium excretion as a surrogate for sodium chloride intake have yielded inconsistent data, with some studies showing no association between dietary sodium intake and renal disease progression and others showing a positive association. A longitudinal study published in 2016, which involved serial 24-h urine collections from 3939 patients with CKD, suggested that the highest quartile of urinary sodium excretion (≥4.5 g per day), as compared with the lowest quartile (<2.7 g per day), was associated with a 45% higher mortality and a 54% higher risk of disease progression. Incrementally worse cardiovascular outcomes were observed when dietary sodium intake exceeded 4 g per day. Observations in the general population suggest a J-shaped association; dietary sodium intake that is higher than 5 g per day and intake that is lower than 3 g per day are each associated with an increased risk of cardiovascular disease and death. Although a daily dietary allowance of less than 2.3 g of sodium (<100 mmol) is often recommended for patients with cardiovascular disease, there is no evidence that patients with kidney disease will benefit from this sodium restriction. Therefore, a daily dietary sodium intake of less than 4 g (<174 mmol) is recommended for the overall management of CKD and its associated risks, with a sodium intake of less than 3 g (<131 mmol) for the specific management of symptomatic fluid retention or proteinuria. Evidence supporting a sodium intake of less than 1.5 g per day (<87 mmol per day) for patients with renal insufficiency is lacking, given the risk

of hyponatremia and adverse outcomes. Once sodium excretion is excessive and blood pressure elevates, the nutrition consultation and repeating 24-h urine measurements of sodium are recommend to make dietary planning more easily [1, 2, 4, 23–25].

Whereas adequate fluid intake may mitigate the risk of kidney disease, patients with renal insufficiency generally have isosthenuria. This is the basis for the recommendation that patients with stage 3 CKD limit fluid intake to less than 1.5 L per day in order to avoid hyponatremia; adjustment of that limit for a hot climate and other conditions associated with high insensible fluid losses is imperative. Adjunctive therapy with loop diuretics is often prescribed, particularly for patients who tend to have symptomatic fluid retention or hyponatremia, given the association of such conditions with poor outcomes in CKD. It should also be noted that diuretics alone might fail because an unrestricted salt intake will overcome the effectiveness of diuretic.

14.3.4 Potassium Intake

Substantial evidence has supported that potassium-rich foods could reduce the possibility of developing chronic diseases, such as hypertension, diabetes, and coronary heart disease. Thus, given the well-established association of higher dietary potassium with lower sodium intake and lower incidences of hypertension, stroke, and kidney disease, a relatively high daily intake of potassium of 4.7 g (120 mmol) was recommended in the general population by guidelines from the Institute of Medicine. However, the causal relationship between dietary potassium and hypertension in patients with CKD was less studied in the previous researches.

Accompanied by renal insufficiency, the kidneys' ability to excrete excess potassium might be impaired. Besides, the impairment in the action of protective hormones (e.g., aldosterone) or use of ACEIs, ARBs, or nonsteroidal anti-inflammatory drugs may also result in the impaired potassium excretion. Therefore, a careful search for other causes of hyperkalemia should be undertaken before restricting dietary potassium. Particularly, drugs that reduce potassium excretion should be eliminated, acidosis should be corrected, and constipation should be relieved. Undoubtedly, more studies are further needed to investigate the advantage and dangers of increasing (or limiting) dietary potassium in patients with CKD.

A higher dietary potassium intake may be associated with a higher risk of kidney disease progression. Among patients with very advanced CKD, the highest quartile of dietary potassium intake, as compared with the lowest quartile, is associated with an increase in the risk of death by a factor of 2.4; the association is independent of the plasma potassium level and other nutritional measures. Therefore, the National Kidney Foundation's expert panel recommended potassium restriction for individuals with advanced CKD (e.g., stage 4 CKD and an estimated GFR <30 mL/min/1.73 m^2). In other epidemiologic studies, both moderately low (<4.0 mmol per liter) and high plasma potassium levels (>5.5 mmol per liter) are associated with more rapid kidney disease progression. Dietary potassium restriction is often recommended in patients with hyperkalemia, especially those with more advanced stages of kidney disease. However, excessive dietary restrictions can expose patients to less heart-healthy and more atherogenic diets and worsen constipation, which may actually result in higher gut potassium absorption. Despite the higher risk of hyperkalemia with the progression of kidney disease, few studies have examined the effects of dietary potassium restriction or methods of extracting potassium during food preparation and cooking. It is not clear whether potassium-binding agents can allow the liberalization of dietary potassium intake with the inclusion of healthier potassium-rich foods. In patients with a tendency toward hyperkalemia (>5.5 mmol of potassium per liter), a dietary potassium intake of less than 3 g per day (<77 mmol per day) is recommended, with the stipulation that the balanced intake of fresh fruits and vegetables with high fiber should not be compromised [1, 2, 4, 23, 24, 26, 27].

14.3.5 Phosphorus Intake

Numerous studies have determined positive phosphate balance and hyperphosphatemia to be the risk factors for vascular calcification, cardiovascular mortality, and left ventricular hypertrophym in chronic kidney disease. Daily dietary phosphorus intake is approximately 1000–1200 mg, of which approximately 950 mg is absorbed. Phosphorus could be removed by two systems, the gastrointestinal tract (150 mg/day) and the urine (800 mg/day). However, as kidney function declines, renal phosphorus excretion might be progressively impaired. Decreased glomerular filtration of phosphorus is initially compensated by decreased tubular reabsorption regulated by parathyroid hormone and fibroblast growth factor 23 (FGF-23). Elevated parathyroid hormone and FGF-23 levels can cause renal bone disease, left ventricular hypertrophy, vascular calcification, and accelerated progression of kidney disease from vascular and tubulointerstitial injury, highlighting the importance of dietary phosphorus management, even in patients without apparent hyperphosphatemia. There is a close relationship between protein and phosphorus intake: 1 g protein brings 13–15 mg phosphate, of which 30–70% is absorbed through the intestinal lumen. High-protein diet may aggravate uremic symptoms and hyperphosphatemia; however, although a low-protein diet also decreases phosphorus intake, the quantity and bioavailability of phosphorus differ according to the type of protein. For example, the phosphorus-to-protein ratios of egg whites and egg yolks (which have 3.6 and 2.7 g of protein per egg, respectively) are 1–2 mg per gram and 20–30 mg per gram, respectively. The gastrointestinal absorption of phosphorus, mostly in the form of phytates, is lower from plants (along with fibers) than that from meat (30–50% vs. 50–70%). Since food additives include readily absorbable inorganic phosphorus, ingestion of processed foods results in an even higher phosphorus burden. Restricting dietary phosphorus intake to less than 800 mg per day (26 mmol per day) is recommended for patients with moderate-to-advanced kidney disease, and the consumption of processed foods with a high phosphorus-to-protein ratio should be minimized. However, in patients with stage 5 CKD who receive dialysis therapy or who are at increased risk for PEW, excessively stringent restriction of protein intake to control hyperphosphatemia may be associated with poor outcomes. Thus, an individualized dietary approach that incorporates ample use of phosphorus binders is optimal [1, 2, 4, 23, 24, 28].

14.3.6 Calcium and Vitamin D

Vitamin D insufficiency and deficiency is widely prevalent in the patients with CKD, which is further exacerbated by the reduced ability to convert 25-(OH) vitamin D into the active form, 1,25 dihydroxy-vitamin D. The associated decline in 1,25-dihydroxy vitamin D may further diminish gastrointestinal absorption of calcium; however, passive diffusion of ionized calcium continues and may lead to a positive calcium balance, which is aggravated by diminished urinary calcium excretion due to secondary hyperparathyroidism. Increased calcium release from bone in hyperactive renal bone disease (increased bone resorption because of secondary hyperparathyroidism) enhances the positive calcium balance and may worsen vascular calcification. Gut calcium absorption varies because of differences in dissociation and bioavailability from one type of elemental calcium to another; for instance, calcium citrate is more readily absorbable than calcium acetate. Two studies suggested that an intake of 800–1000 mg of elemental calcium per day (20–25 mmol per day) can result in a stable calcium balance in people with stage 3 or 4 CKD. Hence, whereas the suggested calcium intake for persons without kidney disease is 1000–1300 mg per day (25–32 mmol per day), 800–1000 mg of elemental calcium from all sources per day should suffice in patients with moderate-to-advanced CKD [1, 2, 4, 23].

Native vitamin D supplementation (cholecalciferol or ergocalciferol) may be offered to patients with CKD and low levels of circulating vitamin D. In some studies, vitamin D analogs have been associated with decreased proteinuria

in addition to the healing of renal osteodystrophy. Notwithstanding inconsistent data on the requirement for and the effect of vitamin D in certain subpopulations of patients with CKD, including black Americans, who have lower total vitamin D levels and higher parathyroid hormone levels than those in white Americans, hydroxylated vitamin D agents may be needed in addition to native vitamin D to control progressive secondary hyperparathyroidism.

14.3.7 Vegetarian Diet, Fiber, and the Microbiome

Plant-based diets, despite containing low amounts of protein, are also rich in potassium and phosphorus, and therefore vegetarianism is believed to be unsuitable for CKD patients. However, numerous clinical studies have recently demonstrated that such a plant-based diet could be beneficial for the patients when they learn how to use it wisely. Plant-based foods are recommended as part of many strategies for the prevention and management of kidney disease because these foods contain smaller amounts of saturated fatty acids, protein, and absorbable phosphorus than meat; they also generate less acid and are rich in fibers, polyunsaturated and monounsaturated fatty acids, magnesium, potassium, and iron. Besides, according to several studies, a plant-based diet was found to delay the progression of CKD, help to control high blood pressure, and decrease proteinuria, while others indicated that high plant protein intake is likely to accelerate CKD progression when compared to animal proteins. Therefore, the National Kidney Foundation recommends vegetarianism, or part-time vegetarian diet as being beneficial to CKD patients.

Besides, constipation can lead to higher retention of uremic toxins and hyperkalemia, whereas loosening stools may enhance fluid loss and removal of nitrogenous products. The protein in a vegetarian diet is less fermentable, and has high fiber content, increasing peristalsis, and the number of bowel movements, and is associated with less uremic toxin production, exposure, and absorption.

Uremia itself, as well as dietary restrictions and pharmacotherapy, including antibiotics, may alter the gut microbiome; this change may affect the symptoms and progression of kidney disease. Gut dysbiosis, which is manifested by qualitative and quantitative changes in host microbiome profile and disruption of gut barrier function, was commonly seen in patients with CKD. Endotoxin derived from gut bacteria can incite a powerful chronic inflammation in the host organism. Furthermore, disruption of gut barrier function in CKD may allow translocation of endotoxin and bacterial metabolites to the systemic circulation, which contributes to uremic toxicity, inflammation, progression of CKD, and associated cardiovascular disease. Therefore, targeted microbiome modulation through nutritional interventions, such as consumption of probiotics, may help to control the production, degradation, and absorption of certain uremic toxins that are fermentation by-products of gut microbial activities, including indoxyl sulfate, *p*-cresol, and trimethylamine [1, 2, 4, 23, 29]. For example, in a study involving 40 patients with moderate-to-advanced CKD, a lower ratio of dietary fiber to protein was associated with higher blood levels of indoxyl sulfate and *p*-cresol. Nutritional and pharmacologic interventions, including the use of absorbent ingestible agents and high-fiber or vegetarian diets, are being tested as a means of reducing gut absorption of uremic toxins to control uremic symptoms and slow disease progression.

14.3.8 Carbohydrate and Fat Intake

National dietary recommendations have promoted high-carbohydrate, low-fat diets to reduce cardiovascular disease risk. These recommendations were based on observational studies in which low fat intake was associated with a low risk for cardiovascular disease, presumably by lowering LDL cholesterol levels. Unrefined carbohydrates account for half the usual daily energy intake, and the proportion may be even higher in a low-protein diet. In patients with kidney disease, carbohydrates should be complexed with high fiber content (e.g., whole-wheat breads,

multigrain cereal, oatmeal, and mixed fruits and vegetables) to help reduce dietary phosphorus and protein as well as urea and creatinine generation. Such a diet may promote a more favorable microbiome with less constipation.

Reducing fat as part of a low-calorie diet is a practical way to reduce energy intake. However, clinical trials of diet therapy to reduce lipids and slow progression of CKD have not been conducted. Dietary fat recommendations for obese patients with CKD should be in accordance with the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII) guidelines (2001) developed for cardiovascular risk reduction. In CKD stages 1 through 4, the KDOQI recommends that 25–35% of the total energy intake comes from fat, with 10% of the total from saturated fat. The recommended cholesterol intake is 200 mg/day. The objective of these guidelines is to control blood lipid levels, minimizing elevated blood glucose and triglyceride levels. Because diets for patients with CKD are sometimes mildly restricted in protein, it may be difficult to provide sufficient energy without resorting to a large intake of high-glycemic index carbohydrates that may increase triglyceride production. Another challenge when addressing fat intake is maintaining recommended macronutrient balances when lowering saturated fat in the diet. When saturated fat is reduced in the diet, it can be replaced with unsaturated fat, protein, or carbohydrates. The optimal means of replacement of saturated fats is not known. Data from dietary intervention trials suggest that a diet low in saturated fat that uses either protein or unsaturated fats to replace carbohydrates can have favorable effects on lipids. Unsaturated fat is the preferred lipid in the diet. Replacement of butter with flaxseed, canola, or olive oil, all of which are rich in unsaturated fatty acids, may be worthwhile. For example, a recent study suggested that dietary unsaturated fatty acid supplementation in patients with diabetes and hypertriglyceridemia may reduce albuminuria and preserve renal function. There is currently no evidence that low-fat diets, recommended by some guidelines, improve kidney disease outcomes. In a low-protein diet, fat and carbohydrates should together account for more than 90% of the daily energy intake requirement of 30–35 kcal per kilogram to avoid PEW. Obviously, in patients with diabetic kidney disease, proper glycemic control should be maintained, but adequate energy intake is needed to mitigate the risk of PEW and hypoglycemia, which increases with worsening kidney function [1, 2, 4, 23].

14.3.9 Dietary Management of Acidosis in Chronic Kidney Disease

Daily acid production results from bicarbonate losses in the gut (20–30 mmol of bicarbonate per day), breakdown of amino and nucleic acids from proteins (20–30 mmol per day), and oxidation of carbohydrates and fats to lactic acid and ketoacids (10–20 mmol per day). The kidney plays an important role in regulating of the acid–base balance. The kidneys regenerate the bicarbonate used for buffering by the excretion of both net acid and acid buffers, including phosphate, and by ammoniagenesis through the deamination of glutamine in the proximal tubule and its synthetization to ammonium in the collecting ducts, with subsequent urinary excretion. Hence, chronic kidney disease and reduced glomerular filtration rate may contribute to the development of chronic metabolic acidosis. Kidney disorders, including renal tubular defects, are often associated with chronic metabolic acidosis. Metabolic acidosis is a relatively common complication in patients with renal failure, particularly in those with GFR falls below 30 mL/min/1.73 m^2. Also, a large amount of evidence identifies acidosis not only as a consequence of, but as a contributor to, kidney disease progression.

Diet plays an important role in acid–base balance. The modern high-protein diets may yield about 1 mmol/kg body weight/day of net endogenous H+ production, while the fruits and vegetables may generate base from the metabolism of organic anions such as citrate and malate. The 24-h urinary excretion of ammonium and titratable acid minus bicarbonate could be used as an indicator of total net acid

excretion (NAE). A well-controlled clinical trial in healthy adults consuming various diets has revealed that pH value in 24-h urine was closely related to the total renal NAE. Moreover, the total urinary NAE can be reasonably estimated from dietary intake, intestinal absorption, and the metabolism of most important inorganic anions and cations in urine. On the basis of these factors, the potential renal acid load (PRAL) can be calculated directly from dietary intakes. While protein-rich foods such as meat, fish, and cheese are the food groups with the highest acid loads, fruits, vegetables, salads, and fruit juices have a high alkalizing potential. An increase in the dietary acid load may be associated with glomerular hyperfiltration. Metabolic acidosis is associated with more rapid kidney disease progression and an increase in the overall risk of death. Hyperparathyroidism, along with chronic buffering of acid by bone, leads to progressive loss of bone minerals and worsening renal osteodystrophy. Hence, reduced protein intake with a greater proportion of diet from plant-based foods to correct acidosis improves bone mineralization and may slow protein breakdown and disease progression. Adjunctive alkali therapy can also be considered to mitigate acidosis in patients with CKD [1, 2, 4, 30].

14.3.10 Trace Elements and Vitamins

PEW has the potential to impact not only macronutrient metabolism but also vitamin and trace element status in patients with CKD. Inadequate food intake may result in an insufficient ingestion of antioxidant vitamins, including vitamins C and E and carotenoids; in addition, patients with advanced renal disease often become deficient in folate, vitamin K, and calcitriol. A micronutrient imbalance in patients with kidney disease may contribute to a higher burden of oxidative stress, inflammation, and cardiovascular disease. Among the trace elements, iron deficiency is most problematic given the high frequency of gastrointestinal blood loss in patients with CKD. Deficiencies of zinc, copper, and selenium may occur, whereas aluminum and magnesium levels may increase. A recent study showed that 800 μg of folic acid per day, when added to enalapril, led to slower disease progression than that with enalapril alone. Experimental models of CKD suggest that vitamin K supplementation may blunt the development of vascular calcification. Daily intake of other vitamins and trace elements at conventional doses is often recommended both for persons at high risk for kidney disease and for those with established renal insufficiency [1, 2, 4].

14.3.11 Practice Strategies

Dietary protein, energy, and micronutrient intakes should be assessed regularly. In addition, 24-h urine collection should be performed to estimate the dietary intakes of protein (based on urinary urea nitrogen), sodium, and potassium; to measure creatinine clearance and proteinuria; and to evaluate adherence to dietary recommendations, with suggestions for improving adherence if necessary. Excessive restrictions may be harmful and should be avoided [4].

14.4 Conclusions

Given the high incidence and prevalence of CKD and the urgent need for alternative disease management strategies, patient-centered and cost-effective nutritional interventions with disease-specific dietary ranges help delay progression of CKD, prolong the dialysis-free interval, improve quality of life, and increase longevity for millions of people worldwide. Nutritional management for renal failure is structured to achieve a lower protein, phosphate, and sodium intake, while supplying with enough energy. In general, the purpose of nutritional management is to improve signs, symptoms, and complications of renal insufficiency, delay the progression of disease, and preserve good nutritional status.

Key Messages

- Nutritional status in patients with CKD should not be evaluated with only a single parameter but with the combined use of valid and complementary parameters.
- Nephrologists, nutritionists, and other interested physicians have a common principle of discussing the underlying research and translation of best practices for the nutritional management and prevention of renal disease.
- The purpose of nutritional management for CKD is to maintain good nutritional status, slow progression, and reduce complications.

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Medication in Chronic Kidney Disease

15

Hongdi Cao

Abstract

Chronic kidney disease (CKD) is a common disorder that is associated with multiple comorbidities and complications. The evidence for medications in patients with CKD is still insufficient. Several factors should be considered when different medications were selected in patients with CKD, such as the altered drug absorption and distribution. Because most pharmacokinetic data are collected from the trials which usually do not include patients with CKD, the evidence and the guidelines for the treatment of a general population might not be suitable for patients with CKD. Commonly used medicines in patients with CKD such as adrenal glucocorticoids, immunosuppressants, diuretics, inhibitors of the renin-angiotensin-aldosterone system, anticoagulation agents, antibacterial agents, and traditional Chinese medicines are described. Patients with CKD often need multiple medications for treatment of complications, and most drugs are excreted through the kidneys of a prototype or metabolite, thus most therapies should be adjusted according to renal function to avoid side effects of drug accumulation.

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15.1 Introduction

Up to 10–15% of the global population is estimated to have some degree of chronic kidney disease (CKD). End-stage renal disease (ESRD) represents the final stage of CKD and ultimately leads to the initiation of renal replacement therapy to treat kidney failure. However, the evidence for medications in patients with CKD is still insufficient, including those with CKD not requiring renal replacement therapy, the patients undergoing hemodialysis or peritoneal dialysis, and those receiving kidney transplants. CKD patients and ESRD patients on dialysis have several comorbidities and complications that require pharmacological management, including diabetes, hypertension, and anemia. To control these comorbidities, CKD or ESRD patients take an average of 12 different medications. The risk of medication-related problems is heightened due to the polypharmacy experienced by CKD patients. In practice, patients with CKD, ESRD, or kidney transplants have often been excluded from most randomized controlled trials (RCTs) testing for drug efficacy. In addition, the relatively few trials that enrolled and were restricted to patients with CKD or ESRD were often negative or inconclusive.

The kidney plays a vital role in metabolism and clearance of drugs. Due to the pharmacokinetics changes in CKD, the pharmacological action intensity and the maintenance time of drugs are also altered. Two main factors must be

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considered when selecting medications for treating patients with CKD: one is the glomerular filtration of drugs which mainly depends on the concentration of free drugs in serum and the glomerular filtration rate, the other one is the metabolic changes of drugs, such as digestion, absorption, distribution, and excretion. For those patients undergoing dialysis, the effect of dialysis itself on the clearance of drugs could not be ignored. Furthermore, multidrug use naturally leads to an increased risk of drug–drug interactions. This chapter discusses in detail in these issues and the commonly used medicines in CKD or ESRD patients.

15.2 Pharmacokinetic Changes in CKD

The kidney plays an important role in the metabolism and clearance of drugs and their metabolites. It is widely known that the medicines which are predominantly excreted by the kidney should be adjusted in patients with CKD. How the decrease of renal function alters the aspects of the pharmacokinetics and pharmacodynamics of several drugs has caused for concern; the rate and extent of drug absorption, distribution among kidney, metabolism, and excretion of pro-drugs, drugs, and their active or toxic metabolites must be considered [1].

Pharmacokinetics in patients with CKD is different from that in general population, which is mainly reflected in the following aspects: (1) Drug absorption: in patients with CKD, the increase of ammonia leading to a relatively alkalinized milieu which might affect the dissolution of certain drugs, thus leading to reduced absorption. Phosphate binders are a classic example of pH-dependent effectiveness. (2) Drug distribution: CKD may cause the loss of protein from urine or the change of protein structure in serum to reduce the affinity with drugs, thus affecting the distribution of the drugs. Edema and fluid overload, especially the cyclic hydration changes in hemodialysis patients may change the volume of distribution for certain drugs. (3) Drug catabolism: the oxidation rate is usually enhanced in patients with CKD. (4) Drug excretion: drug excretion rate slows down and half-life is prolonged accompanied with the decrease of creatinine clearance rate. Therefore, the dosage of drugs should be adjusted according to the degree of renal dysfunction to avoid drug accumulation and poisoning in patients with CKD [2]. A summary of the pharmacokinetic changes in patients with hemodialysis is shown in Table 15.1.

Table 15.1 Summary of pharmacokinetic changes in hemodialysis patients

Pharmacokinetic process	Changes in hemodialysis
Absorption	Increased absorption mediated by: • Paracellular leakage • Decreased efflux transporter activity • Decreased P450 activity
Distribution	Increased free drug concentration mediated by: • Decreased albumin concentration • Uremic toxin-mediated decreases in protein binding
Metabolism	• Decreased Phase I metabolism • Decreased Phase II metabolism
Excretion	• Decreased renal drug excretion • Decreased biliary drug excretion
Hemodialysis	• Dialytic drug clearance leading to decreased plasma concentration • Normalization of non-renal drug clearance pathways

The medication in patients with CKD needs to be made according to the characteristics of the specific drugs and their metabolites, as well as the degree of renal function. Drugs in patients with CKD should be selected and adjusted appropriately. Drug adjustments could be carried out through the following common ways: (1) Dosing adjustment: the initial dose of the drug and the drug interval remain unchanged, while the maintenance amount is reduced. (2) Interphase extension: the dosage of the drug remains unchanged, but the interphase is prolonged. Individualized medication regimens are implemented according to the specific conditions of patients. For special drugs, the regimen needs to be adjusted by monitoring the serum drug concentration. It should be emphasized that drugs with a high risk of renal damage might be banned or used with caution in patients with

CKD. Several publications have focused specifically on recommendations for drug dosing and monitoring of patients with CKD, patients with ESRD who are on renal replacement therapy, and patients on continuous renal replacement therapy.

15.3 Challenge of Evidence-Based Prescribing in CKD

Increasingly, more and more evidence concerning medication in general populations has accumulated and may guide the treatment decisions. The types of patients selected for experimental treatments in clinical trials must be considered. It is worth noting that CKD, especially ESRD, is often an important clinical feature excluded by clinical trials [3]. For example, CKD patients were definitely excluded from approximately 50% of RCTs of interventions in chronic heart failure or acute coronary syndrome. Exclusions of patients with CKD were usually common in the clinical trials of inhibitors of the renin angiotensin-aldosterone system and anticoagulants.

Thus, because most evidence is derived from the trials in the general population, whether such evidence and the resulting guidelines for therapies could be used to guide treatment of patients with CKD or ESRD still need to be confirmed. Whether such extrapolations are appropriate is unclear, and in some instances extrapolation is appropriate, whereas in others it is not. More RCT studies are needed to support medication use in patients with CKD or ESRD.

15.4 Medication Use in Patients with CKD

Commonly used medicines in CKD or ESRD are described in detail below, according to the therapeutic types [4].

15.4.1 Adrenal Glucocorticoids

Adrenal glucocorticoids are commonly used in CKD, especially in primary membranous nephropathy, lupus nephritis, and other immunological nephropathies. The absorption, distribution, metabolism, and excretion of glucocorticoids are different, and there are differences in efficacy and adverse drug reactions. When oral glucocorticoids enter the blood, most bind with cortisol-binding globulin (CBG). Glucocorticoids are mainly metabolized by the liver and excreted by the kidneys with a variety of inactive metabolites, such as tetrahydroxy cortisol. Different glucocorticoids have different anti-inflammatory properties, drug removal half-lives, and durations of efficacy (Table 15.2).

Indications and contraindications should be strictly evaluated before using a glucocorticoid. The dosage, duration, and adverse drug reactions must be closely monitored. Glucocorticoid resistance is defined as a nephrotic syndrome without improvement following sufficient glucocorticoid treatment (e.g. prednisone 1 mg/kg/day) for more than 3 months. The common reasons for glucocorticoid resistance are as follows: co-existing complications, such as infections, thrombosis, and embolism; severe edema leading to abnormalities

Table 15.2 Characteristics of glucocorticoids used in CKD

	Equivalent dose (mg)	Anti-inflammatory properties	Water sodium retention	T1/2 (h)	Plasma binding protein	Duration of efficacy (h)
Cortisone acetate	25	0.8	2	0.5	CBG/Alb	8–12
Hydrocortisone	20	1	2	1.7–2.1	CBG/Alb	8–12
Prednisone	5	4	1	2.9–4.1	CBG/Alb	18–36
Prednisolone	5	4	1	2.7–4.1	CBG/Alb	18–36
Methyl prednisolone	4	5	0	1.6–3.4	Alb	18–36
Dexamethasone	0.75	27	0	4.1–5.4	Alb	36–54

Abbreviations: *CBG* cortisol-binding-globulin, *Alb* albumin

of the digestive and absorptive functions of the gastrointestinal tract; concurrent drug use that reduces glucocorticoid concentrations; and primary kidney disease types which have poor responsiveness to glucocorticoids.

Adverse reactions to glucocorticoids are closely related to dosage and treatment duration. Common adverse reactions include infection; adverse reactions of the skin and soft tissues, such as acne; water and sodium retention; adverse reactions of the cardiovascular system, such as hypertension; adverse reactions of the digestive system, such as peptic ulcers and gastrointestinal bleeding; osteoporosis; elevated blood sugar; adverse reactions of the central nervous system, such as insomnia and euphoria; adverse reactions of the reproductive system, such as menstrual disorders and decreased fertility; and adrenocortical insufficiency such as that seen in patients upon withdrawal of long-term use of glucocorticoids.

15.4.2 Immunosuppressants

Immunosuppressants and immune regulators have been rapidly developed recently, with research focusing on new drugs and combinations of different types of immunosuppressants to reduce adverse reactions. This chapter briefly summarizes the current clinical applications of immunosuppressants in primary and secondary CKD and renal transplantation, including cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, leflunomide, and calcineurin inhibitors. The specific drug characteristics and treatment principles are shown in Tables 15.3, 15.4, 15.5, 15.6, 15.7, and 15.8.

15.4.3 Diuretics

Diuretics are one of the most common medicines used for treating CKD in patients with decreased urine output. Commonly used diuretics include loop diuretics, thiazide diuretics, and potassium-sparing diuretics. The classification and characteristics of the main diuretics are shown in Table 15.9.

Table 15.3 Characteristics and therapeutic principles of cyclophosphamide

Cyclophosphamide
• Alkylating agent
• Gonadal toxicity depends on cumulative doses and increased age
• Gastrointestinal and hematological system toxicities are common
• Increases the risk of malignancy in the hematological system
• Due to the risk of hemorrhagic cystitis and bladder neoplasms, patients should be hydrated during treatment
• Oral dose: 1–2 mg/kg/day
• Impact intravenous doses: 0.5–1.0 g/m^2 surface area
• Routine blood and liver function should be monitored and routine urine output monitored for life
• Cystoscopy is required for non-glomerular-derived hematuria

Table 15.4 Characteristics and treatment principles of azathioprine

Azathioprine
• Purine analog
• Digestive and hematological system toxicity is common
• Dose for kidney transplantation: 3–5 mg/kg/day • Dose for autoimmune disease: 1–2.5 mg/kg/day
• Contraindicated with allopurinol and febuxostat
• Routine blood and urine analyses and liver function should be monitored
• Use with glucocorticoids to reduce glucocorticoid dosage or to maintain treatment

Table 15.5 Characteristics, treatment principles, and precautions of methotrexate

Methotrexate
• An indirect agonist of adenosine
• Dihydrofolate reductase inhibitor
• Adverse reactions in the gastrointestinal, hematological system, and skin mucosa are common
• The liver, hematological system, and lung can have rare but serious adverse reactions
• Dose: 5–30 mg per week
• Daily use of 1–2 mg of folic acid can partially reduce the incidence of adverse reactions or decrease their severity
• Patients with decreased glomerular filtration rate (GFR) or concurrent alcohol use should receive a reduced dose
• White blood cell counts and liver and kidney function should be measured every 4–8 weeks
• Chest radiographs should be obtained before treatment

Table 15.6 Characteristics, treatment principles, and precautions of mycophenolate mofetil (MMF)

MMF
• Inositol monophosphate dehydrogenase (IMPDH) inhibitors
• Gastrointestinal and hemotological system toxicities are common
• Dosage: 1–2 g/day, taken on a separate basis
• Doses should be reduced according to renal function
• Routine blood analyses should be monitored after administration
• The efficacy of this class of drugs is superior to azathioprine in organ transplantation

Table 15.7 Characteristics, treatment principles and precautions of leflunomide

Leflunomide
• Isoxazole derivatives
• May be used in kidney transplantation, autoimmune disease, and primary renal disease
• Active metabolites can inhibit dihydroorotate dehydrogenase (DHODH)
• Gastrointestinal toxicity is common
• Dosage: 50–100 mg/day for 3 days, 20–30 mg/day for maintenance
• Dosage does not require adjustment in impaired renal function
• Liver function should be monitored

Table 15.8 Treatment principles and precautions for calcineurin inhibitors

Calcineurin inhibitors
• Cyclosporine A and tacrolimus (FK506) are commonly used
• May be used in kidney transplantation, autoimmune disease, and primary renal disease
• Inhibition of calcineurin
• Nephrotoxicity and neurotoxicity are most common
• Because the effective treatment concentration range is narrow, blood drug concentrations should be monitored during treatment
• Liver function should be monitored

15.4.3.1 Clinical Application Principles for Diuretics

First, the uses of diuretics must be based on dietary controls that limit Na^+ intake and control of salt intake. Patients with mild and moderate edema require a low-salt diet, and patients with severe refractory edema require a salt-free diet. While edema is not the preferred indication for the use of diuretics, such medications are suitable for use in heart or respiratory function insufficiency, obvious ascites, or in patients with edema who cannot accept a strict salt restriction. A strong diuresis is necessary only in patients with acute pulmonary edema and acute renal failure, while other conditions should adhere to the principle of slow diuresis. Adverse reactions should be closely monitored during diuresis, especially abnormal blood volume, and electrolyte disturbances.

15.4.3.2 Indications of Diuretics

Nephrotic Syndrome

Diuretic treatment in nephrotic syndrome can improve the pathophysiological changes caused by H_2O storage by the kidney, which is one of the basic steps in the treatment of nephrotic syndrome. However, there are two pathophysiological conditions associated with the occurrence of edema in nephrotic syndrome: insufficient circulating blood volume caused by fluid flow to the interstitial fluid, or due to excessive capacity due to kidney sodium. The former may exacerbate primary kidney damage by the use of diuretics. Therefore, it is necessary to carry out a careful assessment of the condition to give correct diuretic treatment.

Acute Kidney Injury (AKI)

A large number of RCTs showed no clinical benefit in the incidence of inpatient mortality and renal replacement therapy for AKI patients. Therefore, diuretics should not be used as preventive or therapeutic drugs when AKI occurs.

Chronic Renal Failure (CRF)

Diuretics can be helpful for the regulation of the total body water, electrolyte disorders, and hypertension in CRF patients.

Renal Tubular Acidosis

Loop diuretics can increase H_2O and NaCl in the downstream nephron and stimulate the secretion of aldosterone and phosphorus excretion. Therefore, loop diuretics increase the discharge of acid.

Table 15.9 Common diuretics and their functional characteristics

Classification	Representative drugs	Characteristics
Loop diuretics	• Furosemide • Bumetanide • Butyric acid • Tolasemi	• Inhibits the active reabsorption of NaCl in the loop • Destruction of the intramedullary mass concentration gradient • Damage of renal dilution function • Damage of renal concentration function • Maximum diuretic effect can reach 20–50% of total Na^+ filtration • Increases urinary potassium excretion • Dilated renal cortical vessels
Thiazide diuretics	• Chlorothiazide • Hydrochlorothiazide • Indapamide	• Inhibition of cortical distal convoluted tubule Na^+ reabsorption • Poor function when creatinine clearance is decreased • Limited renal dilution function • Does not affect the concentration function • Increases urinary potassium excretion • Constricts blood vessels
Potassium-sparing diuretics	• Aldosterone antagonist: spironolactone • Inhibition of potassium extraction: amiloride, aminobenzene	• Potassium-sparing • The diuretic effect is weak and is not used alone

Heart and Liver Diseases

Diuretics can be helpful for improvement of CKD with heart and liver disease, such as acute left heart failure and chronic cirrhosis.

Hypertension

Diuretics can be effective for controlling blood pressure by reducing the circulating blood volume. Thiazide diuretics might be beneficial in the treatment of hypertension; however, the metabolic side effects of thiazides are gradually attracting attention.

15.4.3.3 Adverse Reactions of Diuretics

Adverse reactions of diuretics, especially loop diuretics and thiazide diuretics, include metabolic abnormalities and allergic reactions. Blood volume, hyponatremia, and hypokalemia are the most significant adverse reactions. Therefore, the ensuing changes in volume and electrolytes should be closely monitored during treatment with diuretics.

15.4.4 Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)

Among all oral prescription medications, inhibitors of RAAS have received the most attention in terms of their protective effects in CKD. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are recommended in CKD patients with hypertension and proteinuria, especially in those with diabetic nephropathy. Underuse of these drugs in CKD population seems to be especially common among the elderly and the patients with heart failure. Another topic often be discussed is the lower use of inhibitors of RAAS for secondary prevention after myocardial infarction. Patients discharged from hospitalization for myocardial infarction usually experienced a lower maintenance treatment of beta blockers, statins, and RAAS inhibitors in CKD patients. It is vital to point out that in patients with CKD who receive RAAS inhibitors, serum creatinine, and creatinine potassium should be monitored closely. If the level of serum creatinine exceeds more than 30% over the base value or hyperkalemia is detected, the use of RAAS inhibitors needed to be reassessed or discontinued if necessary.

15.4.5 Anticoagulation Agents

Patients with CKD often need anticoagulation, especially for those patients undergoing hemodialysis. The most widely used anticoagulant therapy for hemodialysis includes heparin and low-molecular

weight heparin. In patients with ESRD, antiplatelet agents such as aspirin and clopidogrel together with thrombolytics do not require dose adjustment. Warfarin could be used for atrial fibrillation or venous thromboembolism in patients with CKD or ESRD, which needed to be dose adjusted according to the international normalized ratio (INR). However, it is important to emphasize that patients with CKD or ESRD might display a greater risk of bleeding with anticoagulation treatment. However, the direct oral anticoagulants still require more study to support their use in patients with CKD or ESRD, which are currently not recommended among such population.

15.4.6 Antibacterial Agents

As similar to antibacterial therapy in the general population, the choice of antibacterial agents is mainly based on the likely source of infection, the types of organism, and the local antibiotic resistance patterns. If sepsis is suspected, broad-spectrum antibiotics should be needed. The most two common infections in patients with CKD or ESRD are catheter-associated infections and lower respiratory tract infections. For catheter-associated infections, for example, for catheter-associated infections in patients undergoing hemodialysis, vancomycin might be selected in combination with another agent. However, due to its nephrotoxicity, vancomycin might be avoided in patients with CKD who are not on dialysis. If methicillin-sensitive *S. aureus*is is present, cefazolin could be selected. Trimethoprim should be avoided due to the high risk of hyperkalemia in patients with CKD or ESRD. Dose adjustments of antibacterial agents in CKD are summarized in Table 15.10 [5].

15.4.7 Traditional Chinese Medicines

There is an increasing evidence supporting the application of traditional Chinese medicines in CKD. Table 15.11 summarizes the primary mechanisms and indications for the use of several commonly used traditional Chinese medicines in CKD.

15.5 Adjustment of Drug Dosage in CKD or ESRD

Patients with CKD often require multiple medications to treat complications. Because most drugs are excreted by the kidneys in the form of a prototype or metabolite, most drugs need to be adjusted according to the renal function of the patient to avoid side effects of drug accumulation [6].

15.5.1 Clinical Manifestations of Drug Accumulation in CKD or ESRD

15.5.1.1 Abnormalities of the Central Nervous System

Antibiotic encephalopathy is the most common drug accumulation response in patients with CKD or ESRD, which is referred to as a brain dysfunction caused by antibiotics poisoning, showing a series of nervous system symptoms, which usually occur 3–10 days after the start of antibiotics. Clinically, cephalosporins and carbapenems are commonly associated with antibiotic encephalopathy.

15.5.1.2 Liver Function and Kidney Function Injury

The capacity of drug metabolism and excretion often decreases following renal function impairment. The accumulation of drugs might increase the burden of the liver and the kidneys, leading to the dysfunctions of these organs. When patients with CKD or ESRD have unexpected clinical manifestations, in addition to the factors of primary morbidity and complications, the possibility of drug accumulation should be considered.

15.5.2 The Main Principles of Dose Adjustment for CKD

Adjustment of the dosage and dosing intervals of drugs in CKD or ESRD patients is vital to avoid drug accumulation and related adverse reactions. These principles should be followed:

Table 15.10 Dose adjustment of antibacterial agents in CKD

Antibacterial agents	$T_{1/2}$ (h)	Dose in general population	50 < GFR < 90 (mL/min/1.73 m^2)	10 < GFR < 50 (mL/min/1.73 m^2)	GFR < 10 (mL/min/1.73 m^2)	HD	PD	CRRT
Ertapenem	4	1.0 qd	100%	50% (GFR < 30)	0.5 qd	0.5 qd after HD		
Imipenem	1	0.5 q6h	0.25–0.5 q6–8h	0.25 q6–12h	0.125–0.25 q12h	After HD	0.125–0.25 q12h	0.5–1.0 bid
Meropenem	1	1.0 q8h	100%	1.0 q12h	0.5 qd	After HD	0.5 qd	
Cefuroxime	1.2	0.75–1.5 q8h	100%	0.75–1.5 q8–12h	0.75–1.5 qd	After HD	0.75–1.5 qd	0.75–1.5 q8–12h
Ceftazidime	1.2	2.0 q8h	2.0 q8–12h	2.0 q12–24h	2.0 q24–48h	Additional 1 g after HD	0.5 qd	2.0 q12–24h
Cefaclor sustained release tablets	1	0.375 po q12h	100%	50%	50%			
Cefoperazone/sulbactam	1.7/1	1/0.5–2.0/1.0 q12h	100%	100%	Sulbactam 0.5 q12h	Additional 1.5 g after HD		
Cefepime	2.2	2.0 q8h	100%	2.0 q12–24h	1.0 qd	Additional 1 g after HD	1.0–2.0 q48h	2.0 q12–24h
Penicillin G	0.5	0.5–4 million U q4h	100%	75%	20–50%	After HD	20–50%	75%
Amoxicillin	1	0.25–0.5 q8h	100%	0.25–0.5 q8–12h	0.25–0.5 qd	After HD	0.25 q12h	0.25–0.5 q8–12h
Ampicillin	1	0.25–2.0 q6h	0.25–2.0 q6h	100%	0.25–2.0 q6–12h	After HD	0.25 q12h	0.25–0.5 q8–12h
Amoxicillin/clavulanate potassium	1.3/1	0.5/0.125 q8h	0.5/0.125 q8h	100%	Amoxicillin 0.25–0.5 q 12h	Additional 0.25–0.5 after HD		
Ampicillin/sulbactam	1/1	2.0/1.0 q6h	2.0/1.0 q6h	100%	2.0/1.0 q8–12h	After HD	2.0/1.0 qd	1.5/0.75 q12h
Piperacillin/tazobactam	0.7–1.2	4.0/0.5 q6–8h	4.0/0.5 q6–8h	100%	2.0/0.25 q6h (<20:q8h)	2.0/0.25 q8h, additional 2.25 after HD	4.0/0.5 q12h	4.0/0.5 q48h
Aztreonam	2	2.0 q8h	100%	50–75%	25%	Additional 0.5 g after HD	25%	50–75%
Ciprofloxacin	3–6	0.5–0.75 po or 0.4 iv q12h	100%	50–75%	50%	0.25 po or 0.2 iv q12h	0.25 po or 0.2 iv q8h	

Levofloxacin	6–8	0.75 qd	100%	20–49: 0.75 q48h	<20: Loading 0.75, following 0.5 q48h	Loading 0.75, following 0.5 q48h	Loading 0.75, following 0.5 q48h	Loading 0.75, following 0.5 q48h
Rifampicin	1.5–5	0.6 po qd	100%	0.3–0.6 po qd	0.3–0.6 po qd	0.3–0.6 po qd	0.3–0.6 po qd	0.3–0.6 po qd
Ethambutol	4	15–25 mg/kg qd	100%	15–25 mg/kg q24–36h	15–25 mg/kg q48h	After HD	15–25 mg/kg q48h	15–25 mg/kg q24–36h
Pyrazinamide	9	25 mg/kg qd	100%	25 mg/kg qd	12–25 mg/kg qd	40 mg/kg, 24 h before dialysis	25 mg/kg qd	25 mg/kg qd
Vancomycin	6	1.0 q12h	100%	1.0 q24–96h	1.0 q4–7d	1.0 q4–7d	1.0 q4–7d	0.5 q24–48h
Teicoplanin	45	6 mg/(kg d)	qd	q 48h	q 72h	q72h	q 72h	q 48h
TMP-SMZ	11/10	TMP: 5–20 mg/(kg d) q6–12h	100%	30–50: 5–7.5 mg/kg q8h; 10–29: 5–10 mg/kg q12h	Not recommended, if used: 5–10 mg/kg qd	Not recommended, if used: 5–10 mg/kg qd	Not recommended, if used: 5–10 mg/kg qd	5–7.5 mg/kg q8h
Amphotericin B	24	0.4–1.5 mg/(kg d)	qd	qd	q24–48h	No adjustment		
Fluconazole	37	0.1–0.4 qd	100%	50%	50%	After HD	50%	0.2–0.4 qd
Itraconazole iv	21	0.2 q12h	100%	Ccr <30mL/min is contraindicated				
Voriconazole iv	Pharmacokinetic nonlinearity	6 mg/kg q12h∗twice to 4 mg q12h	100%	Po or be forbidden				4 mg/kg po q12h
Ganciclovir iv	3.6	5 mg/kg q12–24h	50–100%	0.625–2.5 mg/kg qd	0.625–1.25 mg/kg tiw	After HD	0.625–1.25 mg/kg tiw	
Ganciclovir po	3.6	1.0 po tid	50–100%	0.5–1.0 po qd	0.5 po tiw	0.5 g after HD		
Acyclovir po	2.5	0.2–0.8 q4–12h	100%	75%	0.2 q12h			
Acyclovir iv	2–4	5–10 mg/kg q8h	100%	5–10 mg/kg q12–24h	50% reduced qd	After HD	50% qd	5–10 mg/kg qd
Lamivudine	5–7	0.3 po qd	100%	0.05–0.15 qd	0.025–0.05 qd	After HD	0.025–0.05 qd	0.1∗1d to 0.05 qd

Abbreviation: *HD* hemodialysis, *PD* peritoneal dialysis, *tiw* three times per week, *qd* once per day, *TMP-SMZ* trimethoprim-sulfamethoxazole

Table 15.11 Traditional Chinese medicines in CKD

	Main mechanism	Indications
Emodin	• Anti-inflammatory • Immunosuppressant • Anti-oxidant • Anti-fibrosis	• Various chronic kidney diseases
Cordyceps and its preparations	• Decreases proteinuria • Improves renal fibrosis • Delays progression of renal function	• Various chronic kidney diseases
Tripterygium wilfordii tablet	• Suppresses immunity and inflammation	• Various primary and secondary nephropathies, such as chronic glomerulonephritis, lupus nephritis, nephrotic syndrome, and diabetic nephropathy

1. A familiarity with the pharmacokinetic characteristics of commonly used drugs
2. A correct determination of the degree of renal impairment, nutritional metabolism, and internal environmental stability
3. Defined indications for drug administration
4. Selection of drugs with relatively low renal toxicity as the first line of treatment
5. The adjustment of the dosage regimen according to the degree of renal impairment if drugs with nephrotoxicity are unavoidable
6. The close monitoring of clinical efficacy and toxicity of drug reactions

For those patients undergoing HD or PD, dialysis membrane-permeable drugs must be replenished. Dispersion is the basic principle of solute removal in hemodialysis. Because there is no drug in the dialysate, there is a large concentration gradient between the blood and the dialysate. Therefore, free drugs in the blood can easily be removed by dialysis. In ESRD patients, toxin molecules may replace a highly protein-bound drug at its adhesion site to increase the plasma concentration of free drug. In this case, a large amount of free drug can be removed by dialysis. In general, drugs with lower molecular weights (<500 Da) are more easily dialyzed than those with higher molecular weights. Drugs with a molecular weight ranging between 500 and 20,000 Da can be removed by peritoneal dialysis or high-flux dialysis. Those drugs exhibiting a high degree of protein binding are less susceptible to dialysis. Therefore, influencing the permeability of drugs is complex. The extent of drug removal remains dependent on the molecular weight of the drug, the degree of protein binding, drug water solubility, the volume of drug distribution and the elimination pathway. For example, larger apparent distribution volumes (>250 L) render drug dialysis more difficult. Drugs with poor water solubility are usually distributed between tissues and cannot be easily dialyzed. In summary, hydrophilic or low-molecular weight drugs which weakly bind plasma proteins can be readily dialyzed, while lipophilic or high-molecular weight drugs which significantly bind plasma proteins cannot be easily cleared by dialysis. Furthermore, the characteristics of the dialysis membrane or the dialysis mode might have different degrees of influence on drugs, such as high-flux dialysis [7].

15.6 Summary

CKD is a complex disorder that is associated with multiple comorbidities and complications. Patients with CKD are often prescribed several medications to treat these comorbidities and complications and attempt to improve the quality of life and life expectancy, which increase the risk of drug–drug interactions. Significant drug accumulation occurs in CKD or ESRD patients, which also places patients at an increased risk of adverse medication reactions.

This chapter has summarized the characteristics and principles of commonly used medicines in CKD. Although it has long been appreciated that ESRD patients do not have renal drug excretion

capacity, emerging studies have clearly documented that hepatic clearance of many drugs is decreased in CKD. Studies in both animal models and clinical pharmacokinetic studies in dialysis patients have suggested that kidney disease decreases hepatic metabolism. Unfortunately, these studies have not yet clarified specific metabolic pathways that are altered in patients with CKD. In the past 15 years, there is an abundance of evidence affirming that drug transporters play a critical role in determining the disposition of many medications. Much like metabolism, several clinical pharmacokinetic studies in ESRD patients have demonstrated that drug transport is impaired in ESRD patients. Unlike metabolism, which has many well-established, specific in vivo probe substrates, transporter probes used in vivo in clinical pharmacokinetic studies are nonspecific. Although animal models of CKD have been helpful in this regard, we must be cautioned that there are known differences in the regulation of drug metabolizing enzymes and transporters between rodents and humans. Accordingly, humanized mouse models may provide a useful tool for evaluating the impact of CKD on specific transporter expression and activity. Even with the use of these models, drugs that may be used in patients with CKD should have clinical pharmacokinetic studies prior to use in this patient population [8].

The hemodialysis process itself can have a profound impact on the pharmacokinetics of drugs. The changes in dialysis prescription from low-flux to high-flux dialysis means that we do not have good evidence for the dialytic clearance off or many drugs that are commonly in use today. In general, the implementation of high-flux dialyzers would be expected to increase the dialytic clearance of drugs. It is likely that many drugs are eliminated by dialysis and may not be present at concentrations required to generate therapeutic efficacy. Multiple studies have shown that the hemodialysis process itself can impact the intradialytic pharmacokinetics of drugs. Accordingly, clinical pharmacokinetic studies should be used to determine optimal dosing for patients across the spectrum of CKD and those in ESRD who require hemodialysis.

When encountering a CKD or ESRD patient, clinicians should first search for evidence of drug dosing recommendations in these populations. Indeed, dosage adjustments in CKD may be found in the product monograph. When specific pharmacokinetic data in CKD are not available, the clinician must evaluate all known information on the pharmacokinetics and pharmacodynamics of the drug, as well as what processes are likely to be altered in CKD or ESRD, and prescribe a dosage that is supported by available evidence.

Key Messages

- Several factors should be considered when different medications were selected in patients with CKD, such as altered drug absorption and distribution.
- Commonly used medicines such as adrenal glucocorticoids, immunosuppressants, diuretics, inhibitors of RAAS, anticoagulation agents, antibacterial agents, and traditional Chinese medicines in CKD or ESRD are described in detail in this chapter according to the medicine types.
- Patients with CKD often need multiple medications for complications. Because most drugs are excreted from kidneys in the form of a prototype or metabolite, most therapies should be adjusted according to renal function to avoid side-effects of drug accumulation.

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16 Initiation Timing and Modality Option for Renal Replacement Therapy

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Abstract

The decision of the initiation timing of dialysis is not only due to the stage of chronic kidney disease but also due to the uremic symptoms. The uremic syndrome is a cluster of clinical and metabolic characteristics associated with fluid, electrolyte, hormonal, and metabolic abnormalities that progress as kidney function aggravates. Current KDOQI recommendations on indexes of the initiation of dialysis include *Kt*/*V* and malnutrition. If the symptoms (anorexia, nausea, vomiting, fatigability, and diminished sensorium) and signs (refractory pulmonary edema, metabolic acidosis, foot or wrist drop, and asterixis) of uremia are present, dialysis treatments are emergently indicated. Decisions on modalities of renal replacement therapy depend on not only physical conditions but also lifestyle and psychological conditions of patients.

16.1 Introduction

Therapeutic modalities for irreversible end-stage renal disease (ESRD) include hemodialysis, peritoneal dialysis (PD), and renal transplantation. Every approach to renal replacement therapy (RRT) has its unique risks and benefits. The current prevalence rate of chronic kidney disease (CKD) in China is 10.8%. The incidence and prevalence of ESRD are predicted to continuously increase, and ESRD will affect an estimated 750,000 individuals by 2020 [1, 2]. Furthermore, ESRD care is costly. According to statistical data from Western countries, approximately 2% of patients with CKD will progress to ESRD and require RRT [2]. If every patient receiving dialysis therapy would cost 100,000 RMB per year, all patients would cost 240 billion RMB annually. It should be recognized by physicians and patients that these treatment options can also be complementary, thereby allowing to choose different modality under different clinical conditions. Patients with progressive renal failure should be identified to enable them to make an educated choice that suits their medical situation and lifestyle. Emergency hospitalizations, complications, and costs can be decreased by careful planning. Moreover, early assessment enables the identification of potential living donors, so that preemptive transplantation can be performed.

16.2 Indications for RRT

Other than serum blood urea nitrogen or creatinine level, the symptoms and signs of patients contribute more to the decision as to when dialy-

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sis should be performed [3]. The good points of early initiation of dialysis include the avoidance of fluid retention, malnutrition, and harmful effects of prolonged exposure to high concentrations of phosphorus, β2-microglobulin, and other uremic toxins. Nevertheless, there is no significant benefit of early initiation of dialysis compared with standard care [4, 5]. The absolute indication for dialysis is hyperkalemia unresponsive to medications and dietary restriction accompanied with electrocardiographic changes. Dialysis should be performed to avoid life-threatening arrhythmias. The clinical manifestations of uremic syndrome requiring dialysis treatment include fluid overload refractory to intravenous diuretics, nausea, anorexia, increasing lethargy, and difficulty in concentrating. Complications of brain and heart such as uremic encephalopathy, seizures, coma or pericarditis, and pericardial tamponade should be prevented by prior interventions. Emergency hemodialysis is more costly because of the lack of vascular access and the requirement of prolonged hospitalization.

16.3 Current Kidney Disease Outcomes Quality Initiative (KDOQI) Recommendations for the Initiation of Dialysis

16.3.1 K_rt/V_{urea} (Kt/V)

The weekly renal urea clearance, calculated as K_rt/V_{urea} (r, residual) although not discussed in the 2006 KDOQI clinical practice guidelines [6], was the primary criterion applied to determine the initiation timing of dialysis in the 2000 KDOQI guideline recommendations. Based on viewpoint, an actual weekly $Kt/V < 2$ approximates an estimated glomerular filtration rate (eGFR) of 10.5 mL/min/1.73 m^2 when corrected to total body water. The weekly Kt/V can be calculated to provide an objective functional detection therefore helping to determine the timing for the initiation of dialysis based on urea clearance instead of eGFR, which is creatinine-based. The 24 h urea clearance is used for weekly Kt/V calculating. The urea distribution volume is calculated based on weight and/or total body water estimate or according to standard formulas. A weekly Kt/V of 2 is approximately equal to a urea clearance of 7 mL/min and creatinine clearance between 9 and 14 mL/min/1.73 m^2 [7]. An example of weekly Kt/V calculation for a nondialysis individual is shown in Table 16.1 [8].

A stage-based paradigm that utilizes either eGFR calculated using the Modification of Diet in Renal Disease (MDRD) study equation or an actual measurement of glomerular filtration rate (GFR) have been suggested to apply for the decision of the initiation time of dialysis by the current KDOQI guidelines [9]. These guidelines specifically interpret that patients at stage 4 CKD should be educated about dialysis and that referral for dialysis should be considered after the GFR declines to 15 mL/min/1.73 m^2 (see Table 16.1) [2]. According to these guidelines, it

Table 16.1 Calculation of weekly Kt/V

Steps in calculation	Example of calculation or formula
Calculate the urea clearance for a 24-h period	Urea clearance = U_{urea}/P_{urea} ∗ urine volume/1440 = Urea mL/min
Determine urea clearance in liters, which is equivalent to Kt	L/week = Urea mL/min ∗ number of minutes in week (10,080)/1000 mL/1 L
Determine the urea distribution volume (V) in liters (L)	V (L) men = 2.5 + 0.34 ∗ Wt (kg) + 0.118 ∗ ht (cm) − 0.095 ∗ age (years) V (L) women = −35.3 + 0.18 ∗ W + 0.34 ∗ H or V (L) men = 0.6 ∗ (Wt in kg) V (L) women = 0.5 ∗ (Wt in kg)
Calculate the weekly Kt/V (Kt/V_{week}) week/V (L)	Kt/V_{week} = Urea (mL/min) ∗ number of minutes in week (10,080)/1000 mL/1 L/V (L)
Example: a 70-kg man with 24-h urea clearance of 10 mL/min	U_{urea}/P_{urea} ∗ urine volume = Urea mL/min = 10 mL/min 10 mL/min ∗ 10,080 min/week ∗ 1 L/1000 mL = 100.8 Urea clearance Assess total body water (V) (approx. 0.6 ∗ Wt) = 42 L Kt/V_{week} = 100.8/42 = 2.4

Abbreviations: *Wt* weight, *ht* height (Reproduced with permission from Bessie Ann Young [8])

was shown that dialysis was initiated at a higher mean GFR in 2006 than that in 1994, occurring at a conspicuous cost and also with early loss of residual renal function. Study of the Initiating Dialysis Early and Late randomized trial showed that there was no evident difference in mortality between early initiation of dialysis (eGFR, 10–14 mL/min/1.73 m^2) and late initiation of dialysis (eGFR, 5–7 mL/min/1.73 m^2). Current formulas for the calculation of eGFR are listed in the KDOQI guidelines for CKD, and most laboratories currently include serum creatinine-based eGFR calculated using the four-variable MDRD study equation proposed by Levey et al. (Table 16.2). Table 16.3 shows the KDOQI recommendations for the initiation of dialysis.

Therefore, even if the weekly *Kt*/*V* decreases to 2.0, it is not necessary to immediately start dialysis if the following conditions exist:

1. Absence of edema and no weight gain
2. Nutrition indexes indicating no need for dialysis
3. Absence of clinical symptoms and signs of uremia

However, the initiation of dialysis in patients with CKD in practical works is always later than the KDOQI recommendation. The Netherlands Cooperative Study on the Adequacy of Dialysis investigated the average *Kt*/*V* upon initiation of dialysis in the Netherlands from 1993 to 2000 and reported that the average *Kt*/*V* was 0.5 in 1993 and 0.8 in 2000 [10]. In China, Yang et al. surveyed the conditions of patients in Peking University First Hospital in 2000 and reported that the average creatinine clearance upon initiation of dialysis was 4.2 mL/min. In addition, many patients had complications such as hyperkalemia and acute pulmonary edema when they started dialysis. Liu et al. compared the timing for the initiation of dialysis in 2000 and 2006 in the same hospital and showed that dialysis was initiated earlier in 2006; however, complications were present.

Controversy exists as to whether earlier dialysis can improve the quality of life and prolonged the lifespan. Kazmi et al. analyzed the US Medicare data and showed that a higher eGFR at

Table 16.3 Kidney Disease Outcomes Quality Initiative recommendations for the initiation of dialysis

CKD stage	Recommendation
Stages 1 and 2	• Diagnosis of CKD and initiation of risk factor reduction
Stage 3	• Referral from PCP to nephrologist for the evaluation of CKD and assessment of risk factors for progression
Stage 4	• CKD education, including education about transplant and dialysis • Referral to vascular surgery for AV fistula once estimated GFR <20 mL/min/m^2 • Preemptive transplantation
Stage 5	• Cadaveric transplant wait-listing • PD catheter placement • AV graft placement • Initiation of hemodialysis if uremic symptoms exist

Abbreviations: *CKD* chronic kidney disease, *PCP* primary care provider, *AV* arteriovenous, *GFR* glomerular filtration rate, *PD* peritoneal dialysis (Reproduced with permission from Bessie Ann Young [8])

Table 16.2 Chronic Kidney Disease Epidemiology Collaboration equation for estimating GFR

Race	Sex	Serum creatinine level, μmol/L	Equation
Black	Female	≤62 μmol/L (≤0.7 mg/dL)	$GFR = 166 * (SCr/0.7)^{-0.329} * (0.993)^{Age}$
	Female	>62 μmol/L (>0.7 mg/dL)	$GFR = 166 * (SCr/0.7)^{-1.209} * (0.993)^{Age}$
Black	Male	≤80 μmol/L (≤0.9 mg/dL)	$GFR = 163 * (SCr/0.7)^{-0.411} * (0.993)^{Age}$
	Male	>80 μmol/L (>0.9 mg/dL)	$GFR = 163 * (SCr/0.7)^{-1.209} * (0.993)^{Age}$
White	Female	≤62 μmol/L (≤0.7 mg/dL)	$GFR = 144 * (SCr/0.7)^{-0.329} * (0.993)^{Age}$
or other	Female	>62 μmol/L (>0.7 mg/dL)	$GFR = 144 * (SCr/0.7)^{-1.209} * (0.993)^{Age}$
	Male	≤80 μmol/L (≤0.9 mg/dL)	$GFR = 141 * (SCr/0.7)^{-0.411} * (0.993)^{Age}$
	Male	>80 μmol/L (>0.9 mg/dL)	$GFR = 141 * (SCr/0.7)^{-1.209} * (0.993)^{Age}$

Abbreviations: *GFR* glomerular filtration rate, *SCr* serum creatinine (Reproduced with permission from Bessie Ann Young [8])

the initiation of dialysis indicated a higher risk of death, possibly implying that patients had much more serious complications. However, Beddhu et al. examined the risk of death adjusted for complications and obtained the same results [11]. Current clinical practice guidelines have suggested the timing for the initiation of dialysis according to renal function, nutritional status, and symptoms and signs of uremia. However, the key factor to determine when to institute dialysis is the existence of complications in clinical practice, especially in patients with diabetes. The measurement of residual renal function is helpful for doctors to evaluate the complications of patients and to determine the timing for the initiation of dialysis. More studies are required to confirm the advantages of earlier-onset dialysis.

16.3.2 Malnutrition

RRT should be considered if malnutrition cannot be corrected using standard non-dialysis treatment. According to the KDOQI guidelines, maintenance dialysis or kidney transplantation is recommended for non-dialysis patients with CKD (GFR <15 mL/min/1.73 m^2) if protein–energy malnutrition is persistent or progresses despite treatment in which reasons for malnutrition are absent (viewpoint).

Extensive data showed that mortality and the incidence of complications were significantly increased in patients with protein–energy malnutrition at the initiation of dialysis [12, 13]. Supplementary evidence indicated that the survival rate of patients with ESRD closely correlated with nutritional status. This is true not only in patients on maintenance dialysis but also in patients who are to undergo dialysis. A study investigating 683 patients undergoing dialysis between 1970 and 1989 showed that hypertension, coronary artery disease, and hypoalbuminemia preexisting before dialysis were independent risk factors for mortality. Another study that included 1982 hemodialysis patients indicated that hypoalbuminemia at the start of dialysis was correlated with the risk of death. A study that included 680 PD patients also reported similar results.

Moreover, one study reported the opposite and observed no correlation between serum albumin level and survival rate of patients starting on hemodialysis. However, the sample size was small (n = 139), and 94% were black (83%) or Hispanic (11%) in this study.

Despite controversial conclusions, there was evidence showing that nutritional status improved after dialysis treatment in malnourished patients; however, the improvement in nutritional status did not improve the prognosis. Conversely, in patients with good nutritional status, their nutritional status remained unchanged after dialysis. Accordingly, despite the absence of evidence, the KDOQI guidelines suggest that maintaining good nutrition before dialysis could be helpful for the prognosis of patients.

Patients with CKD are usually prescribed with a "low-protein diet." An inappropriate low-protein diet could result in malnutrition and poor prognosis. Hence, if the nutritional status of patients with CKD (GFR <20 mL/min/1.73 m^2) is aggravated with no firm causes and cannot be corrected by interventions, RRT should be considered even though pericarditis or hyperkalemia is absent.

16.3.3 Indications for Emergency Dialysis

Severe hyperkalemia, acidosis, and acute pulmonary edema are indications for emergency dialysis.

16.4 Modality Option for RRT

16.4.1 Medical Consultations for Patients and Relatives

The purpose of management of patients with CKD in different stages is distinct. Stage 3 CKD is followed by renal anemia, renal osteopathy, electrolyte disturbance, acidosis, cardiovascular disease, and malnutrition. Patients with these must be intensively monitored by renal physicians. Moreover, endocrine and cardiovascular specialists are involved in the management of patients. Dietitians are required to evaluate the nutritional status and institute a low-protein diet

plan to delay the progression of kidney disease. As kidney disease progresses, mental disorders are always accompanied by physical conditions. Therefore, psychologists and social workers are required to participate in the management of patients. Treatments for stage 4 CKD include retardation of progression, management of complications, and physical and psychological preparations for RRT. Studies have shown that quality of life and survival rates were better in patients undergoing appropriate management before dialysis than in those without rational treatment by nephrologist [14–16].

The physical preparations for RRT include correction of anemia, treatment of bone disease, maintenance of electrolyte and acid–base balance, and preservation of good nutritional status [17]. Patients with stage 4 CKD should be followed up every 2 or 3 months if diagnosed with diabetic or nondiabetic nephropathy, respectively.

With respect to psychological preparations for RRT, first of all, doctors should assist patients in eliminating their fear, depression, and anxiety about RRT, and information on CKD, renal failure, and modalities of RRT should be subsequently introduced to them. In addition, patients could be introduced to the hemodialysis or PD settings to help eliminate RRT rejection. Unhealthy mental condition before dialysis correlates with poor prognosis of patients.

16.4.2 Modalities of RRT

Patients at stage 4 CKD should make a decision of dialysis modality with respect to RRT, which is expected to be made during a relatively short period of time, such as during a clinic visit. Many educational facilities such as DVDs, videos, or Internet programs can be used to assist patients and their families in considering which modality best fits their lifestyle and needs. Moreover, to acquire sufficient exposure to diverse available dialysis options, patients are advised to discuss dialysis option selection with a patient peer who is on dialysis or has a transplant and with a trained dialysis social worker who is familiar with all aspects of RRT (transplant, hemodialysis, and peritoneal dialysis). In addition, the economic status of patients should be considered when modality selection is decided. Therefore, patients are suggested to consult with a financial specialist who can evaluate current health insurance dialysis coverage and help patients decide which modality is suitable for them. In China, although majority of dialysis-related healthcare is paid by the China Health Care, it may not cover all care, which may be province-dependent. Transplantation is still the best therapy for irreversible kidney failure, so evaluation for preemptive transplantation before initiating dialysis should be considered for all patients, as should registering for transplantation as soon as possible or simultaneously as patients are being prepared for dialysis.

16.4.2.1 Hemodialysis

Dialysis substitutes two major kidney functions: solute removal and fluid removal. The passive movement of solutes from the blood compartment to the dialysate compartment across a semipermeable membrane, called diffuse, is the predominant mode by which the solute is removed in hemodialysis. The rate of diffusion depends on several coefficients, such as molecular weight of solutes, membrane permeability, blood flow rate, concentration gradient of the solutes between the blood and dialysate, membrane permeability, and flow rate. The clearance of smaller molecules is higher. The greater the concentration gradient between the blood and the dialysate, the more rapidly diffusion occurs. Membrane permeability is determined by several specific membrane characteristics, such as pore size, charge, and quaternary conformation. Higher flow rates facilitate greater solute removal, and the countercurrent of dialysate flow to blood flow will maxim the gradient across the dialysis membrane [18].

Another principle of hemodialysis is convection, which means the spontaneous transport of solutes across the dialysis membrane. Although the convective mass transfer of solutes may not play a dominant role in conventional hemodialysis, convection is mainly responsible for scavenging macromolecules and plays an important role predominantly in high-flux dialysis and continuous venovenous hemofiltration.

Solvent such as water removal in hemodialysis occurs by the process of ultrafiltration. Fluid can

be forced across a semipermeable membrane on a pressure gradient from higher to lower pressures, and the pressure could result from the mechanical hydrostatic pressure or osmotic force. When positive pressure is applied to the blood compartment or negative pressure is applied to the dialysate side of the membrane, ultrafiltration will multiply. The ultrafiltration rate is adjusted to obtain the desired fluid removal during dialysis.

The hemodialysis machine has three main components: (1) the dialyzer (i.e., dialysis membrane); (2) a pump that regulates blood flow; and (3) a dialysate solution delivery system at a constant rate up to approximately 500 mL/min. In addition, the machine has many safety devices to ensure the proper, safe, and reliable delivery of blood and dialysate to the filter where exchange of water and solutes takes place. These devices include monitors to ensure that the pressures inside the extracorporeal circuit are not excessive, a detector for leakage of red blood cells from the blood compartment into the dialysate compartment, an air detector and shut-off device to prevent air embolism, a pump to deliver dialysate, a proportioning system to properly dilute the dialysate concentrate, a heater to warm the dialysate to body temperature, an ultrafiltration controller to precisely regulate fluid removal, and conductivity monitors to check the ionic strength of the dialysate.

Under most conditions, solute removal and fluid removal occur simultaneously. However, if vigorous ultrafiltration is attempted during conventional hemodialysis, patients frequently complain of nausea, muscle cramping, and vomiting. At the same time, systemic vascular resistance may decrease, thereby hypotension develops. Osmotic changes are minimized with isolated fluid removal in the absence of solute removal. Separating ultrafiltration will produce greater hemodynamic stability.

16.4.2.2 Peritoneal Dialysis

In the 1950s and 1960s, peritoneal dialysis (PD) was utilized mainly to treat acute kidney injury. Patients with ESRD were treated almost exclusively by hemodialysis and occasionally by intermittent peritoneal dialysis (IPD). In 1976, the introduction of continuous ambulatory peritoneal dialysis (CAPD) transformed this situation.

Approximately 10% of patients with ESRD in the United States and more than 50% of those in the United Kingdom, Mexico, Canada, and Australia receive CAPD. Compared with hemodialysis, PD obviates the need for vascular access, which is a predominant challenge in patients with diabetes, young children, elders, and patients with severe vascular disease. Furthermore, anticoagulation is not needed in PD so the risk of bleeding decreases. Patients with PD has more stable hemodynamic status as PD is a slow and continuous process compared with hemodialysis, thereby reducing the risk of cardiovascular complications and protecting the residual renal function. PD can be performed by patients at home, thereby giving patients a sense of control and independence. In addition, the diet restriction for salt, potassium, protein, and fluid is not so strict in PD. For children with ESRD, PD is the option of choice because it avoids frequent vascular punctures and, most importantly, allows children to grow. Despite the advantages of PD, there is still controversy about its outcomes compared with those of hemodialysis. PD has been represented with worse, similar, and better mortality compared with hemodialysis, depending on the study design and statistical analysis.

Hemodialysis, PD, and transplantation are the cornerstones of modern renal replacement therapy. It is crucial to understand that these modalities are not mutually exclusive, because patients may transfer from one to another during the course of their treatment. Thus, PD is an excellent option for initial dialysis treatment if a patient will have a transplant within a short period of time. Also, for patients who would like to be in more control of their dialysis, or who intend to do dialysis at home, PD is a good choice.

For PD therapy, the peritoneal membrane is used as the dialyzing surface. Therefore, the function of peritoneal membrane should be evaluated regularly to avoid insufficient dialysis. Unless there is a major contraindication, PD should be considered as the first-line therapy for all patients undergoing preemptive kidney transplantation and other home dialysis therapies.

Table 16.4 lists some recommendations for modality selections (hemodialysis or PD).

Table 16.4 Recommendations for modality selections

Conditions of patients	Recommended modality
Cannot establish vascular access Refractory heart failure Postoperative valve repair Intolerant to HD (severe headache) 0–5 years old Patients' strong wish to undergo PD	PD is strongly recommended
Cardiovascular diseases Chronic diseases Hemorrhagic diseases Myeloma Unstable diabetes HIV infection Hepatitis B or C Preparation for kidney transplantation Fainting during acupuncture	PD is recommended
Diabetes mellitus Peripheral vascular diseases Polycystic kidney Scleroderma Chronic glomerulonephritis Overweight Chronic diverticulitis Severe back pain Hernia Multiple abdominal operations Poor operational capacity Blind	PD or HD, HD is preferred
Diaphragmatic hernia (diaphragmatocele) Malnutrition Abdominal adhesions Urine protein >10 g/day Severe diabetic gastroplegia Severe hypertriglyceridemia Severe COPD Ascites Upper amputation Poor sanitation Poor home environment Infective abdominal diseases	PD is relatively contraindicated
Acute diverticulitis Acute ischemic enteropathy Abdominal abscess Pregnancy	PD is absolutely contraindicated

Abbreviations: *PD* peritoneal dialysis, *HD* hemodialysis, *HIV* human immunodeficiency virus, *COPD* chronic obstructive pulmonary disease

16.4.2.3 Renal Transplantation

Patients can gain best quality of life while successful renal transplantation is performed. After transplantation, because of the restoration of normal renal function, they are free from diet and fluid restrictions, are free to work and travel, and achieve correction of metabolic disturbances and anemia. Moreover, the long-term survival of renal transplantation patients is better than that of hemodialysis patients.

Even though the kidney survival has been improved dramatically nowadays, complications after transplantation and long-term survival are still challenges for surgeons and nephrologists. There are a lot of factors influencing the prognosis of transplantation including ages of donor and recipient, race and sex, major histocompatibility complex (MHC), pre-sensitization to human leukocyte antigen (HLA), kidney disease of recipient, condition and complication before transplantation, compliance of recipient, cold ischemia time, number of nephrons of donor, and immunosuppressive strategy.

For kidney transplantation, the identification of potential candidates is very important. Patients with transplantation aspiration should be added to the list while dialysis initiated. To offer patients with the best quality and quantity of life, it is essential to assess candidates early and, if possible, proceed directly to preemptive transplantation if a living donor can be identified [19, 20]. The evaluations of the recipients include the general condition such as age, body mass index (BMI), primary kidney disease, and immune state of particularly the panel reactive antibodies (PRAs). Additionally, identification of the latent infective diseases like tuberculosis, hepatitis B, and C is also necessary.

Owing to the stage-based approach to the initiation of RRT in patients with stage 5 CKD, opinions on RRT initiation timing have changed significantly over the last decade. Preemptive transplantation is the preferred choice for RRT; even though due to the enlarged number of patients with kidney disease and who will receive

RRT, adequate transplants are not available, and other modalities for RRT are still needed. Besides conventional hemodialysis, other home dialysis modalities such as short daily and nocturnal dialysis are optional methods of RRT but are underutilized [21]. It is notable that some home hemodialysis modalities may approximate the survival found with transplantation thus should be considered as preferred methods of RRT when transplantation is not available. The RRT modalities are not inflexible for one patient, and the study showed that a planned shift for all modes of RRT could improve overall survival and life quality for ESRD patients [22]. Home dialysis treatments including PD should be regarded as first choice for RRT, especially when patients have significant residual renal function or have an impending living donor transplant. Finally, newer home hemodialysis modalities such as daily or nocturnal dialysis may provide better survival for patients who are not immediate transplant candidates.

Key Messages

- The decision as to when dialysis should be performed depends on patients' signs and symptoms rather than absolute blood urea nitrogen or serum creatinine level.
- Current KDOQI recommendations on indexes of initiation of dialysis include *Kt*/*V* and malnutrition.
- Severe hyperkalemia, acidosis, and acute pulmonary edema are indications for emergency dialysis.
- Decisions on modalities of RRT depend on not only physical conditions but also lifestyle and psychological conditions of patients.
- To offer patients with the best quality and quantity of life, it is essential to assess candidates early and, if possible, proceed directly to preemptive transplantation if a living donor can be identified.

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Hemodialysis

17

Hong Ye, Hao Ding, Wei Gan, Ping Wen, Yang Zhou, Hongdi Cao, and Weichun He

Abstract

Hemodialysis (HD) sustains life for more than millions of people worldwide, without which most would die within a few weeks. The life-sustaining treatment depends on an extracorporeal blood device and requires caregivers to in-depth process detailed aspects of dialysis procedure in addition to an understanding of the pathophysiology of the uremic state. Patients with end-stage kidney disease routinely relies on HD to preserve life since half a century ago. Several early pioneers deserve to be remembered for laying the foundation for HD, which had become technically feasible nowadays. The government approval of public funding for HD made the life-sustaining kidney replacement available for virtually all patients. In this chapter, we review the physical, chemical, and clinical principles of HD as they relate closely to the treatment of uremia patients and the complications associated with HD. The descriptions of other replacement therapies, such as transplantation and peritoneal dialysis, are reviewed in the following chapters.

17.1 Introduction

More than a million patients worldwide would die within a couple of weeks without hemodialysis (HD). Several early pioneers laid the foundation for the life-sustaining therapeutic dialysis. Claude Bernard and Milieu Intérieur introduced and described the concept of HD. Thomas Graham (1805–1869) is named the "father of dialysis" because of his discovery of the fundamental process using semipermeable membranes to separate solutes in vitro. John Jacob Abel was the first to present the idea of passing the blood of a living rabbit and dogs over a dialysis membrane and using hirudin extracted from a leech for anticoagulation. Georg Haas started the use of an artificial kidney for dialysis in humans in 1924. In 1944, Willem Kolff successfully used extracorporeal dialysis as a human life-saving treatment for patients with kidney failure; hence, he is often referred to as the "father of artificial organs." In 1960, a blood access device applying plastic tubes inserted into the vein and artery was developed by Belding Scribner, collaborating with Quinton and Dillard at the University of Washington. Subsequently, Brescia and Cimino introduced the more permanent arteriovenous fis-

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tula (AVF). Kolff and Scribner were granted the prestigious Albert Lasker Award for Clinical Medical Research in 2002 for their pioneering work in the field of artificial organs [1, 2].

17.2 Principles

Diffusion: The spontaneous passive movement of solutes across the dialysis membrane is called diffusion (Fig. 17.1). The rate of diffusion depends on several coefficients, such as molecular weight of solutes, membrane permeability, blood flow rate, concentration gradient of the solutes between the blood and dialysate, dialysate temperature, and flow rate.

Convection: The spontaneous transport of solutes across the dialysis membrane is called convection. Convection is mainly responsible for scavenging macromolecules. Factors affecting convection include the screening coefficient of dialysis membrane and membrane pore size, the size and configuration of solute molecules, and the charge of membrane and solute.

Adsorption: Adsorption is a method for removing molecules from the blood or plasma by attachment to a surface incorporated in a module within an extracorporeal circuit. Adsorption occurs fundamentally because of the hydrophobic properties of sorbents. In this group, the sorbents used in different dialysis techniques are charcoal and nonionic macroporous resins. Adsorption occurs by chemical affinity, such as ion-exchange resins and chemisorbents.

Ultrafiltration: A solvent such as water can be forced across a semipermeable membrane on a pressure gradient from higher to lower pressures, and the pressure could result from the mechanical hydrostatic pressure or osmotic force. The solvent carries with it the dissolved solute molecules that are small enough to pass through the membrane pores. This movement of molecules across a semipermeable membrane due to a pressure difference is called ultrafiltration (UF) (Fig. 17.2). If the pressure is hydrostatic, the process is called hydrostatic UF. Conversely, UF due to osmotic pressure is called osmotic UF. For solutes with a sieving coefficient close to diffusion,

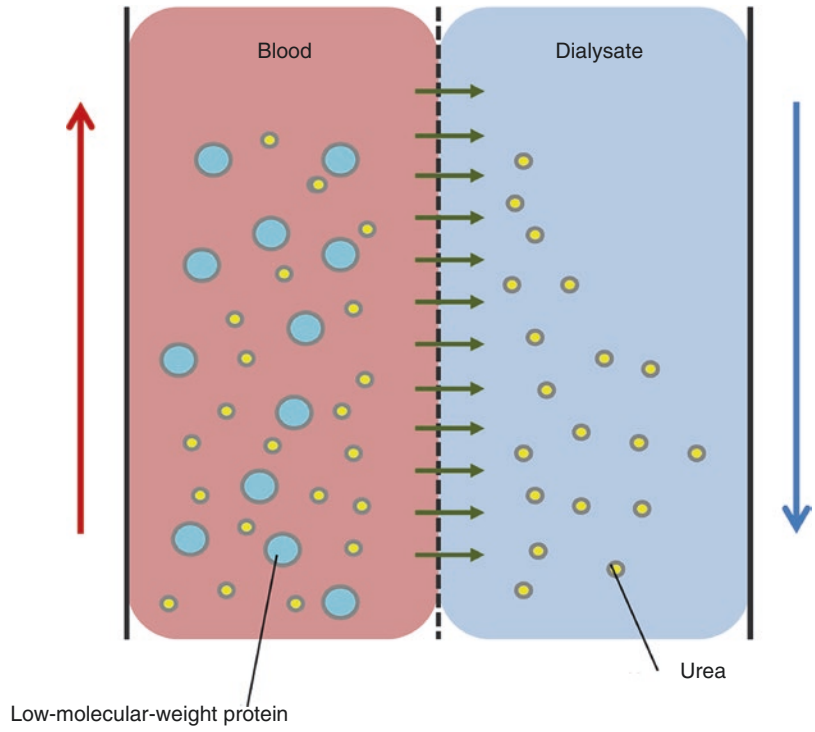

Fig. 17.1 Diffusion across a semipermeable membrane. The driving force for solute diffusion is the transmembrane concentration gradient. Small solutes with higher concentrations in the blood compartment, such as potassium, urea, and small uremic toxins, diffuse through the membrane into the dialysate compartment. Dialysis dissipates this concentration gradient (i.e., the molecular concentration gradient decreases with dialysis). Larger solutes and low-molecular-weight proteins such as albumin diffuse poorly across the semipermeable membrane

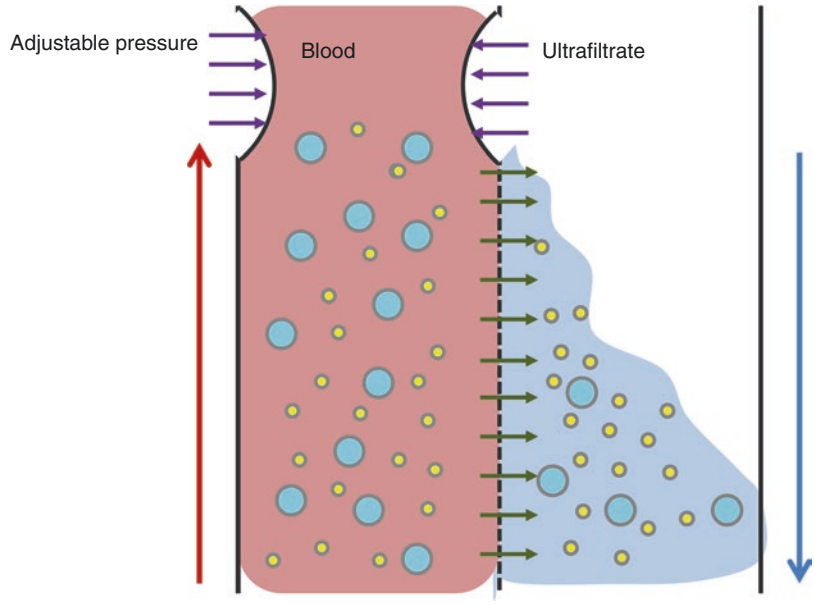

Fig. 17.2 Ultrafiltration across a semipermeable membrane. The driving force for ultrafiltration is the transmembrane hydrostatic pressure. When applied to the blood compartment, solvent flows across the membrane into the dialysate compartment, bringing along solutes

the concentrations of solvent molecules do not change with time.

17.3 Dialysis System

The purpose of HD is to effectively remove uremic toxins and extra fluid from the blood. The dialysis systems are mainly composed by the dialyzer, dialysis machine, extracorporeal blood circuit, and water purification system [3]. The dialysis machine has a blood and dialysate pumps, dialysate mixing and degassing unit, heating system, UF balancing system, as well as monitoring and safety system. Contaminants must be purified from the water for dialysis prior to its use. The final dialysate is produce by the proportioning water purification system.

17.3.1 Dialyzer

The dialyzer controls the transfer of water and solutes across the semipermeable membrane (Fig. 17.3). All dialyzers consist of a series of parallel flow paths designed to provide a large surface area between the blood and membrane and between the membrane and dialysate. There are two basic flow path geometries: (1) rectangular cross section, seen in parallel plate dialyzers, and (2) circular cross section, seen in hollow-fiber dialyzers. Virtually all hemodialyzers in clinical use today are the hollow-fiber type. The hollow-fiber artificial kidneys are by far the most commonly used dialyzers and are available in a wide variety of sizes and membranes. Cellulosic or synthetic tiny hollow fibers are approximately 150–250 μm in diameter. Wall thickness may be as thin as 7 μm, although some synthetics have walls with thickness of 50 μm or more. The blood flows through these tens of thousands of hollow fibers. The contained blood volume is very low in relation to the dialyzer's surface area because of the dialyzer's flow geometry. Resistance to blood flow is low because of the large number of blood passages. Hollow-fiber dialyzers are not compliant; therefore, they do not increase in shape or in the volume that they hold under high transmembrane pressure. UF can be precisely controlled. Hollow-fiber dialyzers can be effectively sterilized using ethylene oxide (ETO), gamma irradiation, or steam. Electron beam (e-beam) is a newly discovered method applied in factory sterilization. As e-beam sterilization does not use chemicals or radioactive materials, it may be an alternative for patients sensitive to ETO.

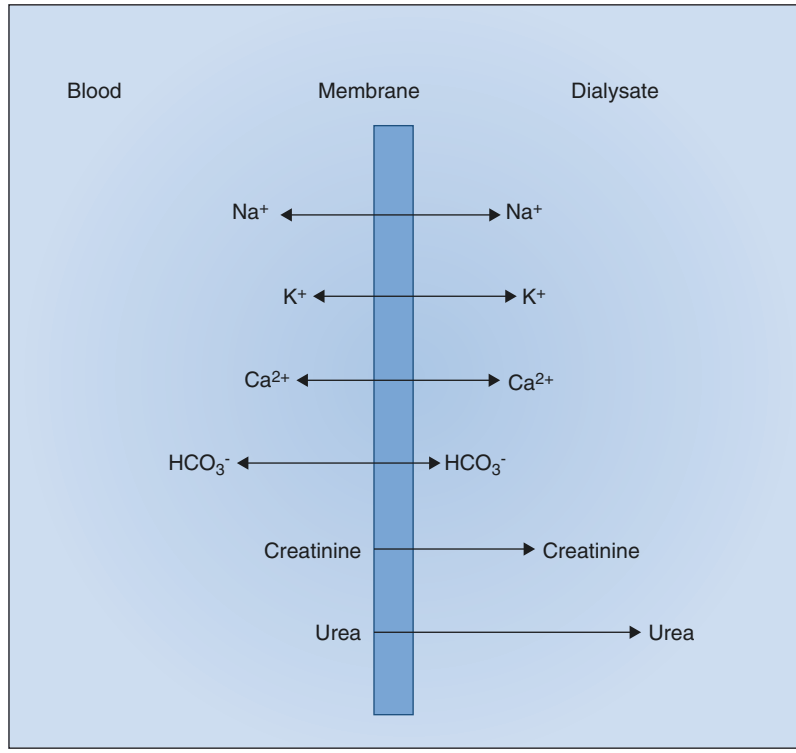

Fig. 17.3 Membrane fluxes in dialysis. Dialysis is the process of separating elements in a solution by diffusion across a semipermeable membrane (diffusive solute transport) down a concentration gradient. This is the principal process for removing the end-products of nitrogen metabolism (urea, creatinine, and uric acid) and for repletion of the bicarbonate deficit of the metabolic acidosis associated with renal failure in humans. The preponderance of diffusion as the result of gradient is shown by the displacement of the arrow

17.3.2 Dialysis Membrane

Membranes vary with respect to biophysical properties such as transport characteristics, chemical structure, and biocompatibility. Cellulose ($C_6H_{10}O_5$) is a complex carbohydrate polymer that is the structural material of plants. Cuprophan has been widely used. The cellulose is treated with ammonia and copper oxide during manufacture; cuprammonium rayon and Hemophan are modifications. Saponified cellulose ester, cellulose acetate, and triacetate are other widely used cellulose materials. One distinct advantage of cellulosic membranes is the fact that they have been used for many years; therefore, their transport characteristics are well known. They are also relatively inexpensive. However, all cellulosic membranes have some degree of bioincompatibility with blood. The synthetic membranes are thermoplastics. They have a thin, smooth luminal surface supported by a sponge-like wall structure. Those used for HD include polyacrylonitrile, polysulfone, polyamide, polymethyl methacrylate, and others (Table 17.1). Convective transfer accounts for their overall mass transport. These membranes mainly remove "middle" and large molecules. All have UF coefficients of 20–70 mL/h/mmHg or more and are well adapted for reuse. Synthetic membranes have much fewer bioincompatibility problems than cellulosic membranes.

Table 17.1 Examples of dialyzer

Material (abbreviation)	Membrane type
Cellulose triacetate (CTA)	Hollow fiber
Polysulfone (PS)	Hollow fiber
Polyethersulfone (PES)	Hollow fiber
Polymethylmethacrylate (PMMA)	Hollow fiber
Polyester polymer alloy (PEPA)	Hollow fiber
Ethylene vinyl alcohol copolymer (EVAL)	Hollow fiber
Polyacrylonitrile (PAN)	Hollow fiber, laminated

Dialyzer performance indices include the following:

1. Biocompatibility of membrane: The biocompatibility of synthetic membrane is superior to that of fiber membrane. After contact with the

blood, the dialysis membrane may produce various reactions, including the activation of complement, slow excitation peptide, white blood cells, platelets, and blood coagulation factor. Membranes with better biocompatibility produce less reaction. Improvement in biocompatibility can reduce the deposition of amyloidosis, which can be characterized by joint disease, bone lesions and pathological fracture, soft tissue swelling, and carpal tunnel syndrome. In addition, it can reduce allergic reactions, reduce the occurrence of dialysis hypotension, improve nutrition, preserve residual renal function, reduce the incidence of cardiovascular disease, and reduce mortality.

2. Permeability of dialysis membrane: Permeability of water is expressed as UF coefficient Kuf, which refers to the UF of unit pressure in unit time. According to Kuf, dialyzers can be divided into three groups: low-flux dialyzer (Kuf <6 mL/mmHg·h) is used in ordinary dialysis; Kuf 7–20 mL/mmHg·h is in flux, the parser that can be used for efficient dialysis; and high-flux dialyzer (Kuf >20 mL/mmHg·h) is used for the removal of water and macromolecules. It is suitable for high-flux HD and hemofiltration (HF).
3. Dialysis membrane solute sieving coefficient: The ability of the dialysis membrane to filter the solute in the convection is related to the molecular weight of the solute.

17.3.3 Water Treatment and Dialysate

A standard 4-h HD session, with a dialysate flow of 500 mL/min, exposes the patient to 120 L of water [3]. Therefore, water quality is of paramount importance for the patient's well-being. Water treatment includes filtration, adsorption (activated carbon filters), softening, reverse osmosis, deionization, and ultraviolet light exposure. The dialysate water must meet the Association for the Advancement of Medical Instrumentation (AAMI) standards for chemical, bacterial, and pyrogen content. Current AAMI standards suggest that the microbial count should be <200 colony-forming units (CFU)/mL, endotoxin concentration should be <2 endotoxin units (EU)/mL, and respective action levels should be 50 CFU/mL and 1 EU/mL (Table 17.2).

Table 17.2 Association for the Advancement of Medical Instrumentation water quality standard for dialysis

Substance	Maximum allowable concentration (mg/L)
Aluminum	0.01
Chloramines	0.1
Copper	0.1
Fluoride	0.2
Nitrate	2.0
Sulfate	100.0
Zinc	0.1
Arsenic	0.005
Barium	0.1
Cadmium	0.001
Chromium	0.014
Lead	0.005
Mercury	0.0002
Selenium	0.09
Silver	0.005
Calcium	2.0 (0.1 mEq/L)
Magnesium	4.0[a] (0.3 mEq/L)
Potassium	8.0[a] (0.2 mEq/L)
Sodium	70.0[a] (3.0 mEq/L)
Antimony	0.003
Free chlorine	0.50
Thallium	0.002

[a]Maximum allowable error

The dialysate carries away the waste materials and fluid removed from the blood by the dialysis procedure, prevents the removal of essential electrolytes, normalizes electrolyte levels, and averts excess water removal during the procedure. Furthermore, the dialysate corrects the acid–base balance in the patient. These functions are achieved by modulating the chemical composition in the dialysate close to that in normal blood.

There are five major components in the dialysate (Table 17.3): sodium chloride, sodium bicarbonate or sodium acetate, calcium chloride, potassium chloride, and magnesium chloride. Glucose is usually included to prevent intradialytic hypoglycemia. Dialysate is currently produced by mixing bicarbonate and acid components, which are provided as liquid or dry (powder) concen-

Table 17.3 Solute concentrations present in the dialysate

Solutes	Concentration (mEq/L)
Sodium	135–145
Chloride	102–106
Bicarbonate	30–39
Dextrose	11
Acetate	2–4
Magnesium	0.5–1
Potassium	0–4
Calcium	0–3.5
pH	7.1–7.3

trates. The bicarbonate component contains sodium bicarbonate and sodium chloride, whereas the acid component contains chloride salts of Na, K, Ca, Mg, acetate (or citrate), and glucose (optional). The potassium concentration in the dialysate may be modulated between 0 and 4 mmol/L according to the predialysis plasma potassium concentration. The calcium concentration in the dialysate in China is 1.5 mmol/L. Higher dialysate calcium concentrations may be used in patients with hypocalcemia associated with secondary hyperparathyroidism or following parathyroidectomy. The usual sodium concentration in the dialysate is 135–140 mmol/L. Lower dialysate sodium concentration is associated with a higher frequency of hypotension, cramping, vomiting, fatigue, and dizziness. Sodium concentration in the dialysate is gradually changed from 145–155 mmol/L to 140 mmol/L (isotonic concentrations) at the end of dialysis treatment and is typically reduced either in steps or in a linear or exponential fashion.

17.4 HD Techniques

Here, HD techniques refer to common blood purification techniques, which include HD, HF, and hemoperfusion (HP) [4–6].

17.4.1 Hemodialysis

HD removes solutes by diffusion based on the concentration gradients of solutes between the blood and dialysate across the semipermeable membrane. For example, urea diffuses from the blood to the dialysate compartment, thereby decreasing the total urea mass in the body and the urea concentration in the plasma. Conversely, the concentration gradient of bicarbonate usually favors diffusion of this ion from the dialysate to the blood compartment. Movement of water-carrying solutes across the dialysis membrane is not necessary for solute transport in this modality, although removal of fluid from the patient's plasma is often desirable because dialysis patients are usually fluid-overloaded. High efficiency in HD refers to a high rate of removal by diffusion of small-sized solutes; high flux in HD refers to a high rate of removal by diffusion of "middle molecules" that are substantially larger than urea. A membrane can be a high-efficiency/high-flux, high-efficiency/low-flux, low-efficiency/high-flux, or low-efficiency/low-flux membrane. The term "conventional dialysis membrane" usually refers to a low-efficiency/low-flux membrane.

17.4.2 Hemofiltration

HF, another form of extracorporeal therapy, removes fluid by convection (i.e., water movement across the large-pore HF membrane into the ultrafiltrate compartment drags along the solutes dissolved in the water). A crucial distinction between HD and HF is that fluid removal, but not the concentration gradient of the solute, is required for solute removal in HF. Removal of fluid with its accompanying solutes results in a loss of the total body mass of the solute, but not necessarily a decrease in the plasma concentration. In order to achieve a substantial decrease in concentration, "clean" replacement fluid devoid of that solute is intravenously infused to replace nearly the large volume of plasma fluid removed in the hemofilter. This modality is analogous to glomerular filtration, in which plasma solutes are removed by convection. In the case of the glomerulus, however, the replacement fluid is water and electrolytes that are selectively reabsorbed from the renal tubules. The term hemodiafiltration (HDF) refers to the combination of HD and HF operating simultaneously using a large-pore

membrane (i.e., solutes are removed by both diffusion and convection).

When HD, HF, and HDF are continuously applied for days to weeks in the presence of acute kidney injury (AKI), they are referred to as continuous renal replacement therapy (CRRT). The terms are further qualified by the forms of vascular access used. For example, continuous HF using an artery for blood supply and a vein for blood return in the extracorporeal circuit is called continuous arteriovenous hemofiltration. Continuous HDF exclusively using veins for vascular access is called continuous venovenous HDF. A rather common form of CRRT is slow (or sustained) low-efficiency HD.

17.4.3 Hemoperfusion

HP is the removal of solutes (usually toxins) from the blood by adsorption onto materials, such as charcoal or resins, in the extracorporeal circuit. HP is primarily used as treatment for acute poisoning. Adsorbents designed to remove specific molecules, such as β2-microglobulin, are not used in routine clinical renal replacement therapies (RRTs).

17.5 Acute Complications of HD

17.5.1 Neurological Complications

17.5.1.1 Disequilibrium Syndrome

Disequilibrium syndrome is a situation that produces neurological and other symptoms soon after a patient begins dialysis treatment. Urea is able to move freely between the cells and serum. Theories suggest that when a severely uremic patient is dialyzed for the first time, as the urea is removed, the plasma becomes more hypotonic, causing water to shift from the plasma into the brain tissue, which is less hypotonic and contains higher amounts of urea. Patients who (1) are treated with HD, (2) have very high blood urea nitrogen levels (usually >60 mmol/L), (3) have severe acidosis, (4) are elderly individuals or children, and (5) have a history of neurological diseases are at risk of disequilibrium syndrome. As the water flows to higher urea concentration, the brain cells begin to swell, causing neurological symptoms that range from headache, nausea, vomiting, restlessness, and twitching to the more severe tremors, disorientation, and convulsions. Treatment includes the administration of a hypertonic solution, such as hypertonic saline, 50% dextrose, or mannitol. The patients' symptoms should be treated. Delivering a less effective treatment using lower blood and dialysate flow rates, decreasing treatment time, or running the patient with a concurrent flow will help minimize these symptoms until the blood urea nitrogen levels stabilize [7, 8].

17.5.1.2 Muscle Cramps

Persistent involuntary skeletal muscle contractions with pain is a common complication during dialysis. It usually occurs near the end of dialysis, may be associated with low blood pressure, and is responsive to treatment with plasma volume expanders. However, cramps do not always rely on significant volume reduction and hypotension and have a positive response to hypertonic saline, mannitol, and hypertonic glucose solutions, which may suggest a role for low osmotic pressure in the pathogenesis of muscle contraction. Muscle cramps is often associated with peripheral vascular disease and the management for symptom includes the following aspects which are aimed at increasing plasma osmotic pressure. It has been shown that parenteral infusion of 25% mannitol (50–100 mL), 23.5% hypertonic saline (15–20 mL), or 50% hypertonic glucose solutions (25–50 mL) is equally effective. Applied before hemodialysis, midodrine hydrochloride tablet may be effective in reducing muscle contraction in patients with symptomatic hypotension during dialysis. Precautions include reducing excessive weight gain between dialysis to avoid rapid UF. Increasing the dry weight may be suggested if interdialytic weight gain is appropriate. It has been found that the use of quinine sulfate (oral, 325 mg) at the onset of HD may significantly reduce the incidence of muscle contraction. Using different sodium modeling strategies (exponential or stepwise), for example, starting

from a dialysate sodium concentration of 145–155 mEq/L and linearly decreasing to 135–140 mEq/L, has led to similar clinical results. The use of internal blood volume UF feedback control system is associated with a lower incidence of muscle contraction. Finally, stretching exercises for affected muscle groups during dialysis may be beneficial [9–11].

17.5.1.3 Convulsion

Convulsion occurs in <10% of patients and more frequently in patients starting HD. Cerebral hemorrhage should be considered when focal neurological signs are positive. Other reasons include hypertensive encephalopathy, disequilibrium syndrome, uremic encephalopathy, acute aluminum poisoning, hypoglycemia, and alcohol withdrawal. Termination of HD should be immediately performed when convulsion occurs, the respiratory tract should be kept unblocked, and the circulation should be maintained stable. Electrolyte and blood glucose levels should be immediately measured, and sedatives should be administrated to stop convulsion. Subsequent treatment needs to be decided according to the process of attack, signs, and results of blood tests.

17.5.2 Allergic Reactions

17.5.2.1 Dialyzer Reactions

Dialyzer reactions are sometimes referred to as "first-use syndrome" because some patients, upon exposure to the dialyzer membrane for the first time, develop allergic-type symptoms. Dialyzer reactions are at present more commonly referred to as type A and B reactions, with type A reactions being more severe and often presenting with anaphylactic-type symptoms. These reactions usually occur within the first 5 min of treatment, with patients experiencing the following symptoms: dyspnea, chest and back pain, feeling of warmth, sense of impending doom, and cardiac arrest. Less threatening symptoms include itching, urticaria, coughing, sneezing, watery eyes, and abdominal cramping. The causes are probably multifactorial and may involve the activation of plasma proteins by dialysis membranes, allergy to disinfectants, or release of noxious substances that have contaminated the dialyzers during the manufacturing or sterilization process. Another cause is the accumulation of vasoactive kinins as a result of enhanced activation of kininogen by dialysis membranes made of copolymers of acrylonitrile and methallyl sulfonate and decreased kinin degradation due to the simultaneous administration of angiotensin-converting enzyme inhibitors, which are also kininase inhibitors. Type A reactions are usually due to the factory sterilant ETO. This type of reaction is currently less common because some dialyzer manufacturers are using alternative sterilization methods such as gamma irradiation as a sterilant, e-beam sterilization, or steam sterilization. For those using dialyzers sterilized with ETO, proper priming of the dialyzer may help prevent pockets of ETO from remaining in the fibers to be released during the patient's dialysis treatment. Type B reactions are less threatening but more commonly seen. The symptoms usually occur as soon as the patient's blood is exposed to the dialyzer and returned to the patient. Symptoms include chest pain, hypotension, and occasionally back pain. The treatment for both types of reactions is based on symptoms. Dialysis treatment should be discontinued until the cause of symptoms is determined and the physician is notified. Oxygen is generally administered for difficulty in breathing. Intravenous antihistamines or epinephrine may be ordered for anaphylaxis. Blood pressure support may also be necessary for hypotension [12].

17.5.2.2 Reuse Syndromes

The reuse reaction is more likely due to other agents such as germicides for re-treatment of dialyzers because most of the remaining ETO is washed out of the dialyzer at "first use." Commonly used germicides include glutaraldehyde, peracetic acid/hydrogen peroxide, and formaldehyde. Formaldehyde is a known allergen and a life-threatening response is observed in HD patients who are positive for the radioactive sorbent formaldehyde test. Disinfection of the water supply system may also result in exposure to residual formaldehyde.

17.5.2.3 Drug-Induced Reactions

Intravenous Iron Dextran

Iron dextran is a mixture of synthetic glucose polymers that is involved in systemic reactions. The allergic reaction to iron dextran is due to this compound, which occurs at 0.6–1% of the recipients. Clinical practice guidelines of the National Kidney Foundation's recommend that resuscitation equipment and healthcare personnel should be available whenever iron dextran is used. High and low molecular weight dextran iron preparations differ in the frequency of allergic reactions, which latter appear to be safer. The exact mechanism of dextran-induced allergic reactions is unclear, but dose-dependent histamine releases from basophils, which may be the cause of cardiovascular failure, seems to occur. Due to this dose-related toxicity, 0.5–1 mg of iron dextran should always be used as a starting test dose so that staff could deal with the reaction in time. If the test dose is safe, a course of treatment with ten doses of 100–200 mg per session of dialysis can be safely provided. An alternative to iron dextran including intravenous administration of iron gluconate and saccharin may cause less allergic reactions, but it has been recognized that free iron released from these drugs can lead to inflammatory reactions.

Heparin

Patients are rarely highly sensitive to heparin preparations, and allergic reaction usually occurs only when beef heparin and porcine heparin are exchanged.

Desferrioxamine

Desferrioxamine or iron chelation in the treatment of aluminum poisoning can lead to hypotension during dialysis, hearing toxicity, bone pain, gastrointestinal disorders, visual loss, or even rare allergic reactions or aggravation of aluminum encephalopathy.

17.5.2.4 Intradialytic Hypotension

Hypotension during dialysis requiring drug intervention occurs in 10–30% of treatments. Although intradialytic hypotension can often be asymptomatic, it may be accompanied by a severe decrease in blood perfusion in vital organ, leading to loss of consciousness, seizures, and even death. There are a lot of reasons for intradialytic hypotension. First, blood volume may decrease excessively. Excessive weight gain between two dialysis sessions or inappropriate dry weight may lead to plasma refilling failure during dialysis, which is a crucial reason that accounts for hypotension. The rapid clearance of uremic toxins results in a low osmotic pressure of interstitial fluid and blood leading to the shift of water into the cells and eventually causes a decrease in blood volume. Second, there may be a decrease in vascular tone. The inability of the body to make a normal compensatory response to hypovolemia, characterized by a central redistribution of blood volume and an increase in peripheral vascular resistance, is a common mechanism of hypotension. Several patient-related factors are involved in the mechanism of the failed compensatory response, which include arrhythmia, taking antihypertensive drugs, structural heart disease, bleeding, anemia, autonomic neurological dysfunction (especially in patients with diabetes and elderly), food intake during dialysis, venous stasis during dialysis, fervescence, and sepsis. Reduced sensitivity to renin-angiotensin, adrenergic, and arginine vasopressin systems may also result in insufficient vasoactive response to hypovolemia induced by HD. Third, a disturbance in cardiac constructive and dilated function can also contribute to intradialytic hypotension.

Hypotension during dialysis should be treated immediately. The rescue measures include placing the patient in Trendelenburg position to facilitate the recovery of perfusion of important organs, preventing accidental inhalation, increasing circulating blood volume by infusion of isotonic saline or hypertonic agents, and reducing or stopping UF. Additional treatments such as use of bicarbonate dialysate, UF volume control, increase of sodium concentration in dialysate, more accurate assessment of dry weight of patients by bioimpedance or vena cava ultrasound, and decrease of dialysate temperature may improve cardiovascular stability and reduce occurrence of hypotension during dialysis.

Table 17.4 Strategies for intradialytic hypotension

Management strategies	Proposed physiologic mechanisms
• Lowering UFR or suspending UF	• Optimizes plasma refill/increases preload
• Trendelenburg position	• Increases cerebral perfusion/augments venous return
• Infusion of saline or albumin	• Restores plasma volume/augments venous return
• Pressor agents	• Increases vascular resistance
• Nasal catheter oxygen inhalation 2–4 L per minute	• Prevents or reduces organ hypoxemia
• Reduction of blood flow and dialysate flow	• Minimizes plasma osmotic gradients

Abbreviations: *UFR* ultrafiltration rate, *BP* blood pressure

Furthermore, sodium modeling can reduce episodes of hypotension, while the effect of low-salt albumin is not better than that of normal saline and the cost is higher. The effectiveness of online blood volume monitoring technique is controversial even if it has been used to control intradialytic hypotensive episodes. There are other strategies for preventing intradialytic hypotension, including avoiding food ingestion before and during dialysis, stopping antihypertensive drugs before dialysis, correcting anemia and hypoalbuminemia, treating congestive heart failure and arrhythmia, searching for other reasons such as pericardial effusion, and counseling patients on weight gain. Lastly, the use of selective alpha-1-adrenergic receptor agonist midodrine prior to a session of dialysis can effectively and safely reduce the severity and frequency of intradialytic hypotension. L-Carnitine and sertraline are also pharmacological options [13]. Common measures for the treatment of intradialytic hypotension are listed in Table 17.4.

17.5.2.5 Intradialytic Hypertension

Hypertension during dialysis is one of the risk factors for cardiovascular disease morbidity and mortality, which occurs in 8–30% of treatments. Although volume control remains the primary pillar of blood pressure (BP) management in patients with HD, as many as 50% of patients have not achieved the ideal BP control. Several volume-indepentent factors associated with hypertension during dialysis include activation of renin-angiotensin system owing to decreased blood volume and hypokalemia, increased inotropism and vascular tone induced by hypercalcemia, and preexisting hypertension. Other hypothesized mechanisms for hypertension in dialysis include increased sympathetic tone and cardiac output in response to fluid removal, especially in patients with cardiac dysfunction. It has been shown that long-term usage of recombinant human erythropoietin (rHuEPO) is also related to hypertension.

In the absence of signs or symptoms of volume contraction, it is reasonable to reduce dry weight by 0.5 kg and observe the clinical response, followed by reevaluating periodically. Increased dialysis or UF time and/or frequency can promote volume removal. Detection value of atrial natriuretic peptide shows that the true dry weight is not achieved in most patients with refractory hypertension during dialysis. Altering the approach of rHuEPO administration from the intravenous to the subcutaneous route is associated with improved BP control in patients with hypertension during dialysis. Finally, consideration should be given to the use of minimal doses of antihypertensive drugs that cannot be cleared by dialysis such as carvedilol, clonidine, calcium channel blockers, and angiotensin II receptor blockers.

17.5.2.6 Cardiac Arrhythmias

Atrial and ventricular arrhythmias often occur in patients undergoing HD, while the etiology of these arrhythmias is multivariate. Potential conditions frequently encountered include uremic pericarditis, ischemic or hypertensive heart disease, silent myocardial ischemia, left ventricular hypertrophy and dysfunction, and conduction system calcification. Furthermore, rapid or slow changes in the homestasis of fluids, electrolyte, and acid-base during HD may aggravate the arrhymogenic effects of digitalis preparation, antiarrhythmic medications, and other

drugs. Arrhythmias may only be caused by increased transport or consumption of oxygen in the myocardium, such as volume overload or intradialytic hypotension.

Measures that can be used to prevent arrhythmias include the use of bicarbonate dialysate and tight monitoring of potassium and calcium levels in dialysate. Because of the possibility arrhythmogenesis, zero potassium dialysate should be banned, and an adjusted concentration of potassium in dialysate may be helpful.

17.5.3 Hematological Complications

17.5.3.1 Hemolysis

Hemolysis (lysis of red blood cells) may be due to thermal, chemical, or mechanical events, resulting in the release of intracellular potassium. Chemical causes of hemolysis include exposure of the blood to chemicals, such as sodium formaldehyde, nitrates, hypochlorite, or copper. Thermal hemolysis is caused by exposure of the blood to overheated dialysate. Dialysate temperatures >42 °C are considered dangerous. Mechanical causes of hemolysis include kinking of blood lines, overocclusion blood pumps, excessive negative pressure from a small-gauge needle with a high blood flow rate, and a poorly positioned needle. Other causes of hemolysis include dialyzing the patient against a hypotonic bath and blood transfusions. The diagnosis of severe hemolysis is not difficult (blood from the dialyzer appears bright red); however, chronic and mild hemolysis is difficult to diagnose unless a diagnostic test for HD is performed. Treatment consists of discontinuation of dialysis and the blood in the blood circuit must not be returned. In addition, it is common to collect blood samples to detect blood potassium levels.

17.5.3.2 Acute Bleeding

Hemorrhagic tendency is aggravated by the use of anticoagulant agents during HD in uremic patients. Monitoring the bleeding time is the best method to evaluate hemorrhagic tendency. Platelet dysfunction is another cause of bleeding, and maintaining an acceptable hemoglobin level and HD adequacy could help correct platelet dysfunction. For patients with severe hemorrhagic tendency, heparin-free dialysis can be considered to reduce the risk of anticoagulant-related bleeding. The method in detail is as follows: the dialysis pipeline should be rinsed using 100–200 mL of 0.9% sodium chloride every 15 or 30 min (the UF volume should be increased). The blood flow rate should be increased, whereas the UF rate should be decreased to avoid coagulation when heparin is not used. Regional citrate anticoagulation (RCA) is an effective approach to reduce the risk of bleeding.

17.5.4 HD Technique-Associated Complications

17.5.4.1 Air Embolism

An air embolism, also known as a gas embolism, is a blood vessel blockage caused by air or a large amount of foam in the patient's circulatory system. Air embolism can occur when blood or saline infusion bags run dry or when arterial or venous lines become disconnected. The patient may complain of chest pain or tightness or shortness of breath and may cough. If the patient is sitting upright, air may be introduced into the cerebral venous system and causes neurological symptoms, such as visual problems, loss of consciousness, and convulsions. Dialysis should be stopped immediately, and patients should be placed on their left side in a head-down position (to trap air at the apex of the right ventricle) once an air embolism is suspected. After this, endotracheal intubation with oxygen flow at high rate should be started. Swan–Ganz catheter may be used to aspirate air from the right ventricle in some severe cases.

17.5.4.2 Loss of Blood

Loss of blood is usually due to disconnections of needles, catheters, and junctions of the artery or vein to the dialyzer along the extracorporeal circulation pathways and sometimes results from failure characteristics of products such as rupture of pump tubes.

17.6 Chronic Complications of HD

17.6.1 HD-Associated Infections

Infection is the second leading cause of death after cardiovascular diseases among patients with chronic HD. Many factors contribute to the susceptibility of patients to infectious agents such as impaired cellular immunity, defective neutrophil function, and complement activation. Infections transmit to susceptible patients either from an infected healthcare worker (professional to patient transmission) or from another infected patient (patient to patient transmission) through contaminated equipment, supplies, intravenous medications, environmental surfaces, or hands of healthcare workers. Moreover, intermittent hospitalizations and surgeries increase the opportunities for exposure to non-community acquired infections.

17.6.1.1 Microbial Contaminants in HD Systems

Several microbiological parameters were neglected in the design of many dialysis machines and corresponding water supply systems. Gram-negative water bacteria (e.g., *Burkholderia*, *Flavobacterium*, *Pseudomonas*, *Ralstonia*, *Serratia*, and *Sphingomonas*) are commonly detected in water supplies used for HD. Under certain circumstances, these microorganisms can persist and multiply in aqueous environments associated with HD equipment, and they can adhere to surfaces and form biofilms (glycocalyx), which are virtually impossible to eradicate. This can directly or indirectly affect patients by septicemia or endotoxemia. Control strategies are designed not to eradicate bacteria but to reduce their concentration to relatively low levels and prevent their regrowth.

While the incoming tap water flows through each component of the water treatment system in turn, which is composed of prefilters, a water softener, carbon adsorption tanks, a particular filter for the protection of the reverse osmosis membrane, and a reverse osmosis unit, it becomes more chemically pure while avoiding high levels of microbial contamination. Under the conditions of a thoroughly sterilized and regularly maintained system, the microbial content of water should be well within the recommended limits.

Increasing data suggest that the use of ultrapure water and dialysate would benefit maintenance dialysis patients, and the microbial quantity of HD fluids acts on the alleviation of chronic inflammatory response syndrome, management of anemia, retardation of residual renal function decline, and improvement in serum albumin level in patients with HD.

17.6.1.2 Vascular Access Infections

Vascular access-related infections remain a major cause of morbidity and mortality in this population, owing to disseminated bacteremia, dysfunction of or even loss of vascular access. Some local signs near the vascular access may indicate infections such as erythema, swelling and tenderness, induration, skin breakdown, warmth, loculated fluid, and purulent exudates. As the initial reported by the surveillance project performed by Centers for Disease Control and Prevention (CDC), the frequency of bacteremia associated with vascular access was 1.8 overall per 100 patient-months, and it varies among different types of access: 0.25 for fistulas, 0.53 for grafts, 4.8 for permanent catheters with tunnel and cuff, and 8.7 for temporary catheters without tunnel and cuff. On the basis of a later report from survey data collected by this system between 1995 and 2005, the average frequency of infection ranged from 10.1 for temporary catheters to 0.6 for fistulas per 100 patient-months, and the total frequency was 3.1.

According to the frequency of pathogens causing vascular access infections, 32–53% of cases were *Staphylococcus aureus*, 20–32% coagulase-negative *staphylococci*, 10–18% Gram-negative bacilli, 10–12% other Gram-positive cocci (including *enterococci*), and <1% of case were fungi infection. *Staphylococcus aureus* infection is more common in patients with fistulas or grafts, while coagulase-negative *staphylococci* accounts for a higher proportion of patients who use catheters.

The type of vascular access is the major risk factor for infection associated with access, as catheters, grafts, and native AVFs having the highest, moderate, and the lowest risk of infection,

respectively. Other potential risk factors for vascular access infection include (1) immunosuppression; (2) diabetes; (3) older age; (4) chronic inflammatory state; (5) access location in the lower extremity; (6) scratching over the access site, dermatitis, trauma, or hematoma; (7) recent vascular access surgery; (8) poor needle puncture technique; (9) poor patient hygiene; (10) intravenous drug use; and (11) iron overload. Based on the relative risk of both infectious and noninfectious complications, it is recommended that native AVFs be more commonly used and HD catheters less commonly and that no more than 10% of patients should be maintained with permanent catheter-based HD treatment. To minimize infectious complications, patients should be referred early for the creation of an implanted access, thereby decreasing the time for dialysis using a temporary catheter. Additionally, catheters should be used only in patients for whom a permanent access is impossible.

To reduce infections associated with vascular access, several recommendations have been made by the National Kidney Foundation and CDC as follows: (1) avoiding preventive use of antibiotic; (2) avoiding to replace catheter routinely; (3) following the principle of aseptic technique strictly during catheter placing; (4) restricting the service life of temporary catheter to 3–4 weeks; (5) avoiding usage of catheter for other purpose beyond HD; (6) allowing only skilled staff to participate in catheter manipulation; (7) changing dressing on catheter-site during each dialysis session or if damp, lose, or soiled; (8) sterilizing the skin with a 2% chlorhexidine-based preparation before catheter insertion and dressing replacement; (9) offering a catheter-site care which is compatible with catheter material. To reduce catheter-related bloodstream infections in HD patients, some researchers adopt an antimicrobial lock strategy. Two meta-analyses have drawn conclusions from these studies, that is, bloodstream infections associated with catheter could be dwindled by this antimicrobial lock strategy, and in clinical practice, in combination with other prevention methods, this treatment strategy should be considered routinely. Nevertheless, the long-term effect of routine antibiotic use with catheter lock solutions remains unknown. In spite of promising results from these studies, a routine antimicrobial lock solution use is not recommended by the CDC for fear of antimicrobial resistance.

The Infectious Diseases Society of America recommends a nasal mupirocin treatment for documented *S. aureus* carriers who are suffered from catheter-related bloodstream infection and continues to require a catheter. Apart from this, neither the CDC nor National Kidney Foundation recommends a routine use of nasal mupirocin in dialysis patients with catheters.

17.6.1.3 Chronic Infections

Hepatitis B Virus (HBV) Infection

HBV infection is one of the most frequent and morbid viral infections in HD patients. In the early times, HBV infection spread regionally in dialysis unit and outbreak frequently. Since the introduction of vaccination and improvements in infection control, the incidence and prevalence of HBV infection rates among HD patients in the USA have sharply declined, being 0.12% and 1%, respectively, in 2002. Skin (i.e., through skin puncture) or mucous membrane (direct contact with mucous membrane) exposed to infectious blood or body fluids containing blood is the main route of transmission of HBV.

HBV is resistant to the external environment and able to stay viable for more than 7 days on environmental surfaces at room temperature. HBsAg could be detected on hemostats, scissors, dialysis machine control panels, and door knobs in dialysis facilities. By this way, blood contaminated apparatuses without routinely cleaning and sterilization could turn into a reservoir for HBV transmission. In addition, HBV could be transmitted to susceptible patients from an infected health care worker.

In most cases, HBV infection outbreaks among HD patients were induced through (1) environmental surfaces, instruments, or equipment without routinely cleaning and sterilizing after each use; (2) using one multiple-dose intravenous solution or vial for more than one patient; (3) intravenous medications prepared close to

areas where blood samples were handled; (4) health care workers providing medical service to both infected and susceptible patients simultaneously. If there are certain factors which promote HBV transmission among patients being identified, the following measures for control are recommended: (1) serological test for screening HBV infection in both HD patients and health care workers; (2) setting up an isolated area for all HBsAg-positive patients; (3) avoiding assignment health care workers to HBsAg-positive patients and to HBV-susceptible patients during the same shift; (4) separating dialysis equipment for HBV-susceptible patients from that for HBsAg-positive patients; (5) routinely assigning a supply tray to each patient no matter what serological status is; (6) cleaning and sterilizing of instruments that are not disposable such as clamps, scissors, and hemostats before they are used for another patient; (7) wearing gloves regardless of touching dialysis equipment or not and changing gloves between each station and between each patient; (8) cleaning and sterilizing equipment and environmental surfaces routinely.

In the acute care setting, HD has also been found associated with HBV infection among patients. Other related risk factors include sexual and household exposure, multiple sexual partners, male homosexual activity, drug injection, and perinatal exposure. Staff of dialysis unit should educate patients about these and inform infected patient's sexual partners and household of vaccine inoculation.

There are three pairs of antigen–antibody systems found associated with HBV infection, including HBsAg and antibody to HBsAg (anti-HBs); hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and hepatitis B early antigen (HBeAg) and antibody to HBeAg (anti-HBe). These serological biomarkers can be detected in different combinations at different stages of infection. The other screening test for HBV infection is qualitative or quantitative analysis for HBV DNA. Routine screening for HBV infection should be performed for all HD patients, and in order to ensure that the patients are properly managed in a timely manner, their test results should be reviewed promptly.

Machines, equipment, and supplies for HBsAg-positive patients should be dedicated and placed in an isolated area. Since the transmission of HBV occurs via occupational contact with blood, and repeated use of dialyzers in HBsAg-positive patients increases the risk of infection among staff members susceptible to HBV, repeated use of dialyzers should be avoided. Chronic HBV-infected patients, that is, HBsAg-positive, total anti-HBc-positive, and IgM anti-HBc-negative, who are at a high risk of chronic liver diseases are major source of infection. Moreover, assessment based on current clinical practice guidelines is preferred for HBsAg-positive patients. The hepatitis A virus vaccine inoculation should be considered for people with chronic liver disease to prevent further impairment of liver. Although routine follow-up tests in chronic HBV-infected patients do not improve the control of infection, it is reasonable to test HBsAg annually for the small proportion of HBV-infected patients whose HBsAg may shift to negtive.

HCV Infection

Another common viral infection in dialysis unit is a single-stranded RNA virus named hepatitis C virus (HCV) which belongs to the Flaviviridae family. HCV is another efficiently transmitted blood-borne viral pathogen in the dialysis setting. Incidence and prevalence of HCV infection varies greatly in different dialysis unit of the world. HCV remains relatively stable when exposed to external environment and able to survive for more than 16 h in a dry environment at room temperature. Direct percutaneous exposure to blood plays a pivotal part in HCV transmission; similar to HBV, chronic infected patients play a key role in the spread of HCV. Risk factors for HCV infection among HD patients include blood transfusions from unscreened donors, intravenous drug abuse, low staff-to-patient ratios, and years on dialysis. The number of years on dialysis is the major risk factor independently associated with higher rates of HCV infection. The prevalence rate of HCV infection increased with the increase of dialysis time, and the average rate of patients receiving dialysis <5 years was

12%, while that of patients receiving dialysis >5 years was 37%.

There were several media identified associated with cross-infection among HD patients, including (1) medical instruments and supplies without sterilization after use; (2) shared drug cart for preparing and distributing medications at patient stations; (3) contaminated multiple-dose vials after repeated use; (4) polluted priming buckets without cleaning and sterilization; (5) machine surfaces that were not routinely cleaned and disinfected between patients; and (6) spilled blood containing HCV. There are some other risk factors for HCV infection such as intravenous medication, blood transfusion, exposure to a HCV-infected sexual partner or household contact, number of sexual partners, and vertical transmission.

Recombinant immunoblot assay (RIBA) and nucleic acid test (NAT) for HCV-RNA are the only two methods used for the diagnosis of HCV infection approved by the Food and Drug Administration. More often than not, an initial enzyme-linked immunosorbent assay (ELISA) anti-HCV screening is used for saving cost of detecting. Note worthily, the ELISA anti-HCV test result should be interpreted with caution for each of the following cases: (1) a false-negative test result in nearly 10% of HCV-infected population; (2) previous acute HCV infection; (3) in the acute phase of HCV infection, there may be a prolonged interval between the onset of illness and seroconversion; and (4) a high rate of false-positive in people with low infection rate. Therefore, a positive anti-HCV screening test is not reliable to make a diagnosis of HCV infection.

An initial ELISA-based screening test is suggested as a routine test, while anti-HCV assay using RIBA or HCV-RNA test could serve as a supplement for positive ones. It has been recommended that anti-HCV routine examination be performed every 6 months in patients with HD.

It is not necessary to separate HCV-positive patients (defined as a positive anti-HCV screening test result with a high signal-to-cutoff ratio; or a positive anti-HCV screening test result with RIBA or NAT positivity; or a positive anti-HCV screening test result with NAT negativity and RIBA positivity) from other patients or restrict them to dedicated dialysis machines. Routine test could both monitor virus transmission in dialysis unit and judge whether established preventive measures are efficiently executed or not. HCV-positive patients should be evaluated (by consultation or referral, if appropriate) for the presence or development of chronic liver disease according to the current medical practice guidelines and should receive information on how they can prevent further injury to their liver and transmitting HCV to others. Those with chronic liver disease should be vaccinated against hepatitis A, if susceptible [14, 15].

17.6.2 Hypertension

Hypertension is one of the common complications of chronic kidney disease (CKD). With the decline of glomerular filtration rate, the prevalence of hypertension increases gradually, and more than 80–90% of patients have hypertension at the start of dialysis. There is a U-shaped relationship between BP and cardiovascular disease outcomes in the dialysis population, with increased cardiovascular disease events and mortality at both markedly elevated postdialysis systolic BP (SBP >180 mmHg) and lower SBP (<110 mmHg). Certainly, hypertension does not appear entirely benign in dialysis patients, and it is an independent risk factor for ischemic heart disease, LVH, heart failure, and cerebral hemorrhage. Although it is generally considered that UF to dry weight is an initial treatment for hypertension, there is no evidence to support any BP target or even the best method to achieve a specific BP target in this population.

17.6.2.1 BP Target for HD Patients

According to the suggestions of the Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in the United States with respect to the staging and treatment of hypertension, normal

BP is <120/80 mmHg. HD treatment makes BP variation more complex. Partial patients (40–50%) have decreased BP, whereas some have increased BP. Some studies show significant associations between SBP before HD and LVH, whereas other investigations reported good correlation between ambulatory BP monitoring and interdialytic BP. With respect to clinical practices for cardiovascular diseases, the Kidney Disease Outcomes Quality Initiative (KDOQI) suggested that the BP should be <140/90 mmHg and <130/80 mmHg before and after dialysis, respectively.

17.6.2.2 Measures to Control BP

High blood volume is the main factor for hypertension in patients undergoing maintenance HD, and approximately 50% of patients are volume-dependent. The Hemodialysis (HEMO) study suggested that the volume affected the BP both before and after dialysis. Therefore, accurate evaluation of dry weight is an important strategy to control hypertension in HD patients. Sodium and liquid intake should be restricted to avoid excessive weight gains. In addition, hypercalcemia and usage of erythropoietin can contribute to hypertension.

The usage of antihypertensive agents and adjustment of dosages are essential for BP control. A combination of two or more antihypertensive agents is needed to achieve BP targets for HD patients. According to the KDOQI guidelines, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are preferentially selected because they can inverse LVH, reduce the excitability of sympathetic nerves, decrease the pulse wave velocity, improve endothelial function, and reduce oxidative stress. Another principle is to choose long-acting drugs. For difficult-to-control hypertension in HD patients, beta receptor blocker, calcium channel blocker, adrenergic blocker, and vasodilator agent can be used to control BP. Additionally, pharmacokinetics of the antihypertensive agents should be considered in HD patients (e.g., the clearance of drugs in HD treatment) [16].

17.7 Vascular Access

Maintenance of vascular access is a major challenge in chronic HD. An adequate vascular access should permit blood flow to the dialyzer at a rate of 200–500 mL/min in adults, depending on patient size. In the United States, there is a tendency to use blood pump speeds of 350–500 mL/min, whereas speeds of 200–250 mL/min are common in Asia. This discrepancy is partly due to the smaller body size in the Asian population, longer dialysis sessions in some countries, and uncertainty as regards the clinical benefits of very high clearances of small solutes in chronic HD. A large-diameter venous catheter is necessary to perform acute HD in the absence of a functional permanent vascular access. Under these circumstances, a double-lumen catheter is placed, usually in the internal jugular vein or femoral vein. One lumen is used to extract the blood from the patient (the so-called arterial side, even though it comes from the patient's vein), and the other lumen is used to return the blood to the patient ("venous" side). Femoral catheters are seldom left in place for more than one dialysis session unless the patient is confined to bed, because catheters in this location are prone to kinking, dislodgement, and infection [17].

17.7.1 Arteriovenous Fistula

Long-term vascular access for HD is usually established by the creation of an AVF in an upper extremity, although a lower extremity or even an axillary vessel may sometimes be employed. After AVF is established, the venous will receive a large flow of arterial blood so the venous segment will dilate and develop a thickened wall (arterializes) over time. As the KDOQI guidelines suggested, the AVF is the best vascular access method up to now. A literature review by the KDOQI groups determined that the AVF has the "longest life with least complications" and a "longer intervention-free life" than any other vascular access method. The radial artery and cephalic vein at the wrist are the most commonly

used vessels for fistula (radiocephalic fistula) (Fig. 17.4).

When a distal fistula has failed to creation or distal vessels are unavailable, the upper arm veins can provide other options. Both the cephalic and basilic veins can be applied to fistula creation; however, it is noteworthy that the basilic vein courses the upper arm in deep fascia, thereby an additional procedure of transposition is required. Fistulas should not be used for 6 weeks after their creation because their use prior to the maturity of the venous wall can shorten their life.

17.7.2 Arteriovenous Graft (AVG)

If a native AVF cannot be created, tubal material can be grafted under the skin between the artery and vein and be used as blood access. The use of several graft materials (autogenous, heterogeneous, and synthetic) has been attempted, including saphenous vein, bovine carotid artery, and polytetrafluoroethylene (PTFE). Partly due to the ease of placement and the short time required from the placement of an AVG to the initiation of puncture, PTFE accesses are highly prevalent. An AVG can be placed as a straight tube or as a loop between an artery and an appropriately matched vein, and it can be created almost anywhere in the arm (sometimes in the thigh if vessels in the arm are not available) (Fig. 17.5). Usually, a minimum waiting period of 2–3 weeks is recommended prior to use. However, a new material graft with trilayer sealing properties can be used after 24 h of implantation. Some complications of graft are similar to AVF, but the incidence rate of infection, stenosis, and thrombosis is higher. The most common cause of flow problems is intimal hyperplasia that leads to stenosis at the venous anastomosis. AVGs need more monitoring and intervention treatment to maintain a longer patency.

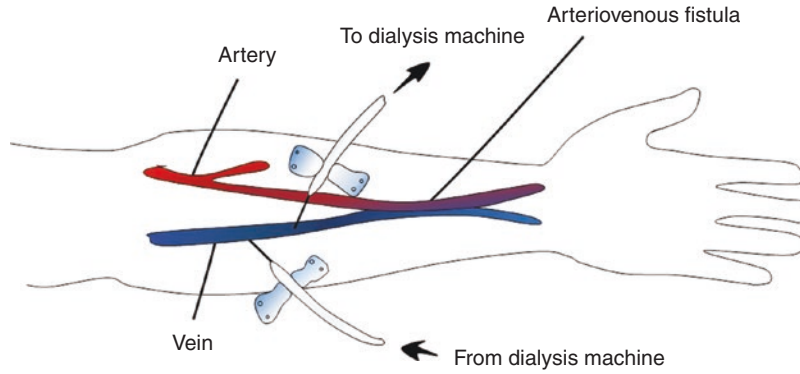

Fig. 17.4 Arteriovenous fistula. Arteriovenous fistula is established by surgical anastomosis of a peripheral artery with a larger subcutaneous vein

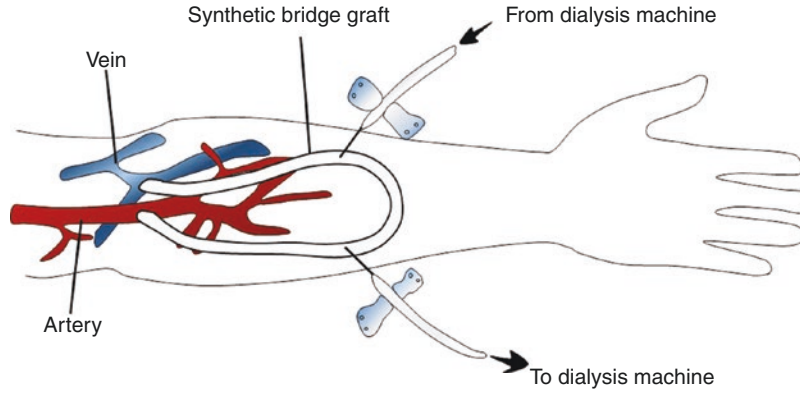

Fig. 17.5 Arteriovenous grafts. Arteriovenous grafts might be necessary when the patient's vascular status does not support a fistula. Polytetrafluoroethylene grafts are commonly used and can be repetitively punctured for hemodialysis

Stenosis at the outflow tract of AVFs, especially AVGs, frequently occurs and represents the major cause of failure of these accesses. Stenosis is almost exclusively due to neointimal hyperplasia, which is composed of proliferating myofibroblasts, and deposition of extracellular matrix, similar to that observed in coronary artery restenosis. Partial obstruction of the dialysis access impedes the flow of cleansed blood from the dialyzer back to the central veins; as a result, the blood recirculates back to the "arterial" (afferent) limb of the fistula and decreases the amount of fresh systemic blood delivered to the dialyzer, diminishing the overall efficiency of the dialysis process.

Several methods can be used to detect stenosis of AVFs and AVGs. Obstruction of the vascular access outflow tract leads to an increase in pressure inside the "venous" (efferent) tubing during HD, which has been used as a clue to the presence of fistula outflow stenosis. Techniques involving noninvasive devices and the dilution principle have been developed to assess the total blood flow through AVFs or AVGs. These monitoring techniques are performed during HD, and the monitoring equipment is sometimes built-in as a component of the dialysis machine. Gradual decrease in blood flow rate through the fistula or graft over time provides a clue and allows earlier detection of stenosis. Duplex ultrasonography is also useful for the diagnosis of vascular access stenosis. Nevertheless, the predominance of evidence suggests that regular monitoring of blood flow rates and prophylactic angioplasty intervention do not prolong the useful life of HD grafts. An angiogram (also called a "fistulogram" for AVFs) with contrast dye injection remains the gold standard for the confirmation and anatomic definition of vascular access stenosis. The fistulogram is also helpful in searching for collateral veins, which are impediments for the growth and maturation of the native fistula. Improvement in duplex ultrasonography techniques has diminished the use of contrast fistulograms, unless an angioplasty procedure is being planned in conjunction with the fistulogram.

Fistula or graft stenosis can be surgically treated by replacing or bypassing the stenotic segment. Alternatively, stenosis may be relieved by percutaneous balloon angioplasty with or without the placement of a stent to keep the lumen patent. Although angioplasty temporarily restores the flow and usefulness of the vascular access, a major problem with it is that the trauma induced by the balloon actually predisposes the vessel wall to further stenosis, setting up a vicious cycle. If left untreated, most stenotic vascular accesses eventually become totally occluded by thrombi. The value of systemic antiplatelet agents or anticoagulants to prolong the useful life of an AVF or AVG is unproven. Various pharmacologic and radiation strategies are being investigated to prevent dialysis graft stenosis and make synthetic grafts a better option. Until those strategies materialize, the native AVF remains the preferred vascular access.

17.7.3 Central Venous Catheters (CVCs)

Despite guidelines suggesting the early placement of an AVF and restraining CVCs to no more than 10% of all prevalent accesses, the usage of CVC is still prevalent. Currently, 82% of patients in the United States initiate dialysis with a CVC, and 19–25% use a CVC as their permanent access. The materials of current catheters include silicone, polyurethanes, or copolymers. Silicone is soft and flexible, while polyurethane is more rigid than silicone and is thermoplastic (i.e., more plastic when heated to body temperature), making it easier to insert, especially for emergent HD. The most efficient shaft design for dual-lumen catheters is the "double D." The size of current dual-lumen catheters ranges from 12F to 16F, and larger sizes are used for tunneled catheters. Current tunneled catheters can be adjusted to adapt to blood flow rates of 300–400 mL/min. For acute HD, especially unstable patients like patients with sepsis, the best suitable catheter is dual-lumen, noncuffed temporary catheter. The three main anatomical locations for catheter insertion are the femoral, jugular, and subclavian vein. For patients requiring extended HD or maintenance HD, tunneled cuffed catheters are preferred to be

utilized. It takes longer time to insert cuffed catheter and fluoroscopy is often required to ensure proper placement with the arterial port of the catheter at the entrance to the right atrium. Compared with AVF, catheters provide more rapid access to the circulation and can be placed in most patients in many different locations. However, it is notable that catheter placed for a long period could lead to stenosis and even occlusion of the placed vessel. Therefore, the internal jugular vein on the contralateral side of the planned AVF is preferred and used to avoid complications of central vein stenosis. Compared with arteriovenous access, CVCs are associated with more hospitalizations, higher morbidity and mortality, and higher overall annual per-person costs.

17.8 HD Anticoagulation

As an extracorporeal circulation treatment, anticoagulation is required during HD and CRRT to prevent clotting in the extracorporeal circuits. The ideal use of anticoagulants should not only ensure sufficient anticoagulation during HD but also avoid excessive anticoagulation leading to bleeding. The usage of anticoagulation therapy includes the evaluation of coagulation status, individualized selection of appropriate anticoagulants, and regular monitoring of coagulation state. Common anticoagulation methods are as follows: standard heparin anticoagulation, low-molecular-heparin anticoagulation, argatroban anticoagulation, local citric acid anticoagulation, and heparin-free anticoagulation.

17.8.1 Standard Heparin Anticoagulation

Unfractionated heparin (UFH) remains the most commonly selected anticoagulant during HD. The loading dose is given at the start of HD and then continued to be replenished into the blood through the heparin pump until 30 min before the end of HD. When there is no clinical risk of hemorrhagic disease and plasma antithrombin III activity >50%, UFH might be the first choice for HD. UFH for anticoagulation during HD can be monitored by monitoring the activated partial thromboplastin time (APTT). The value of APTT 1.5–2.0 times above the baseline during HD is recommended. UFH can reduce the platelet count (<100,000/mL), called heparin-induced thrombocytopenia (HIT), which is closely related to the immune response mediated by the anti-platelet factor 4–heparin complex.

17.8.2 Low-Molecular-Weight Heparins (LMWHs)

LMWH is derived from UFH via chemical or enzymatic depolymerization and is one third of the molecular weight of UFH. LMWH acts as an anticoagulant by inhibiting the activity of X factor, which has been thought to be safer in bleeding than UFH. Intravenous injection of 60–80 U/kg is administered before treatment, and no additional dosage is required for HD. The European Renal Best Practice guidelines for HD has recommended the use of LMWH for HD anticoagulation; nevertheless, UFH remains the most common anticoagulant for HD in China. Although cost might be the main factor against the use of LMWH in HD, their safety remains a matter of concern. The hemorrhagic risk of LMWH was not significantly different compared with UFH. To date, LMWH has been considered to be the anticoagulant as safe as UFH in HD [18].

17.8.3 Argatroban

Argatroban, a new thrombin inhibitor, can be reversibly combined with thrombin, which is mainly used in anticoagulation therapy for patients with acute cerebral ischemic infarction. Argatroban is highly selective for thrombin. Argatroban is a direct thrombin inhibitor derived from arginine that is used for anticoagulation of HD in patients with contraindications to UFH or LMWH. Clinically, if there are obvious bleeding tendencies in HD patients; or

plasma APTT, prothrombin time, and international normalized ratio are significantly prolonged; or HIT is suspected; or antithrombin III activity is below 50%, argatroban might be preferred in HD anticoagulation. It could be administered as an initial dosage of 100–250 μg/kg followed by a maintenance infusion of 0.5–2.0 μg/kg/min, which could be stopped at 20–30 min before the end of HD. The dose of argatroban should be adjusted according to the plasma APTT.

17.8.4 Regional Citrate Anticoagulation

Hemorrhagic events have been reported in more than 30% of critically ill patients with AKI receiving renal replacement. Regional citrate anticoagulation (RCA) has been shown to prolong the circuit life and reduce the incidence of hemorrhagic complications (Fig. 17.6). Citrate is infused into the proximal portion of the dialysis circuit, which combined with the circulatory ionized calcium prevents thrombin activation to achieve full blood anticoagulation. At the same time, calcium solution is infused at venous to supplement ionized calcium. Due to the anticoagulant effect only in vitro, RCA is especially suitable for patients in high risk of bleeding. The 2012 KDIGO clinical practice guidelines for AKI have recommended RCA as the preferred anticoagulation modality for CRRT in patients without contraindications for citrate. However, for patients with liver insufficiency, citric acid should be used with caution [19].

17.8.5 Heparin-Free HD

Heparin-free HD was developed for use in patients at high risk of bleeding or with bleeding complications. In heparin-free dialysis, preflushing the blood line with heparin saline and flushing the dialyzer with physiological saline every 15–30 min may help prevent clotting. Both the blood lines and the dialyzer need to be pretreated in heparin-free HD; the cumulative volume of saline administered should be removed from the body during dialysis. Nursing plays a vital role in heparin-free HD, with carefully monitoring of arterial and venous pressure alarms to detect early clotting. With the devel-

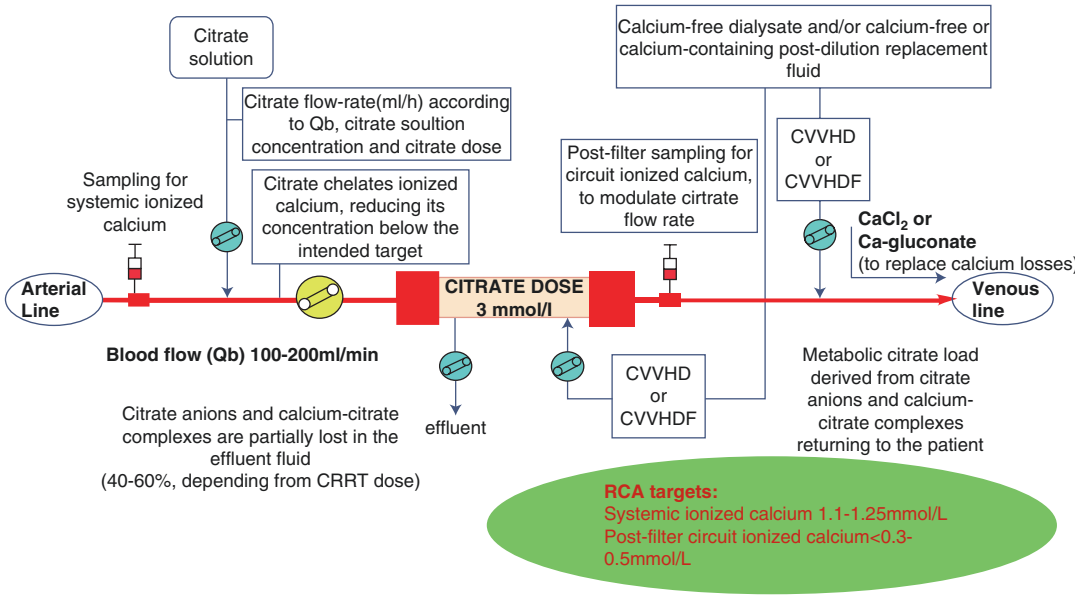

Fig. 17.6 Basic principles of regional citrate anticoagulation in continuous renal replacement therapy. *CRRT* continuous renal replacement therapy, *CVVHD* continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration, *RCA* regional citrate anticoagulation

opment of RCA application for patients at high risk of bleeding, the clinical application of heparin-free dialysis is gradually decreasing.

17.9 Adequacy of Dialysis Dose

Dialysis adequacy mainly relies on the solute mass balance achieved during HD, with the objective of restoring the homeostasis of the patient and without sodium and water overload. Efficacy of dialysis refers to the delivery of treatment which is sufficient to achieve an optimal long-term outcome. An adequately treated HD patient with a good quality of life is usually physically active, euvolemic, well nourished, and normotensive.

Different types of uremic toxins could be used to understand the relationship between HD prescribed parameters and uremic toxin clearance. The dose of uremic toxin clearance could be divided into three types: (1) dose of water-soluble toxin clearance, (2) dose of middle molecule clearance, and (3) dose of protein-bound toxin clearance. The dose of water-soluble toxin clearance has been identified with urea, and Kt/V_{urea} is the commonly used dose parameter. β2-Microglobulin is the widely used marker solute for middle molecules, and the dose of middle molecule clearance is related to the membrane pore size. Serum urea and β2-microglobulin could be detected routinely in clinical conditions. Due to the complexity of detection methods, the clearance of protein-bound toxins is difficult to be applied. *P*-cresol or *p*-cresol sulfate might be the most common marker used to categorize protein-bound toxin clearance. Because the relationship between long-term outcome and protein-bound solute clearance has not been clarified definitely, this specific class of toxins will not be further discussed here.

17.9.1 Randomized Controlled Clinical Trials on HD Adequacy

So far, there has been three randomized controlled clinical trials (RCTs) evaluating HD adequacy, the National Cooperative Dialysis Study (NCDS), HEMO study, and Membrane Permeability Outcome (MPO) study. The first two studies evaluated the effect of increased clearance of both water-soluble toxins and middle molecules such as β2-microglobulin. The results from NCDS demonstrated that small solute clearance was an important clinical predictor of HD patients. On the basis of NCDS, the urea kinetics as the measure of HD dose was established. The MPO study showed that HD patients appeared to gain no major benefit from a dialysis dose higher than that recommended by the current guidelines. There was no other benefit from the application of high-flux membrane either. In the MPO study, it was demonstrated that the use of high-flux membranes displayed a significant survival benefit among patients with hypoalbuminemia [20–22].

17.9.2 Assessment of Dialysis Dose with Water-Soluble Toxin Clearance

The clearance of water-soluble toxin by HD is primarily limited by the blood flow rate to the dialyzer, the dialysate flow rate, and the surface area of the HD membrane. In clinical practice, dialysis dose is often expressed as *Kt*/*V* or urea reduction ratio (URR).

17.9.2.1 *Kt*/*V*

Kt/*V* is a tool widely used to assess the delivery of dialysis dose. In clinical practice, *Kt*/*V* is used almost for urea, where *K* is the dialyzer urea clearance (liters per hour), *t* is the dialysis session time (hours), and *V* is the urea volume distribution (liters). A delivered *Kt*/*V* of 1.0 demonstrates that the volume of plasma cleared of urea ($K \times t$) during a dialysis session is equal to urea distribution volume (*V*). In daily clinical practice, single-pool *Kt*/*V* (*spKt*/*V*) is the most widely used parameter to assess dialysis dose.

$$spKt/V = -\ln\left(R - 0.008 \times t\right) + \left(4 - 3.5 \times R\right) \times \mathrm{UF}/W$$

where "ln" is the natural logarithm, "*R*" is the post-dialysis/pre-dialysis circulatory urea ratio, "*t*" is the HD session time (hours), "UF" is the

ultrafiltration volume (liters), and "*W*" is the patient's post-dialysis body weight (kilograms).

17.9.2.2 Urea Reduction Ratio

Urea reduction ratio (URR) refers to the dialysis-related reduction in circulatory urea concentration and is computed simply: URR = $1 - (C_t/C_0)$, where C_0 is the concentration of pre-dialysis serum urea and C_t is the concentration of post-dialysis serum urea. URR is a simple but an imprecise method of quantifying dialysis dose because it does not consider the urea generation during the dialysis and convective urea removal by UF. Even so, URR has been the widely accepted method to the evaluation of dialysis adequacy. It has been shown that URR is correlated well with the dialysis outcome. A minimum URR of 65–70% has been recommended for adequate HD.

17.9.2.3 Evaluation Criteria for the Adequacy of Dialysis Dose

- Good well-being
- Fewer complications of HD
- Better control of BP and extracellular fluid volume
- Electrolyte and acid–base balance maintained in the normal range
- Adequate nutritional status
- More effective removal of solute

17.9.3 Recommendations for the Adequacy of Dialysis Dose

Many expert groups have proposed clinical practice guidelines based on the three above-mentioned RCT studies. For example, the 2012 KDOQI clinical practice guidelines recommend that the dialysis dose should be monitored using *spKt*/*V* and the minimum dose be 1.2 with a target dose of 1.4 was suggested. However, the European Renal Best Practice guidelines recommend that the dialysis dose might be monitored using *eKt*/*V* and that the target dose be 1.2. These two recommendations are similar because a target *eKt*/*V* of 1.2 is approximately equal to a target *spKt*/*V* of 1.4. Once URR is used, average URR of 65% might be equivalent to a *Kt*/*V* of 1.2. The delivered dose of HD should be monitored at least once per month in all HD patients.

Key Messages

- Aside from renal transplantation and peritoneal dialysis, HD is the most popular RRT for patients with end-stage renal disease. Diffusion and convection are its main principles. The main components of the dialysis system include the extracorporeal blood circuit, dialyzer, dialysis machine, and water purification system.
- Acute complications of HD include neurological complications, allergic reactions, cardiovascular complications, hematological complications, and HD technique-associated complications; HD-associated infections and hypertension are the main chronic complications of HD.
- AVF is by far the best vascular access method for HD, having the "longest life with least complications" and a "longer intervention-free life" than any other vascular access method.
- Anticoagulation is required during HD to prevent clotting in the extracorporeal circuits. Several anticoagulants have been described, including systemic anticoagulation, regional citrate anticoagulation, and anticoagulation-free dialysis.
- Adequacy of dialysis dose refers to the dialysis dose considered sufficient to promote an optimal long-term outcome. The 2012 KDOQI clinical practice guidelines recommend that the dialysis dose should be monitored using *spKt*/*V* and suggest with a target dose of 1.4.

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Peritoneal Dialysis

18

Jia Di

Abstract

Peritoneal dialysis (PD) is an effective, convenient, and economical modality for patients with renal failure, and its characteristic is that the treatment of PD can be done at home. PD utilizes the peritoneum as a biological dialysis membrane to remove metabolites from the body to the peritoneal cavity and to correct the abnormality of the fluid and electrolyte by diffusion and ultrafiltration simultaneously. The main components of PD system include peritoneal and abdominal cavity, dialysate, peritoneal catheter, and connecting devices. In this chapter, we mainly introduce the principles of PD, indications and contraindications for PD, PD modalities, evaluation methods of PD, and its applications and complications.

18.1 Introduction

For patients with acute and chronic renal failure, peritoneal dialysis (PD) is one of the main modalites of renal replacement therapy. Overall, there exists no evidence on significant differences in critical outcomes between PD and hemodialysis (HD), although it is widely accepted that PD could more effectively preserve the residual renal function than HD. Most studies indicate the survival advantage of PD for individuals without diabetes and younger individuals with diabetes who have no other coexisting medical conditions [1]. Therefore, PD is the first choice of stage 5 chronic kidney disease (CKD) for individuals with residual renal function, children aged 2 years or older, and adults without serious complications. On the contrary, the worse overall health of the patient is, the lesser survival advantage with PD becomes. The health-associated quality of life provided by PD to patients is similar to that provided by HD; however, PD patients are more satisfied with their care but are more likely to switch to HD because of technique failure.

18.2 Peritoneal Barrier

The mechanism of PD is to remove uremic toxins and excess fluid by using a system of biological membranes and the dialysis fluid infused into the peritoneal cavity. Peritoneal cavity is the largest serosal cavity in the human body, the surface area of which is about 1–2 m^2 [5].

There are five different resistance barriers that are contained in the peritoneum:

1. The interstitial space
2. The unstirred fluid layers in the peritoneal cavity
3. The capillary wall (endothelium and basement membrane)

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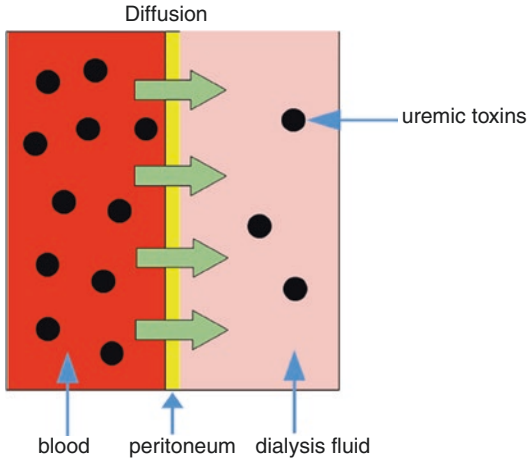

Fig. 18.1 Diffusion is driven by the concentration gradient over the membrane

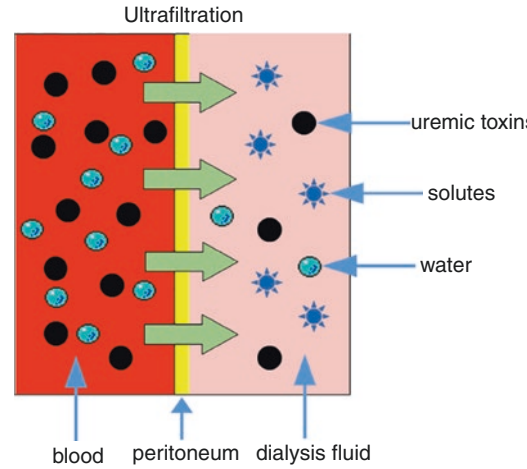

Fig. 18.2 Ultrafiltration driven by the osmotic agent over the membrane

Table 18.1 Compositions of commonly used glucose lactate dialysate

	Glucose ($C_6H_{12}O_6 \cdot H_2O$) (g)	Osmotic pressure (mOsmol/L)	pH	Ion concentration				
				Na	Ca	Mg	Chloride	Lactate
1.5% glucose lactate dialysate	1.5	346	5.2 (4.5–6.5)	132	1.75/1.25	0.25	95–106	35–40
2.5% glucose lactate dialysate	2.5	396						
4.25% glucose lactate dialysate	4.25	485						

4. The unstirred fluid layer in the capillaries
5. The mesothelium and its basement membrane

The major transport barrier for transperitoneal exchange is recognized as the capillary wall. The interstitium of the capillary wall is particularly important in long-term PD patients whose submesothelial tissues are markedly of increased thickness. On the contrary, the mesothelium is not an important transport barrier because of its highly permeable character [5].

In the process of PD, diffusion is the main way for solutes to be bidirectionally transported through the peritoneal barrier. The concentration gradient over the membrane can drive diffusive transport through membrane (Fig. 18.1). To a lesser extent, solutes are transported into the peritoneal cavity by convection because of osmotic disequilibrium resulted from osmotic agent and hydrostatic pressure differences (Fig. 18.2). Furthermore, accompanied by convective fluid absorption, the solute is transported into the surrounding tissues from the peritoneal cavity and to the blood via the lymphatic vessels.

Lactate dialysates with different concentrations of glucose, thereby with different osmotic pressure, are used in clinical practice. Composition of commonly used glucose lactate dialysates is shown in Table 18.1.

18.3 Catheter Design and Insertion Techniques

Several different types of catheters and catheter insertion techniques are used in PD. The advantages and disadvantages of different techniques for catheter insertion are summarized in Table 18.2.

Flexible catheters—As the gold standard for PD access, Tenckhoff catheter is the most widely used in patients with chronic dialysis.

Table 18.2 Advantages and disadvantages of different catheter insertion techniques

	Advantages	Disadvantages
Percutaneous (bedside)	• Can be performed at bedside, allowing rapid initiation of dialysis	• Risk of bowel or bladder injury
	• Physician or nurse can be trained to perform the procedure	• Not suitable for patients with previous midline surgical scars or risk of adhesions
Open surgical	• Available in most centers	• Requires surgical scheduling, with available operating theater time at a premium
	• Lower cost of consumables than that with laparoscopy	
Laparoscopic	• Lower incidence of leakage	• Requires skilled personnel
	• Ability to perform adjunctive procedures	• High cost of consumables
	• Ability to place the catheter in the pelvis under vision	

Rigid catheters—By using a trocar device, the catheter can be inserted directly to the iliac fossae. Dialysis using these catheters is less efficient although they are easy to be inserted. Also, this catheter design tends to generate some complications, such as bladder or bowel perforation, bleeding, leakage of dialysate, and obstruction owing to the small side holes and lumen [4].

18.4 Indications and Contraindications for PD

18.4.1 Indications

PD is recommended as the first-line treatment modality of renal replacement theraphy for the following patients with CKD stage 5: (1) children aged ≥2 years, (2) individuals with residual renal function, and (3) adults with no significant related comorbidities.

18.4.2 Contraindications

Contraindications for PD are summarized in Table 18.3.

Table 18.3 Contraindications for peritoneal dialysis

Absolute	Relative
• Loss of peritoneal function	• Recent abdominal aortic graft
• Producing inadequate clearance	• Ventriculoperitoneal shunt
• Adhesions blocking the dialysate flow	• Intolerance to intra-abdominal fluid loading
• Surgically uncorrectable abdominal hernia	• Large muscle mass
• Abdominal wall stoma	• Morbid obesity
• Diaphragmatic fluid leakage	• Severe malnutrition
• Inability to perform exchanges in the absence of suitable assistant	• Skin infection • Bowel disease

18.5 PD Modalities

Several major PD modalities exist, which include the following:

1. Continuous ambulatory peritoneal dialysis (CAPD)—Patients undergo PD throughout the day.
2. Continuous cycling peritoneal dialysis (CCPD)—Patients undergo PD throughout the day, which is assisted by automated machines overnight.
3. Intermittent peritoneal dialysis (IPD)—Patients undergo intermittent PD.
4. Automated peritoneal dialysis (APD)—Patients undergo PD assisted by automated machines.

Since the invention of Tenckhoff catheter in 1968 and appearance of wearable/portable equilibrium dialysis technique in 1976, CAPD has

been used as a feasible modality of renal replacement therapy in the long-term treatment of patients with end-stage renal disease (ESRD). Twin bags are used in CAPD patients to reduce the number of connections and disconnections required to be established everyday [5].

CCPD is suitable for patients requiring help (such as children, blind individuals, and the elderly) or daytime workers. Patients can carry out their own activities and work with the peritoneal dialysate in the abdominal cavity throughout the day and have good sleep assisted by automated machines overnight.

IPD is applied to acute or chronic renal failure for the initial 3–10 days of CAPD. IPD removes more water, is associated with fewer complications of peritonitis, and can discharge more nitrogen.

The advantage of APD is that it needs less intensive nursing care, but the disadvantage is that it increases the financial burden. During APD, a variety of highly efficient treatment arrangements can be provided by the use of high flows of dialysate, individualized intraperitoneal fluid volumes, and short residence times.

Overall, there exists no evidence on significant differences in critical outcomes among modalities, such as quality of life, mortality, adverse events, nutritional status, and technique survival for patients treated with CAPD and APD. Therefore, adults and children can opt for CAPD, CCPD, or APD. However, APD has been recommended as the preferred option for infants and children on a liquid diet based on clinical experience. The National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF–DOQI) guidelines recommended Kt/V target of 2.0 for CAPD and 2.1 for CCPD every week in 1997. Because higher daily dialysis solution volumes can be easier and more convenient delivered by using automated machines, cycler utilization is increased in order to achieve these high targets. Nevertheless, in recent NKF–DOQI guidelines, the Kt/V targets for CAPD have been mildly reduced to 1.7. The use of APD has significantly increased since its reintroduction, probably because its use promotes positive changes in the lifestyle of dialysis patients [2].

18.6 Assessment

18.6.1 Peritoneal Equilibration Test (PET)

The most commonly used method for evaluating the transport characteristic of peritoneal membrane is PET. As a simple clinical method, PET is widely used to assess the rapidity of urea, creatinine, and other solutes diffusion across the peritoneal membrane. It has become a routine method for the evaluation of clinically important alterations in peritoneal transport characteristics. In this test, the dialysate to plasma solute concentration (D/P) ratio for particular solutes is measured during an exchange with conventional PD fluid [5].

The standard procedure for PET is listed below [8]:

1. After total drainage of the prior dwell (if CAPD, typically 8 h), perform this test in the morning.
2. Use dextrose dialysate (2.5%) to instill the usual fill volume.
3. After infusion, immediately (0 h) and at 2 and 4 h, collect dialysate sample to determine the concentrations of glucose, creatinine, and urea.
4. After dialysate infusion, collect blood sample at 2 h to determine the concentrations of glucose, creatinine, and urea.
5. Record the drainage volume when the dialysate is drained at 4 h. Calculate the D/P ratios for urea and creatinine at 2 and 4 h.
6. Calculate and compare the dialysate glucose concentrations at 2 and 4 h to the beginning concentration (D/D_0).
7. Draw these on standard PET graphs to determine the peritoneal membrane type.

This protocol is usually simplified in clinical practice. Dialysate samples are collected immediately after infusion, and then collected 2 and 4 h later. The dialysate is drained and the volume is recorded after 4 h. At 2 h dwell time a blood sample is drawn. The drainage volume of dialysate which is used as a measure for evaluating ultrafiltration capacity, the D/D_0 ratio for glucose and the D/P ratio

for creatinine, are usually compared to standard values. The D/D_0 for glucose and D/P for creatinine from the PET will be closely correlated with the diffusive mass transport coefficient for these solutes.

This test can categorize patients into four different transport groups according to Twardowski's initial classification: high transporters, high average transporters, low average transporters, and low transporters. Because of faster glucose absorption, high transporters and high average transporters have poorer net ultrafiltration, but they have more rapid creatinine equilibration. On the other hand, low transporters and low average transporters have lower solute transport, leading to slower glucose absorption and higher net ultrafiltration but lower peritoneal clearances for larger solutes and creatinine.

This test provides evidence for further refining the dialysis prescription. Low transporters can maintain volume control on a standard CAPD prescription even when the residual renal function has lost. High transporters require short, frequent exchanges to acquire adequate ultrafiltration. Clinical management and outcomes of PD patients are significantly affected by their peritoneal transport characteristics. Similarly, optimal dialysis prescriptions in regard to ultrafiltration and small solute clearances are greatly affected by the peritoneal small solute transport characteristics of patients. In addition, an important risk factor for both PD technique failure and mortality is thought to be a high peritoneal transport rate.

18.6.2 Kt/V_{urea} Measurement

Kt/V_{urea} measurement (urea clearance over time) is often used to assess the dose and/or efficacy of PD, where, K = volume of dialysate drained multiplied by dialysate/plasma urea concentration, t = dialysis duration, V = urea distribution volume (total body water calculated as 0.5 [for females] or 0.6 [for males] multiplied by body weight), and Kt/V_{urea} is the main indicator used to evaluate the adequacy of PD and nutritional status of PD patients. Kt/V_{urea} and total creatinine clearance must be determined in clinically stable patients. The NKF–DOQI guidelines recommended a weekly Kt/V target above at least 1.7. Increasing the dialysis dose by increasing the number of exchanges is a common technique to increase Kt/V.

18.6.3 Residual Renal Function

Residual renal function refers to the clearance and endocrine function of renal tissues after injury and is an important parameter that most likely changes with time in PD patients. As residual creatinine clearance could be overestimated by the secretion of creatinine when the renal function is low, it is recommended to express this as the mean of urea and creatinine clearances. The residual creatinine clearance rate is significantly higher in PD patients with residual renal function than in those without. The residual renal function is directly related to the survival rate and prognosis of PD patients. Preserving the residual renal function can effectively improve the quality of life of dialysis patients. However, as the duration of PD increases, the residual renal function gradually decreases.

18.7 PD for Acute Kidney Injury (AKI)

In the 1920s, PD was first used in the treatment of AKI patients. At present, PD is still a treatment modality often used for AKI in developing world. There are many superiorities for PD to treat patients with AKI. Several studies have suggested that outcomes with PD can be comparable to that with extracorporeal renal replacement therapy [2].

18.7.1 Advantages

PD has minimal equipment requirements and is of lower cost and technically simple. PD is a better modality especially for patients at risk of bleeding, with difficult vascular access or increased intracranial pressure. PD has been thought to be less inflammatory and more physiological than

extracorporeal therapies. There is a considerable interest that toxic cytokines in sepsis can be removed by using high cut-off membranes for hemofiltration. PD may provide a great advantage over conventional HD and filtration because of the large pores in the peritoneal membrane allowing the clearance of these molecules [2].

18.7.2 Disadvantages

Nevertheless, there are still critical concerns about PD for AKI, including primarily risk of peritonitis, possible inadequate solute clearances, and potentially unpredictable fluid removal rates. Furthermore, hyperglycemia from glucose-containing dialysate, glucose absorption, and excessive protein loss through the peritoneal membrane are other potential PD-specific problems. Additionally, reduced functional residual capacity coming from impaired diaphragmatic movement is also a problem, particularly among mechanically ventilated patients [2].

18.8 PD for ESRD

PD has long been established as an alternative method for renal replacement therapy in patients with ESRD. The percentage of PD ranges from 0 to 30% in adults with changes in local practice and resources and reaches >50% in children. PD is the preferred initial modality of renal replacement therapy for patients with ESRD and is particularly the best option for infants and small children with ESRD. The 2011 National Institute for Health and Care Excellence (NICE) clinical guideline suggested PD to be the primal choice for dialysis treatment of CKD stage 5 in children ≥2 years, adults without significant associated comorbidities, and individuals with residual renal function [3].

Peritoneal membrane function should be regularly monitored at least every 6 months using PET or its equivalent. If clinically or biochemically indicated or to achieve clearance targets, it could be more frequently measured in adults and children. The NICE recommends that the minimal treatment doses for adults should be a combined urinary and peritoneal Kt/V_{urea} of 1.7/week or a creatinine clearance of 50 L/week/1.73 m^2. If patients are experiencing uremic symptom, the dialysis dose should be increased. A continuous 24-h PD regimen is preferred over an intermittent regimen for patients with anuria [3].

The success of a PD program depends on specialized nurses. They have appropriate skills in assessing and training patients for PD and in monitoring treatment. They also have sufficient resources to provide continued care in the community. In 2012 the National Renal Workforce Planning Group suggested a caseload of up to 20 PD patients for every nurse. The requirement for specialized nurses with skills to deal with complex patient educational issues has been highlighted in the 2016 International Society for Peritoneal Dialysis (ISPD) guidelines on teaching PD to patients and caregivers. In order to promote PD as a therapeutic option and develop clinical management policies, a designated lead clinician for PD in each unit is needed[1].

18.9 Complications of PD

A number of potential complications are associated with the use of PD. The following are briefly discussed:

- PD-related infections
- Encapsulating peritoneal sclerosis (EPS)
- Mechanical or catheter-related problems

18.9.1 PD-Related Infections

18.9.1.1 Category

PD-related infections include PD-related peritonitis and PD catheter infection.

- PD-related peritonitis
- PD-related peritonitis is diagnosed by the presence of fever, abdominal pain, cloudy dialysate, and a leukocyte count >100 cells/μL (or polymorphonuclear cells >50%) after a 2-h dwell time. The

peritoneal fluid culture suggests the species of organisms [3].
- PD catheter infection
- PD catheter infection includes exit-site and tunnel infections. Exit-site infection is defined as the presence of pain, swelling, erythema, and serous discharge at the exit site. Tunnel infection is defined as the presence of pain, tenderness, erythema, induration, or any combination of these signs and symptoms present over the subcutaneous tunnel of the catheter [3].

18.9.1.2 Causes

Touch contamination, catheter-related problems, bowel pathology, gynecological disease, or systemic bacteremia.

18.9.1.3 Results

Complications resulting from PD-related peritonitis and catheter infections include hospitalization, switching to HD (either permanently or temporarily), catheter loss, and death. Peritonitis is probably the most important cause of technique failure in PD patients.

18.9.1.4 Prevention Strategies

Preventing exit-site infections is appropriate to reduce the rate of peritonitis. The NICE recommended in 2017 that patients undergo regular revision of their technique. Antibiotic prophylaxis should be administered during initial catheter insertion, and mupirocin and gentamicin should be used to reduce the frequency of exit-site infection and peritonitis [3].

18.9.1.5 Treatment

- PD catheter infection
- Exit and tunnel infections can lead to peritonitis and must therefore be treated aggressively. The treatment course is at least 2 weeks or until the exit site appears normal. The ISPD guidelines emphasize that in case of refractory PD-related peritonitis, PD catheter should be timely removed. Furthermore, when a *Pseudomonas* infection or associated tunnel infection is present, PD catheter removal or swap is required in refractory exit-site infections and may be required earlier. Initial treatment regimens should cover Gram-negative and Gram-positive bacteria, including *Pseudomonas* species until getting the results of culture and antibiotic sensitivities are obtained. Although methicillin-resistant *Staphylococcus aureus* require systemic treatment, oral antibiotics are as effective as intraperitoneal injection [7].
- PD-related peritonitis
- The ISPD guidelines recommend the use of first- and third-generation cephalosporins for empiric therapy. If patients have prior infections resistant to first-generation cephalosporins, vancomycin can be used with a third-generation cephalosporin. Intraperitoneal administration is recommended, and intravenous administration should be considered for hospitalized and acutely ill patients. The treatment course should be lasted for 2 weeks. However, peritonitis caused by *S. aureus*, *Enterococcus* sp., *Pseudomonas*/*Stenotrophomonas* sp., or multiple organisms needs 3 weeks of treatment. If no organisms are detected, Gram-negative coverage can be stopped at 96 h if the patient is clinically better, and Gram-positive coverage can be lasted for 2 weeks. In the case of relapsing peritonitis (recurrence of peritonitis because of the same organism within 4 weeks of therapy completion), it is recommended to remove catheter [7].

Fungal peritonitis occurs in patients undergoing PD at a rate of 0.01–0.19 episodes for each dialysis-year. Frequent episodes of bacterial peritonitis, recent antibiotic therapy, and immunosuppression are main risk factors for fungal peritonitis. Patients are usually seriously ill with significant abdominal tenderness. Once fungi are identified, it is recommended to remove catheter immediately.

18.9.2 EPS

18.9.2.1 Diagnosis

EPS is defined as a potential and rare complication of long-term PD, always occurring in patients on PD for more than 5 years. It is diagnosed by a combination of bowel obstruction and features of

encapsulation due to peritoneal fibrosis. The common symptoms of EPS are anorexia, nausea, vomiting, and weight loss. Additionally, it is important to recognize the stepwise process of symptom progression.

18.9.2.2 Management

Some strategies to reduce the risk of EPS include the following [6]:

1. Minimizing dialysate glucose exposure but ensuring that the fluid volume status is not consequently compromised.
2. Using interventions recommended by the ISPD guidelines for peritonitis to preventing acute PD-related peritonitis.
3. Using neutral-pH, low-glucose degradation product PD solutions (low-grade evidence only).

Early monitoring of nutritional status and dietetic referral are essential for patients with EPS. Such nutritional support is often provided by oral, enteral, or parenteral supplementation. Using any medical therapy to treat EPS has not been recommended in any clear evidence. Immunosuppressants, corticosteroids, and tamoxifen have been used to treat EPS at the physician's discretion. Decisions about the duration of therapy should be tailored to the individual patient. Clinical and social factors as well as the patient's wishes and the principles outlined in the ISPD guidelines should be followed [6].

18.9.3 Mechanical or Catheter-Related Problems

Catheter obstruction may come from displacement and omental wrapping of the catheter or fibrin blockage of the catheter. In the latter situation, flushing the catheter with sterile saline may dislodge the blockage. Once the flow is reestablished, 500–1000 units of heparin need to be added to each liter of PD fluid.

Methods for manipulating displaced PD catheters could include guidewire (blind or fluoroscopic) manipulation and laxative use. The catheter should be replaced if these methods fail.

Key Messages

- PD is a major dialysis modality recommended as the initial renal replacement therapy for CKD stage 5 in individuals with residual renal function, children aged ≥2 years, and adults without significant associated comorbidities.
- Tenckhoff catheter is the gold standard for PD access, and open surgical catheter insertion is most widely used in PD centers.
- PD is a safe and effective method for blood purification and fluid removal in AKI.
- Overall, there are no significant differences in critical outcomes between CAPD and APD.
- The NICE recommends that the minimal treatment doses for adults should be a combined urinary and peritoneal Kt/V_{urea} of 1.7/week.
- PD-related infections, EPS, and mechanical or catheter-related problems are major complications associated with PD.

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Transplantation

19

Hao Ding and Junwei Yang

Abstract

Renal transplantation is the best modality of renal replacement therapy available for most patients with end-stage renal disease and is one of the breakthroughs in medical science in recent decades. Our knowledge of HLA typing, cross-match testing, recipient preparation, donor management, and postoperative care have advanced and brought widespread benefits, and these are crucial for clinicians to formulate an appropriate treatment regimen. Great effects should be paid to selection and preparation of kidney transplant recipients because of the risks from immunosuppressive therapy. Reducing acute rejection episodes and minimizing ischemic damage is the main goal of immunosuppressive therapy. The general concepts that most clinicians agree useful include induction therapy and maintenance treatment. Delayed graft function after kidney transplantation is usually defined as the need for dialysis during the first postoperative week, anuria, or failure of prompt azotemia resolution, and most studies suggest that patients with DGF have worse long-term outcomes than patients with immediate function. Although the outcomes of renal transplant patients have improved over the years, this population continues to show significant morbidity and mortality due to infection. Transplantation team should attempt to achieve a balance between preventing allograft rejection and maintaining immune system integrity.

19.1 Introduction

End-stage renal disease (ESRD) represents a growing global public health epidemic, and the prevalence of ESRD may rise sharply over the next few decades. Renal replacement therapy is available as three different modalities, i.e., hemodialysis, peritoneal dialysis, and a kidney transplant. Renal transplantation is one of the pioneering advances in medicine. It not only improves quality of life of patients with ESRD but also has been proven to prolong life [1]. Renal transplantation is a relatively young field of medicine, with the successful induction of immunological tolerance in rats by Peter Medawar and his colleagues at University College London in 1953 and the first successful kidney transplantation by Joseph Murray and his colleagues at Harvard in 1954.

Our knowledge of HLA typing and cross-match testing, immunosuppression, recipient preparation, donor management, and postoperative care has advanced and brought widespread

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benefits. The acute immune response to the transplanted tissue can now be controlled such that short-term graft survival has improved impressively. Nonetheless, this progress has not been accompanied with the improvement of long-term graft survival, and antibody-mediated rejection (AMR) has adverse long-term effects on the graft. Managing transplant recipients is challenging even for the most experienced transplant physicians, who need to understand not only the relevant basic research but also clinical transplant medicine.

With the invention of novel immunosuppressive drugs, kidney transplantation has made great progress in recent years. Unfortunately, the shortage of donated organs remains a major limiting factor, and the issues associated with organ donation, retrieval, and preservation are still challenging. Furthermore, the immune system poses many problems that have yet to be resolved, and donor-specific tolerance, which is the ultimate goal of transplantation, has still a long way to go. Clinical xenotransplantation—a procedure holding promise to solve the shortage of human donor organs—and engineered allografts are unlikely to be realized in the near future.

19.2 Histocompatibility Testing

The recipient's lymphocytes recognize the cell surface proteins of the transplanted tissue that are different from those of the recipient and trigger inflammatory events that cause allograft injury. Once the patient is determined to be a suitable transplant candidate, HLA typing and antibody screening tests are performed by the methods described in the following sections.

The histocompatibility test should be considered a risk assessment before transplantation. Therefore, a complete risk assessment of any donor–recipient pair must take into account HLA typing and possibly involve multiantibody detection methods. In addition, antibody analysis is increasingly being carried out posttransplant as a noninvasive predictor of acute and chronic alloimmune complications. Understanding the complexity and interactivity of these histocompatibility methods and their interpretation parameters is crucial for clinicians to formulate appropriate treatment interventions.

19.2.1 ABO Incompatibility

The ABO blood group antigen system is the most important immune barrier for successful transplantation. At the time of transplantation, ABO-incompatible kidneys can be rejected immediately. Nevertheless, in some cases, a transplant with a different ABO blood type is possible. Several research groups have already developed protocols for transplanting kidneys across major ABO barriers. These programs are based on various techniques and drugs to reduce the amounts of anti-A or anti-B antibodies. These antibody reduction methods help to expand the number of patients who may receive a kidney from a living donor [2].

19.2.2 HLA Typing

HLA typing quantifies the number of HLA antigen mismatches between donor and recipient, and it is one of the most important risk assessment tools for predicting non-self-HLA recognition. Serological tests have been performed in small plastic trays with a grid of small flat-bottomed wells containing antibodies. If lymphocytes from an individual have antigens on their surface that the antibodies can bind, then complement is activated and vital dyes are absorbed into those cells on which the membrane attack complex forms. Serological typing can yield rapid results, which are important for deceased donor typing. Nonetheless, small amino acid differences in HLA proteins may have strong immunological consequences and are not easily detectable by serological methods. In addition, the number of HLA alleles increases annually, and it is difficult to find high-quality serum samples with sufficient antibody to identify.

It is now more common to type individuals by DNA-based rather than serological methods. Advantages of molecular typing include greater

accuracy and reproducibility of the reagents. Aside from lymphocytes, typing can be performed on tissues containing other nucleated cells. Today's next-generation sequencing (NGS) has become an everyday research tool to address HLA-typing tasks. NGS offers more powerful higher-throughput sequencing, and the protocol is getting simpler for clinical laboratories. The ultimate goal of accurate high-resolution typing is to improve transplant outcomes.

- Past: RFLP (restriction fragment length polymorphism)
- Present: SSOP (sequence-specific oligonucleotide probes), reverse SSOP, real-time PCR, NGS
- Future: NGS

19.2.3 HLA Antibody Screening

Sensitization to HLA antigens occurs during pregnancy or in patients who had received blood transfusion or a previous transplant. Patients with circulating anti-HLA antibodies are at a high risk of rejection. Therefore, sensitive and specific detection of anti-HLA antibodies is necessary for the identification of the sensitized recipients. By considering all relevant antibodies and avoiding false-positive cross-matching of antibodies that are not clinically relevant, the anti-HLA antibody screening process must ensure a true negative cross-match with the intended donor. Over the past 40 years, various methods for detecting and characterizing anti-HLA antibodies have been developed:

- NIH-CDC
- AMOS modified
- Antiglobulin-augmented AHG-CC
- ELISA
- Flow cytometry
- Luminex

The complement-dependent lymphocyte toxicity (CDC) assay is the most popular method for anti-HLA antibody screening. B cells and T cells which have variable HLA types incubated with patient's serum, complement will be activated if the serum contains antibodies that bind to the cell surface at sufficient density, and the absorption of vital dyes allows for easy identification of dead cells. For example, in a 50-cell group, the positive reaction to 30 cells represents 60% of PRA. The CDC PRA assay has serious limitations. For example, the percentage of PRA may vary according to the cell group employed in the screening. In addition, substantial false-positive results and false-negative results may be obtained. Finally, it is almost impossible to compile an accurate and complete antibody-specific list in this way.

Due to the limitations of the CDC assay, there is an urgent need for more sensitive analytical methods. Solid-phase analysis by means of affinity-purified HLA antigens is now available for a variety of platforms. These methods involve only soluble or recombinant HLA molecules that are applied to solid-phase media platforms (ELISA) or beads; therefore, the solid phase will bind HLA antibodies only when recipient serum is added. Neither viable lymphocytes nor complement fixation is required, and target HLA specificity can be determined next by using a panel of HLA antigens from individual donors or by means of a single HLA antigen. The outputs of the solid-phase analysis can show substantial interlaboratory differences because there is considerable controversy as to what thresholds should be considered a cutoff for positive results. To determine whether the recipient has a donor antibody, the solid-phase antibody screening data should be analyzed in conjunction with cross-matching results [3].

19.2.4 Cross-Matching

The cross-match test is the final pretransplantation immunological screening step. Cross-matching determines whether the recipient has antibodies against donor. Just as cytotoxic PRA, cytotoxic cross-matching may miss low-titer antibodies, resulting in false negatives or detection of false-positive antibodies. To address this issue, serum samples from patients with IgM autoantibodies should be heated or treated with dithioth-

reitol to eliminate IgM prior to final cross-pairing. Flow-cytometric cross-match (FCXM) assays are more sensitive to complement-binding antibodies than standard complement-dependent cytotoxicity assays. Nonetheless, the thresholds of positivity may differ between laboratories. Therefore, there is considerable interlaboratory variability in the routine methods of FCXM. The status of FCXM remains controversial, and its role in the assessment of patients' immune risk has not been confirmed. Furthermore, these tests may not be available in all laboratories.

19.2.5 Non-HLA Antibodies

In some cases, antibody-mediated results are histopathologically or clinically suspicious while circulating anti-HLA antibodies have not been detected. Those immunity-associated, non-HLA antibodies may contribute to these cases, and detection of these non-HLA antibodies is still being studied.

19.3 Selection and Preparation of the Living Kidney Donor

Renal transplant is the best treatment for patients with ESRD; however, it cannot be performed without kidney donors. Both living and deceased donors contribute critically to the success of the transplantation endeavor on the individual, national, and international levels. Nevertheless, the shortage of cadaveric kidney transplants has caused patients to wait for longer periods to reap the benefits of transplantation. In comparison with deceased donor transplantation, live donor transplantation has the following advantages:

- Better long-term outcomes
- The procedure can be performed preemptively, thereby helping to avoid dialysis
- This procedure is elective and allows for optimization of the recipient
- Low rates of delayed graft function (DGF)

Even when corrected for ischemic times and DGF, live donor source is one of the strongest factors associated with good graft survival. The use of live kidney donors varies widely, and agreements to evaluate potential donors may vary widely among medical centers. On the other hand, many published expert recommendations can serve as the basis for most living donor experiments, including the United States guidelines and the Amsterdam living kidney donor guidelines.

19.3.1 Informed Consent

An important part of living kidney donation involves informed consent. According to the consensus conference, living donors should be willing to donate, be under no coercion, be suitable according to medical and social psychology, and must fully understand the risks, benefits, and alternative treatments available to the recipient. Donor advocates should ensure that potential donors fully and undeniably understand the immediate and long-term team risks and benefits of organ donation, so that donors can independently decide whether to perform a donation assessment.

19.3.2 Risks to Donors

Laparoscopic technique is associated with decreased discomfort and postsurgical pain and most transplant centers perform this technique. Two studies in the United States have estimated perioperative mortality at ~0.02–0.03%. The most common causes of death are a pulmonary embolus and cardiac events. In addition, there has been concern about the possibility that patients with a single kidney may develop glomerular hyperfiltration, hypertension, proteinuria, and renal insufficiency long-term. Living kidney donors are at a small but significantly increased risk of ESRD as compared with nondonors [4].

19.3.3 Evaluation of Living Kidney Donor

Living-donor evaluation includes a complete medical history taking, past medical history tak-

ing, physical examination, laboratory tests, serological screening for infectious diseases, renal scintigraphy, radiological imaging, and appropriate cancer screening. Furthermore, people being considered for the donation should be healthy or have only mild diseases that do not cause functional limitations.

19.3.4 Renal Function Evaluation

Serum creatinine and creatinine clearance testing is employed to estimate glomerular filtration rate (GFR) in most centers, whereas practice varies widely around the world. In the UK, GFR should be measured by an isotopic method, most often involving ^{51}Cr-EDTA, and normalized to body surface area (mL/min/1.73 m^2). In the USA and many European countries, GFR is often estimated from creatinine clearance calculated via 24-h urine collection. Renal echography and sequential scintigraphy are helpful for assessing morphological and function characteristics of the two kidneys. Imaging of arterial and venous anatomy includes

- Intra-arterial angiography
- Spiral computed tomography (CT) angiography
- Magnetic resonance (MR) angiography (less accurate than CT)

Spiral CT angiography has largely replaced intra-arterial angiography because this technique helps to avoid the complications of arterial puncture and provides accurate arterial and venous phase images. Furthermore, 3D reconstruction of spiral CT is helpful for planning laparoscopic nephrectomy.

19.3.5 Summary

Comprehensive assessment and education of living kidney donors is a complex and time-consuming process requiring a thoughtful approach and extensive detailed communication among all members of the transplant team. There is an urgent need for new studies on donor and recipient outcomes after transplantation in contemporary cohorts [5].

19.4 Selection and Preparation of the Recipient

Kidney transplantation is the treatment of choice for patients with ESRD, and there are few conditions that are absolute contraindications for kidney transplantation. Proper selection and preparation of kidney transplant recipients are important goals of the transplant team due to the risks associated with immunosuppressive therapy. The goal of pretransplantation assessment is to obtain maximal benefits from transplantation which in turn leads to an increase in quality of life and life expectancy of the patients.

19.4.1 Timing of Referral and Contraindications of Transplantation

In ideal circumstances, preparation for transplantation begins as soon as progressive CKD is recognized. Increased cardiovascular risk, which is a major determinant of posttransplantation morbidity and mortality, can be recognized as soon as the serum creatinine level is elevated. It is well known that preemptive renal transplantation leads to improved patients' and allograft outcomes. Compared with patients who have been on dialysis for more than 2 years, patients who have not undergone dialysis (or have been on dialysis for less than 6 months) have longer graft survival time.

Contraindications to transplantation are listed below:

- Active or metastatic cancer
- Untreated current infection
- Severe irreversible extrarenal disease
- Uncontrolled psychiatric illness impairing compliance or consent
- Active substance or alcohol abuse
- Recalcitrant treatment noncompliance
- Aggressive recurrent native kidney disease
- Limited, irreversible rehabilitative potential
- Primary oxalosis

19.4.2 Complete Medical History and Physical Exam

A complete medical history of the transplant candidate is crucial. The history may be useful to ascertain whether the renal disease has a hereditary or familial origin, and a general screening examination should be conducted when a full medical history is obtained.

19.4.3 Evaluation of Renal Disease

The history of kidney disease should be reviewed with a focus on the nature and duration of primary kidney disease. All forms of glomerulonephritis may recur after transplantation and may lead to graft failure, but the risks of disease recurrence and its consequences differ among the various subtypes of glomerulonephritis.

19.4.4 Screening for Cardiovascular Disease

Cardiovascular disease occurs early after transplantation, and these events are the most common cause of death after renal transplantation. Almost half of the deaths of patients who have functional grafts within 30 days after transplantation are due to a cardiovascular event, mainly acute myocardial infarction. Careful study of the cardiovascular system and proper treatment of aberrations before placement of candidates on an active waiting list are necessary because cardiovascular disease is the main cause of late graft loss and long-term mortality.

19.4.5 Screening for Infectious Diseases

Infection may worsen with immunosuppressive drug application which is the second most common cause of death among patients with ESRD. Kidney transplant candidates must be screened to determine the presence of infection, and pretransplantation screenings are designed to eliminate any infections that may reactivate during the posttransplant period.

19.4.6 Screening for Cancers

Nine to 12% of deaths among kidney transplant recipients are caused by cancer. At baseline, patients with ESRD are at a higher risk of cancer than is the age-matched control population. Therefore, detecting cancer and reducing risk factors of cancer are important components of pretransplant evaluation. In addition, immunosuppressive drug application increases the risk of cancer, and existing cancer may turn more aggressive.

19.5 Immunosuppressive Medication and Protocols for Kidney Transplantation

Management of renal transplant recipients to achieve long-term survival is the main goal of transplant physicians. An immunosuppressant treatment that reduces acute rejection reactions and minimizes ischemic damage is the cornerstone of successful management of these delicate organs. Prevention of rejection while favoring the development of an immunological adaptation is the main goal of immunosuppressive therapy. More potent and specific immunosuppressive agents have enabled a significant reduction in the incidence and severity of rejection.

19.5.1 History of Immunosuppression and Transplant

The ability of the immune system, particularly T lymphocytes, to mediate acute rejection of organs transplanted between genetically nonidentical individuals was well known before the first successful renal transplant, in 1954. In the absence of any means of suppressing the immune system, this first transplant was performed between identical twins.

Whole-body irradiation was used for the first attempt at immunosuppression; azathioprine was introduced in the early 1960s and was soon followed by prednisone. Polyclonal antilymphocyte globulin and antithymocyte globulin came onto the scene in the 1970s. The introduction of cyclosporine in the 1980s was a seminal milestone, which reduced the acute rejection rate significantly and transformed the kidney transplantation scenario, with improvement in 1-year graft survival to more than 80%. In 1985, the first monoclonal antibody OKT3 was introduced into clinical practice because of the ability to treat the first acute rejection. Tacrolimus and mycophenolate mofetil (MMF), which are two other major developments, then followed. In 1999, sirolimus was introduced, and later, everolimus was approved in 2007. Due to the constant research into the immune system, tremendous progress has been made in kidney transplantation. The short-term survival and mid-term survival of kidney transplants are now satisfactory.

19.5.2 Induction Immunosuppression

Induction therapy is a boost of immunosuppression for approximately several days immediately after the surgical operation (although it usually starts immediately before the operation) in order to "shut down" the immune system after transplantation to reduce the possibility of accelerated rejection and acute rejection. There are several important reasons for the use of induction therapy. First, induction agents can significantly reduce the rate of acute rejection and improve 1-year graft survival. Second, induction therapy is important for preventing early calcineurin inhibitor (CNI)-induced nephrotoxicity. In addition, these drugs are also considered for high-risk patients such as those with multiple HLA mismatches, with organ transplant history, or with preformed antibodies.

Induction therapeutic agents are pharmacologically classified as monoclonal or polyclonal antibodies. Nevertheless, it is more accurate to classify them as depleting or nondepleting proteins. The use of specialized induction agents has increased over time, with 87% of patients undergoing kidney transplantation in the Unites States in 2012 receiving such medication according to Organ Procurement and Transplantation Network data. Two T-cell-depleting agents—rabbit antithymocyte (rabbit ATG, thymoglobulin) and alemtuzumab (Campath)—and one nondepleting agent, basiliximab (Simulect), are used for induction therapy in most cases. The advantages and disadvantages of depleting-antibody induction are outlined in Table 19.1.

Table 19.1 Potential advantages and disadvantages of depleting-antibody induction

Potential advantages
• Improved graft survival for high-risk patients
• Onset of first rejection is delayed
• Period of delayed graft function may be foreshortened
• May allow for less aggressive maintenance regimen
Potential disadvantages
• Risk of first-dose reactions
• May prolong hospital stay and increase cost
• Higher incidence of cytomegalovirus infection
• May increase mortality

19.5.3 Maintenance Immunosuppression

Maintaining immunosuppression is intended to prevent acute and chronic immune system-mediated graft injury. Continuous development of immunosuppressive drugs has led to several new options that can further prevent rejection and improve outcomes in the long run. Immunosuppressive drug application requires careful selection and dose titration to balance the risks of rejection and toxicity. Table 19.2 lists maintenance agents used in clinical practice.

The immunosuppressive treatment regimens for transplant centers vary, and the 2009 KDIGO guidelines on maintenance immunosuppression suggest the use of a CNI, antimetabolite, and corticosteroid in combination. This drug selection method also helps to minimize drug-related adverse events [6]. Selecting a suitable immuno-

Table 19.2 Maintenance agents in renal transplantation [7]

Calcineurin inhibitors
• Cyclosporine • Tacrolimus
Antimetabolites
• Mycophenolate mofetil • Azathioprine
mTOR inhibitors
• Sirolimus • Everolimus
Corticosteroids

Reproduced with permission from Kennedy et al. [7]

suppressive agent should be patient specific. The most important adverse effects of generalized immunosuppression are cancer and infection, including opportunistic infections. Individual drugs have a specific profile of adverse effects.

19.5.4 Monitoring the Levels of Immunosuppressive Drugs

The avoidance of over-immunosuppression and under-immunosuppression is a major challenge in clinical practice. Patients are routinely monitored for signs of drug toxicity by means of serum drug levels including CNI concentrations, mammalian target of rapamycin inhibitor (mTORi) levels, and at certain centers, MMF/MPA concentrations. Nevertheless, extreme drug levels are helpful but not definitive in the diagnostic process. Moreover, dosing of immunosuppressive drugs remains rather empirical, and there is no test for biological activity of the drugs used in transplantation.

19.5.5 Conclusion

Kidney transplantation has greatly evolved and has seen many advances in immunosuppressive therapy, with an increasing number of immunosuppressive agents available for use in various combinations allowing for more options and personalization of immunosuppressive therapy. When selecting an induction immunosuppressive agent, a clinician must carefully consider several factors including immunological risk of the patient, the cumulative immunosuppression burden, concomitant maintenance immunosuppression, and additional patient factors including age and comorbidities such as cardiovascular disease, pulmonary disease, and prior cancer. T-cell-depleting agents such as rabbit ATG or alemtuzumab are associated with lower acute rejection rates but higher rates of leukopenia and infection as compared to basiliximab. An individual patient's risk of rejection should be carefully weighed against potential complications due to overimmunosuppression and/or drug-related toxicities. Maintenance immunosuppressive therapy has greatly evolved too. Although CNI-based therapy with tacrolimus, mycophenolate, with or without corticosteroids continues to be the standard (most commonly utilized) regimen ensuring low rates of acute rejection, the associated medication-related toxicities continue to contribute to morbidity and mortality.

19.6 Allograft Dysfunction

With a living donor kidney transplant, the graft usually begins to function soon after the vascular anastomosis is complete. Although immunosuppressive agents, surgical techniques, and histocompatibility tests have improved, allograft dysfunction remains the most common complication of renal transplantation [8].

19.6.1 Immediate Posttransplant Period

With a living donor kidney transplant, the graft usually begins to function soon after the vascular anastomosis is complete. Impairment of graft function is suggested by a decrease in urine output and/or a rise in creatinine levels. The definition of DGF varies among transplantation centers, and the most common definition is dialysis that is required within 7 days. On the other hand, the current definition of DGF does not enable clinicians to distinguish the causes of DGF from other types of graft dysfunction and can lead to misclassification of patients. Furthermore, there are different criteria for dialysis prescription among nephrologists. The main causes of DGF are listed in Table 19.3.

Table 19.3 Main causes of DGF

Prerenal
• Hypotension, hypovolemia
• Arterial thrombosis, venous thrombosis
Parenchymal
• Acute tubular necrosis (Ischemia, drug)
• Rejection (hyperacute, acute)
• Thrombotic microangiopathy (CNIs, mTOR inhibitors)
• Recurrence of original disease (FSGS, HUS, primary hyperoxaluria)
Postrenal
• Ureteral obstruction (ureteral kinking, ureteral stenosis, blood clots, lymphocele)
• Urine leakage
• Urine fistula

DGF delayed graft function, *CNI* calcineurin inhibitor, *mTOR* mammalian target of rapamycin, *FSGS* focal segmental glomerulosclerosis, *HUS* hemolytic uremic syndrome

Table 19.4 Main measures for preventing DGF

Donor
• Normovolemia
• Maintain blood pressure
• Optimize cardiac output
• Adequate kidney perfusion
Kidney perfusion
• Selection of renal preservation solution[a]
• The use of pulsatile machine perfusion
Cold ischemia time
• Maintain <12–24 h when possible
Ischemia-reperfusion injury
• Multiple anti-inflammatory and antioxidant therapies[a]
Recipient
• Check blood volume
• Low-dose dopamine
• Loop diuretics

DGF delayed graft function
[a]Requires more research

19.6.2 Management of DGF

Patients with DGF show longer hospitalization and are at a higher risk of occult rejection or other undiagnosed insults to the graft. Most studies suggest that patients with DGF have worse long-term outcomes than patients with immediate function. Great efforts should be made to reduce the damage during the transplantation process; these measures include optimal management of donors, a precise surgical technique, optimizing allograft perfusion, minimizing cold ischemia time, and ensuring adequate preparation of the recipient (Table 19.4).

Table 19.5 Causes of allograft dysfunction in the early postoperative period

Prerenal
• Transplant artery stenosis
• Hypovolemia/hypotension
• Renal vessel thrombosis
• CNIs
Parenchymal
• Acute thrombotic microangiopathy
• Acute allergic interstitial nephritis
• Recurrence of primary disease
• Acute rejection
• Acute CNI nephrotoxicity
• Toxic/ischemic acute renal tubular necrosis
• Acute pyelonephritis
Postrenal
• Urine leaks
• Urinary tract obstruction

CNI calcineurin inhibitor

19.6.3 Early Posttransplant Period

Early posttransplant allograft dysfunction is often defined as a sustained increase in plasma creatinine concentration, and the reasons are listed in Table 19.5 [9].

19.6.4 Late Posttransplant Period

There is an apparent overlap between the causes and assessment of acute allograft dysfunction in the late period (3–6 months after transplantation) and those of early acute dysfunction [9]. The reasons of late chronic allograft dysfunction are listed in Table 19.6.

19.6.5 Management of Late Allograft Dysfunction

The main focus of the current research in this field is the prevention of chronic allograft dysfunction. The medical history should be carefully

Table 19.6 Reasons of late chronic allograft dysfunction [10]

Prerenal
• Heart failure
• Transplant renal artery stenosis
Parenchymal
• Chronic active antibody-mediated rejection (ABMR)
• Chronic active T-cell-mediated rejection (TCMR)
• Drug and radiocontrast nephrotoxicity
• Hypertension
• Interstitial fibrosis and tubular atrophy, no specific etiology
• Chronic BK virus nephritis
• Donor-related disease and/or perioperative injury
• Chronic CNI toxicity
• Chronic BK virus nephritis
• Late recurrence of primary disease
• Diabetic nephropathy
• New disease
Postrenal
• Urinary tract obstruction

CNI calcineurin inhibitor (Reproduced with permission from Magee et al. [10])

examined, especially with respect to primary kidney disease, early posttransplantation course, acute rejection episodes, degree of hypertension, CNI levels, and compliance. Urinalysis and renal ultrasonography should be performed to rule out primary kidney disease and obstructive cause. Allograft biopsy is often performed because endogenous nephropathy is the leading cause of dysfunction [10].

If there is a histological evidence of acute TCMR components, pulsed steroids are usually prescribed, and baseline immunosuppression is increased. How to manage chronic TCMR is not clear. If there is evidence of an acute AMR component, plasmapheresis and/or IVIg protocol may be performed. How to manage chronic AMR is not clear either. In most cases, when allograft injury due to CNI toxicity, and with no evidence of active rejection, reducing the CNI dose is a reasonable action. Alternative medication such as MMF or sirolimus may be initiated as a replacement, but it is important to pay close attention to late acute rejection of patients. ACE-I/angiotensin receptor blockers are commonly used in renal transplantation although there are no randomized controlled trials. When GFR deteriorates, patients should be ready to resume dialysis. Erythropoietin, vitamin D therapy, and other ancillary measures should be applied. The "CKD management" of patients who fail in transplantation may be difficult due to the adverse effects of immunosuppressive agents [10].

19.7 Updated Banff Classification Categories

Among living and deceased donor transplant recipients, the incidence of acute rejection within the first year posttransplant decreased to 7.9% for both categories during 2013 and 2014. The development of donor-specific antibody (DSA) and AMR negatively affects graft survival, and the present-day diagnosis of AMR in the absence of peritubular capillary C4d staining has been incorporated into the Banff classification system [11]. Updated Banff classification categories are listed in Table 19.7.

19.8 Infection After Kidney Transplantation

Although the outcomes of renal transplant patients have improved over the years, this population continues to show significant morbidity and mortality due to infection. Infection accounts for 15–20% of deaths after transplantation, and it is the second most common cause of hospital admission among kidney transplant patients in the first year posttransplant [12]. Therefore, a transplantation team attempts to achieve a balance between preventing allograft rejection and maintaining immune system integrity for defense against pathogens. In addition to immunosuppressive agents, several factors contribute to a decrease in immune status, including uremia, nutrition, diabetes, dialysis, age, and ESRD-related malnutrition.

Table 19.7 Updated Banff classification categories

Category 1: Normal biopsy or nonspecific changes	
Category 2: Antibody-mediated changes	
Acute/active ABMR: three features are required	
Histological evidence of acute tissue injury (inflammation, TMA, ATN)	
Linear C4d staining	
Serological evidence of DSA	
Chronic active ABMR: three features are required	
Histological evidence of chronic tissue injury	
Linear C4d staining	
Serological evidence of DSA	
C4d staining without evidence of rejection	
Category 3: Borderline changes	
Category 4: TCMR	
Acute TCMR	
Grades	
IA	Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma) and foci of moderate tubulitis
IB	Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma) and foci of severe tubulitis
IIA	Mild to moderate intimal arteritis
IIB	Severe intimal arteritis comprising >25% of the luminal area
III	Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation
Chronic active TCMR	
Chronic allograft arteriopathy	
Category 5: Interstitial fibrosis and tubular atrophy	
Grades	
I	Mild interstitial fibrosis and tubular atrophy (≤25% of cortical area)
II	Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
III	Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)
Category 6: Other changes not considered to be rejection	
BK virus nephropathy	
Posttransplant lymphoproliferative disorders	
CNI nephrotoxicity	
Acute tubular injury	
Recurrent disease	
De novo glomerulopathy	
Pyelonephritis	
Drug-induced interstitial nephritis	

ABMR antibody-mediated rejection, *TMA* thrombotic microangiopathy, *ATN* acute tubular necrosis, *DSA* donor-specific antibody, *TCMR* T-cell-mediated rejection, *CNI* calcineurin inhibitor

19.8.1 Pretransplant Recipient and Donor Evaluation

Before transplantation, appropriate evaluation and treatment of patients are required, starting with a detailed medical history taking and physical examination. The goal is to assess the condition or exposure that causes the candidate to be susceptible to future complications, especially those requiring treatment or prevention. Predonation kidney transplant donors have also been tested several times. Donors can harbor infectious diseases that can be transmitted to recipients via donor organs.

19.8.2 Timing of Posttransplant Infections

Infection after kidney transplantation is divided into three stages: 0–1 month, 1–6 months, and after 6 months. The recipients are susceptible to certain infections due to the different levels of immunosuppression and environmental factors in each period. Table 19.8 lists the timeline and relevant infectious microorganisms after a kidney transplant.

19.8.3 Evaluation of Fevers

Although a fever is not always present in an infected immunosuppressed patient, it remains the most common manifestation of an infection in a transplant patient. A number of clinical, laboratory, and radiological tests on a febrile transplant patient are recommended. Both infection and rejection can lead to fever in the transplant recipients, and the first differential diagnosis should be between infection and rejection. Medical tests for a renal transplant recipient with a fever are listed in Table 19.9, and Table 19.10 lists bacterial, viral, and fungal infections common among renal-transplant recipients.

Table 19.8 Timeline and infectious organisms after a kidney transplant [13]

0–1 month	1–6 months	After 6 months
Nosocomial infection Pneumonia Urinary tract infection Bloodstream infections Wound Herpes viruses Oral candidiasis	Cytomegalovirus Polyomavirus Pneumocystis Cryptococcus Nocardia *Toxoplasma gondii* Listeria monocytogenes Candida species Aspergillus species Histoplasmosis Coccidioidomycosis Mycobacteria Other herpes viruses Hepatitides B and C	Community infections Cytomegalovirus retinitis Cryptococcus Herpes virus Polyomavirus Mycobacteria

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Table 19.9 Medical tests for a renal transplant recipient with fever

Rejection	Infection
• Creatinine • Urinalysis • Graft ultrasonography • Renal biopsy	• Blood cell analysis • Cultures (blood, urine, secretions) • Chest X-ray imaging • Echocardiogram • Urinary ultrasonography (Graft, native kidney) • Neurological evaluation • Cerebrospinal fluid • Cerebral CT • Intestinal–hepatic tests • CMV antigenemia • Anti-legionella, -candida, or -mycoplasma antibodies

Table 19.10 Bacterial, viral, and fungal infections

Bacterial infections	Viral infections	Fungal infections
• Urinary tract infections • Sepsis • Wound infections • Nocardiosis • Listeriosis	• Herpes virus infections • Hepatitis viruses • Influenza • HIV • Polyomaviruses	• Candidiasis • Cryptococcus • Aspergillosis • Mucormycosis • Histoplasmosis • Coccidioidomycosis

Key Messages

- Chronic rejection and overimmunosuppression remain significant clinical problems. The development of more specific treatments accompanied by reduction in toxicity requires further work.
- Antibody analysis is increasingly carried out posttransplant as a noninvasive predictor of acute and chronic alloimmune complications. Understanding the complexity and interactivity of these histocompatibility methods and their interpretation parameters is crucial for clinicians to formulate an appropriate treatment regimen.
- Comprehensive assessment and education of living kidney donors require communication among all members of the transplant team which is a complex and time-consuming process.
- Great effects should be paid to selection and preparation of kidney transplant recipients because of the risks of immunosuppressive therapy.
- Kidney transplantation has greatly evolved and has seen many advances in immunosuppressive therapy, with an increasing number of immunosuppressive agents available for use in various combinations allowing for more options and personalization of immunosuppressive therapy.
- DGF after kidney transplantation is usually defined as the need for dialysis during the first postoperative week, anuria, or failure of prompt azotemia resolution. DGF increases

the risk of allograft rejection by 50% as compared with prompt graft function.
- The development of DSA and AMR adversely affects graft survival. The modern diagnosis of AMR in the absence of peritubular capillary C4d staining has been incorporated into the Banff classification system.
- Although the outcomes of renal transplant patients have been great improved in recent years, infectious complications after a transplant may induce allograft injury or graft loss and are a major cause of morbidity and mortality.

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