Management of Chronic Kidney Disease

A Clinician's Guide

Mustafa Arıcı
Editor

Second Edition

Springer

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To the 100th anniversary of the Republic of Turkey, founded by Mustafa Kemal Atatürk, where I received free public education, lived in a secular and free state…

To my patients, students, colleagues, professors, and mentors from whom I have learned and continue to learn…

To my mother, father, and brothers who have supported me since my childhood and enlightened my path...

To my lovely daughters Ayşe and Zeynep and my beautiful wife Esra... beyond the tolerance and patience they have shown me despite the time I stole from them...for their continuous love and support…

Preface

It is my pleasure and honor to present to you the second edition of the *Management of Chronic Kidney Disease: A Clinician's Guide*, the first edition of which was published in 2014. This book is intended to help family physicians, internal medicine and nephrology residents, and specialists from primary to tertiary care for the management of chronic kidney disease, which globally has a prevalence of approximately 10% and will rank fifth among the causes of mortality on the global burden of disease list by 2040.

Considering that the number of CKD patients seen from early to late stages is almost 100 times the number of dialysis and kidney transplant patients, this book addresses the management of a much wider CKD patient population. As noted in the preface to the first edition, this book filled an important gap by providing a comprehensive, guideline-based, practice-oriented management plan for physicians who consistently care for adult CKD patients. Since the book is written with a multidisciplinary approach, it will serve as an essential source for physicians in many disciplines like cardiologists and endocrinologists who frequently encounter CKD patients in their daily practice.

The second edition of the book is not a simple update of the first edition. The book, which had 37 chapters in the first edition, has reached 39 chapters with 2 new chapters in this edition. Of the 78 authors featured in this edition, 39 are entirely new. The 12 chapters in this issue were written by entirely new authors. Therefore, it would not be wrong to say that the book is quite new and up to date.

The second edition also covers the diagnosis of CKD, risk factors, the relationship between CKD and cardiovascular diseases, complications of CKD, and the management of CKD patients in special circumstances from a practical perspective. Disease management programs and preparing a CKD patient for dialysis and kidney transplant form the final part of the book. This book also covers important but often neglected topics such as sleep disorders, whether a CKD patient should be vegetarian or vegan, pain management, depression and suicide risk, disease education, and quality of life in CKD patients. The book covers the management of chronic kidney disease from the first to the last step in a structured perspective.

The editor of this book is aware that times are changing so fast, the digital transformation is now almost complete, and artificial intelligence has entered our lives, including academic writing. In this regard, there may be some who think that this book is outdated on the day of its publication. Yes, books

cannot change information as fast as digital platforms, but the information that enters the books is permanent information filtered from the retort. Unlike small pebbles dragged by a fast-flowing stream, books are the big rocks left behind, can be considered non-dynamic, but the knowledge that is permanent and should stay is always in the books. In this context, I am confident that this book contains basic information that will assist you in the treatment of many patients in your daily practice.

The preparations for the second edition of the book began during the days when the world was battling with the Covid-19 pandemic. The book has reached you after a very long and difficult preparation process. A significant number of authors from the first edition have shown their dedication to contributing to the second edition of the book during the fight against the epidemic. The authors who did not agree to contribute to the second edition were replaced with new ones with great devotion. This book would not have been possible if the authors of this book had not devoted their most precious time to this book in their busy work schedule. Therefore, I would like to express my sincere thanks to all of them.

I would like to acknowledge my late Professor Sali Cağlar and Professor John Walls, who were my mentors in Nephrology, and Professor Garabed Eknoyan who is not only a great teacher but also inspired me to become a "different Professor." I should also thank all of my friends and patients, specifically the ones in Ankara, Hacettepe University, Türkiye, and the ones living in different parts of the world, who always make me feel content and strong. Last but not least and most importantly, my deepest gratitude extends to my family, wife, and daughters, whose support cannot be expressed in words.

The main purpose of this book is to reduce the burden of chronic kidney disease on patients, stop or slow the progression of kidney disease, and provide a better quality of life as well as a longer life. As the editor of this book, I feel indebted to my patients for achieving these goals. The editor and authors will feel that their efforts for the book are rewarded if readers apply these principles to their clinical practice. After that, it is up to you, the readers…

Ankara, Turkey Mustafa Arıcı

Contents

What Is Chronic Kidney Disease?

1

Aditi Sen and Rajeev Raghavan

Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) is defined as having abnormalities of kidney structure or function for at least 3 months for implications to the health of the individual.
- CKD is classified based on the cause (C), GFR category (G; G1 to G5), and albuminuria (A; A1 to A3).
- CKD is a treatable, major public health problem worldwide.
- CKD may be diagnosed from abnormalities in the urinalysis, estimated GFR (eGFR) calculated from serum creatinine and/or cystatin C, kidney ultrasound, or kidney histology.
- There is a strong graded and consistent relationship between the severity of the two hallmarks of CKD: reduced eGFR and increased albuminuria.
- CKD is more common in the elderly, males, and individuals with a family history of CKD.
- Genetic testing is non-invasive emerging modality that can diagnose or predict development of kidney disease.
- Diabetic kidney disease (DKD) is the leading cause of CKD.

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1.1 Introduction

Diseases of the kidney have afflicted humans from time immemorial. Medical interest in the detection and treatment of kidney disease can be traced to antiquity, but all past efforts have been fragmentary and based on its symptomatic manifestations as a change in urine color (hematuria) and flow (obstruction) or pain due to stones or obstruction. It is only in the past three decades that the actual burden of kidney disease has been documented and identified as a global public health problem [1–5].

The traditional lineage of detecting and defining kidney disease is traced to Richard Bright (1789–1858), who in 1827 described the autopsy findings of the kidneys in 24 albuminuric, dropsical patients who had died of kidney failure [1]. Bright considered his disease an inflammatory lesion (nephritis) that was rare as reflected in his statement that "Inflammation of one or both kidneys, as a primary idiopathic disease, is less frequently met than most other forms of phlegmasia." In his textbook on the practice of medicine published in 1839, he devotes most of the discussion of nephritis to calculous or obstructive diseases rather than the rare disease he had identified. In the century that followed, the acute and chronic forms of Bright's disease were defined, their diagnosis from urinalysis was refined, and their microscopic renal lesions were described, but its therapy remained symptomatic and the outcome

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fatal much as it had been in 1827 when Bright described his eponymous disease [2]. It was the conceptual and technical advances in medicine during and after the Second World War that was to change it all, most notably the introduction of the artificial kidney that transformed the fatal disease of Bright into a treatable one, a milestone achievement that catapulted the growth of nephrology in the closing decades of the past century [1].

Ironically, it was the treatment of Bright's end-stage kidney disease (ESKD) with dialysis that focused attention on the broader and more significant issue of chronic kidney disease (CKD). Dialysis started as an exploratory effort to sustain the life of patients with acute kidney injury (AKI) during the Second World War. It evolved in the 1970s into a lifesaving therapy for patients whose CKD had progressed to kidney failure necessitating renal replacement therapy (RRT) with dialysis. As administrative data from national dialysis registries accrued in the 1980s, it became evident that the care of patients with ESKD should have been started well before they presented for dialysis having sustained already the ravaging consequences of progressive loss of kidney function. It was this concern that at the turn of the century prompted the first efforts at the definition, classification, and evaluation of CKD [1, 2].

1.2 Definition of CKD

In 2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) developed guidelines for a working definition of CKD, independent of the cause of the disease, based on the presence of either kidney damage (proteinuria, abnormal kidney biopsy, or imaging studies) or a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for more than 3 months [3]. The guidelines also proposed a classification of CKD based on severity determined by the level of kidney function calculated from the serum creatinine and expressed as the estimated GFR (eGFR). It proposed the classification of CKD into 5 stages: stages 1 and 2 as a covert disease requiring the presence of kidney damage (proteinuria, abnormal urinalysis, biopsy, or imaging studies) and stages 3, 4, and 5 as overt diseases (i.e., when the eGFR was less than 60 ml/min/1.73 m^2) with eGFR of 30–59, 29–15, and <15 ml/min/1.73 m^2, respectively.

This numerical staging or grading system for CKD was created on arbitrarily chosen bands of eGFR values, not based on biologic variations of GFR (Fig. 1.1). For example, arbitrarily asserting that an eGFR <60 ml/min per 1.7 m^2 represents disease. The conceptual model of CKD used in proposing this classification is shown in Fig. 1.2. The five stages of CKD classification do not appear in this cartoon. Rather, stages 1 and 2 are grouped together and implicitly represented in the ellipse-labeled "injury" and flagged for albuminuria, and stages 3 and 4 in the ellipse-labeled "decreased GFR" and flagged <60 ml/min/1.73 m^2. These guidelines were a major step forward in the evolution of our understanding of kidney disease by providing a uniform definition whereby kidney disease could be discussed across different studies, regions, and countries.

In 2007, stage 3 CKD was sub-divided into 3A and 3B for an eGFR of 45–59 and 30–44 ml/min/1.73 m^2, creating four equally divided quartiles of 15 ml/min below 60 ml/min [7]. This change also allowed clinicians to account for an age-related reduction in GFR or eGFR, as these were typically confined to CKD stage 3A. In 2014, the addition of albuminuria to the staging added granularity because this laboratory assessment is strongly tied to the progression of the disease [8]. Conversely, the response to therapy of CKD can be assessed from the reduction of albuminuria in response to therapeutic interventions. The random urine albumin to creatinine ratio (UACR) has become a standard tool to quantify and describe albuminuria, being much easier to obtain than a 24-hour urine collection. Albuminuria is defined as A1 (<30 mg/g), A2 (31–300 mg/g), and A3 (>300 mg/g). Table 1.1 identifies how the clinician may utilize both albuminuria and GFR to identify, detect, and prognosticate kidney disease among patients.

The four-variable MDRD formula was published in 1999 using a U.S. population of patients

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Fig. 1.1 Staging and prognosis of chronic kidney disease (CKD) by glomerular filtration rate and albuminuria (Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) [6])

with known CKD. The CKD-EPI formula was published ten years later, touting better accuracy particularly at a higher GFR. The CKD-EPI was modeled using a larger, more heterogenous patient population [4]. All eGFR formulae are computed using a freely filtered endogenous marker, such as the serum creatinine (eGFRcr), cystatin C (eGFRcys), or both (eGFRcr-cys). The serum Cystatin C may be more reliable as it is produced by all nucleated cells, unlike the serum creatinine, which varies with muscle mass. However, Cystatin C is a less widely available laboratory test. Estimating equations that utilize both markers may have better accuracy in estimating the GFR [5]. The other three variables used to estimate the GFR for these MDRD and CKD-EPI formulae include age, gender, and the patient's self-reported race [4]. It is important to note that the GFR declines by 1 ml/min/m^2 beginning in the third decade of life, hence, by age 70, an individual may have lost over 40% kidney function, often corresponding to CKD Stage 3A.

Patient self-reported race was tabulated and used in deriving the MDRD and CKD-EPI estimating equations. This was inherently problematic because race is a social construct, without a coherent definition. Incorporating race into an equation falsely implies differences in biology among individuals, propagating racism in medicine. In 2020, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) created a joint task force to re-calibrate these estimating equations. In 2021, the joint task force reconfigured the MDRD and CKD-EPI estimating equations, using original patient data, to remove the race modifier [9]. It is expected that laboratories will implement race-free equations when reporting eGFR to patients and clinicians.

A uniform definition of CKD allows society guidelines to recommend initiation or cessation of therapeutics, frequency of screening (e.g., hemoglobin for anemia), and prognosis (e.g., transplant referral). However, **the clinician must individualize decisions, particularly with vul-**

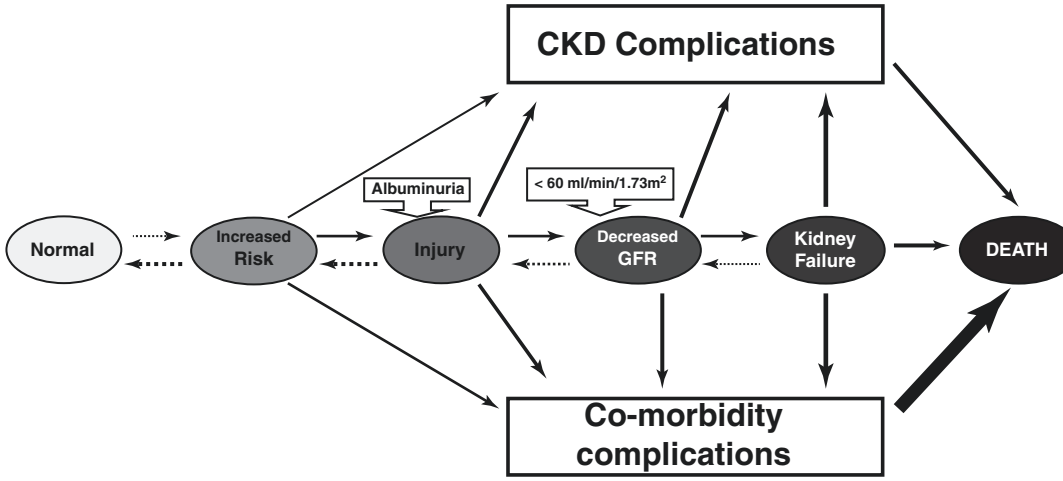

Fig. 1.2 A conceptual model of the course, complications, and outcomes of chronic kidney disease. The ellipses represent the progressive stages and consequences of progressive chronic kidney disease (CKD). The first two ellipses are antecedent stages representing cohorts at increased risk of developing CKD. The next two ellipses are flagged for the two hallmarks used in the definition and staging of CKD: albuminuria (stages 1 and 2) and a glomerular filtration rate of <60 ml/min/1.73 m^2 (stages 3 and 4). The gradually increasing thickness of the *arrows* connecting the ellipses reflects the increasing risk of progressing from one stage to the next stage of CKD as the disease progresses. The *dotted arrows* connecting the ellipses indicate the potential for improvement from one stage to its preceding stage due to treatment or variable natural history of the primary kidney disease. The rectangle at the top indicates the complications of CKD (anemia, mineral and bone disorders, hypertension, hyperparathyroidism). The rectangle at the bottom indicates the risk multiplier effect of CKD of coexistent comorbidities, principally that of cardiovascular disease. The gradually increasing thickness of the *arrows* connecting the ellipses to the upper and lower rectangle represents the increased risk of the complications as the CKD progresses from one stage to the next (Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) [6])

Table 1.1 Use of the glomerular filtration rate (GFR) and albuminuria in chronic kidney disease (CKD)

Utility	GFR	Albuminuria
Significance	Index of kidney function Normal: 100–125 ml/min/1.73 m^2 in young adult	Marker of kidney damage[a] Normal: <30 mg/day in young adults
Measurements	Calculation: estimate GFR (eGFR) using gender, age, serum creatinine (eGFRCr), and/or cystatin C (eGFR cr-cys or eGFRcys) Calculation: measure GFR (mGFR, mClcr) using serum creatinine, timed urine creatinine, and timed urine volume	Calculation: spot urine albumin to creatinine ratio (UACR)[b] or 24 h urine albumin
Definition of CKD	eGFR <60 ml/min/1.73 m^2	UACR >30 mg/g or timed albuminuria >30 mg/day, for >3 months
Risk predictors of disease progression	Decline in slope of eGFR >30% or mean reduction in eGFR slope >0.5 ml/min/1.73 m^2 per year	Persistent albuminuria >300 mg/g

[a] Other markers of kidney damage include hematuria, pyuria, electrolyte derangements, imaging abnormalities, or pathological abnormalities
[b] The UACR utilizes urine albumin in milligrams and urine creatinine in grams

nerable or atypical populations such as pediatrics, transgender patients, and the very elderly.

Methodological issues associated with the initial definition of CKD have been addressed and to some extent resolved. Serum creatinine mea-

surements have now been standardized, the equation to calculate eGFR refined, and nearly all clinical laboratories now reporting eGFR in their laboratory results. The standardization and reporting of urinary albumin measurements are under active investigation but remain to be refined.

In defining CKD as kidney damage for at least 3 months, the guidelines also set the stage for the identification of another form of kidney disease, the potentially reversible forms of acute kidney disease (AKD) of less than 3 months duration, specifically that of acute kidney injury (AKI) of less than 7 days duration. A discussion of AKI or AKD is beyond the scope of this chapter, but familiarity is essential for the care of CKD patients. Patients with pre-existing CKD are most susceptible to AKD, and nearly 1 in 3 patients who develop AKD will not regain kidney function, resulting in increased morbidity, mortality, and accelerated progression to ESKD [10].

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines documented the increased number of systemic complications (anemia, hypertension, mineral and bone disorders), morbidity, and mortality associated with declining eGFR and described the greater risk of death of CKD patients from cardiovascular disease than from their progression to kidney failure and ESKD [9–12]. During the decade that followed the issue of these guidelines, epidemiologic data has validated, refined, and provided convincing evidence that CKD is common, harmful, treatable, and a major public health problem worldwide [9–11].

CKD is prevalent in 10% of the general population and increases in high-risk populations (diabetic, hypertensive, obese, elderly), some ethnic groups (Latin Americans, African Americans, Pima Indians), and those with predisposing genetic composition. Some of the heterogeneous risk factors that contribute to the progression of CKD are potential therapeutic targets (Fig. 1.3).

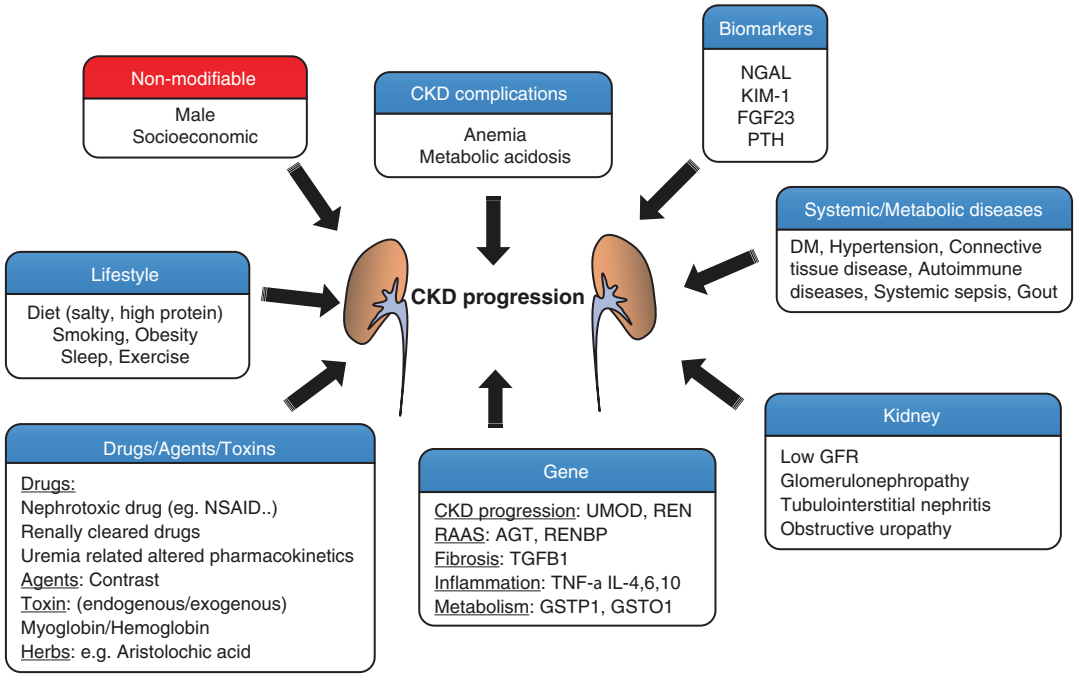

Fig. 1.3 Risk factors associated with progression of CKD. Non-modifiable risk factors for CKD progression include male, socioeconomic status, and genetics. Modifiable risk factors include lifestyle, metabolic disease, and exposure to potentially nephrotoxic drugs/agents/toxins. In addition to the cystatin C or serum creatinine, biomarkers such as NGAL or KIM-1 may allow for earlier detection of kidney injury. Reproduced with permission from [13]

Modifiable risk factors linked to CKD progression include unhealthy diet, sleep deprivation, and use of tobacco. Genetic testing is non-invasive (e.g., saliva) and the cost for a 'kidney panel' is affordable enough for this to be a first-line option in cases without an identifiable cause [14].

The interaction of chronic diseases such as hypertension, diabetes, obesity, and/or atrial fibrillation can be viewed as an overlap phenomenon whereby the presence of CKD emerges as a risk multiplier of the morbidity and mortality of the other major chronic diseases [10, 13, 15]. The risk of each disease increases in the areas of their overlap with CKD, and the magnitude of this detrimental effect is related to the severity of CKD [10]. Thus, detection and treatment of both CKD and comorbid conditions are essential to reducing the global burden of disease.

1.3 Staging of CKD

One of the major milestones in Nephrology was the creation of a uniform language to define and classify CKD in 2002. At the time, a major limiting factor was the quality and quantity of evidence then available. Nonetheless, the classification schema allowed for improved organization of subsequent research and the ability for scientific publications and clinicians to communicate clearly with one another. Apart from information on the epidemiology and outcomes of CKD, the new evidence revealed a strong, graded, and consistent relationship between the severity of the two hallmarks of CKD: reduced eGFR and increased albuminuria [8]. As a result KDIGO released a new guideline for the staging of CKD that integrates albuminuria as a determinant of the severity of the disease. The guideline refines the definition of CKD as abnormalities of kidney structure or function, present for >3 months, with implications for the health of the individual, and classifies CKD based on the cause (C), GFR (G), and albuminuria (A) category (CGA) [6]. The classification of CKD by the level of eGFR and albuminuria (the GA of C **GA**) and their impact on prognosis is shown in Fig. 1.1. That the cause (C) is based on the presence and absence of systemic diseases and the location of the disease within the kidney (glomerulus, tubule, vasculature, cystic, or genetic).

The importance of considering the cause (the C of **C**GA) of CKD, now part of the 2012 definition, is highlighted in the conceptual model of CKD shown in Fig. 1.2. The dotted arrows in the figure reflect the potential for reversibility at each stage of CKD. This improvement may be part of the natural course of some diseases but is also and to a greater extent the result of detection and proper treatment of individual cases. Thus, a patient with malignant hypertension and CKD who presents with AKI requiring dialysis can recover sufficient kidney function after control of the blood pressure to cease requiring maintenance dialysis and revert to an earlier stage of CKD [10]. Similarly, a patient with congestive cardiomyopathy, who requires dialysis at presentation, can recover sufficient kidney function following treatment of the heart failure to perfuse the kidneys well enough to revert to an earlier stage of CKD. The same argument can be made for all CKD patients whose kidney function is aggravated by poor management of the comorbid conditions with which it overlaps. By the same token, improvement of kidney function with regression to an earlier stage can be achieved by the proper therapy (e.g., steroids, immunosuppression) of the cause of the kidney disease in selected cases (e.g., lupus nephritis, IgA nephropathy) or the reduction of the magnitude of their albuminuria with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), SGLT2 inhibitors, and antihypertensive agents. Whereas albuminuria is used in the grading of CKD, the evaluation of the individual patient with CKD should include all abnormalities detected on urinalysis that are usually equally important in diagnosis and affect CKD outcomes, especially that of hematuria. In those whose CKD continues to progress, their outcomes can be improved by preventing the complications of continued loss of kidney function (anemia, mineral, and bone disorders) to forestall the otherwise serious systemic ravages of CKD. This underscores the vital importance of detecting

kidney disease in its earliest stages before the onset of serious and irreversible complications.

1.4 Epidemiology of CKD

Recognition of the global burden of CKD was prompted by the epidemiologic studies launched after the creation of a uniform definition of CKD in 2002. Factors that aided in wider recognition of CKD include: (1) the ease of diagnosing CKD from spot albuminuria and/or the eGFR from a single serum creatinine measurement; (2) substantial epidemiologic data indicating that overt kidney disease (stages 3B–5) is the tip of an iceberg of covert disease (stages 1, 2, and 3A); (3) recognition of the near exponential increase in the prevalence of two major causes of kidney disease, diabetes mellitus and obesity (Fig. 1.3); (4) identification of attempts to control the cost and improve the outcomes of renal replacement therapy by the early detection of overt CKD for the amelioration of its course and prevention or treatment of its complications; (5) accruing compelling evidence of the major role of CKD in increasing the risk of cardiovascular disease as well as that of other chronic diseases that have prompted active interest in the detection of CKD by non-nephrologists; and (6) the verification of effective measures to prevent the progression of CKD, reduce its complications, and ameliorate its outcomes. While these factors render control of CKD an achievable goal of healthcare planning in the developed world, the problems they delineate in the developing world are challenging and remain to be adequately addressed.

Chronic kidney disease is an important contributor to the morbidity and mortality from noncommunicable diseases. Cause of CKD depends on the environment with diabetes and hypertension being the most common causes, while diseases like HIV and heavy metal toxicity also contribute to pathology. In some instances, the cause remains unknown. The Global Burden of Disease, Injuries and Risk Factors Study with its broad collection of data sources can deliver global estimates of the disease [16]. In 2017, the prevalence of CKD was estimated at 9.1% in the world population: stages 1 and 2 accounted for 5%; stage 3 for 3.9%; stage 4 for 0.16%; stage 5 for 0.07%; dialysis for 0.041% and kidney transplantation for 0.011%. The global standardized mortality rate was 1.39 times higher amongst males than amongst females per 100,000 population [17]. Kidney disease was listed as the 12th leading cause of death in 2017 [17].

These statistics highlight the importance of access to renal replacement therapy, both to initiate and maintain access to dialysis. In certain low-income parts of the world, despite initiation of kidney replacement therapy, most patients are forced to withdraw due to the inability to pay for ongoing dialysis.

Public health policies have a major role to play in educating health personnel on the early kidney disease detection, implementation of kidney protective treatments and appropriate treatment of risk factors like hypertension and diabetes. One approach could be screening for chronic kidney disease in patients, especially the elderly and those with risk factors. Studies have suggested that such screening protocols can be a cost-effective approach in reducing mortality and progression to ESKD [18].

The number of people needing kidney replacement therapy worldwide is 2.5 million; and this is estimated to grow to 5.4 million by 2030 [19]. Unfortunately, there is a shortage of renal replacement therapy in many countries and an estimated 2.3–7.1 million adults died prematurely from lack of access to this treatment [20].

Data from the National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of CKD is rising, particularly in stage 3, probably due to the increased prevalence of obesity and diabetes (Fig. 1.3). Between one-quarter to one-third of diabetics will develop diabetic kidney disease, which is the leading cause of CKD [6]. It is estimated that the number of people worldwide diagnosed with diabetes will rise from 171 million in 2000 to 366 million in 2030, resulting in additional millions of new cases of CKD. A change to a "Western" diet and the rising rates of obesity along with genetic predisposition are all consid-

ered as potential etiologies that account for the rising incidence of these chronic diseases [21]. Another contributing factor to the rise in CKD is the increase in cases of AKI. In the past two decades, there has been an increase in the incidence of AKI severe enough to require dialysis. Two suspected reasons are (1) procedures or novel therapies using nephrotoxic agents and (2) survival from severe sepsis, a major risk factor for AKI and AKD. Furthermore, all patients with an AKI hospitalization (regardless of whether there is underlying CKD) have a risk of either ESKD (5%) or death (25%) in the year following their hospitalization [7].

The onset and progression of CKD depend on the occurrence of both modifiable (obesity, smoking, poorly controlled hypertension or diabetes, diet) and non-modifiable (age, gender, race, genetics) risk factors. Old age is a well-established risk factor for CKD, but there has been ongoing debate as to whether the age-related GFR decline is "normal" or pathological. The age-related decline in GFR, which affects up to 40% of people aged over 65 years, could lead to overestimating the actual burden of CKD because many of these elderly people have impaired but stable kidney function [8]. However, the treating physician must be aware that such patients are at increased risk of drug toxicity and worsening comorbid chronic diseases (Fig. 1.2). Thus, with increasing age, especially in patients above 75 years, the likelihood of death outweighs the risk of developing ESKD even when the eGFR is severely reduced (below 29 ml/min/1.73 m^2) [11].

Gender represents one non-modifiable risk factor for CKD. The data comparing the prevalence of CKD in men and women is a topic of controversy. Feminine hormones have been proposed to favorably alter the onset, course, and progression of chronic kidney disease, through alterations in the renin–angiotensin system, reduction in mesangial collagen synthesis, modification of collagen degradation, and upregulation of nitric oxide synthesis [22]. The USRDS database indicates that women have a 22% lower risk of being diagnosed with CKD ($p < 0.001$) and a lower incident rate of ESKD, but the definite worldwide effect of gender in CKD remains to be determined [8].

Ancestry and genetics represent other non-modifiable risk factors. CKD has a higher incidence among African Americans and Latin Americans in the USA than among their Caucasian counterparts. Even after adjusting for known genetic causes of CKD (such as polycystic disease or Alport Syndrome), family members of dialysis patients tend to have a higher prevalence of CKD [23].

1.5 Etiology of CKD

In the USA and worldwide, most CKD cases are secondary to diabetes mellitus, influenced by the increasing rates of obesity across all developing countries. Apart from its association with diabetes and hypertension, obesity per se is linked to earlier onset and faster progression of CKD in general [17]. The importance of weight control in all CKD obese patients cannot be overemphasized.

Disparities in the prevalence of CKD are affected by geographic and economic factors (Table 1.2). In developing countries, chronic glomerulonephritis (GN) and interstitial nephritis are a more frequent cause of CKD, in many cases reflecting kidney disease secondary to environmental exposure or a bacterial, viral, and parasitic infection [21]. The incriminated infectious agents include tuberculosis (200 million affected worldwide), streptococcal infections, hepatitis C virus (170 million), human immunodeficiency virus (40 million), and schistosomiasis (200 million), depending on the region. IgA nephropathy is common in Southeast Asia and the Pacific region accounting for up to 35–45% of glomerulonephritides [21]. Focal segmental glomerulosclerosis (FSGS) is another common cause of CKD in developing countries such as India, possibly because of the low nephron mass associated with low birth weight. Finally, the magnitude of environmental pollution's contribution on CKD remains debatable: an association has been documented only for occupational exposure to lead, cadmium, and mercury.

Table 1.2 Prevalence of CKD and deaths associated with CKD from different parts of the world in 2017

	Number and prevalence of CKD (95% CI)	Prevalence of death attributed to CKD
Global estimates	697,509,472 [9.2%]	1,230,168 [2.1%]
Europe		
United Kingdom	5,636,676 [8.5%] (5,233,735–6,135,943)	6766 [1.26%] (6628–6903)
Germany	9,046,875 [10.9%] (8,323,728–9,881,743)	26,754 [2.8%] (24,215–29,510)
Spain	4,233,637 [9.08%] (3,900,640–4,624,353)	10,605 [2.49%] (9890–11,361)
Russia	26,981,655 [18.67%] (24,997,909–29,311,266)	11,361 [0.62%] (11,135–11,621)
Italy	6,163,048 [10.18%] (5,684,428–6,714,537)	14,292 [2.21%] (13,318–15,333)
Australia	2,919,853 [11.67% of entire population] (2,708,028–3,164,634)	5228 [3.24%] (4833–5656)
America		
Canada	3,467,822 [9.35%] (3,213,111–3,766,495)	6087 [2.1%] (5681–6544)
USA	38,816,706 [11.9%] (36,156,443–41,956,816)	84,944 [3.02%] (83,154–86,756)
Mexico	14,556,534 [11.6%] (13,572,422–15,614,239)	65,033 [10.7%] (63,122–66,615)
Asia		
India	115,069,914 [8.6%] (106,818,767–124,130,281)	223,821[2.2%] (207,938–235,529)
Japan	21,411,356 [16%] (19,946,798–23,210,020)	35,709 [2.6%] (33,921–38,263)
China	132,324,202 [9.5%] (121,756,611–143,737,211)	175,891 [1.7%] (160,601–183,366)
South America		
Brazil	16,777,334 [8.07%] (15,579,858–18,107,349)	35,350 [2.8%] (34,607–36,148)
Africa		
Nigeria	12,681,837 [6.6%] (11,675,878–13,853,971)	13,740 [0.6%] (10,420–18,751)

The definition of CKD includes persons with estimated glomerular filtration rate (eGFR <60 ml/min/1.73 m^2) or albuminuria. The prevalence rate of CKD is quite similar across all countries with the global average percentage of 9.2% [24]

1.6 Progression of CKD

The treatment of specific causes of CKD will be detailed in later chapters of this textbook. However, **regardless of the cause, kidney fibrosis including nephrosclerosis and tubulointerstitial fibrosis constitutes the final pathway of cellular injury**. Myofibroblasts are the main cell type that produce the extracellular matrix. A novel concept called partial epithelial-mesenchymal transition (EMT) involves tubular epithelial cells developing mesenchymal characteristics despite retaining their attachment to basement membrane has been proposed to play a pathogenic role in CKD.

After an acute kidney injury, there is enhanced expression of mesenchymal markers (e-cadherin, a smooth muscle actin) and upregulation of pro-fibrotic factors (TGF-B, connective tissue growth factor). These factors lead to cell cycle arrest and this in turn upregulates pro-fibrotic factors, leading to a vicious cycle culminating in fibrosis progression [25, 26]. Fatty acid oxidation, which is the main source of energy of proximal convo-

luted tubule (PCT) is halted by these inflammatory factors resulting in lipid accumulation in the PCT cells which is a characteristic feature of EMT. This enhances inflammation, activates innate immunity to cause apoptosis, cytokines, and chemokines [26].

Epigenetic modifications like DNA methylation and histone modification also participate in the regulation of partial EMT. Agents inhibiting these could be a novel therapeutic solution to retard the progression of CKD.

1.7 Genetics of CKD

The precise molecular and cellular mechanisms underlying CKD pathogenesis are poorly understood. **It is estimated that 20% of individuals with CKD in the US harbor potential identifiable and causal mutations in a single gene** [27]. **Studies suggest that disease-causing genetic variations are identifiable in 10% adults and 20% children with CKD** [28]. **Identification of these causes may provide personalized treatments, enable counseling of an at-risk population, guide family planning, and/or identify patients who need treatment for systemic diseases**. For screening, broad gene panels may provide comprehensive analysis. Understanding the testing patterns will enable better understanding of the scope of various detection panels.

One next generation sequencing broad-based panel includes over 300 known mutations for cystic, tubulointerstitial, glomerular, tubular, and structural disorders of the kidney. The panel is ordered per discretion of the nephrologist and can be done utilizing saliva or blood. A study of over one thousand patients utilizing this test found a positive disease-causing variant in 21.1% [29]. The most common genetic abnormalities identified include: PKD1, APOL1, and COLA4/5. Apart from diagnostic significance, there are prognostic and therapeutic benefits as well. For example, the finding of a PKD1 mutation may prompt the clinician to start an ADH-antagonist earlier in the course of disease or could influence family planning. In another example, the finding of a COLA4/5 mutation in a patient with histologic evidence of FSGS could re-classify the cause and avoid unnecessary immunosuppression. FSGS is also associated with genetic variants such as INF2, CD2AP, PAX2, and WT1. And discovery of the HNFB1 gene has been linked to hypomagnesemia, gout, and progressive renal disease in patients previously deemed "idiopathic CKD." As a result, recent guidelines recommended a classification system that included the incorporation of genetic confirmation. Genetic testing also has the potential to reduce the need for kidney biopsy in diagnosis, thus avoiding potential complications and costs. In patients of West African origin, an APOL1 G1 allele is strongly associated with development of non-diabetic kidney disease [29].

One limitation today is that a negative genetic test may miss currently unknown variants. Nevertheless, it is certainly the way forward for detection of genetic diseases and could result in a more personalized treatment for patients with kidney disease.

1.8 Detection

CKD is potentially a progressive disease with the distinct likelihood of ongoing loss of kidney function even after the initial injury is no longer present. **Patients with CKD are often asymptomatic until they reach the more advanced stages. Hence, it is intuitive that earlier detection will facilitate timely treatment, disease awareness, and promote the necessary lifestyle and medication changes to retard the progression of CKD and prevent its complications**. Diagnostic tests employed to detect latent CKD are the dipstick urinalysis for albuminuria, serum creatinine (to calculate eGFR), the kidney ultrasound, and the blood pressure. Although relatively cheap, these have not proven cost-effective when applied to the screening of the general population. Targeting specific susceptible subpopulations, for example, patients with diabetes, hypertension, obesity, or cardiovascular disease, is a more economical approach to screening to detect CKD. Recommendations regarding which

"high-risk" group should be screened vary between national and international organizations (Table 1.3). Attempts at diligent detection and early identification are just a beginning; unfortunately, there is frequently failure to achieve therapeutic targets, due to the lack of awareness of available clinical practice guidelines or their ineffective implementation. Planned programs at detection must incorporate the next important step of proper follow-up and therapy.

Although the worldwide epidemic of obesity and diabetes extend to children, screening for kidney disease in this population is also controversial. The most used and cost-effective screening tool in children is urinalysis for blood and albumin. Two challenges facing mass screening campaigns are (1) determining the right popula-

Table 1.3 Select international guidelines in screening specific adult populations for CKD

Organization	Population	Screening test
American Diabetes Association (ADA)[a] https://diabetesjournals.org/care/article/28/7/1813/27976/Screening-for-Kidney-Disease-in-Adults-With	Adults with diabetes	Initial assessment measures albumin excretion on at least 1 occasion over a 6-month period. Further testing involves assessment of serum albumin creatinine ratio and eGFR evaluation
Japanese Society of Nephrology[a] https://jsn.or.jp/en/guideline/pdf/guideline2009.pdf	Adults with diabetes	Serum creatinine (with eGFR) and urinary albumin–creatinine ratio (UACR) in a spot urine sample
National Institute for Health and Clinical Excellence (NICE)[a] https://www.nice.org.uk/guidance/ng203	Adults with diabetes, hypertension, cardiovascular disease, structural renal tract disease, renal calculi, prostatic hypertrophy, multisystem diseases with potential kidney involvement (e.g., lupus), family history of hereditary kidney disease or stage 5 CKD	Offer CKD testing with urinary albumin–creatinine ratio (UACR) and/or serum creatinine based eGFR measurement
	Adults prescribed nephrotoxic drugs or receiving long-term systemic nonsteroidal anti-inflammatory drug (NSAID) treatment	Measurement of eGFR creatinine
	Obese individuals	No specific screening recommended
Kidney Disease: Improving Global Outcomes (KDIGO)[a] https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf	Adults with CKD	Assessment of GFR through CKD-EPI serum creatinine and cystatin C measurement
United States Preventative Task Force (USPTF)[a] https://www.uspreventiveservicestaskforce.org/uspstf/document/RecommendationStatementFinal/chronic-kidney-disease-ckd-screening	Asymptomatic adults	No specific screening recommended
National Kidney Foundation (NKF)[a] https://www.kidney.org/kidneydisease/siemens_hcp_quickreference	Adults at "increased risk" of CKD	Recommends use of spot urine for albumin- creatinine ratio (UACR) and use of serum creatinine to estimate GFR

[a] Last reviewed on July 24, 2022. The Canadian Society of Nephrology follows KDIGO guidelines for assessment and treatment of chronic kidney disease and associated complications like hypertension, anemia, metabolic bone disease etc

Table 1.4 Goals of a school screening program to detect CKD

1. Program should be based on relatively simple tests that have been documented to provide reproducible results
2. Tests should have a high level of sensitivity (to avoid missing cases of CKD) and preferably associated with high specificity (to reduce number of false positives)
3. Infrastructure of screening program should be set up in such a way to identify abnormal results and schedule confirmatory tests in a short period of time
4. Close communication with the parents of children with abnormal results should be maintained throughout all stages of the screening program
5. Appropriate consultation with a pediatric nephrologist should be expedited for all children who have persistently abnormal results
6. Cost-effectiveness of the program should be confirmed periodically to maintain enthusiasm for the program

tion (such as children's age or country of origin) to screen and (2) assuring the accuracy of random urinalysis. Detection of proteinuria is most accurate with the first morning void; hence, all persons who screen positive on a random sample should have a confirmatory urinalysis done on a first-void morning specimen shortly thereafter.

The goals of implementing a school screening program for children are listed in Table 1.4 [30]. Mass urinary screening programs were initially implemented in France and have been routine practice in Asian countries such as Japan, Taiwan, and Korea for decades. Perhaps due to the high prevalence of IgA nephropathy, childhood screenings in Japan have been reported as "successful" [30]. In 2002, 246,000 elementary and 115,000 junior high school Japanese children were screened. Proteinuria was detected in 0.11% and confirmed on repeat urinalysis in 0.05% of the elementary school children; the results of junior high school screens were 0.6 and 0.32%, respectively. The number of Japanese adolescents who develop ESKD has decreased between 1984 and 2002 suggesting that screening children has the potential to reduce the incidence of ESKD. However, there seems to be a movement away from mass screening in North America and Europe due to issues of its cost-effectiveness. In the USA, the American Academy of Pediatrics (AAP) does not recommend urinalyses during childhood to screen for kidney disease.

Given this data, all children with risk factors for CKD, including those who are obese, are hypertensive, or have relocated from areas of the world with a high endemic burden of CKD, should have a screening urinalysis and if abnormal should be followed by a repeat first morning urinalysis.

Before You Finish: Practice Pearls for the Clinician

- CKD is a major public health problem that is common, harmful, and treatable.
- Detection of CKD is best accomplished with serial measurements of blood pressure, serum creatinine, and urinalysis in select populations at a higher risk of disease
- CKD staging combines albuminuria (A) and cause (C), with GFR (G), to improve prognostication
- The two principal hallmarks of CKD that affect its outcomes are levels of reduced eGFR and increased albuminuria.
- Because of the epidemic of obesity and diabetes, the incidence of CKD is increasing, particularly for persons with overt stage 3 disease (eGFR 30–59 ml/min/1.73 m^2).
- The eGFR declines as age increases resulting in an eGFR of 45–59 ml/min/1.73 m^2 or CKD Stage 3A for many individuals over age 70

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2 Clinical Assessment of a Patient with Chronic Kidney Disease

Sinem Girgin and Mustafa Arici

Before You Start: Facts You Need to Know

- A focused history and physical examination are essential in the assessment of patients with chronic kidney disease (CKD).
- A CKD patient's history should differentiate CKD from acute kidney disease, define duration and chronicity, find a causative or contributory disease, and assess complications and comorbidities.
- Physical examination should cover all systems but has a special emphasis on blood pressure and orthostatic changes, volume assessment, and cardiovascular examination.
- Serum creatinine and estimation of glomerular filtration rate (GFR) with a serum creatinine based equation should be done as a part of initial assessment in all CKD patients.
- A complete urinalysis and measurement of albumin/creatinine ratio in the urine should be carried out in all CKD patients.

2.1 History and Physical Examination of a Chronic Kidney Disease Patient

Chronic kidney disease (CKD) is usually a silent condition. Signs and symptoms, if present, are generally nonspecific (Box 2.1) and unlike several other chronic diseases (such as congestive heart failure, chronic obstructive lung disease), they did not reveal a clue for diagnosis or severity of the condition. Typical symptoms and signs of uremia (Box 2.2) appear almost never in early stages (Stage 1 to 3A/B, even Stage 4) and develop too late *only in some patients* in the course of CKD. Still, all newly diagnosed CKD patients, patients with an acute worsening in their kidney function, and CKD patients on regular follow-up should have *a focused history and physical examination*. This will be the key to perceive *real* "implications of health" associated with decreased kidney function in CKD.

Box 2.1 Symptoms and Signs of Early Stages of CKD

- Weakness
- Decreased appetite
- Nausea
- Changes in urination (nocturia, polyuria, frequency)
- Blood in urine or dark-colored urine

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- Foamy or bubbly urine
- Loin pain
- Edema
- Elevated blood pressure
- Pale skin

Box 2.2 Symptoms and Signs of Late (Uremic) Stages of CKD

- General (*lassitude*, *fatigue*, *elevated blood pressure*, *signs of volume overload*, *decreased mental acuity*, *intractable hiccups*, *uremic fetor*)
- Skin (*sallow appearance*, *uremic frost*, *pruritic excoriations*)
- Pulmonary (*dyspnea*, *pleural effusion*, *pulmonary edema*, *uremic lung*)
- Cardiovascular (*pericardial friction rub*, *congestive heart failure*)
- Gastrointestinal (*anorexia*, *nausea*, *vomiting*, *weight loss*, *stomatitis*, *unpleasant taste in the mouth*)
- Neuromuscular (*muscular twitches*, *peripheral sensory and motor neuropathies*, *muscle cramps*, *restless legs*, *sleep disorders*, *hyperreflexia*, *seizures*, *encephalopathy*, *coma*)
- Endocrine-metabolic (*decreased libido*, *amenorrhea*, *impotence*)
- Hematologic (*anemia*, *bleeding diathesis*)

In a newly diagnosed CKD patient, the history should be focused *to differentiate an acute kidney injury/disease from CKD* and get clues for duration and chronicity of kidney dysfunction. Any previous kidney function tests, urine findings, and imaging studies should be obtained and reviewed. If CKD diagnosis is confirmed, history should be focused *to find an underlying cause*. Patients should be questioned for any sign or symptom of an underlying (causative or contributory) disease(s) for CKD. All medications (including current and prior medications, over-the-counter, and non-prescription medications) should be carefully reviewed and documented. Any previous surgical intervention, especially genitourinary interventions, should be reviewed. A detailed family history should be obtained to exclude presence of a familial, hereditary kidney disorder (Box 2.3).

Box 2.3 Clues to the Underlying (Causative or Contributory) Disease in a CKD Patient

Previous lab tests, imaging, or biopsy findings (*provide definite evidence for CKD if they show previously decreased GFR and/or presence of kidney damage*, *presence of bilateral small kidneys*)

System review:

- Cardiovascular (*history of myocardial infarction*, *coronary intervention*, *and heart failure provide evidence for cardiorenal connection and impaired renal perfusion*)
- Immunologic/infectious (*provide evidence for autoimmune or infectious causes of CKD*)
- Gastrointestinal (*history of hepatitis*, *cirrhosis*)
- Genitourinary (*frequent urinary tract infection*, *recurrent kidney stones*, *and urinary symptoms related to bladder neck obstruction provide evidence for pyelonephritis*, *obstruction*, *and stones*)

Past medical history (*history of diabetes or long- standing hypertension*, *glomerulonephritis in early childhood*, *kidney complications during pregnancy*, *any previous acute kidney injury episode*, *any previous urologic intervention*)

Family history (*anyone with CKD diagnosis among first-degree relatives*)

Medication history (*frequent use of NSAIDs or pain killers*, *long- term exposure to nephrotoxic antibiotics*, *frequent exposure to radiocontrast agents*, *chemotherapeutic use*, *etc.*)

Source: Reprinted from KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification [1], Copyright 2002, with permission from Elsevier. Available from: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm

In each visit, the *stage of CKD and presence of any comorbidity and complications* related to loss of kidney function and *cardiovascular status* should be evaluated. All body systems should be thoroughly reviewed as CKD may have various manifestations in any of them. Patients should be specifically questioned for dermatological, pulmonary, cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, genitourinary, musculoskeletal, and neurological symptoms. *Potential risk factors for sudden deterioration and progression* of CKD, along with *a careful review of medications*, should be sought in each visit.

Physical examination of a CKD patient includes a few specific points beyond general rules. Patient's general health, nutritional status, appetite, and weight changes should be determined in each visit. Blood pressure and pulse should be assessed both in upright and supine positions for determining orthostatic changes. Hypertensive or diabetic changes in the eye should be examined by fundoscopy. Patients should be examined for signs of hypovolemia or volume overload. Skin should be evaluated for finding an underlying disease and signs of CKD (anemia, pruritus, sallow appearance). A careful evaluation of the cardiovascular system is important. The abdomen should be palpated for large kidneys and bladder distention. Abdominal bruits should be noted for potential renovascular disease. Costovertebral tenderness may be a sign of infection and/or stone disease in kidneys. In men, rectal examination is required for determining prostatic enlargement. Neurological evaluation should be focused on signs of neuropathy and muscular problems. Examination for any sign of a systemic disease causing or contributing to CKD should be carefully sought. Findings consistent with uremia should be determined and followed in each visit (Box 2.4).

Box 2.4 What the Guidelines Say You Should Do: History and Physical Examination

- Review past history and any previous measurement for GFR or markers of kidney damage to determine the duration of kidney disease.
- Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease.

Source: Data from KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [2]

2.2 Estimating or Measuring Glomerular Filtration Rate in CKD

Glomerular filtration rate (GFR) is usually accepted as the best index of kidney function. Persistently decreased GFR (<60 ml/min/1.73 m^2) is a hallmark for CKD, even in the absence of any marker for kidney damage. GFR usually correlates well with the prognosis and complications of CKD like anemia, mineral-bone disorders, and cardiovascular disease. GFR should be determined for confirming diagnosis, staging the disease, estimating the prognosis and making decisions about treatment in all CKD patients. GFR level may also be used to decide appropriate timing to start renal replacement therapies. GFR should be regularly monitored in CKD patients according to the stage and severity of CKD. There is, however, no consensus on the monitoring frequency of GFR in various stages (Table 2.1).

GFR is traditionally measured as renal clearance of an "ideal" filtration marker, such as inulin

Table 2.1 How often should GFR be monitored in CKD?

Stage	Testing frequency (once in every)[a]
Stage 1 and 2	6–12 months
Stage 3A	4–6 months
Stage 3B	3–4 months
Stage 4	2–3 months
Stage 5	1 month

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2] and National Institute for Health and Clinical Excellence (NICE) [3]. Available from: http://www.kdigo.org/clinical_practice_guidelines/CKD.php and https://www.nice.org.uk/guidance/ng203

[a] Testing frequency may change according to progression rate and albuminuria level in each stage. All CKD patients should have GFR measurements during any intercurrent illness, any operation, any hospitalization, and any radiocontrast administration

from plasma. This measured GFR is considered *the gold standard* but is not practical for daily clinical use due to complexity of the measurement procedure. Estimating GFR based on a filtration marker (usually serum creatinine) is now widely accepted as an initial test. Several GFR prediction equations that use serum creatinine or some other filtration markers along with certain patient characteristics (like age, gender, and race) are giving precise estimates of GFR in various clinical settings [4].

1. *Serum creatinine*, *Creatinine clearance*, *and GFR estimating equations*: These are the most common methods used for assessing kidney function in clinical practice.
   (a) *Serum creatinine measurement* is a very convenient, cheap, and readily available technique. It is, therefore, the most commonly used parameter to evaluate kidney function in routine clinical practice. Serum creatinine (SCr) levels are largely determined by the balance between its generation and excretion by the kidneys. Creatinine generation is affected by muscle mass and dietary meat intake. Age, gender, and racial differences in creatinine generation depend to changes in dietary intake and muscle mass. Reduced protein intake, malnutrition, and muscle wasting may reduce creatinine generation in a CKD patient. These factors may blunt the rise of serum creatinine in spite of a decrease in GFR levels, especially in late stages of CKD.

   Creatinine is freely filtered through the glomerulus and is also secreted by the proximal tubules (5–10% of the excreted creatinine). Tubular secretion and increased extrarenal elimination of creatinine increases with decreasing kidney function. Both factors lead to underestimation of kidney function by using only serum creatinine levels. In early stages of CKD, serum creatinine usually stays in normal limits despite large reductions (~30–40%) in real GFR due to increased tubular secretion and extrarenal elimination of creatinine [5].

   Serum creatinine is commonly measured by alkaline picrate (Jaffé method), enzymatic, or high-performance liquid chromatography (HPLC) methods. These different methods of measuring serum creatinine are recently standardized to the isotope dilution mass spectrometry (IDMS). Standardized measurements usually yield 5% lower values for serum creatinine concentrations. The alkaline picrate method is subject to interference by various serum constituents and drugs. The differences in assays and inter- and intra-laboratory variability may also affect the accuracy of serum creatinine measurements [6].

   All these factors (differences in creatinine generation, tubular secretion, extrarenal elimination, and variations in assay methods) may affect diagnostic sensitivity and correct interpretation of serum creatinine. *Serum creatinine alone is not anymore accepted as an adequate marker of kidney function.*

   (b) *Creatinine clearance* (*Ccre*) *measurement* is a frequently used clinical method for measuring GFR. Its calculation depends on 24-h urine collection. This is a cumbersome procedure, especially

in elderly. An incomplete or prolonged collection of urine alters the accuracy of the results. If creatinine generation is stable and there is no extrarenal elimination of creatinine, a complete collection may be determined by calculating total excretion of creatinine in the urine as follows:

$$\text{Urine creatinine} \times \text{urine volume} = 20-25\,\text{mg/kg/day for men}, 10-15\,\text{mg/}kg\text{/day for women}$$

Calculation of creatinine clearance assumes that all of the filtered creatinine (equal to the product of the GFR and the serum creatinine concentration (SCr)) is equal to all of the excreted creatinine (equal to product of the urine creatinine concentration (UCr) and the urine flow rate) and ignores the tubular secretion of creatinine. In this condition, the formula is as follows:

$$Ccre = \left[UCr \times V\right] / SCr, \text{where } Ucr\left(\text{Urine creatinine}\right)\text{is mg/ml}, V\left(\text{urine volume}\right)\text{is ml and } SCr\left(\text{Serum creatinine}\right)\text{is mg/dl.If the finding is divided to 1440}\left(24\,\text{h} \times 60\,\text{min}\right), \text{creatinine clearance is expressed as ml/min}.$$

Creatinine clearance formula overestimates true GFR by approximately 10–20% because of disregarding tubular secretion. As already mentioned, tubular secretion of creatinine increases with decreasing kidney function causing higher overestimations in late stages of CKD.

(c) The *reciprocal serum creatinine concentration* (*1/SCr*) *curve* is used to follow changes in the kidney function of patients with CKD. It assumes that GFR is inversely proportional to the serum creatinine. If creatinine generation, extrarenal elimination, and tubular secretion remain stable, a plot of 1/SCr against time will be linear with a constant decrease in GFR. Due to several caveats, this method is not popular anymore for following progression among CKD patients.

(d) *GFR estimating equations based on serum creatinine* were developed in order to eliminate several limitations of serum creatinine use. These equations were derived from different studies and populations and usually combine serum creatinine levels with other determinants of GFR like age, gender, and race and body size. The most common equations used are the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) Study, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

(e) The *Cockroft- Gault equation* is the oldest (developed in 1973) but simplest equation for everyday clinical use. It has been derived using data from 249 men with a creatinine clearance ranging from approximately 30 to 130 ml/min [7].

$$Ccre\left(\text{ml/min}\right) = \left\{\left[\left(140 \;\; \text{age}\right) \times \text{body weight}\right] / \left(72 \times Scr\right)\right\} \times \left(0.85\,\text{if female}\right),$$

where age is expressed in years, weight in kilograms, and serum creatinine $\left(Scr\right)$ in milligrams per deciliter.

This equation was derived when standardized creatinine assays were not in use. In labs where standardized creatinine assays were used, this equation will cause an overestimation (10–40%) of actual GFR. This equation has not been adjusted for body surface area. It is less accurate in obese patients (overestimate), in patients with normal or mildly decreased GFR (underestimates), and in the elderly (underestimates) [6, 8].

(f) The *MDRD Study equation* was developed in 1999 by using data from 1628 CKD patients (primarily white subjects, with nondiabetic kidney disease) with a GFR range between 5 and 90 ml/min/1.73 m^2. The equation was re-derived in 2006 for use with the standardized serum creatinine assays [9, 10].

$$\text{GFR}\left(\text{mL}/\text{min}/1.73\,\text{m}^2\right) = 186.3 \times Scr^{-1.154} \times \text{age}^{-0.203} \times \left(0.742\,\text{if female}\right) \times \left(1.210\,\text{if African American}\right), \text{where } Scr \text{ is expressed in mg/dL and age is expressed in years.}$$

$$\text{GFR}\left(\text{mL}/\text{min}/1.73\,\text{m}^2\right) = 175 \times Scr^{-1.154} \times \text{age}^{-0.203} \times \left(0.742\,\text{if female}\right) \times \left(1.210\,\text{if African American}\right), \text{where a standardized } Scr\left(\text{mg}/\text{dL}\right) \text{measurement is done.}$$

MDRD equation is the most widely used formula in recent years. Many laboratories automatically report MDRD equation GFR estimate along with serum creatinine measurements. This equation is more accurate in estimating GFR than 24-h urine creatinine clearance and Cockroft-Gault formula. It is also more accurate in patients with lower GFR levels (<60 ml/min/1.73 m^2). Its accuracy differs in various ethnic groups. It is less accurate in obese patients and in patients with normal or mildly decreased GFR.

(g) *The CKD-EPI equation* has been derived in 2009 from a large study population that included patients with or without kidney disease with a wide range of GFR. When compared with MDRD, CKD-EPI was more accurate in people especially with higher GFR levels (>60 ml/min/1.73 m^2) [11].

GFR (ml/min/1.73 m^2) = 141 × min(SCr/κ, 1)α × max(SCr/κ, 1)–1.209 × 0.993Age × (1.018 if female) × (1.159 if African American), where SCr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1

Female	≤ 0.7 mg/dl	$\text{GFR} = 144 \times \left(Scr/0.7\right)^{-0.329}$
	> 0.7 mg/dl	$\text{GFR} = 144 \times \left(Scr/0.7\right)^{-1.209} \times \left(0.993\right)^{\text{Age}} \times 1.157\left[\text{if black}\right]$
Male	≤ 0.9 mg/dl	$\text{GFR} = 141 \times \left(Scr/0.9\right)^{-0.411}$
	> 0.97 mg/dl	$\text{GFR} = 141 \times \left(Scr/0.9\right)^{-1.209}$

The CKD-EPI equation has been found to result in lower prevalence estimate of CKD across a broad range of populations and categorized mortality and ESRD risk better than MDRD. Given the data on the improved performance, especially in general population at higher levels of GFR, "*KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease*" *recommends to use CKD-EPI equation for GFR estimation*.

Race-free CKD-EPI equation with the realization that race is only a social terminology and not a biological construct. Health professionals began to demand the removal of variables by race from clinical algorithms. With this perception, the race variable was removed and the CKD EPI 2021 creatinine equation was revealed [12, 13].

There is information that Black individuals are classified in a lower category and non-Black individuals in a higher category in CKD staging using the race-independent CKD EPI 2021 equation. Although the use of the CKD EPI 2021 equation increases the prevalence of CKD in Black individuals, it is thought that its suitability for medical treatments and contrast-based procedures will need to be evaluated. It may increase nephrology and vascular access referrals, and transplantation and donor eligibility assessments may be affected [14].

The performance of race-free equation was found to be poor in white subjects with a significant underestimation of CKD, especially in European populations. A viewpoint by European Renal Association has not proposed to adopt this new race-free CKD-EPI equation before its better performance in European populations is shown [15]. A new European Kidney Function Consortium equation (EKFC) has been developed mostly from European cohorts with a full age spectrum, i.e., applicable from children >2 years to the elderly population [16].

(h) *The Berlin Initiative Study (BIS) equation* was developed to make an accurate estimation of GFR in elderly population. Two new equations were created, one based on creatinine (BIS1) and one based on creatinine and cystatin c (BIS 2). GFR is estimated more accurate with BIS equations in elderly patients (≥70 years) especially when eGFR is greater than 30 mL/min per 1.73 m^2 [17].

All GFR equations have some imprecision and do not provide an accurate estimate of GFR due to several limitations. Some of the limitations are related to the serum creatinine itself (Box 2.5) and some are linked to the populations and studies that the equations have been derived. All GFR equations should be used in stable settings where serum creatinine has no rapid alterations (i.e., not used in acute kidney injury/disease). They are not recommended for use in patients under the age of 18, in patients with extremes in body size or muscle mass, in patients with severe alterations in dietary intake (vegetarians, using creatine supplements), in very elderly (>85 years), or in pregnant patients. It should be noted that GFR equations have a large standard deviation. They are very useful in large group/ population estimates, but may lead to misinterpretations in some individual assessments. Where wide variations in an individual's estimated GFR exists, or where a more accurate assessment of GFR is required, good clinical judgment and measurement of GFR (see below) is recommended.

In elderly population, MDRD equation predicts higher eGFR than CKD stage compared to CKD EPI and Cockroft-Gault equations. MDRD equation overestimates GFR in the elderly population due to decreased muscle mass. One reason is that the MDRD study population is younger and excludes people

over 70 years of age. However, the CKD EPI collaboration study included older adults as well. GFR estimation with cystatin c (see below) is more reliable in the elderly population where muscle mass reduction is common. Cystatin c-related equations are more advantageous in estimating moderate GFR reductions in this age group, and the only disadvantage is the cost of the measurement.

Box 2.5 Sources of Error by Using Serum Creatinine in GFR Estimation

- Non-steady state (*e.g.*, *acute kidney injury*)
- Variable creatinine generation (*e.g.*, *race*, *extremes of muscle mass*, *extremes of body size*, *high protein diet*, *creatinine supplements*, *muscle wasting*)
- Variable tubular secretion (*e.g.*, *decrease by trimethoprim*, *cimetidine*, *fenofibrate*)
- Variable extrarenal elimination (*e.g.*, *decrease by inhibition of gut creatininase by antibiotics*, *increase by large volume losses*)
- Higher GFR (*e.g.*, *higher measurement errors in patients with higher GFR*)
- Interference with assay (*e.g.*, *spectral interferences from bilirubin and some drugs or chemical interferences from glucose*, *ketones*, *bilirubin*, *and some drugs*)

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2]. Copyright 2013. Available from: http://www.nature.com/kisup/index.html

2. *Blood urea and Urea clearance*: Urea is the most well-known nitrogenous waste and it was used as one of the first indicators to measure GFR. It is also measured as an indicator of uremic burden and uremic symptoms in late stages of CKD. Although blood urea nitrogen (BUN) has an inverse relationship with GFR, it is not an ideal filtration marker. Urea production is variable and is largely dependent on protein intake. BUN concentration increases as its production increases with high protein intake, tissue breakdown, trauma, hemorrhage, or glucocorticoid use. In contrast, BUN concentration decreases when its production decreases with low protein intake or in liver disease.

   Urea is freely filtered from the glomerulus, but 40–50% is reabsorbed in the tubules. Urea reabsorption increases substantially in states of decreased renal perfusion (volume depletion, congestive heart failure, diuretic use). In all these conditions, BUN levels will increase out of proportion to a decrease in GFR and will result in an increased ratio of BUN to SCre. Increased BUN-to-SCre ratio is suggestive of a prerenal state and may indicate an acute deterioration in a CKD patient.

   Urea clearance is not a reliable indicator of GFR also due to variable tubular reabsorption rates of urea. GFR may be underestimated almost as half as the real level by urea clearance. *The only clinical setting where urea clearance use has been advocated is the late stages of CKD for deciding appropriate timing of dialysis* [18]. As urea clearance underestimates and creatinine clearance overestimates GFR, it is recommended that the average of these two clearances (*GFR* = (*creatinine clearance* + *urea clearance*)/2) is preferred for estimating GFR in advanced CKD. The use of this formula is also compromised by problems related to proper urine collection.
3. *Serum cystatin C and GFR equations*: Limitations inherent to the use of serum creatinine are the major drive for seeking alternative filtration markers in the serum. Among them, cystatin C is considered to be a potential alternative to serum creatinine for estimating GFR. Cystatin C is a low molecular weight (13-kDa) cysteine protease inhibitor that is produced by all nucleated cells. It is freely filtered by the renal glomerulus. It is reabsorbed and completely catabolized by tubular cells. In contrast to creatinine, cystatin C does not undergo

any tubular secretion. The generation of cystatin C was believed to be less variable and affected less by age and sex. Later epidemiological studies, however, have suggested that cystatin C generation rate and serum levels have been influenced by age, sex, cell turnover rate, steroid use, body mass index, inflammation, and diabetes. Studies have also shown that there is an extrarenal elimination of cystatin C at low levels of GFR. Serum cystatin C measurements are not standardized yet and still evolving. Studies have shown that cystatin C measurements also have higher intraindividual variation than serum creatinine.

Several studies have shown that cystatin C concentrations may correlate more closely with GFR than serum creatinine. Similarly, GFR estimates based on cystatin C may be more powerful predictors of clinical outcomes than creatinine-based eGFR. These findings have been the strongest for mortality and CVD events, and the prognostic advantage of cystatin C is most apparent among individuals with GFR >45 ml/min/1.73 m^2. Recently, a single equation combining both serum creatinine and cystatin C has been found to be more accurate in determining GFR [19]. The role of cystatin C measurements or use of cystatin C-based equations in CKD care has yet to be determined. "KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease" has recommended to measure cystatin C to confirm CKD in adults if eGFR based on serum creatinine was between 45 and 59 ml/min/1.73 m^2 without any markers of kidney damage. KDIGO recommends to use either cystatin C-based eGFR equation or cystatin C and creatinine-based eGFR equations in confirming the presence of CKD. The use of cystatin C equations has also several limitations (Boxes 2.6 and 2.7). A new race free creatinine and cystatin C based eGFR equation without race has also been defined. It more accurately estimated measured GFR than equations with either the creatinine or cystatin alone. The use of creatinine and cystatin C based eGFR equation led to smaller differences from measured GFR between race groups [12].

Box 2.6 Sources of Error by Using Serum Cystatin in GFR Estimation

- Non-steady state (e.g., *acute kidney injury*)
- Variable cystatin generation (e.g., *race*, *thyroid function disorders*, *corticosteroid use*, *diabetes*, *obesity*)
- Variable extrarenal elimination (e.g., *increase by severe decrease in GFR*)
- Higher GFR (e.g., *higher measurement errors in patients with higher GFR*)
- Interference with assay (e.g., *heterophilic antibodies*)

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2]. Copyright 2013. Available from: http://www.nature.com/kisup/index.html

Box 2.7 What the Guidelines Say You Should Do: Glomerular Filtration Rate

- Use serum creatinine and a GFR estimating equation for initial assessment.
- Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone.
- Understand clinical settings in which eGFRcreat is less accurate.
- Clinical laboratories should report eGFRcreat in adults using the 2009 CKD-EPI creatinine equation.
- Clinical laboratories that measure cystatin C should report eGFRcys and eGFRcreat-cys in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.

Source: Data from KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [2]

CKD-EPI Cystatin C equation:

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73\,m^2}\right) = 133 \times \min\left(\mathrm{SCysC}/0.8,1\right) - 0.499 \times \max\left(\mathrm{SCysC}/0.8,1\right) - 1.328 \times 0.996^{\mathrm{Age}} \left[\times 0.932 \text{ if female}\right]$$

where SCysC is serum cystatin C (in mg/l), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.

CKD-EPI Creatinine-Cystatin C equation:

$$\mathrm{GFR}\left(\mathrm{ml/min/1.73\,m^2}\right) = 135 \times \min\left(\mathrm{SCr}/\kappa,1\right)^{\alpha} \times \max\left(\mathrm{SCr}/\kappa,1\right) - 0.601 \times \min\left(\mathrm{SCysC}/0.8,1\right) - 0.375 \times \max\left(\mathrm{SCysC}/0.8,1\right) - 0.711 \times 0.995^{\mathrm{Age}} \left[\times 0.969 \text{ if female}\right] \left[\times 1.08 \text{ if black}\right]$$

where SCr is serum creatinine (in mg/dl), SCysC is serum cystatin C (in mg/l), κ is 0.7 for females and 0.9 for males, α is –0.248 for females and −0.207 for males, min(SCr/κ, 1) indicates the minimum of SCr/κ or 1,and max(SCr/κ, 1) indicates the maximum of SCr/κ or 1; min(SCysC/0.8, 1) indicates the minimum of SCysC/0.8 or 1 and max(SCysC/0.8, 1) indicates the maximum of SCysC/0.8 or 1.

All these equations may be reached in various websites as electronic calculators, such as http://touchcalc.com/bis2.html or http://www.hdcn.com/calcf/gfr2.htm or https://www.kidney.org/professionals/kdoqi/gfr_calculator

4. *Measuring GFR with exogenous markers*: In clinical settings where GFR estimates from serum creatinine or creatinine-based GFR estimating equations cannot be performed (such as pregnancy, acute kidney disease, etc.) or when there is a need for a more precise determination (such as for living donor assessment) of GFR, clearance measurements should be performed with several filtration markers (inulin, iothalamate, iohexol, DTPA, or EDTA) [20]. Measuring GFR with the use of these markers is complex, expensive, and difficult to do in clinical practice. The measurement of GFR with these markers has also some limitations and rarely used in clinical practice for CKD care except research settings. In a CKD patient, a measured GFR may only be required if the patient is chronically ill with severe reduction in muscle mass, if there will be a prolonged exposure to nephrotoxic drugs, or if there is a discrepancy between severely reduced eGFR and symptoms of uremia before deciding to start renal replacement therapy.

   There is also a new method for calculating GFR by transcutaneous measurement of a new exogenous renal marker, FITC-sinistrin (fluorescein isothiocyanate). GFR is calculated by measuring FITC-sinistrine tested in rodents, and its elimination from the skin with a miniaturized instrument. The advantage of this method over conventional plasma clearance measurements is that it does not require repetitive measurements with blood samples and allows repetitive GFR measurements in a short time period [21, 22]. There are also studies for real-time monitoring of GFR via transdermal measurement of fluorescent tracers [23].
5. *Novel biomarkers*: There is still ongoing research for finding one or more potential,

alternative markers for estimating GFR. In this sense, several low molecular weight molecules such as beta-trace protein (BTP), beta(2)-microglobulin (B2M), and symmetric dimethyl arginine have been investigated. BTP and B2M have been found to be more accurate than serum creatinine in some studies. Proenkephalin A 119–159 (PENK) is a newly identified marker of renal function. It is a good biomarker in showing kidney function because it does not bind to proteins in plasma and can be filtered from the glomerulus. Plasma PENK concentration has been shown to correlate with GFR in many patient populations (critical illness, sepsis, heart failure, CKD patients, kidney transplant recipients and donors) [24]. It is yet to be determined whether one or several of them have a role in CKD patients alone or in combination with creatinine or cystatin C.

2.3 Urinalysis and Albuminuria in CKD

Urinalysis and assessment of albuminuria are very informative, noninvasive tests for both screening and diagnosing CKD. Albuminuria is also an important measure for defining severity of kidney dysfunction, estimating prognosis of CKD-related outcomes, and associated cardiovascular risk. The presence of albuminuria and its severity also guides treatment alternatives in CKD.

1. *Urinalysis*: A complete urinalysis should be carried out in the first examination of all CKD patients. Along with a targeted history and physical examination, urinalysis provides important information for differential diagnosis of acute and chronic kidney disease. Urinalysis may also provide clues for underlying etiologies of chronic kidney disease. There is, however, no evidence-based information whether urinalysis is required in each follow-up visit of a CKD patient.

   A detailed discussion of the diagnostic uses of urinalysis or specific tests of urine (metabolic diseases, urine electrolytes, etc.) is beyond the scope of this chapter and may be found in other sources. Here, only essential features of urinalysis for the care of CKD patients will be covered.

   An accurate urine analysis should start with a proper collection of a urine sample. First-void (early) morning urine is usually preferred as formed elements will more likely be seen in concentrated urine with a low pH. The sample should be analyzed within 2–4 h from collection.

   A complete urinalysis consists of three components, as physical (gross) examination, chemical (dipstick) analysis, and microscopic evaluation of the urinary sediment. In routine clinical practice, most of the physical and chemical parameters are examined by a dipstick. A dipstick provides a semiquantitative examination of several urinary characteristics by a series of tests embedded on a reagent strip. Among physical parameters, color (usually normal in CKD), turbidity (usually normal in CKD), and specific gravity (usually a fixed, isosthenuric urine is produced in CKD, i.e., specific gravity is 1010) are assessed. In chemical analysis, urine dipstick assesses pH (low or normal in CKD), glucose (usually normal in CKD), ketones (usually normal in CKD), bilirubin and urobilinogen (usually normal in CKD), nitrite and leukocyte esterase (usually normal in CKD), blood, and protein. *The dipstick test for blood* detects peroxidase activity of erythrocytes. The dipstick test is commonly considered to be sensitive for detection of microscopic hematuria. False-negative results are unusual, i.e., a negative dipstick for blood excludes hematuria. However, myoglobin and hemoglobin also will catalyze this reaction, so a positive test result may indicate hematuria, myoglobinuria (from rhabdomyolysis), or hemoglobinuria (from intravascular hemolysis). When it is positive, visualization of intact erythrocytes on microscopic examination of the urinary sediment should be done for confirmation of hematuria. Hematuria may be observed in patients with CKD due to various underlying

causes. *The dipstick test for protein* is most sensitive to albumin and may not detect low concentrations of globulins, tubular proteins, and Bence Jones proteins. The dipstick measurement of urine protein allows only an approximate quantification of urine albumin, expressed on a scale from negative trace to 1(+) to 4(+). Dipstick tests for trace amounts of protein yield positive results at concentrations of 5–10 mg/dl—lower than the threshold for clinically significant proteinuria. Dipstick protein may miss moderately increased albuminuria levels in the range of 30–300 mg/day (formerly called microalbuminuria) in most cases. A result of 1+ corresponds to approximately 30 mg of protein per dl and is considered positive; 2+ corresponds to 100 mg/dl, 3+ to 300 mg/dl, and 4+ to 1000 mg/dl. In addition, dipstick protein measurement is dependent on the concentration of the urine specimen, where concentrated urine may give false-positive and dilute urine may give false-negative results. Thus, it is important to quantify the amount of proteinuria detected on urine dipstick analysis with other methods. Protein can be quantified in random samples, in timed or untimed overnight samples, or in 24-h collections. Although 24-h urine protein amount represents the gold standard method, problems related with 24-h collection (over or under collection) are a major source of error. It is also a cumbersome procedure for many patients. Still, adequately collected 24-h urine protein concentrations are accepted as the most accurate way to monitor proteinuria under active treatment (such as active immunosuppressive use). A complete collection may be determined by the amount of expected 24-h urine creatinine excretion (see above). *Protein-creatinine ratio* (*PCR*) in a random urine sample is accepted as an alternative to 24-h urine collection. PCR may correct problems arising from variability of urine volume and concentration. It is easy to obtain and showed a strong correlation with 24-h urine collection. However, when urine protein levels are greater than 1 g/l, spot protein-creatinine correlation with 24-h urine may not be accurate. Thus, spot protein-creatinine level may act as a simple screening for proteinuria, i.e., if it is negative, there is no need for a 24-h urine collection.

In cases where presence of non-albumin proteins (such as gamma globulins, Bence Jones proteins) is suspected, other precipitation methods like sulfosalicylic acid test should be used. Trichloroacetic acid can be used in place of sulfosalicylic acid to increase the sensitivity to gamma globulins.

Microscopic examination of urine sediment should be done in all patients with CKD and in patients with high risk for CKD. In the urine sediment, cellular elements (red blood cells, white blood cells), casts, and crystals should be thoroughly examined. Some findings in the urine sediment may help to diagnose some underlying causes of CKD. There is, however, no characteristic finding in the urinary sediment of a CKD patient, except broad casts which are typically associated with advanced stages of CKD.

Urine flow cytometry is an alternative to automated microscopic methods. It has more advanced cell counting and accuracy. It provides rapid detection of urine microorganisms and allows more accurate results by evaluating the dilution parameters. Early detection of urothelial cancer is one of its advantages. Rapid detection of urinary tract pathogens is also possible with the matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS) method [25].

2. *Albuminuria*: Albumin is the predominant protein in major proteinuric diseases causing CKD. Albumin measurement in urine has greater sensitivity and improved precision for the detection of low levels of proteinuria compared to protein measurements. It is therefore accepted as a more sensitive method for screening/diagnosing not only diabetic but also nondiabetic CKD. Most of the recent studies also showed strong evidence linking increased albuminuria and outcomes of CKD.

Urinary concentrations of albumin <150 mg/l are below the detection limit of the "dipstick" tests used in routine urinalysis. Albumin in the urine may be detected by radioimmunoassay, immunoturbidimetric technique, and nephelometry, ELISA, or HPLC. Reagent strip methods were also developed for urine albumin screening but have increased false-positive or false-negative ratios.

Twenty-four-hour urine collection is also the gold standard for the detection of high albuminuria (formerly, microalbuminuria). Albuminuria screening however may be done with spot early morning urine collections, timed urine collections, or as a ratio of albumin to creatinine in the urine (ACR). The ACR is the preferred method as it does not require timed collections, it correlates with the 24-h urine values over a large range of proteinuria, it is cheap to perform, and repeat values can be easily obtained to be certain that high albuminuria, if present, is persistent. A value of 30–300 mg/g of creatinine (or, using standard (SI) units, 3.4–34 mg/mmol of creatinine) suggests that albumin excretion is between 30 and 300 mg/day and therefore that high albuminuria is probably present. A false reading for ACR may occur after vigorous exercise, in the presence of fever, urinary infection, congestive heart failure, acute severe elevations of blood pressure or blood sugar, or menstruation. There are some other sources of error in the assessment of ACR (Box 2.8) [26].

Box 2.8 Sources of Error When Using ACR for Albuminuria

- Transient, false elevations in albuminuria (e.g., *menstrual blood contamination*, *urinary tract infection*, *fever*, *exercise*, *orthostatic*, *severe uncontrolled hyperglycemia*, *or hypertension*)
- Variability due to sample storage (*e.g.*, *degradation of albumin before analysis*)
- Variability in creatinine excretion (*e.g.*, *lower in children*, *women*, *or elderly*, *higher in black*, *lower due to decreased muscle mass*, *variability due to non-steady state*)
- Interference with assay (*e.g.*, *samples with very high albumin levels may falsely be reported as low or normal due to antigen excess effect in some assays*)

Source: Adapted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [2]. Copyright 2013. Available from: http://www.nature.com/kisup/index.html

Most national and international guidelines (including KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease) recommend ACR measurement with an early morning urine sample over other methods. Albuminuria assessment is recommended to be done at least annually in CKD patients. The frequency of assessment of albuminuria may depend on clinical situation, i.e., rate of progression or monitoring the effect of anti-albuminuric treatment (Boxes 2.9 and 2.10).

Box 2.9. What the Guidelines Say You Should Do: Albuminuria

- Use the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred):
  - Urine albumin-to-creatinine ratio (ACR)
  - Urine protein-to-creatinine ratio (PCR)
  - Reagent strip urinalysis for total protein with automated reading
  - Reagent strip urinalysis for total protein with manual reading

- Confirm reagent strip-positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible
- Confirm ACR >30 mg/g (>3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample
- Measure albumin excretion rate or total protein excretion rate in a timed urine sample for a more accurate estimate

Source: Data from KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [2]

Box 2.10 Relevant Guidelines

1. *KDIGO Guideline*: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3: 1–150. http://kdigo.org/guidelines/ckd-evaluation-and-management
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2.4 Other Lab Tests in CKD

CKD patients may need further tests as a part of their general assessment or for finding any other marker of kidney damage like renal tubular disorders or for assessment of the complications of CKD (such as anemia, mineral-bone disorders, malnutrition, neuropathy, cardiovascular tests). These tests will not be covered in detail here. It is, however, important to note that some tests need a cautious interpretation especially in patients who are in the late stages (Stages 4 or 5) of CKD. Among those tests, there are serum ALT, AST, amylase, lipase concentrations, troponins, and BNP/NT-proBNP levels which may have diagnostic and/or therapeutic importance. With a decrease in GFR, there is a trend of false alterations in these tests: Liver transaminases tend to decrease to very low levels, pancreatic amylase and lipase, troponins, and BNP/NT-proBNP levels tend to increase above cutoff concentrations. All these alterations should be interpreted carefully, and "real" implications of test results should be assessed within the clinical context of the patient.

Before You Finish: Practice Pearls for the Clinician

- In each visit, a CKD patient should be assessed for general well-being, for progression and any factor for acute deterioration of CKD, for presence of any complications or comorbidity, and for cardiovascular health.
- Patients who are in late stages of the disease should be assessed for the presence of any uremic symptom, and the need for renal replacement therapy should be evaluated.
- Blood pressure, orthostatic changes, volume, and cardiac status should be checked in all visits.
- CKD patients should have an assessment of eGFR and albuminuria as a part of their initial assessment. eGFR and albuminuria should be rechecked at least annually in all CKD patients.
- eGFR should be calculated by 2009 CKD-EPI equation derived from serum creatinine. Patients who are in the late stages, who have a higher risk for progression, who have any intercurrent illness/medication use/operation, and who have changes in treatment may have frequent eGFR assessments.
- Keep in mind the limitations of eGFR or ACR measurements mostly caused by creatinine measurements.
- The use of direct methods to measure GFR should be considered in clinical situations in which estimation equations are known to be suboptimal.
- Albuminuria should be assessed by albumin-creatinine ratio measured from an early morning urine sample. Patients who have severely increased albuminuria or patients who are under antiproteinuric treatment may have frequent albuminuria assessments.

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Imaging in Chronic Kidney Disease

3

Yousef W. Nielsen, Peter Marckmann, and Henrik S. Thomsen

Before You Start: Facts You Need to Know

- Imaging examinations where glomerular filtration of the agent is an integrated part of the examination cannot be performed in patients with reduced renal function (GFR <30 ml/min/1.73 m^2).
- Appropriate precautions to avoid adverse reactions to contrast agents should be taken; all departments should have guidelines for the handling of patients at risk.

3.1 Diagnostic Imaging in CKD

The patients with chronically reduced kidney function can undergo exactly the same imaging examinations as patients with normal kidney function with one important exception, namely when glomerular function is part of the examination as it is in renography, intravenous urography, CT-urography, and magnetic resonance imaging urography where excretion of the contrast agent is an integrated part of the examination.

In most cases the process towards end-stage kidney failure is long. Diabetic nephropathy rarely occurs before the patient has had diabetes mellitus for 10 years. Multiple cysts can be seen in patients with adult dominant polycystic kidney from the early 20's, whereas end-stage kidney failure first occurs in the 50's. Thus the major work for radiology/nuclear medicine in patients with chronic kidney failure is not imaging of the kidneys themselves, but the complications to uremia, e.g., vascular problems (arteriography, venography), cardiac incompensation (chest X-ray), infections, cerebral diseases. In any case the patient should always be referred to the most optimal imaging to verify or rule out a suspected lesion. When there is reduced glomerular filtration rate or it is absent, other ways to visualize the lumen of the upper urinary tract than the usual imaging method, e.g., CT-urography cannot be performed. One has to inject the contrast medium directly into the ureter/pelvis and/or bladder using a catheter. When the contrast medium has been injected, CT or plain films should be done. Alternatively MR-hydrography using the water in the urinary tract should be performed. There may be instances where MR and CT are equal with regard to diagnostic workup; in those cases MR should be chosen for patients with chronic kidney disease so radiation is avoided.

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3.2 Radiological Investigations

3.2.1 Conventional Radiography

A plain film of the urinary tract gives information about the calcifications within and outside urinary tract as well as various medical devices, e.g., nephrostomy tube, double J-stent, and artificial sphincter (Fig. 3.1). A chest X-ray is used like in any other patients to evaluate heart size, pulmonary congestion, pneumonic infiltrations, pneumothorax, location of catheters, and fluid in the pleural space (Fig. 3.2). It is frequently used in patients with severely reduced kidney function or on dialysis as they easier develop chest problems (e.g., pulmonary stasis, inflammations) than patients with normal renal function.

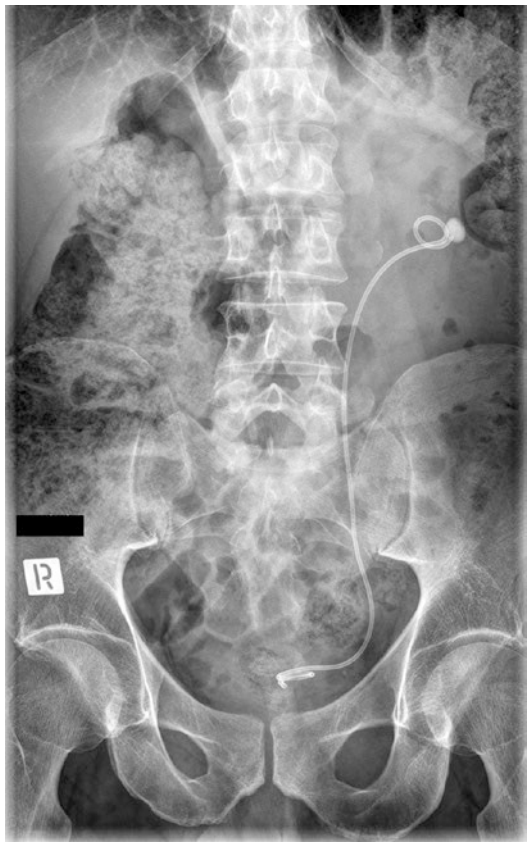

Fig. 3.1 A plain film of the urinary tract showing a left-sided double J-stent

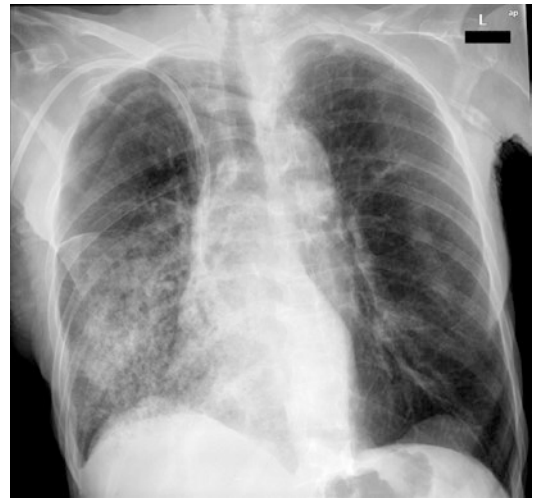

Fig. 3.2 Chest X-ray. Right-sided pneumonia in a CKD patient

Intravenous urography or pyelography has no longer a role in patients with reduced renal function or on dialysis as the kidneys cannot filter enough contrast agents per time unit to enhance the lumen of the urinary tract for imaging. Visualization of the urinary tract (lumen) is possible using conventional imaging methods like direct pyelography where the contrast medium is injected through a catheter inserted percutaneously (nephrostomy) or via catheter placed in the ureter during cystoscopy. These examinations are called antegrade pyelography and retrograde pyelography, respectively (Fig. 3.3). They are rarely used today as most information can be obtained by magnetic resonance imaging and CT-scanning. However, direct pyelography does not include intravascular injection and the patient has no risk of contrast nephropathy.

3.2.2 Ultrasound

Ultrasonography is frequently used in patients with reduced kidney function. It can give information about the size of the kidney and presence of hydronephrosis (Fig. 3.4). However, the absence of hydronephrosis does not exclude obstruction. Doppler can provide information

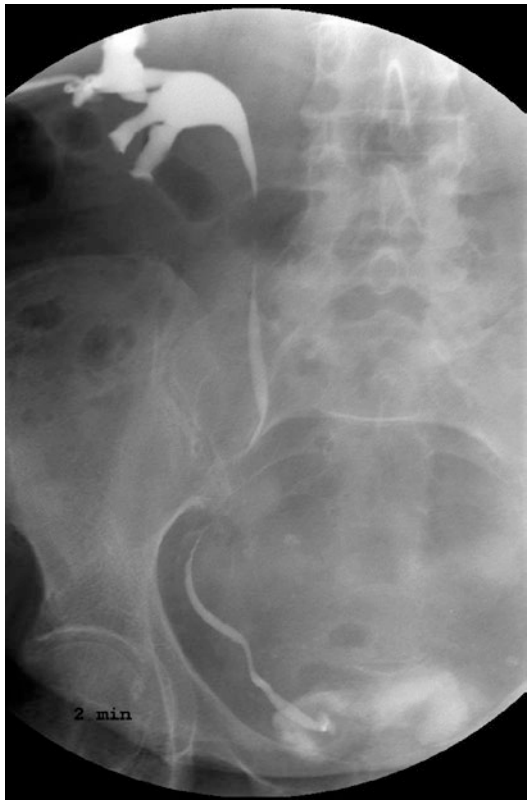

Fig. 3.3 Normal antegrade pyelography. Note the nephrostomy tube

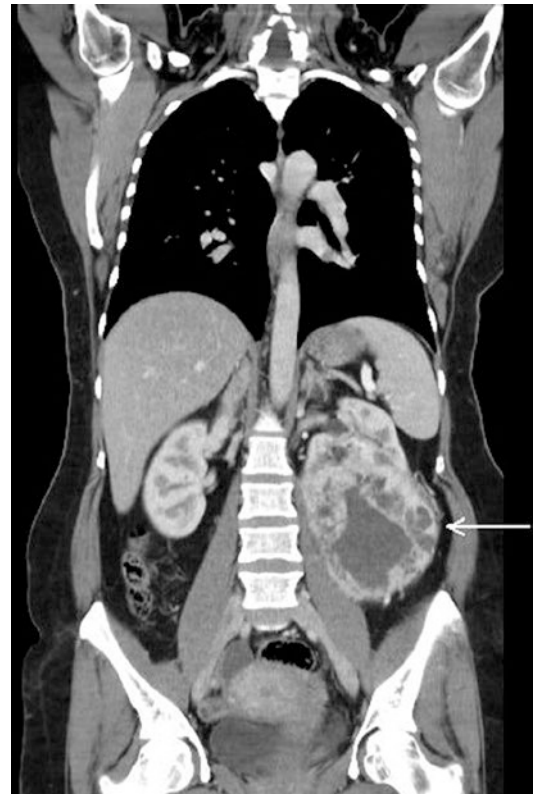

Fig. 3.4 Contrast-enhanced CT showing a large renal cell carcinoma on the left kidney (arrow). There is central necrosis in the tumor

about the vascularization of the kidney. Resistive index (RI) determined by Doppler in CKD patients is considered as a marker of kidney function, histological damage, and kidney prognosis. RI > 0.65–0.70 is associated with severe interstitial fibrosis and arteriosclerosis and kidney function decline, acute tubular necrosis, and more.

3.2.3 CT Imaging

CT imaging can be performed with or without administration of intravenous iodine-based contrast media. Unenhanced CT imaging can be performed in CKD patients without the need of special precautionary measures. **For many years (>70 years) it has been believed that contrast-enhanced studies may result in contrast medium-induced nephropathy (see later). Due to the fear of contrast nephropathy the role of enhanced CT imaging in CKD patients has been limited**.

Unenhanced CT may show obstruction, tumors, cysts or calculi. Both level and degree of urinary tract obstruction can in some cases be clearly visualized, but if the kidney function has been low for longer time periods (months/years), the pelvic cavity may not enlarge in response to urinary tract obstruction. Therefore, a normal sized pelvic cavity does not exclude obstruction in patients with poor kidney function. Some renal tumors can be detected with unenhanced CT, however, the detection of small renal cell carcinomas requires contrast media administration (Fig. 3.5a, b). The presence of a normal contoured kidney does not exclude malignancy in the kidney parenchyma. It may be very difficult to detect small tumors in the upper urinary tract

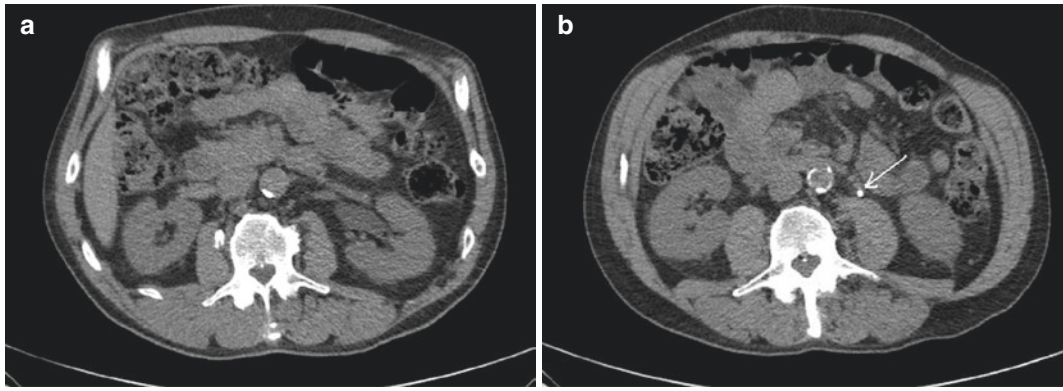

Fig. 3.5 Unenhanced CT showing left-sided hydronephrosis (**a**). The cause was a 6 mm calculus (arrow) in the left proximal ureter (**b**)

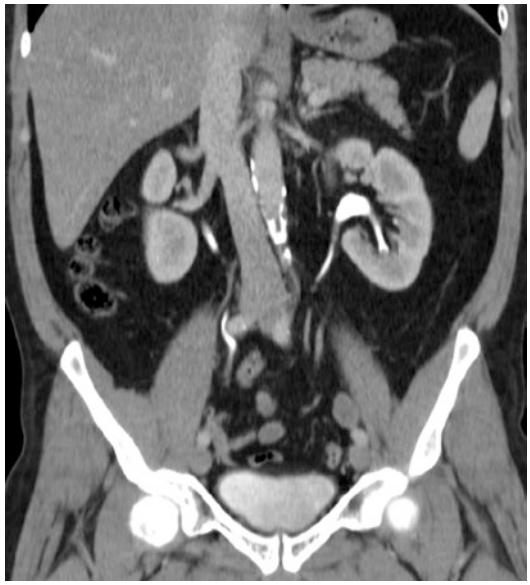

Fig. 3.6 CT-urography. After intravenous contrast administration, there is enhancement of the renal parenchyma as well as contrast in th urinary tract

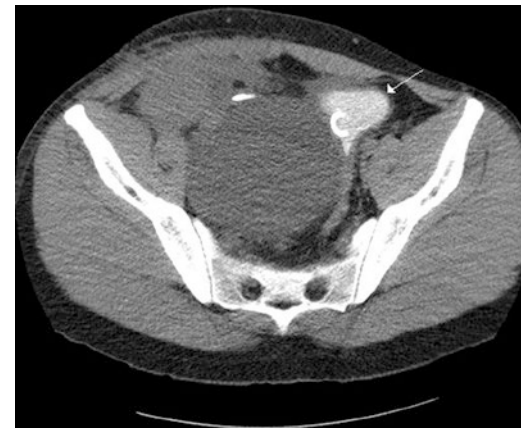

Fig. 3.7 Post-transplant complication. A large lymphocele is present in the pelvis. The bladder (arrow) is compressed and displaced by the lymphocele

without the use of contrast medium; this applies also to patients with acquired cystic disease. The presence of fat within renal lesions is suggestive of angiomyolipoma, but again small amounts of fat may be found in renal cell carcinomas. Unenhanced CT is the best imaging method for detection of urinary tract calculi (Fig. 3.6).

Contrast-enhanced CT performed as CT-urography is the method of choice to detect renal as well as urothelial carcinomas outside the bladder (Fig. 3.7). The strength of CT-urography is the excellent enhancement of renal parenchyma combined with contrast filling of the collecting system and ureters. The major drawback in CKD patients is that the method requires glomerular filtration of the contrast medium. Thus, it is not possible to perform CT-urography when GFR is reduced.

Other indications for contrast-enhanced CT in CKD patients are by large related to vascular diseases. CT-angiography performed in modern multislice CT scanners is suitable for detection of renal artery stenosis, as well as peripheral and coronary artery disease (see later).

In kidney transplant patients, CT may be used in problem solving of post-transplant complications (fluid collections or hematomas) (Fig. 3.8a, b).

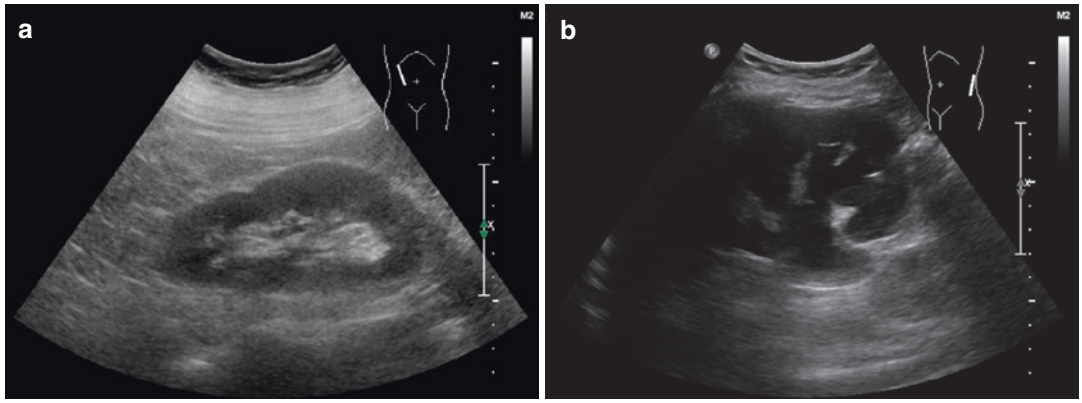

Fig. 3.8 Ultrasound showing a normal kidney (**a**), and a kidney with hydronephrosis (**b**)

The key point in each CKD patient is whether or not the diagnostic question can be answered with unenhanced or enhanced CT. If unenhanced CT fails in answering the question, and enhanced CT is ruled out because of the fear of contrast medium-induced nephropathy, other imaging studies (MRI or ultrasound) should be performed. However, this does not apply to all parts of the body, e.g., the mediastinum and the lungs in workup a lung cancer.

One should remember that in the anuric patients (no urine excretion at all), iodine-based CM can be administered without any problems.

3.2.4 MR Imaging

MRI can be used to image the urinary tract in CKD patients. Similar to CT, MRI can be used to evaluate structural abnormalities such as tumors, cysts, and obstruction. However, compared with CT, MRI is relatively insensitive for detecting urinary tract calculi, so an unenhanced CT may be complementary to the MRI. Other disadvantages of MRI include long imaging times, susceptibility for motion artifacts, and lower spatial resolution than CT and radiography. A considerable advantage of MRI is that no ionizing radiation is used and its soft tissue visualization.

Typical MRI techniques used for imaging the urinary tract are MR-hydrography and excretory MR- urography. For the rest of the body the same examinations for patients with normal kidney function are done in patients with CKD; the only issue is whether it should be enhanced or not as gadolinium-based contrast media may only be used with caution in patients with a glomerular filtration rate below 30 ml/min/1.73 m^2. The technical foundation of MRI is complicated and in depth description of MR-hydrography and excretory MR-urography falls beyond the scope of this chapter. The basic principle of the imaging methods is presented.

In MR-hydrography the so-called T2-weighted imaging sequences (that renders water/urine bright) are used to produce MR urograms. The method was the earliest means of urinary tract MRI. MR-hydrography does not rely on excretion of contrast media, and is therefore useful for visualizing the collecting system of an obstructed, poorly excreting kidney. MR-hydrography can be performed in CKD patients to evaluate if any obstruction is present, but it is dependent on whether the kidney can generate a pressure that enlarges the pelvic cavity. If one is suspicious of an obstructed normal sized pelvic cavity, the only way to solve the issue is to catheterize the pelvic cavity and see whether the kidney function improves. In patients with normal renal function renography often can answer the question.

Excretory MR-urography is similar to CT-urography. A contrast medium is injected intravenously and subsequently images are acquired in the renal excretory phase. In excre-

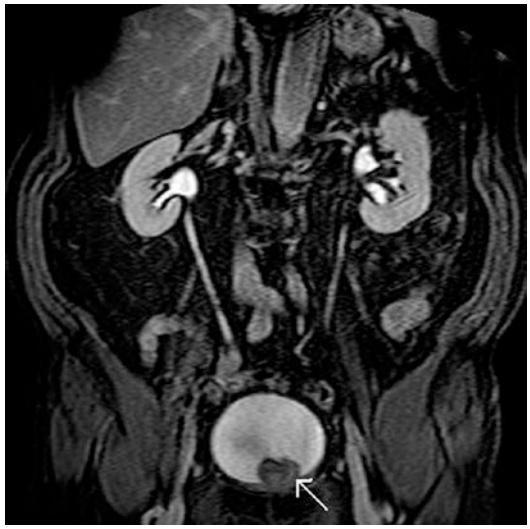

Fig. 3.9 Excretory MR-urography. There is contrast-enhancement in the renal parenchyma as well as contrast material in the ureters and bladder. Note the tumor in the bladder (arrow)

tory MR-urography gadolinium-based MRI-contrast agents are used, as opposed to iodine-based contrast media in CT-urography. However, the pharmacokinetic profiles of the contrast agents are similar, with the agents being eliminated by renal filtration. T1-weigheted images are used to produce bright MR urograms (Fig. 3.9). The reason for this is that the paramagnetic effects of gadolinium shorten T1-relaxation times in adjacent tissue. A common problem in excretory MR-urography is that gadolinium becomes concentrated in the urine. This leads to inhomogeneity in the magnetic field and signal loss on the MR urogram. In order to reduce this problem a lower dose of gadolinium contrast agent should be used for excretory MR-urography as compared to other contrasted-enhanced MRI procedures (typical 0.05 mmol/kg body weight in MR-urography vs. standard MRI dose of 0.1 mmol/kg).

Furthermore, the image quality of excretory MR-urography can be improved by administration of a small dose of diuretics (5–10 mg furosemide in adults), except in anuric patients. The diuretic administration improves image quality as urine flow is enhanced and the contrast material is diluted and more uniformly distributed throughout the urinary tract. The role of excretory MR-urography in CKD patients is limited, as the kidney (s) cannot filtrate enough contrast medium per min in order to obtain an adequate visualization of renal pelvis, ureter, and bladder administration.

3.2.5 Angiography

In patients with renovascular hypertension, it is relevant to perform angiography to rule out renal artery stenosis. Angiography can be performed as conventional X-ray based angiography with direct arterial puncture or as CT- and MR-angiography (CTA, MRA).

Today, most diagnostic studies of the renal arteries are performed as CTA or MRA (Fig. 3.10). The sensitivity and specificity of both CTA and MRA for detection of renal artery stenosis are close to that of conventional X-ray angiography (the gold standard method). Both CTA and MRA utilize contrast media injection and fast images techniques ensuring acquisition during the arterial transit phase, i.e., the arterial first-pass phase that follows intravenous injection of contrast media. However, recent technical improvements in MRA have caused that the use of contrast media is not necessary in all patients for showing the vasculature.

Conventional X-ray angiography, typically performed via the femoral artery, is rarely applied for diagnostic studies after the introduction of CTA and MRA. However, conventional angiog-

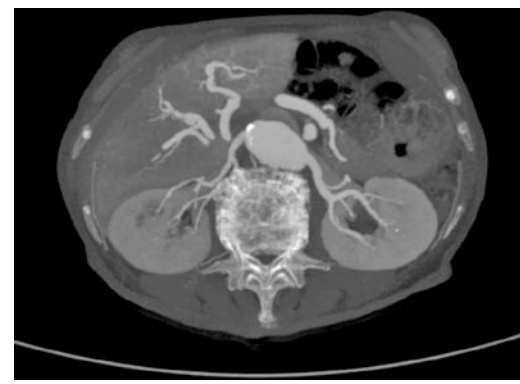

Fig. 3.10 Renal CT-angiography. Normal

raphy combined with interventional procedures (percutaneous transluminal angioplasty—PTA) is applicable for the treatment of renal artery stenosis. Doppler ultrasound suffers from high interobserver variation, but in highly experienced hands it may be useful.

CTA or MRA of the iliac arteries may be relevant in pre-transplant CKD patients to rule out significant stenosis of the vessels that are going to be connected to the transplant kidney, in patients with symptoms and sign of vascular disease.

3.3 Nuclear Scanning

Nuclear medicine also has an important role in patients with reduced renal function. Primarily it is used for determination of the glomerular filtration rate. Although it can be calculated from scintigraphic data, the method using blood sampling at various times after the injection is used in most cases. For the examination both ^{51}Cr-EDTA and ^{99m}Tc-DTPA can be used as they are exclusively excreted through glomerular filtration. They provide better determination of the kidney function than estimated glomerular filtration rate based on serum creatinine measurements and are easier to perform than the optimal, but cumbersome inulin-clearance.

The scintigraphic examinations include renography and renal scintigraphy. For renography ^{99m}Tc-DTPA and ^{99m}Tc-MAG_3 can be used. Renography provides information about the perfusion, excretion, and split function. However, excretion data cannot be obtained in patients with severely reduced kidney function; furosemide (diuresis renography) has no effect. DPTA is purely excreted by glomerular filtration, whereas MAG_3 is also secreted via the tubular cells; the more the poorer the kidney function is. ^{99m}Tc DMSA is taken up by the tubular cells. It provides information about the size and contours of the kidney(s). Split function can also be determined. It has a long image window.

Nuclear imaging includes injection of isotopes. Thus, the whole body is subject to radiation and not only the part of the body that is subject to imaging as it is regarding radiography including CT-scanning. With reduced kidney function isotope retention and exposure lasts longer than in patients with normal renal function.

3.4 Contrast Medium-Induced Nephropathy in CKD

Contrast medium-induced nephropathy is defined as a condition in which a decrease in kidney function occurs within 3 days of the intravascular administration of contrast media. It is a diagnosis of exclusion. Other causes of a sudden decrease in kidney function, in particular prerenal and postrenal causes should be excluded. An increase in serum creatinine levels from pre-injection measurement of 0.3 mg/dl (26 μmol/l), 0.5 mg/dl (44 μmol/l), 1.0 mg/ml (88 μmol/l), 25%, 50%, or 100% has been used to define contrast nephropathy. However, fluctuations in levels of serum creatinine are naturally occurring, more in in-patients than out-patients, and more in acute than in elective examinations. Several researchers have challenged the existence of contrast medium-induced nephropathy after demonstrating comparable fluctuations in patients exposed and not exposed to a contrast medium. If contrast-induced nephropathy does indeed exist, it is believed that it is caused by combination of direct iodine toxicity (chemotoxicity) on the tubular cells and an increased vascular resistance due to a change in the balance between vasoconstrictors and vasodilators in the kidney vessels.

Traditionally, contrast-induced nephropathy was considered more likely to occur in case of pre-existing renal insufficiency. Therefore, one should still consider alternatives to iodine-based imaging in patients with reduced renal function. If it is decided that enhanced radiography including CT is the way to go, one should use the smallest amount of a non-ionic agent necessary for a diagnostic result.

3.5 Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a serious adverse event to some gadolinium-based contrast media. Fibrosis may develop in most parts of the body. It may be a little plaque to be almost generalized. The lower extremities are almost always involved whereas the head is spared. The first signs may come within the first 24 h after injection, and most symptoms develop within the first 3 months. However, a few cases have appeared years after the last Gd exposure. The patient typically develops pain, pruritus, swelling, and erythema in the lower extremities, and later hardening of the skin and subcutaneous tissues with an almost woody texture and brown color. The diagnosis requires documentation of previous Gd exposure, typical skin changes as observed by clinical examination, and characteristical histological findings in deep skin biopsies. Demonstration of gadolinium in the skin may be indicative of nephrogenic systemic fibrosis, but in itself it is not evidence for the presence of nephrogenic systemic fibrosis. Whether hemodialysis of dialysis patients immediately after Gd exposure reduces the risk of nephrogenic systemic fibrosis is unknown, but it has been estimated that it requires about 12 h of effective hemodialysis to eliminate the Gd-containing contrast medium from the body of a dialysis patient. With peritoneal dialysis, it takes weeks to remove the agent.

For more than 30 years, it has been known that the heavy metals including Gadolinium (Gd) belonging to the lanthanide group in the periodic table could cause changes in the skin, and that they are extremely toxic. Lanthanides are not naturally occurring in the human body. Around 0.1 mmol/kg of gadolinium chloride is enough to kill a human being. Also approximately 30 years ago, other researchers found that one gadolinium was excellent for magnetic resonance imaging due to its high relaxativity compared to other ions under similar conditions. In order to detoxify Gd, it was necessary to chelate gadolinium which also increased the relativity significantly. Two principally different chelates were used: (1) the linear chelate DTPA known for years from nuclear medicine where it was used together with ^{99m}Tc and (2) the cyclic chelate DOTA which cages around the ion. Both chelates became available in an ionic and non-ionic version. In order to lower the osmolality which had been shown to be a major step forward in patient safety and comfort regarding iodine-based contrast media, two amid groups replaced two carboxyl groups in the linear chelates. Amid groups hold the gadolinium less strongly that carboxyl groups do and they introduce weak binding points for the gadolinium on plain chelate. Thus, they increase the risk of transmetallation with one of free ions in the blood, e.g., Zn^{++}. When liberated from the chelate in the body, gadolinium binds to phosphate and calcium. Unbound gadolinium is not circulating in the plasma. Instead, it may precipitate in several tissue, including skin, liver, lymph nodes, and bone. The longer the less stabile gadolinium-based contrast media are in the blood, the more gadolinium can be liberated from the chelate through transmetallation. More than 98% of injected extracellular agent is renally cleared within 24 h in patients with normal kidney function, whereas it may take weeks for patients with severely reduced kidney function.

Very quickly after the link between exposure to less stable gadolinium-based contrast agents (agents based on non-ionic linear chelates) and the development of nephrogenic systemic fibrosis was discovered, it became clear that two factors were in play in patients who got the disease/adverse event: (1) non-ionic linear chelates had been used in the vast majority of NSF patients and (2) their kidney function was severely impaired (GFR <30 ml/min/1.73 m^2 in large majority of cases). However, not all patients with poor kidney function developed nephrogenic systemic fibrosis after exposure to a non-ionic linear chelate agent. Furthermore, some patients developed NSF after low-dose exposure (0.1 mmol/kg = standard dose for magnetic resonance imaging), whereas other patients tolerated much higher and repeated doses without developing NSF. Some other still unknown factors besides type of Gd-agent and kidney function thus seem to influence the risk of NSF. The good thing is that the adverse event has been almost erased after the less stable agents have been abandoned and replaced by the more

stable agents (the cyclic ones). Today the authorities have contraindicated the use of the least stable agents in patients with reduced kidney function or on dialysis. The long-term consequences of using the less stable agents in patients with normal or moderately reduced kidney function are still unknown. There are patients with reduced kidney function who develops nephrogenic systemic fibrosis years after last exposure to a gadolinium-based contrast agent. Long-term consequences may also be other adverse reactions than nephrogenic systemic fibrosis.

The fear of nephrogenic systemic fibrosis should not lead to inadequate imaging in patients with symptoms of a serious disease. **One should never deny a patient a clinically well-indicated enhanced magnetic resonance imaging examination with the smallest amount of contrast medium necessary for a diagnostic result**. Sadly, many radiologists still deny giving patients with eGFR below 30 or even 60 ml/min/1.73 m^2 gadolinium-based contrast medium despite clinical symptoms and signs of disease and no diagnostic solution based on the unenhanced scan.

Before You Finish: Practice Pearls for the Clinician

- In patients with chronic kidney disease nephrogenic systemic fibrosis is a serious adverse reaction to Gd-containing contrast agents.
- Nephrogenic systemic fibrosis is only seen after some gadolinium-based agents. These agents are no longer approved for clinical use.
- One should not deny a patient with obvious symptoms and signs of a serious disease an enhanced examination if the unenhanced study was inadequate from diagnostic point of view. This applies to all parts of the body.

What Guidelines Say to Do

KDIGO Level 1 recommendations exist on contrast nephropathy. However, these do not differ significantly from the ESUR guidelines. No KDIGO recommendations exist on prevention of nephrogenic systemic fibrosis.

Key points of current ESUR guidelines on contrast nephropathy:

- Identify the patient at risk of contrast nephropathy at time of the referral.
- The risk of contrast nephropathy is lower with intravenous than intra-arterial iodinated contrast media.
- eGFR of 30 ml/min/1.73 m^2 is considered contrast nephropathy risk threshold for intravenous contrast medium and 45 ml/min/1.73 m^2 for intra-arterial injection; we have only limited knowledge regarding low kidney function as many patients with eGFR below 30 are not offered an examination where contrast agents are used.
- Hydration with either saline or sodium bicarbonate reduces contrast nephropathy incidence and should be used in patients at risk.
- Patients with eGFR ≥30 ml/min/1.73 m^2 receiving contrast medium intravenously can continue metformin normally.

Key points of current ESUR guidelines on nephrogenic systemic fibrosis:

- Patients with GFR below 30 ml/min/1.73 m^2 have increased risk of developing NSF
- Low stability gadolinium contrast media show the strongest association with NSF; they are no longer used in EU
- Following the guidelines regarding gadolinium-based contrast agents minimizes the risk of NSF
  - Use only intermediate or low risk agents
    - These agents should be used with CAUTION in patients with CKD 4 and 5 (GFR <30 ml/min)
    - There should be at least 7 days between two injections
    - Pregnant women: can be used to give essential diagnostic information

Lactating women: the patient should discuss with the doctor whether the breast milk should be discarded in the 24 h after contrast medium.

Relevant Guidelines (AMA Reference Format)

European Society of Urogenital Radiology (ESUR) guidelines

Stacul F, van der Molen AJ, Reimer P, et al. on behalf of the Contrast Media Safety Committee of the European Society of Urogenital Radiology. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol. 2011;21:2527-41.

Thomsen HS, Morcos SK, Almén T, et al. Nephrogenic Systemic Fibrosis and Gadolinium based Contrast Media: Updated ESUR Contrast Medium Safety Committee Guidelines. Eur Radiol. 2013;23:307-18.

www.esur.org

KDIGO guidelines

Fliser D, Laville M, Covic A, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial Transplant. 2012; 27: 4263-72.

Further Reading

1. Blaufox MD, Aurell M, Bubeck B, et al. Report of the Radionuclides in Nephrourology Committee on Renal Clearance. J Nucl Med. 1996;37:883–90.
2. Stacul F, van der Molen AJ, Reimer P, et al. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. Eur Radiol. 2011;21:2527–41.
3. Morcos SK, Thomsen HS. Urogenital imaging. A problem-oriented approach. West Sussex: Wiley-Blackwell; 2009.
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5. Thomsen HS, Morcos SK, Almén T, et al. Nephrogenic systemic fibrosis and gadolinium based contrast media: updated ESUR Contrast Medium Safety Committee Guidelines. Eur Radiol. 2013;23:307–18.
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4 Diabetic Kidney Disease: Increasing Hope with Transformative Therapies

Sylvia E. Rosas and Samer Nasser

Before You Start: Facts You Need to Know

- Diabetic kidney disease is the most common cause of kidney failure and the number of people affected continues to grow.
- Albuminuria is frequently the first clinical manifestation of DKD.
- DKD screening includes annual urine albumin to creatinine ratio and measurement of estimated glomerular filtration rate (eGFR).
- Hyperglycemia triggers glomerular hyperfiltration, SGLT-2 receptor overexpression, and endothelial dysfunction.
- Mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis are frequent pathological findings of diabetic nephropathy.

4.1 Epidemiology

The 2022 Centers for Disease Control and Prevention (CDC) National Diabetes Statistics Report estimates that 130 million Americans live with diabetes or prediabetes. The percentage of diagnosed diabetes was highest among adults of Hispanic origin (11.8%), non-Hispanic Black (12.1%), non-Hispanic Asian (9.5%), and American Indian/Alaska Native (14.5%) compared to non-Hispanic White people (7.4%) in 2018–2019. More than a third of individuals with kidney disease have diabetes [1]. Diabetes is the most common cause of kidney failure and is higher among minoritized populations [2]. Adults with a family income below the federal poverty level have the highest diabetes prevalence for both men (13.7%) and women (14.4%) [3].

There are significant racial disparities in the prevalence and complications of diabetes and chronic kidney disease (CKD) driven by the impact of social determinants of health (SDOH) [4]. Although the prevalence of CKD among Hispanic populations is similar to non-Hispanic, the prevalence of kidney failure is 50% higher in the Hispanic population and 300% higher in African Americans [5].

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M. Arıcı (ed.), *Management of Chronic Kidney Disease*,
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4.2 Diagnosis

Diabetic nephropathy or diabetic kidney disease (DKD) is a pathologic diagnosis confirmed through kidney biopsy. Because of its high prevalence in patients with diabetes type 1 (T1D) and type 2 (T2D), diagnosis of DKD is usually made clinically in the setting of albuminuria and diminished GFR in the presence or absence of other diabetic microvascular complications such diabetic retinopathy. Patients with diabetes and reduced eGFR or albuminuria should undergo evaluation for other non-diabetes causes of chronic kidney disease. Diabetic kidney disease occurs in around 30% of patients with T1D and T2D. Although development and progression of diabetic kidney disease has been mostly studied in T1D, the progression is similar in T2D. The prevalence of DKD can be overestimated because individuals with diabetes and CKD rarely get biopsies and are assigned the diagnosis in registries. Moreover, 25% of T2D patients with decreased GFR and minimal or absent proteinuria have confirmed diabetic nephropathy findings on kidney biopsy, hypothetically as a result of treatment with renin angiotensin aldosterone system (RAAS) blockade [6]. The ADA guidelines recommend screening for CKD at least annually with both urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and eGFR in individuals with T1D with duration of >5 years and in individuals with T2D regardless of treatment. DKD diagnosis is made if urine albumin excretion is ≥30 mg/day or a spot random urine albumin to creatinine ratio of ≥30 mg/g or if there is a GFR persistently <60 mL/min/1.73 m^2. with or without albuminuria [7].

Subsequent follow-up of kidney function with albuminuria and eGFR is based on the stage of CKD. Referral to a nephrologist is recommended when the diagnosis is uncertain, albuminuria is severe, kidney function decline is progressive, or patients are approaching renal replacement therapy.

Some clinical clues can help in the diagnosis of DKD in T1D but not for T2D. First, if albuminuria develops within 5 years since or 25 years after the diabetes diagnosis, other etiologies for the albuminuria should be entertained. Also 95% of T1D patients with diabetic nephropathy have retinopathy. The absence of retinopathy in T1D should trigger suspicion for another cause of CKD or albuminuria [8]. Since it is always difficult to determine the time of development of T2D, it is more difficult to determine if the kidney disease manifestations are related to diabetic nephropathy or not; moreover, retinopathy is not as frequently seen in patients with diabetic nephropathy in T2D patients.

Reports of non DKD on biopsies in patients with CKD and T2D have varied between 33 and 72% [9]. The high incidence of non-diabetic kidney disease (NDKD) alone or in combination with DKD on biopsies is related to selection bias of patients with atypical presentation. The spectrum of kidney diseases ranged from acute tubular necrosis, FSGS (secondary more than primary), hypertensive nephrosclerosis, IgA nephropathy, membranous nephropathy, pauci-immune crescentic GN, acute interstitial nephritis, amyloidosis, myeloma cast nephropathy, post-infectious GN, and atheroembolic disease.

There are no specific criteria for kidney biopsies in patients with DKD but indications may include sudden worsening in GFR, absence of retinopathy in T1D, sudden change in proteinuria, unusual time of onset of proteinuria, nephrotic syndrome, hematuria, active urinary sediment, and/or positive serologies on work-up of CKD. While some findings on NDKD would not result in changing management, other etiologies on NDKD may alter the management improving kidney function [10].

4.3 Pathophysiology

Hyperglycemia is the initial trigger of diabetic changes in the kidney. At the nephron level, hyperglycemia causes hyperfiltration where there is increased renal plasma flow and increased glomerular filtration. Hyperfiltration is seen in different prevalences among type 1 and type 2 diabetes mellitus patients. It is hypothesized that hyperfiltration precedes albuminuria and kidney

function decline. The increased filtered glucose through the filtration barrier induces increased reabsorption of glucose through proximal tubules requiring increased energy consumption to upregulate transporters. This increase in oxygen demand leads to relative ischemia and increase in stress markers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM1) [11].

Most of the glucose and sodium are reabsorbed at the proximal tubule through sodium-glucose co-transporter 2 (SGLT-2). Due to increased filtered glucose, SGLT-2 is over-expressed and sodium is massively co-transported into the proximal tubule leading to reduced sodium chloride reaching the macula densa and hence deactivating the tubuloglomerular feedback. The resultant dilation of the afferent arteriole and renin induced vasoconstriction of the efferent arteriole leads to increased single nephron GFR and hyperfiltration and glomerular hypertension and activation of the RAAS system [12]. The molecular mechanisms of action of SGLT2 inhibitors (SGLT2i) are not completely elucidated. However, investigators have recently proposed the suppression of mTORC1-signaling which integrates cellular energy state signals mostly in distal nephron segments thus reversing the diabetes induced metabolic changes as an important treatment benefit [13].

The glomerular hypertension induces tumor growth factor-beta (TGF-beta) release causing elongation of proximal tubule, which is responsible for the nephromegaly seen in early diabetic nephropathy. Glomerular pressure decreases after hypertrophy but the hyperfiltration persists. Hyperfiltration is correlated to the degree of hyperglycemia as HbA1C control was shown to decrease the filtration rate modestly [14]. Obesity, a frequent comorbidity, on the other hand, increases the filtration rate independent of the diabetes control. Another effect of hyperglycemia is upregulation of mineralocorticoid receptor (MR) which is also induced by obesity, salt intake, and insulin resistance. The activation of MR by aldosterone results in the activation of profibrotic cascade of events [15].

Chronic hyperglycemia leads to endothelial dysfunction in various organs and is the underlying pathogenic mechanism of diabetes in several of the microvascular and macrovascular complications of DM. Hyperglycemia damages the endothelial glycocalyx thus increasing permeability, which in turn leads to albuminuria. As an established correlate and risk factor of cardiovascular disease, albuminuria is a manifestation of endothelial dysfunction in the vascular system [16]. Glomerular basement membrane thickening is an early histologic finding of DKD caused by remodeling of extracellular matrix through injured endothelial cells and podocytes and mesangial cell expansion. While GBM thickening and mesangial cell expansion are seen in DKD, their role in the disease is not demonstrated [17]. Hyperglycemia also affects the structure of podocytes and induces their apoptosis and detachment from the GBM. Progressive podocyte loss manifests as severe albuminuria leading to glomerulosclerosis [18].

Renal Pathology Society classified DKD providing insight into progression and prognosis of the disease. Histopathological spectrum of DKD ranges from glomerular basement membrane thickening (Class I) to mesangial expansion whether diffuse (Class II) or nodular (Kimmelstein Wilson nodules) (Class III), to glomerulosclerosis and arteriolar hyalinosis (Class IV) which carries the worst prognosis and higher risk of progression to end-stage kidney disease (ESKD) (Fig. 4.1). Those findings are frequently seen in patients with T1D and T2D [19]. However, T2D patients with CKD have pathologic evidence of other diseases and this can be attributed to the longevity of these patients and other disease comorbidities. The pathology can be attributed to primary GN's, age related kidney function decline, previous episodes of AKI [9]. In addition, patients with non-albuminuric kidney disease in T2D patients with CKD had a more heterogeneous pattern on pathology compared to T2D patients with albuminuria who mostly had typical diabetic glomerulopathy [20].

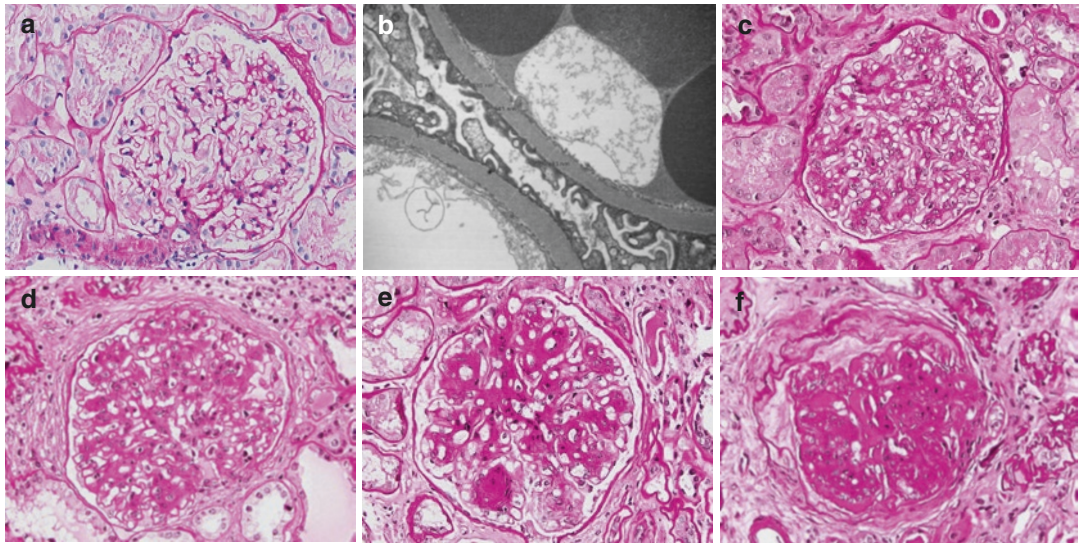

Fig. 4.1 (**a**) Class I "mild or non-specific changes by light microscopy with glomerular basement membrane thickening." Note the absence of unequivocal mesangial expansion. (**b**) Ultrastructural examination is the definitive technique for measuring GBM thickness. In general, measurements exceeding 395 nm in females and 430 nm in males, establishes thickening in adults. Note the preserved foot processes (transmission electron microscopy, original magnification = 15K×). (**c**) Class IIa with "mild mesangial expansion." It is defined as an increase in mesangial matrix that exceeds the width of two mesangial cell nuclei in at least two glomerular lobules, but not exceeding the mean area of a capillary lumen. (PAS, original magnification = 40×). (**d**) Class IIb: "severe mesangial expansion." Defined as an increase in mesangial matrix that exceeds the mean area of a capillary lumen in more than 25% of the total mesangium observed in the biopsy. (PAS, original magnification = 40×). (**e**) Class III: "nodular sclerosis." Defined as the presence of at least one Kimmelstiel-Wilson nodule (7'o clock), with less than 50% of the glomeruli showing global sclerosis. The adjacent nodule (5'o clock) shows a commonly associated finding, mesangiolysis. This lesion, reflecting microvascular injury, may contribute to the formation of K-W nodules (PAS, original magnification = 40×). (**f**) Class IV: "advanced diabetic glomerulosclerosis." Defined as the presence of greater than 50% global glomerulosclerosis that is attributable to diabetic nephropathy. Hyalinosis may be more prominent when the sclerosis is secondary to diabetic nephropathy. (PAS, original magnification = 40×)

4.4 Disease Progression

DKD progression to ESKD has remained at 0.25% per year over the past two decades despite medical interventions [21].**The earliest clinical manifestation of DKD is albuminuria**. Around half of patients with mild albuminuria progress to having severe albuminuria, which poses a 10-fold risk of progression to ESKD compared to patients without any albuminuria. The risk factors for worsening albuminuria include high A1C and elevated blood pressure but not a low GFR.

The incidence of albuminuria in T1D and T2D are similar at 30% but it is usually associated with hypertension in DM2 patients. Hyperglycemia is the driver for albuminuria in both populations. Other risk factors for DKD include morbid obesity, low birth weight, and genetic susceptibility, which explains why not all patients with DM develop DKD [22].

Untreated DKD progression in patients with T1D manifests with proteinuria 11–23 years after diagnosis of T1D, while serum creatinine elevation and ESRD 13–25 and 18–30 years, respectively, after diagnosis. After the development of sensitive methods to detect albuminuria, protein was detected in the urine 5–10 years after the diagnosis of T1D [23] (Fig. 4.2).

The timeline of development of diabetic nephropathy in type 2 diabetics is similar but since it is difficult to assess the timing of the diagnosis of type 2 diabetes, some patients may develop proteinuria even before the diagnosis of T2D. Another difference is the incidence of cardiovascular disease and death, which can occur at any point since the diagnosis of type 2 DM while

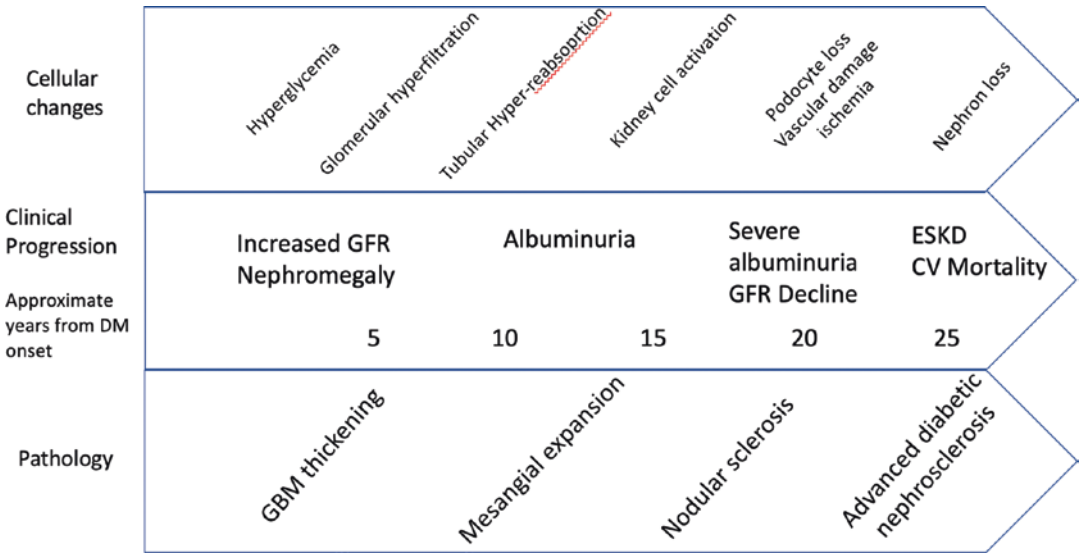

Fig. 4.2 Cellular, pathologic, and clinical progression of diabetic kidney disease: from the onset of diabetes mellitus type 2, cellular and pathologic changes commence prior to any clinical findings such as albuminuria and reduced GFR. The cellular changes due to hyperglycemia will cascade from nephromegaly to eventual nephron loss over time. On the pathological level, concomitantly what starts as GBM thickening will eventually result in advanced diabetic nephrosclerosis. Clinically, the initial manifestation of hyperfiltration on the same timeline will end up as severe albuminuria, reduction in GFR, and eventual ESKD

macrovascular complications in type 1DM do not occur until the development of severe kidney disease. However, this trend in T2D patients with DKD has changed in more recent clinical trials due to the advancements in treatment and prevention of cardiovascular disease.

Proteinuria is the greatest predictor of kidney function decline in DKD. After kidney function starts to decline, patients with diabetic nephropathy continue to progress to ESKD at a rate of 7–12 ml/min year. However, treatment with RAAS inhibitors delays the progression by 3–6 ml/min/year [24].

4.5 Prevention and Treatment

The only proven primary prevention interventions for DKD are glycemic and blood pressure control. While we will be highlighting novel therapies for patients with diabetes and CKD, the management of these complex patients requires a multidisciplinary team to provide education and support in order to achieve lifestyle goals in diet, physical activity, smoking cessation, and weight management.

4.5.1 Glycemia

Glucose control reduces the risk or slows the progression of chronic kidney disease for both T1D and T2D [25–30]. While the target for most adults is HbA1c <7% in order to avoid microvascular complications, this requires modification as the risk of hypoglycemia increases as kidney function declines. There is a delay between intensive glucose control and improvement in kidney outcomes. The benefits of glycemic control are greater with preserved kidney function and with well-controlled blood pressure [31].

4.5.2 Sodium-Glucose Co-transporter 2 Inhibitor (SGLT2i)

SGLT2i lower plasma glucose concentration by inhibiting Na+-glucose-coupled transport in the proximal tubule. In addition to kidney function dependent decrease in glycemia, there are modest decreases in weight and blood pressure [32]. All kidney outcome SGLT2i clinical trials [CREDENCE, DAPA-CKD, and EMPA-Kidney]

have shown that SGLT-2i offer kidney and cardiovascular organ protection [33–35]. In the DAPA-CKD trial that included individuals with and without T2D, a primary outcome event (sustained decline in the estimated GFR of at least 50%, ESKD or death from renal or cardiovascular causes) occurred in 9.2% of participants in the dapagliflozin group compared to 14.5% in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51–0.72; $P < 0.001$; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15–27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, ESKD, or death from renal causes was 0.56 (95% CI, 0.45–0.68; $P < 0.001$). The relative risk reduction for the primary composite outcome with dapagliflozin was consistent in participants with T2D (hazard ratio [HR] 0·64, 95% CI 0.52–0.79) [36]. In the EMPA-KIDNEY trial, the hazard ratio for the comparison of empagliflozin with placebo with respect to progression of kidney disease was 0.71 (95% CI, 0.62–0.81). Given similar results in the kidney endpoint trials, the organ protective effects are considered a class effect. It is important to note that most patients were also on RAS blockade in these trials. Current guidelines recommend a SGLT2i with proven kidney or cardiovascular benefit for patients with T2D, CKD, and eGFR >20 mL/min/1.73 m^2 independent of HbA1c values. Once initiated, the SGLT2i can be continued at lower levels of eGFR [37].

The benefits of SGLT2i are seen across all GFR categories [38] but absolute benefit is more pronounced in the lower GFR categories [39]. A drop in eGFR is frequently seen in patients initiating therapy but a drop >30% is rare [40]. The long-term eGFR trajectories as well as overall and kidney safety profiles during canagliflozin treatment were similar regardless of the initial eGFR drop. SGLT2i reduce the incidence of acute kidney injury [38]. The benefits of SGLT2i are seen across all levels of albuminuria, but absolute benefits are greatest among those with severe albuminuria [38, 41].

SGLT2i reduce the risk of serious hyperkalemia (hazard ratio, 0.84 [95% CI, 0.76–0.93]) in people with type 2 diabetes and CKD without increasing the risk of hypokalemia [42].

In Europe, SLGT2i is approved for individuals with Type 1 diabetes and BMI more than 27 kg/m^2 when insulin monotherapy does not provide adequate glycemic control [43]. A modest improvement in HbA1c was found [44]. In a retrospective study of two European centers, there was a decrease in urinary albumin-to-creatinine ratio (UACR) in those with levels >15 mg/g by 16.6 mg/g [45]. No severe hypoglycemia was detected but 3.5% of individuals developed DKA. Genital infection was reported in 22% of individuals.

Given the risk of euglycemic DKA, several algorithms have been studied including the STICH protocol [46] and the STOP-DKA protocol [47].

4.5.3 Glucagon-Like Peptide 1 Receptor Agonists (GLP1RA)

Glucagon-like peptide 1 receptor agonists (GLP1RA) decrease HbA1c by stimulating glucose-dependent insulin secretion and by reducing glucagon secretion, gastric emptying, and appetite. GLP1RA have been approved for the treatment of T2D. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, there was a lower rate of nephropathy events (defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease) in the liraglutide group compared to placebo (1.5 vs. 1.9 events per 100 patient-years of observation; hazard ratio, 0.78; 95% CI, 0.67–0.92; $P = 0.003$) [48]. New-onset persistent severe albuminuria occurred in fewer patients in the liraglutide group than in the placebo group (161 patients [3.4%] vs. 215 [4.6%]; hazard ratio, 0.74; 95% CI, 0.60–0.91; $P = 0.004$) but there was no difference in the incidence of kidney failure [49].

GLP1RA reduced the composite kidney outcome (defined as development of severe albuminuria, worsening kidney function [doubling of

serum creatinine or 40% or greater decline in eGFR], ESKD and kidney-related death) by 17% (HR 0.83, 95% CI 0.78–0.89) [50]. GLP1RA reduced the relative risk of the composite kidney outcome significantly by 18% (HR, 0.82; 95% CI, 0.75–0.89; $P < 0.001$) mainly secondary to decrease in severe albuminuria.

The FLOW study [ClinicalTrials.gov Identifier: NCT03819153] will determine if semaglutide decreases time to first occurrence of a composite primary outcome event defined as persistent eGFR decline of greater than or equal to 50% from trial start, reaching ESKD, death from kidney disease or death from cardiovascular disease.

4.5.4 Blood Pressure Control

Strict blood pressure control decreases the progression of CKD. In addition, achieving a SBP less than 130 mmHg delays the onset of albuminuria and improves retinopathy.

Uncontrolled blood pressure has been associated with increased mortality in individuals with diabetes, even among the prehypertensive patients. Observational studies showed an association between elevated blood pressure and development of albuminuria and kidney function decline. The United Kingdom Prospective Diabetes Study showed that a 10 mmHg decrease in the SBP was associated with a 12% decrease in the risk of diabetic complications. The risk decreases when the SBP is less than 120 mmHg. However, the study did not show benefit on kidney outcomes such as a decrease in proteinuria and a decrease in kidney function decline [27]. The Irbesartan Diabetic nephropathy trial (IDNT) on the contrary revealed that a BP of <120/85 was associated with a higher CV event rate. Kidney benefit also reached a plateau when the blood pressure was less than 130 mmHg [51].

Appropriate Blood Pressure Control in Diabetes (ABCD) trial compared intensive vs. moderate control of blood pressure in individuals with diabetes over 5 years and there was a decrease in the development of proteinuria in the intensive group but no benefit on creatinine clearance, which was the primary outcome of the study [52]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to compare intensive blood pressure lowering (<120 mmHg) vs. moderate lowering (<140); there was no benefit of lowering the blood pressure from <120 mmHg compared to 140 mmHg in terms of cardiovascular outcomes. While there was a reduction in albuminuria, there was no decrease in the incidence of ESKD in the intensive vs. moderate lowering of BP. Based on these studies there is a benefit of lowering the blood pressure to prevent complications of diabetes including kidney events, but it seems that the benefit plateaus below a systolic blood pressure <130 mmHg [53]. The SPRINT trial recently showed intensive blood pressure lowering <120 mmHg lowers risk of all cause mortality when compared to standard lowering of <140 mmHg. The SPRINT trial, however, excluded patients with diabetes [54]. In the glycemic arm of the ACCORD-BP trial, intensive BP control resulted in decrease in mortality but this arm also excluded patient with CKD. For similar BP reductions, the risk of kidney injury and incident CKD in individuals living with diabetes in the ACCORD-BP was higher than in patients without diabetes in the SPRINT trial. While this may mean that intensive blood pressure lowering worsens DKD, KDIGO's 2021 stance was to target SBP less than 120 mmHg if tolerated in patients with CKD with or without diabetes, extrapolating the evidence of the improved cardiovascular outcomes from the SPRINT trial, despite the absence of the diabetic CKD subgroup from the study [55].

4.5.5 RAS Blockade

RAS blockade with angiotensin converting enzyme inhibition, angiotensin receptor blockade, and mineralocorticoid inhibition have been efficacious in delaying progression of kidney disease in animal models with diabetic nephropathy. Clinical trials have evaluated whether RAS blockers are beneficial to prevent albuminuria onset, overt proteinuria development and progression of kidney

disease in T1DM and T2DM patients. ACE-I and ARB remain the standard of care since all novel therapy trials were performed on patients who were on these medications. The goal is to titrate to the maximum tolerated dose of the medication to achieve BP and albuminuria goals.

RAS blockade has been studied on T1D and T2D without albuminuria for the prevention of incident albuminuria. More than one study has failed to show benefit of RAS blockade in T1D to prevent development of albuminuria. In the HOPE trial, ramipril did not meet this endpoint in individuals with T2D. In individuals with T2D and hypertension, The Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) showed benefit in preventing albuminuria in the ACE-I group [56]. Observations from the Randomised Olmesartan and Diabetes Microalbuminuria prevention (ROADMAP) trial showed that olmesartan decreased onset of albuminuria when compared to placebo, in addition to lowering BP but increased cardiovascular death [57].

In individuals with T2D and mild albuminuria without any RAS blockade also benefit from initiation of RAS blockers to prevent development of severe albuminuria when they were started on irbesartan compared to those individuals started on placebo. There was also a dose dependent benefit in a subgroup analysis (150 mg vs. 300 mg) [58].

As for the prevention of progression, of kidney disease, RAS blockade with captopril 25 mg 3 times a day in T1D with diabetic nephropathy with a creatinine less than 2.5, reduced risk of doubling of the serum creatinine [59].

In patients with T2D, two major studies examined the effect of ARBs on progression of diabetic nephropathy. IDNT investigated the effect of Irbesartan vs. amlodipine vs. the placebo arm. Over the course of 2.6 years, irrespective of blood pressure control, irbesartan reduced the composite outcome of progression of kidney disease (doubling of serum creatinine), ESKD, or death as compared to amlodipine or placebo alone [60]. The RENAAL followed up T2DM with overt proteinuria for around 3.4 years showing the losartan was superior to placebo to reduce risk for the same composite outcome as IDNT [61]. Despite the proven RASi benefit the use of RASi declines with worsening GFR and is lowest in the USA compared to other countries [62].

Dual therapy with ACE-I and ARB was hypothesized to have incremental kidney protection benefit. However, randomized controlled trials ONTARGET and VA NEPHRON-D that studied combination ACE-I and ARB, vs. ARB alone vs. placebo showed a higher rate of the kidney composite endpoint such as doubling of serum creatinine, death, dialysis therapy as well as higher risk of hyperkalemia. Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) studied the combination of Aliskerin with ACE-I or ARB was prematurely terminated because of higher proportion of hyperkalemia, and hypotension in the aliskiren group [63].

An initial higher reduction in albuminuria with RAS therapy is independently associated with less eGFR slope decline. Therefore, it is recommended that therapy should be targeted to reduce albuminuria in patients with DKD [64].

4.5.6 Nonsteroidal Mineralocorticoid Receptor Antagonist (nsMRA)

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist has increased affinity for the MR. It is also associated with lower risk of hyperkalemia compared to steroidal MRA [65]. In the FIDELIO-DKD trial, individuals with T2D, albuminuria and GFR 25–75 ml/min/1.73 m^2 had a primary outcome event [kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes] in 17.8% in the finerenone group compared to 21.1% in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; $P = 0.001$) [66]. Severe hyperkalemia (>6 meq/lt) was seen in 4.5% of the individuals randomized to finerenone compared to 1.4% of those on placebo.

A potential benefit of finerenone in the delay of progression of nonproliferative diabetic retinopathy, independent of baseline HbA1c has also been reported [67].

The cardiorenal benefits of finerenone are independent of SGLT2 inhibitor use. However, patients using this combination are less likely to have

hyperkalemia [68]. The cardiorenal benefits of finerenone are independent of GLP1RA use [69].

In a randomized open-label crossover trial in patients with urinary albumin excretion ≥100 mg/24 h, eGFR 30-90 ml/min/1.73 m^2 combining dapagliflozin with eplerenone resulted in an additive UACR-lowering effect of −53% (95% CI, −61.7 to −42.4) [70]. Two thirds of the individuals in this trial had T2D. The COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE) trial will determine if the combination of nsMRA and SGLT2i reduce albuminuria better than each independently [71] (Table 4.1).

4.5.7 Weight Management

An increase in waist circumference increases the risk of albuminuria in patients with T2D [72]. Weight management is recommended in management of T2D and possibly diabetic nephropathy. Weight loss is achieved through intense lifestyle changes, medical therapy, and bariatric surgical intervention.

The Look AHEAD randomized control trial studied the impact of intensive lifestyle modification vs. diabetes support and education. Intensive life style modification resulted in an 8.6% more weight reduction and there was a 30% risk reduction in development of high risk CKD [73].

GLP1RA and SGLT-2 inhibitors have been shown to achieve weight reduction [74]. Liraglutide at higher doses helped decrease weight by 6% vs. 2% and reduced proteinuria by 18% vs. 6% for placebo. Other studies showed the effect of liraglutide on weight loss and improvement in the GFR. Tirzepatide is a GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptor agonist has superior weight loss and glycemic control compared to other GLP1RA [75].

Bariatric surgery especially with Roux En Y gastric bypass (RYGB) procedures have resulted in the resolution of albuminuria, CKD stage improvement and persistence of the improvements over a 10-year period. When the surgery types were compared RYGB had the highest reduction in proteinuria over time probably due to the success of these surgeries over time [76].

Table 4.1 Evidence based intervention for diabetic kidney disease by risk factor management

Patient with diabetic kidney disease	Intervention	Evidence
GFR <60 ml/min Albumin/creatinine >30 mg/g BP >130/80	BP control SBP<130 mmHg Delayed onset proteinuria Delayed progression	ACCORD-BP Irbesartan IRMA-2, olmesartan ROADMAP captopril trial, IDNT, RENAAL
BMI> 30	Weight loss	Look AHEAD Study Group
Diabetes management	Glycemic control	ACCORD ADVANCE-ON GLP-1 agonists (LEADER)
Albuminuria, CKD and on RASi[a]	SGLT-2 inhibitors	CREDENCE, DAPA-CKD, EMPA-KIDNEY
ACR >30 mg/dL GFR>25 K < 4.8 Maximum tolerated dose RAS-I	MRA finerenone	FIGARO, FIDELIO

[a] Ranges were different per study

4.5.8 Protein Restriction

Dietary modifications are an important part of diabetic management in patients with diabetic nephropathy. The American Dietary Association recommends a low protein diet in the treatment of advanced CKD and diabetic nephropathy inT1D and T2D. The reason behind the low protein diet stems from the hypothesis that high protein diet induces glucagon production, which in term dilates afferent arterioles and increases intraglomerular pressure leading to proteinuria. High protein load can also activate RAAS. A metanalysis of 11 RCT however concluded that a low protein diet did not improve the albuminuria or GFR in diabetic nephropathy patients whether in T1D or T2D. KDOQI guideline opines insufficient evidence to recommend one protein type

over the other to prevent progression of DKD [77]. Low protein diet does not need to be a recommendation for patients with diabetic nephropathy to prevent DKD progression or to decrease proteinuria.

Before You Finish: Practice Pearls for the Clinician

- Screening and early treatment of DKD can prevent disease progression leading to kidney failure.
- Guideline guided therapy includes glucose control, blood pressure control, and reduction of albuminuria.
- Selection of therapy should be patient centric based on glucose control, weight reduction goals, and cardiovascular-kidney benefits
- Avoid treatment inertia and treatment usually includes a combination of RAS blockade with ARB or Ace-inhibitors, SGLT2i, ns-MRA, and GLP1RA for most patients with Type 2 diabetes.

Refer to nephrology for evaluation of albuminuria, rapid course of eGFR loss, or when the diagnosis is not certain such as does with hematuria or lack of diabetic retinopathy.

4.6 Conclusion

Diabetic kidney disease is prevalent among individuals living with T1D and T2D presenting with albuminuria and/or GFR decline and can result in ESKD. Screening with albumin to creatinine ratio and eGFR is recommended. Albuminuria is a predictor of progression of kidney disease, CVD, and mortality. Optimal glycemic control, blood pressure control, lipid profile, and weight can help decrease risk of progression. RAS blockade is the initial therapy for BP and albuminuria control. SGLT2 inhibitors and mineralocorticoid antagonist add benefit in reducing albuminuria and delaying progression of diabetic kidney disease as well as cardiovascular benefit. Benefits from GLP1RA for kidney function protection are still unknown but the cardiovascular benefit has been established and therefore still important for patients with DKD.

What the Guidelines Say You Should Do

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease and ADA American Diabetes Association (ADA) "Standards of Care in Diabetes (2023)

- Comprehensive strategy requires a multidisciplinary team with a foundation on lifestyle modification and self-management
- Optimize glucose and blood pressure control to reduce the risk or slow the progression of chronic kidney disease
- In people with CKD with severe albuminuria (≥300 mg/g urinary albumin), a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression
- ACE-I/ARB should be initiated in patients with diabetes, hypertension, and albuminuria and titrated to the maximum tolerated dose
- In addition to glycemic control medications, SGLT2i, GLP1-RA, and nsMRA have cardiorenal protective effects and need to layered as needed per patient characteristics.
- Modest drop in eGFR (≤30%) after SGLT2i administration should not prompt discontinuation of therapy.
- Glycemic targets are individualized based on patient characteristics (such as life expectancy, severity of CKD, and episodes of hypoglycemia)

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Hypertension and Chronic Kidney Disease

5

Panagiotis I. Georgianos and Rajiv Agarwal

Before You Start: Factors You Need to Know

- Among patients with CKD, hypertension is highly prevalent, remains often inadequately controlled and is associated with increased risk of adverse cardiovascular outcomes and faster progression of kidney injury to ESKD.
- The interrelation between hypertension and CKD is bidirectional, such that hypertension may be either a cause or the consequence of CKD.
- The pathogenesis of hypertension in CKD is complex and includes multiple mechanisms, such as sodium retention and extracellular volume expansion, sympathetic overdrive, overactivation of the renin-angiotensin-aldosterone axis, endothelial dysfunction, and oxidative stress.
- The achievement of adequate BP control is an established and guideline-directed therapeutic strategy to slow the progression of kidney damage and improve cardiovascular outcomes in the CKD population.

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Hypertension is a major public health problem affecting approximately one third of the adult population in the USA [1]. Hypertension is by far the most common comorbidity in patients with chronic kidney disease (CKD). For example, 85.7% and 98.9% of patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study had office blood pressure (BP) levels at baseline ≥140/90 mmHg and ≥130/80 mmHg, respectively [2]. Despite the fact that high BP in patients with CKD is commonly treated with the administration of multiple antihypertensive medications, BP is often inadequately controlled [2]. Sustained uncontrolled hypertension remains a leading cause of end-stage kidney disease (ESKD) worldwide. Uncontrolled BP is also associated with increased risk for adverse cardiovascular events and all-cause mortality [1]. There is therefore a critical unmet need to improve the management of hypertension in the CKD population with the aim to slow the progression of kidney injury, prevent the development of ESKD, and reduce the risk of cardiovascular morbidity and mortality.

Hypertension and CKD are two closely interlinked pathophysiological conditions, such that hypertension may be either a cause or a consequence of CKD [3, 4]. The mechanisms through which hypertension leads to progressive loss of kidney function have been described mainly in preclinical studies. Normally, the glomerular capillary loops are protected from elevated sys-

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temic arterial pressures with a process called "auto-regulation." However, in hypertension, the chronically elevated systemic arterial pressures induce remodeling of the afferent arteriole, and these alterations impair its ability to constrict and dilate. The impaired auto-regulatory process results in the transmission of elevated systemic arterial pressures to the level of glomerular microcirculation, leading to intra-glomerular hypertension, nephrosclerosis, and progressive decline in kidney function [3, 4]. Conversely, CKD may also be a cause of new-onset hypertension or a cause of worsening of pre-existing hypertension. This occurs through several putative mechanisms that often act in a synergistic manner to disrupt normal BP regulation, such as sodium retention, increased activity of the renin-angiotensin-system (RAS), sympathetic overdrive, impaired nitric oxide synthesis, endothelial dysfunction, and oxidative stress [3, 4].

There is an established belief that severity of hypertension travels hand-in-hand with the staging of CKD. However, accumulated evidence suggests that albuminuria—not the levels of estimated-glomerular-filtration-rate (eGFR)—is a stronger determinant of hypertension in CKD. A 2005 study that incorporated office, home, and 24-h ambulatory BP measurements in 232 veterans with CKD showed that among 17 risk factors tested in multivariate models, the spot urinary albumin-to-creatinine ratio (UACR) was the strongest determinant of systolic BP [5]. The strength of the association between albuminuria and systolic hypertension was irrespective of the technique of BP measurement. Most importantly, this strong interrelation was clearly independent from the levels of eGFR [5]. Further analyses showed that regardless of CKD stage, even small increments in the levels of albuminuria exert a dramatic impact on the mean levels of 24-h ambulatory BP and are more closely associated with disrupted circadian variation of arterial pressure [6]. The strong association of albuminuria with the severity of hypertension is difficult to be mechanistically explained. Albuminuria may simply be a marker of worse kidney damage and endothelial dysfunction, but it could act as a mediator as well.

In this chapter, we provide an overview of the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the assessment and management of hypertension in patients with CKD not yet on dialysis. We explore the scientific basis of these recommendations, discussing evidence from observational studies and major randomized controlled trials.

5.1 BP Measurement

Box 5.1 What the Guidelines Say You Should Do: KDIGO 2021 Recommendations for the Techniques of BP Measurement [7]

- We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults. (**1B**)
- We suggest that out-of-office BP measurements with ambulatory BP monitoring or home BP monitoring be used to complement standardized office BP readings for the management of high BP. (**2B**)

5.1.1 Office-Based BP Measurements

The diagnosis and optimal management of hypertension necessitate an accurate assessment of patient's true BP as well as evaluation of hypertension-related target-organ damage. Office-based BP recordings taken either with the use of the auscultatory or the oscillometric method have some inherent limitations, including the "white-coat" effect, a transient elevation in BP seen in a proportion of patients when a medical personnel is present in the room [8]. Standardization of the technique of BP measurement is an essential first step to minimize the error and imprecision introduced by routine office-based BP recordings. At least two BP recordings should be obtained after 5 min of

quiet rest with a validated oscillometric device that is calibrated on a regular basis. A cuff with appropriate size should be placed on the arm at the level of the atrium. Patients should be also instructed to avoid caffeine consumption and smoking 30 min before BP assessment [1]. It has to be noted that all guideline-directed treatment recommendations, such as those provided by KDIGO, are based on evidence from clinical trials that used serial BP recordings obtained in the office environment under standardized conditions.

The Systolic Blood Pressure Intervention Trial (SPRINT) was a landmark trial that demonstrated an impressive 25% reduction in the risk of cardiovascular morbidity and mortality when systolic BP was targeted to levels <120 mmHg as compared with a conservative systolic BP target of <140 mmHg [9]. However, over the course of SPRINT, office BP was measured with a research-grade technique that prespecified a 5-min seated rest period followed by three oscillometric measurements taken without the presence of an observer in the room [9]. In a diagnostic-test study, 275 patients with CKD had their office BP assessed with the research-grade methodology used in SPRINT [10]. On the same day, a single office BP measurement was obtained without specification of a seated rest and with the presence of an observer in the room. Research-grade systolic BP underestimated routine systolic BP by 12.7 mmHg with wide 95% limits of agreement (−46.1 to 20.7 mmHg). Research-grade systolic BP also underestimated daytime ambulatory systolic BP by 7.9 mmHg, once again with wide 95% agreement limits (−33.2 to 17.4 mmHg) [10]. Whereas systolic BP recorded with all three techniques was related to echocardiographically-documented left ventricular hypertrophy, the strength of the association was greater for research-grade office and daytime ambulatory systolic BP as compared with routine office systolic BP [10]. Taken together, these observations indicate that the implementation of SPRINT results into daily clinical practice will require serial office BP measurements with the research-grade technique that was used in this trial. Intensive BP-lowering with the guidance of routine BP recordings in the office environment may be harmful.

5.1.2 Out-of-Office BP Monitoring

Patients with CKD often exhibit abnormal 24-h BP profiles, such as increased short-term BP variability, lack of a normal nocturnal decline in BP or a reverse-dipping BP pattern [11]. Therefore, defining the hypertension control status based solely on office BP recordings is challenging. An earlier meta-analysis of six studies showed that 30% of patients who had CKD and were thought to be hypertensive, in fact had normotension outside of the office [12]. Most alarming, 40.4% of patients who had CKD and were considered to have normotension (or adequately controlled hypertension), in fact had hypertension at home [12]. In an attempt to minimize the misclassification of BP control status, the 2021 KDIGO guidelines recommend the use of home or ambulatory BP monitoring in conjunction with standardized office BP measurements for the management of hypertension in CKD [7].

Home BP measurements represent a practical approach to monitor the BP-lowering response to antihypertensive therapy over a long-term period in daily clinical practice [13]. Patients should be advised on an optimal monitoring schedule and should be educated to measure their BP in a standardized manner with the use of validated automatic home BP devices [14]. Diagnostic-test studies have suggested that among patients with CKD, home BP monitoring is superior to routine office BP recordings in diagnosing uncontrolled hypertension [15]. Prospective observational studies have shown that home BP is a stronger predictor of the risk for progression of CKD, adverse cardiovascular events, and all-cause mortality [16, 17]. In addition, randomized controlled trials have provided evidence that as compared with office-based management of hypertension, the use of home BP monitoring in decision-making has the potential to improve therapeutic inertia and lead to a small, but clinically meaningful improvement in BP control [18]. These benefits may be enhanced when home BP-guided

antihypertensive therapy is accompanied by plans to monitor and treat high BP, such as with the use of telemonitoring [18].

Ambulatory BP monitoring is held to be the "gold standard" technique to diagnose hypertension both in the general population and in patients with CKD [19]. During ambulatory BP monitoring, an appropriate-sized cuff is fitted to the non-dominant arm for 24 h, whereas BP measurements are scheduled every 15–20 min during the daytime period and every 30–60 min during the nighttime period [19]. As compared with office-based BP measurements, BPs obtained from ambulatory BP monitoring exhibit a much closer association with indices of hypertension-related target-organ damage [20]. Ambulatory BP recordings are also of much greater value in prognosticating the risk for adverse cardiovascular and kidney failure outcomes [16, 21]. In contrast to the technique of home BP monitoring that typically assesses BP during periods of resting, ambulatory BP monitoring enables the evaluation of BP during periods of activity. Another unique advantage of ambulatory BP monitoring is that this technique can record BP during the period of sleep, enabling the diagnosis of nocturnal hypertension and identification of non-dipper/reverse-dipper BP patterns [19]. Lastly, when office-based BPs are assessed together with ambulatory BP monitoring, patients on antihypertensive treatment can be classified as having controlled hypertension (i.e., normal office and ambulatory BP), white-coat uncontrolled hypertension (i.e., high office but normal ambulatory BP), masked uncontrolled hypertension (normal office but high ambulatory BP), and sustained uncontrolled hypertension (high office and ambulatory BP) [19].

The prevalence of BP phenotypes in the CKD population varies considerably according to the definition and methodology of out-of-office BP monitoring. In a prospective observational study that included 333 veterans with stage 2–4 CKD and normal office BP (<140/90 mmHg), the prevalence of masked uncontrolled hypertension was 26.7% by daytime ambulatory BP ≥135/85 mmHg, 32.8% by 24-h ambulatory BP ≥130/80 mmHg, but the burden of masked uncontrolled hypertension was as high as 56.1% when hypertension was defined as either daytime BP ≥135/85 mmHg or nighttime BP ≥120/70 mmHg [22]. When the technique of home BP monitoring was applied to determine the BP control status, the prevalence of masked uncontrolled hypertension was shown to be 50.8% [22]. The near twofold higher prevalence of masked uncontrolled hypertension when either daytime or nighttime BPs were considered in the definition should not come as a surprise. Circadian BP patterns and rhythms are commonly disrupted in patients with CKD [23]. Isolated nocturnal hypertension was the exclusive BP abnormality in nearly 50% of the patients enrolled in this cohort.

The reproducibility of masked uncontrolled hypertension diagnosis also varies, depending on the technique of BP measurement. When the assessment of BP was repeated 4 weeks apart in the aforementioned observational study, the agreement in the diagnosis of masked uncontrolled hypertension was 75–78% (k-coefficient: 0.44–0.51) with the use of ambulatory BP monitoring [22]. In contrast, the phenotype of masked uncontrolled hypertension was less reproducible with the application of home BP monitoring (rate of agreement: 63%; k-coefficient: 0.25) [22]. The prevalence of masked uncontrolled hypertension increased progressively with increasing levels of office systolic BP: 2%, 17%, 34%, and 66% in the subgroups of patients with office systolic BP of 90–110 mmHg, 110–119 mmHg, 120–129 mmHg, and 130–139 mmHg, respectively. Accordingly, the suspicision of masked uncontrolled hypertension should be raised in CKD patients who have office BP within the prehypertensive range. Surprisingly, home BP was not superior to office BP in the detection of masked uncontrolled hypertension. One plausible explanation could be the fact that self-monitoring of

home BP is often performed without standardization of the technique (i.e., 5 min of seated rest before BP measurement). Therefore, ambulatory BP monitoring is necessary for the confirmation of the diagnosis of masked uncontrolled hypertension in the CKD population [22].

Identification of abnormal ambulatory BP profiles and classification of the severity of hypertension enable the better stratification of cardiorenal risk. The most robust data are derived from a large analysis of 1502 patients participating in the CRIC study [24]. As exposures, this study evaluated ambulatory BP phenotypes, mean levels of office and ambulatory BP as well as the diurnal variation in BP [24]. As outcomes, the analysis included a cardiovascular endpoint (defined as the composite of myocardial infarction, cerebrovascular event, heart failure, and peripheral arterial disease), a kidney endpoint (defined as the composite of ESKD or an at least 50% decline in eGFR), and all-cause mortality [24]. Over a mean follow-up of 6.72 years, as compared with the referent category of controlled hypertension, masked uncontrolled hypertension was independently associated with a higher risk of the cardiovascular and kidney outcome, but not with excess all-cause death risk. Increasing mean levels of 24-h systolic BP were associated with higher risk of cardiovascular outcome, kidney outcome and all-cause mortality, risk associations that persisted independently from the levels of office BP. As compared with the referent group of dippers, patients with a reverse-dipper pattern in diurnal BP variation exhibited a significantly higher risk of the kidney outcome [24]. It has to be noted, however, that the observational nature of these data precludes the opportunity to derive a direct cause-and-effect risk association between ambulatory BP phenotypes and clinical outcomes. Long-term clinical trials are warranted to fully elucidate whether targeting ambulatory versus office BP is a more effective therapeutic strategy to improve "hard" clinical outcomes in the CKD population.

5.2 BP Management in Patients with CKD, With or Without Diabetes, Not Receiving Dialysis

5.2.1 BP Targets

Box 5.2 What the Guidelines Say You Should Do: KDIGO 2021 Recommendations on the Optimal Levels at Which BP Should Be Targeted [7]

- We suggest that adults with high BP and CKD be treated with a target systolic BP of <120 mmHg, when tolerated, using standardized office BP measurement. (**2B**)

The optimal BP target for patients with hypertension and CKD is an issue that is surrounded by substantial controversy [11]. The 2012 KDIGO guidelines recommended disparate BP targets, depending on the degree of albuminuria: a conservative BP goal of <140/90 mmHg when the levels of UACR are <30 mg/day and a tighter BP goal of <130/80 mmHg when the levels of UACR are ≥30 mg/day [25]. These recommendations were based largely on evidence from three major randomized controlled trials that were conducted specifically in patients with CKD and compared an intensive versus a standard BP target.

The Modification of Diet in Renal Disease (MDRD) trial followed a 2 × 2 factorial design and randomized 840 non-diabetic patients with CKD (GFR: 13–55 ml/min/1.73 m^2) to a usual-protein diet or a low-protein diet and to a usual or a lower BP goal (mean BP of either ≤107 or ≤92 mmHg) [26]. Over a mean follow-up of 2.2 years, there was no difference in the rate of kidney function decline between the standard- and intensive BP groups [26]. In the African American Study of Kidney Disease and Hypertension (AASK)

[27], 1094 African Americans with hypertensive CKD (GFR: 20–65 ml/min/1.73 m^2) were randomized to a standard or an intensive BP target (mean BP of either 102–107 or ≤92 mmHg) and to initiate an antihypertensive regimen including metoprolol (50–200 mg/day), ramipril (2.5–10 mg/day), or amlodipine (5–10 mg/day) in a 2 × 3 factorial design. The results of AASK were in accordance with MDRD; the mean GFR slope from baseline through 4 years of follow-up in the intensive BP arm was not different from the rate of GFR decline in the standard BP arm. Intensive BP-lowering did not improve the composite outcome of sustained ≥50 reduction in GFR from baseline, ESKD or death [risk reduction: 2%; 95% confidence interval (CI): −22% to 21%] [27]. In the Ramipril Efficacy in Nephropathy 2 (REIN-2) trial [28], 338 non-diabetic patients with proteinuric CKD already receiving background therapy with ramipril were randomly assigned to either conventional (diastolic BP <90 mmHg) or intensified (BP <130/80 mmHg) control of hypertension. REIN-2 trial was prematurely terminated for reasons of futility. Over a median follow-up of 19 months, the proportion of patients who progressed to ESKD was identical in the conventional and intensified BP groups [hazard ratio (HR): 1.0; 95% CI: 0.61–1.64] [28].

Taken together, till the completion of their randomized phase, these three trials failed to prove that intensive BP-lowering is an effective strategy to retard the progression of kidney injury or prevent the development of ESKD. However, lower-quality evidence from subgroup analyses of these trials suggested a potential kidney protective effect of intensified BP control in patients with greater proteinuria at baseline. A benefit of a lower versus a standard BP target on GFR slope was observed over the course of the MDRD trial; this benefit was greatest in the subgroup of patients with proteinuria >3 g/day, moderate in the subgroup of patients with proteinuria 1–3 g/day, but totally missing in those with proteinuria <1 g/day at baseline [26]. After completing the randomized phase, patients enrolled in AASK were invited to participate in a post-trial observational study with an extended follow-up ranging from 8.8 to 12.2 years. In the overall analysis of both trial and cohort phases, there was no significant difference between the intensive BP and standard BP arms in the composite outcome of doubling of serum creatinine, ESKD or death from any cause (HR: 0.91; 95% CI: 0.77–1.08) [29]. However, severity of proteinuria at baseline appeared to be a treatment effect modifier, with a potential benefit of intensive BP-lowering in the subgroup of patients with a urinary protein-to-creatinine ratio of >0.22 (HR: 0.73; 95% CI: 0.58–0.93) [29]. Similarly, after the termination of the main phase of MDRD, patients were inserted in a post-trial observational phase with a long-term follow-up of 10.7 years after the initial randomization [30]. In the overall analysis that included both randomized and post-trial observational data, initial assignment to an intensive BP target was associated with a long-term reduction of 32% in the risk of kidney failure (HR: 0.68; 95% CI: 0.57–0.82) as well as with a reduction by 23% in the composite outcome of kidney failure or all-cause mortality (HR: 0.77; 95% CI: 0.65–0.91) [30]. However, given the post-hoc nature of these data, no causal relation between intensive BP-lowering and long-term improvement in kidney outcomes can be demonstrated.

SPRINT was a landmark trial that randomized 9361 non-diabetic patients with office systolic BP ≥130 mmHg and an increased cardiovascular risk to a systolic BP target of <120 mmHg (intensive arm) or to a target of <140 mmHg (standard arm). SPRINT was terminated early after a median follow-up of 3.26 years for reasons of efficacy. In a prespecified subgroup analysis that included 2646 SPRINT participants with CKD at baseline, treatment effects of intensive BP-lowering remained unmodified by the CKD status (*P* value for interactions ≥0.30) [31]. As compared with standard systolic BP target of <140 mmHg, targeting a systolic BP <120 mmHg improved by 19% the primary composite cardiovascular outcome of myocardial infarction, other acute coronary syndromes, stroke, heart failure, and death from cardiovascular causes (HR: 0.81; 95% CI: 0.63–1.05). Intensive BP-lowering also provoked a 28% reduction in the all-cause death risk (HR: 0.72; 95% CI: 0.53–0.99) [31]. Intensive BP control in SPRINT saved lives and

protected the heart, but was not effective in slowing the progression of CKD. However, the kidney failure events were few. The prespecified composite outcome of sustained ≥50 decrease in eGFR from baseline or ESKD occurred in only 15 patients in the intensive arm versus 16 patients in the standard arm (HR: 0.90; 95% CI: 0.44–1.83). With respect to safety, intensive BP-lowering was associated with a higher incidence of acute kidney injury (HR: 1.41; 95% CI: 1.10–1.95), but the majority of these events were hemodynamically-mediated reversible reductions in eGFR rather than true injury to the kidney [31].

Based largely on the impressive cardioprotective benefit of intensive BP-lowering that was demonstrated in SPRINT [31], the 2017 American Heart Association/American College of Cardiology (AHA/ACC) guidelines reappraised the definition of hypertension and recommended a tighter BP target of <130/80 mmHg for the majority of patients at high cardiovascular risk, including those with CKD [1]. However, the results of SPRINT may not be directly generalizable to the whole spectrum of the CKD population, mainly because patients with specific characteristics (i.e., diabetes mellitus, advanced stage 4+ CKD or proteinuria >1 g/day) were not eligible in this landmark trial. The benefit/risk ratio of intensive BP control in these subgroups of CKD patients remains an area of uncertainty.

Another issue is the algebraic manipulation of the intensive systolic BP target that was implemented in SPRINT. For example, the 2017 AHA/ACC guidelines adjusted their recommendation to a 10-mmHg higher systolic BP target aiming to counteract the mean difference between standardized (research-grade) BP recordings that were used in SPRINT and routine measurements often taken in daily clinical practice [1]. However, diagnostic-test studies showed that the 95% limits of agreement between research-grade and routine office systolic BP measurements are wide, ranging from 46.1 mmHg lower up to 20.7 mmHg higher [10]. Accordingly, algebraic adjustment of any degree is insufficient to counteract the large BP variability from patient to patient. The 2021 KDIGO guidelines take a more straightforward position on this crucial issue, recommending that systolic BP should be targeted to levels <120 mmHg (as in the intensive arm of SPRINT), given that intensification of antihypertensive therapy will be guided by standardized office BP measurements [7]. Therefore, the best approach to improve care for patients with hypertension and CKD is at least to measure BP in the clinic following the standardized methodology that is recommended by guidelines.

5.2.2 Treatment with Antihypertensive Drugs, Including RAS-Inhibitors

Box 5.3 What the Guidelines Say You Should Do: KDIGO 2021 Recommendations on Pharmacotherapy of Hypertension in Patients with CKD [7]

- We recommend starting an angiotensin-converting-enzyme-inhibitor (ACEI) or an angiotensin-receptor-blocker (ARB) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes. (**1B**)
- We suggest starting an ACEI or an ARB for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes. (**2C**)
- We recommend starting an ACEI or an ARB for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2, and A3) with diabetes. (**1B**)
- We recommend avoiding any combination of ACEI, ARB, and direct renin inhibitor therapy in patients with CKD, with or without diabetes. (**1B**)

In 2001, two landmark clinical trials, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) demonstrated the superiority of RAS-blockade over placebo or active-treatment with

other classes of antihypertensive medications in patients with type 2 diabetes and overt nephropathy [32, 33]. In RENAAL, the ARB losartan lowered by 16% (95% CI: 2–28%) the risk of doubling of serum creatinine, ESKD or death from any cause as compared with placebo. In IDNT [32], the ARB irbesartan improved the primary composite kidney outcome by 19% relative to placebo [relative risk (RR): 0.81; 95% CI: 0.67–0.99] and by 24% as compared with amlodipine (RR: 0.76; 95% CI: 0.63–0.92) [33]. These kidney protective effects were accompanied by a parallel reduction in the risk of hospitalization for decompensated heart failure. Evidence to support the efficacy of RAS-blockade in non-diabetic patients with proteinuric CKD was provided by the AASK trial [27]. As compared with metoprolol and amlodipine groups, ramipril improved the composite outcome of sustained >50 decrease in GFR from baseline, ESKD or all-cause death by 22% (95% CI: 1–38%) and 38% (95% CI: 14–56%), respectively [27].

Subsequently, large-scale outcome trials were designed to test the hypothesis whether dual RAS-blockade is more effective than monotherapy in retarding the progression of diabetic kidney disease. In the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) trial [34], 8561 patients with type 2 diabetes and CKD, cardiovascular disease or both, who were receiving background therapy with an ACEI or an ARB, were randomized to add-on treatment with the direct renin inhibitor aliskiren or matching placebo. This trial was prematurely terminated due to safety reasons. Over a median follow-up of 32.9 months, the incidence of hyperkalemia was significantly higher in the aliskiren group than in the placebo group (11.2% vs. 7.2%, $P < 0.001$). Similarly, the proportion of patients with reported hypotension was significantly higher with dual RAS-blockade than with monotherapy (12.1% vs. 8.3%, $P < 0.001$) [34]. In the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial [35], patients with type 2 diabetes and albuminuric CKD already treated with losartan at a dose of 100 mg/day were randomized to add-on therapy with lisinopril (10–40 mg/day) or placebo. Once again, this trial was terminated early, because combination therapy was associated with increased risk of serious adverse events. When VA Nephron-D was closed, there was a trend for a slower progression of kidney injury to ESKD with dual RAS-blockade as compared with monotherapy (HR: 0.66; 95% CI: 0.41–1.07) [35]. However, this potential signal of renoprotection was counteracted by excess risk of hyperkalemia (HR: 1.70; 95% CI: 1.3–2.2) and acute kidney injury (HR: 2.8; 95% CI: 1.8–4.3) [35]. After the premature termination of VA Nephron-D trial due to safety reasons, all international guidelines have consistently recommended that combination therapy with an ACEI and an ARB is contraindicated in the whole spectrum of patients with hypertension [1, 7].

As an alternative approach to enhance the cardiorenal protection afforded by monotherapy with an ACEI or an ARB, short-term clinical trials tested the safety and efficacy of add-on treatment with a steroidal mineralocorticoid-receptor-antagonist (MRA), such as spironolactone and eplerenone [36]. An updated 2020 Cochrane meta-analysis of 44 studies involving a total of 5745 patients showed that as compared with placebo or standard care, add-on MRA therapy may be associated with favorable effects on urinary albumin excretion [standardized mean difference (SMD): −0.51; 95% CI: −0.82 to −0.20, $n = 14$ studies], eGFR slope [weighted mean difference (WMD): −3.0 ml/min/1.73 m^2; 95% CI: −5.51 to −0.49, $n = 13$ studies] and office systolic BP (WMD: −4.98 mmHg; 95% CI: −8.22 to −1.75, $n = 14$ studies) [37]. However, these potential benefits on surrogate endpoints of cardiorenal disease were accompanied by excess risk of adverse effects. As compared with placebo or standard care, the addition of spironolactone or eplerenone to an ACEI/ARB increased the risk of hyperkalemia (RR: 2.17; 95% CI: 1.47–3.22, $n = 17$ studies), acute kidney injury (RR: 2.04; 95% CI: 1.05–3.97, $n = 5$ studies), and gynecomastia (RR: 5.14; 95% CI: 1.14–23.23, $n = 4$ studies) [37]. Most importantly, none of the studies that were included in this meta-analysis was adequately powered to detect treatment effects of add-on MRA therapy on patient-level clinical out-

comes, such as progression to kidney failure, adverse cardiovascular events and all-cause mortality [37].

Despite the fact that RAS-inhibitors are recommended by guidelines as a first-line antihypertensive therapy in patients with high BP, CKD, and moderately-to-severely increased albuminuria, pharmacoepidemiologic studies have shown that these agents are often underutilized in daily clinical practice [38–40]. Hyperkalemia is an important factor that limits the optimal RAS-blockade, particularly in patients with moderate-to-advanced CKD. The use of newer therapies that bind potassium in the gut can mitigate the risk of hyperkalemia, possibly enabling the more persistent use of ACEIs/ARBs at optimal doses in this high-risk patient population. Preliminary evidence to support the efficacy of this therapeutic strategy was provided by the Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER) trial [41]. In this phase 2b trial, 295 patients with stage 3b/4 CKD (eGFR: 25 to <45.0 ml/min/1.73 m^2) and uncontrolled resistant hypertension were randomized to double-blind therapy with the potassium binder patiromer (8.4 g/day) or placebo, in addition to open-label spironolactone (at a starting dose of 25 mg/day) and their baseline antihypertensive medications. Over 12 weeks of follow-up, as compared with placebo, patiromer enabled more patients to tolerate and remain on spironolactone with less severe hyperkalemia (between-group difference: 19.5%; 95% CI: 10.0–29.0%) [41]. Just five patients needed to be treated with patiromer to enable the administration of spironolactone in 1 more patient. Add-on therapy with spironolactone was accompanied by a clinically meaningful reduction of 11–12 mmHg in unattended automated office systolic BP over the course of the AMBER trial [41]. Whether this therapeutic strategy offers a downstream benefit on end-organ protection that is translated into a long-term improvement in cardiorenal outcomes is an important research question that will remain unexplored in the foreseeable future. The Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND) was a phase 3 trial that was originally designed to investigate the impact of patiromer-enabled optimization of RAS-inhibitor therapy on the composite outcome of cardiovascular death or cardiovascular-related hospitalization in patients with heart failure with reduced ejection fraction [42]. Unfortunately, DIAMOND failed to provide a clear answer, because the trial was prematurely terminated due to a lower than expected recruitment rate during the COVID-19 pandemic.

Whereas the efficacy of currently established steroidal MRAs in patients with CKD remains unknown, a novel non-steroidal MRA named finerenone has recently received regulatory approval with the indication of cardiorenal protection in patients with CKD associated with type 2 diabetes [36]. Unlike spironolactone and eplerenone, this novel agent offers potent and selective inhibition of the mineralocorticoid receptor with a more favorable side-effect profile [36]. The safety and efficacy of finerenone was demonstrated in two complementary phase 3 clinical trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) [43, 44]. In a prespecified, individual patient-level combined analysis of these two trials, the treatment effects of finerenone (10–20 mg/day) relative to placebo were explored in a total of 13,026 patients with type 2 diabetes and a broad spectrum of CKD [45]. All these patients were receiving optimized background therapy with maximum tolerated doses of an ACEI or an ARB prior to randomization. Over a median follow-up of 3.0 years, as compared with placebo, finerenone improved by 14% the composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or heart failure hospitalization (HR: 0.86; 95% CI: 0.78–0.95) [45]. The cardioprotective benefit of finerenone was primarily driven by a 22% reduction in the risk of heart failure hospitalization (HR: 0.78; 95% CI: 0.66–0.92). Furthermore, finerenone provoked a placebo-subtracted reduction of 23%

in the composite outcome of kidney failure, sustained ≥57% decrease in eGFR from baseline or death from renal causes (HR: 0.77; 95% CI: 0.67–0.88) [45]. As expected, the incidence of hyperkalemia was higher with finerenone than with placebo. However, hyperkalemia-related adverse events with clinical impact occurred rarely; hyperkalemia leading to permanent discontinuation of the trial regimen was observed in only 1.7% of patients in the finerenone group vs. 0.6% in the placebo group [45]. It has to be noted that 40% of patients enrolled in the FIDELIO-DKD and FIGARO-DKD trials had an eGFR >60 ml/min/1.73 m^2 and were identified for inclusion because urine analysis indicated the presence of albuminuria. Therefore, screening for albuminuria to identify at-risk patients with type 2 diabetes who are candidates for finerenone treatment facilitates the long-term improvement in both cardiovascular and kidney failure outcomes.

Lastly, sodium-glucose co-transporter 2 (SGLT-2) inhibitors are guideline-directed antidiabetic therapies proven to be effective in improving cardiorenal outcomes in CKD patients with or without type 2 diabetes [46–48]. The main mechanism of their hypoglycemic action is the blockade of reabsorption of sodium and glucose in the proximal tubule. The resulting natriuresis and osmotic diuresis have been suggested to contribute to a clinically meaningful BP-lowering effect, although other mechanisms may be also involved [49]. In a meta-analysis of seven randomized controlled trials involving a total of 2381 patients with type 2 diabetes and preserved kidney function, SGLT-2 inhibitor therapy was associated with a placebo-subtracted reduction of 3.62 mmHg (95% CI: −4.29 to −2.94) in 24-h ambulatory systolic BP and with a reduction of 1.70 mmHg (95% CI: −2.13 to −1.26) in 24-h ambulatory diastolic BP [50]. A similar in magnitude BP-lowering effect was seen with the SGLT-2 inhibitor canagliflozin over the course of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [51]. This trial included 4401 patients with type 2 diabetes and albuminuric CKD, of whom 3361 (76.4%) had baseline office systolic BP ≥130 mmHg, and 1371 (31.2%) had resistant hypertension. Between baseline and week 3 of follow-up, canagliflozin lowered office systolic BP by 3.50 mmHg (95% CI: −4.27 to −2.72) [51]. This BP-lowering effect was sustained till the completion of the trial and was similar across BP and BP-lowering therapy subgroups. In addition, canagliflozin reduced by 32% the necessity for intensification of background antihypertensive therapy over the course of the CREDENCE trial (HR: 0.68; 95% CI: 0.61–0.75) [51]. Therefore, SGLT-2 inhibitors may be useful as an adjunct BP-lowering therapy in addition to their kidney and cardiovascular protective benefits in CKD patients with or without type 2 diabetes.

Before You Finish: Practice Pearls for the Busy Clinician

- BP measurements in the office should be obtained in a standardized fashion, as recommended by guidelines, as an essential first step for accurate diagnosis and optimal management of hypertension.
- Out-of-office BP monitoring in conjunction with standardized office BP recordings facilitates the identification of white-coat and masked hypertension and enables the better stratification of cardiorenal risk.
- Current evidence suggests that among patients with CKD, targeting office systolic BP to levels <120 mmHg as compared with a conservative systolic BP target of <140 reduces the risk of adverse cardiovascular events and all-cause mortality, given that intensive BP-lowering is guided by standardized office BP measurements.
- Among diabetic or non-diabetic patients with high BP, CKD and moderately-to-severely increased albuminuria, ACEIs and ARBs are first-line antihypertensive therapies, based on solid clinical-trial evidence demonstrating their effectiveness in retarding the progression of CKD and in improving cardiovascular morbidity.
- Dual RAS-blockade has been associated with excess risk of hyperkalemia, hypotension, and

acute kidney injury; therefore, the combination of an ACEI with an ARB is contraindicated.

- Screening for albuminuria is a simple and cost-effective diagnostic test to identify at-risk patients with type 2 diabetes who are eligible for treatment with the non-steroidal MRA finerenone. This therapeutic approach facilitates the long-term reduction in both cardiovascular and kidney disease burden in this high-risk patient population.
- SGLT-2 inhibitors are guideline-directed antidiabetic therapies with proven benefits on cardiorenal outcomes in CKD patients with or without type 2 diabetes. Their natriuretic action is also accompanied by a clinically meaningful reduction of 3–5 mmHg in systolic BP, indicating that SGLT-2 inhibitors may be also useful as an adjunct antihypertensive therapy in addition to their kidney and cardiovascular protective effects.

Conflicts of Interest R.A. reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals, Akebia Therapeutics, Boehringer Ingelheim, Eli Lilly, Relypsa, Vifor Pharma, Lexicon and Reata; is a member of data safety monitoring committees for Vertex and Chinook and a member of steering committees of randomized trials for Akebia Therapeutics, Bayer and Reata; has served as an associate editor of the American Journal of Nephrology and Nephrology Dialysis and Transplantation and has been an author for UpToDate; and has received research grants from the National Institutes of Health and the US Veterans Administration.

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Dyslipidaemia in Kidney Disease

6

Charles J. Ferro

Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) is strongly associated with increased cardiovascular risk and is associated with substantial health and economic costs.
- Declining glomerular filtration rate has been established as a risk factor for cardiovascular events.
- Impaired kidney function results in profound dysregulation of several lipid metabolism pathways and is associated with a more atherogenic profile with low levels of high-density lipoprotein cholesterol, hypertriglyceridaemia, and highly oxidised and carbamylated low-density lipoprotein cholesterol.
- Dyslipidemia treatment is highly effective in preventing cardiovascular events in the general population with increased cardiovascular risk. As CKD patients have a very high risk for cardiovascular events, dyslipidemia treatment in CKD patients is also justified.

There is a graded inverse relationship between glomerular filtration rate and cardiovascular disease that is not explained by age, sex, and other traditional cardiovascular risk factors. This relationship is present even with minor levels of renal dysfunction and is highest in patients with end-stage kidney disease (ESKD) requiring dialysis therapy [1].

Patients with kidney disease are an extremely heterogenous population with multiple aetiologies, levels of kidney function and proteinuria, comorbidities, especially concomitant diabetes mellitus, renal replacement therapies and treatments all of which can have a significant impact on both the levels and properties of circulating lipids [1]. Lipid metabolism is a complex process involving multiple organs, tissues, and cells (Fig. 6.1). All these processes can be affected by kidney dysfunction. Generally, abnormal kidney function alters circulating lipids towards a more atherogenic profile. Patients with chronic kidney disease (CKD) stage 3 or worse typically have hypertriglyceridaemia, low high-density lipoprotein (HDL)-cholesterol, and variable concentrations of low-density lipoprotein (LDL) cholesterol and total cholesterol. Plasma levels of lipoprotein(a) (Lp(a) (Fig. 6.2) increase early in CKD owing to decreased clearance and can be raised 4-fold in patients on dialysis [1, 2].

Separate to changes in glomerular filtration rate (GFR), increasing levels of albuminuria are associated with a dyslipidaemia that is exemplified in patients with nephrotic syndrome. Characteristically, these patients have markedly raised total cholesterol and LDL-cholesterol,

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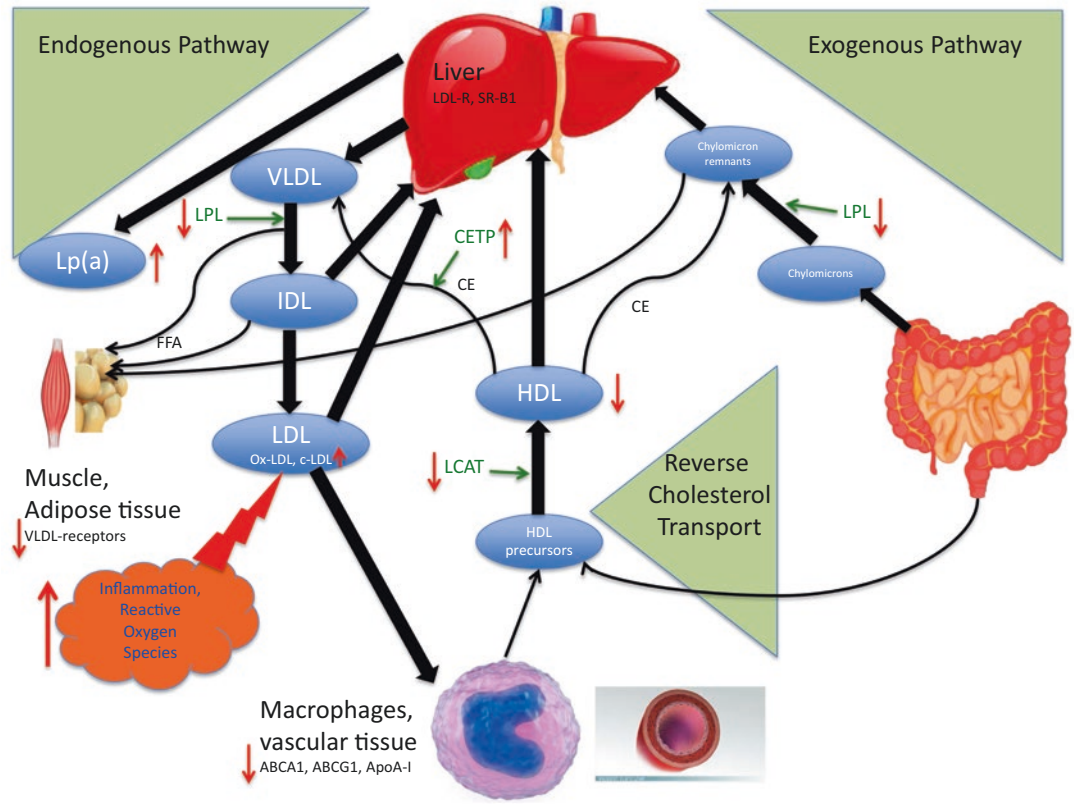

Fig. 6.1 Lipoprotein metabolism in chronic kidney disease. In the exogenous pathway, chylomicrons, rich in triglycerides transport ingested lipids absorbed from the bowel. Chylomicrons are catabolized by lipoprotein lipase, generating free fatty acids that are taken up by liver, muscle, and adipose tissue. Chylomicrons quickly reduce in size becoming chylomicron remnants that are taken up by the liver via the LDL Low density lipoprotein (LDL)-receptor. In the endogenous pathway, the liver produces very low-density lipoprotein (VLDL) particles that transport triglycerides to peripheral tissues. Triglycerides are hydrolysed by lipoprotein lipase, the VLDL particles decrease in size to become intermediate density lipoprotein particles and finally LDL particles, which retain considerable amounts of cholesterol. The LDL particles transport cholesterol to the liver and peripheral tissues and are cleared by the LDL receptor (LDLR), as well as other specific receptors and scavenger receptors such as scavenger receptor B1 (SR-B1). In the process of reverse cholesterol transport, high density lipoprotein (HDL) particles transport cholesterol from peripheral cells to the liver. With worsening kidney function, a gradual qualitative and quantitative shift occurs towards a more atherogenic uraemic lipid profile, characterized by high triglycerides, low HDL cholesterol and variable levels of oxidised LDL (ox-LDL) and carbamylated LDL (c-LDL) cholesterol. The lipid profile is also further modified by comorbidities including diabetes mellitus and nephrotic syndrome. *ABCA1* ATP- binding cassette transporter A1, *ABCG1* ATP- binding cassette transporter G1, *ApoAI* apolipoprotein AI, *CETP* cholesteryl ester transfer protein, *LCAT* lecithin–cholesterol acyltransferase, *Lp(a)* lipoprotein (a)

hypertriglyceridaemia, and low-to-normal HDL-cholesterol [1]. Many kidney disease patients, including kidney transplant recipients and patients with autoimmune or inflammatory conditions require treatment with immunosuppressant medication. Corticosteroids dose-dependently increase circulating levels of LDL-cholesterol and triglycerides, as well as inducing insulin resistance. Calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors increase circulating LDL-cholesterol [1].

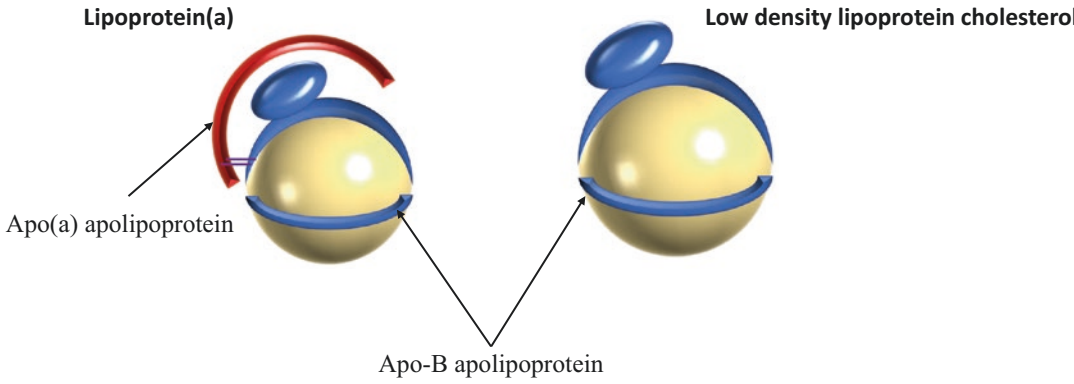

Fig. 6.2 Illustration of the similarities and differences between low density lipoprotein-cholesterol and Lipoprotein(a). Lipoprotein(a) and low density lipoprotein-cholesterol both have a lipid core and an Apo-B apolipoprotein. Lipoprotein(a) also has an Apo(a) apolioprotein of varying sizes. The variability of the Apo(a) apolipoprotein makes direct measurement and quantification of lipoprotein(a) difficult

6.1 Lipids and Cardiovascular Disease

In people without kidney disease, there is a clear linear relationship between plasma LDL-cholesterol and the risk of myocardial infarction and ischaemic stroke. For every 1 mmol/L increase in LDL-cholesterol, the risk of ischaemic heart disease increases by 40% [1]. However, in patients with ESKD on dialysis, LDL-cholesterol has a negative association with all-cause and cardiovascular mortality at below average levels and a flat or weakly positive association at higher levels [1]. A potential explanation for this observed inverse relationship is the development of a unique cardiovascular phenotype in patients with CKD, and especially in those with ESKD, with proportionally less deaths due to atheromatous vasculo-occlusive processes but more deaths attributed to heart failure and sudden cardiac death [3]. The triad of a specific pattern of myocardial fibrosis, increased left ventricular mass and either diastolic or systolic left ventricular dysfunction known as CKD-associated or uraemic cardiomyopathy is the pathophysiological basis for this cardiovascular phenotype [4]. This unique phenotype is supported by a secondary analysis of the Study of Heart and Renal Protection (SHARP) that included 9270 patients with moderate to advanced kidney disease, including 3015 patients on dialysis [5]. A linear relationship was found between LDL-cholesterol levels and the risk of major atheromatous vasculo-occlusive (Hazard Ratio 1.14 95% confidence intervals (95%CI) 1.06–1.22/0.6 mmol/L increase in LDL-cholesterol) events [1]. However, there was an inverse association of LDL-cholesterol with non-atheromatous events, such as arrythmias and heart failure (HR 0.90 95%CI 0.83–0.97 per 0.6 mmol/L increase in LDL-cholesterol). Thus, studies that do not distinguish between the different aetiologies of cardiovascular disease in patients with CKD can be misleading.

Increased HDL-cholesterol concentrations in the general population are associated with decreased cardiovascular risk. However, RCTs have not shown a decrease in cardiovascular events by increasing HDL-cholesterol. Low concentrations of HDL-cholesterol are common in patients with CKD and ESKD but they do not appear to be associated with an increase in cardiovascular events after adjustment for traditional cardiovascular risk factors [1].

Higher levels of circulating triglycerides are associated with increased cardiovascular risk in the general population, although the association is far weaker than that observed with LDL-cholesterol. Hypertriglyceridaemia is common in patients with CKD and ESKD, especially in those with diabetes and on those on peritoneal dialysis [1].

Lipoprotein(a) is a unique, highly atherogenic lipoprotein with a central LDL-like core containing a single molecule of apolipoprotein-B (ApoB) linked by a disulphide bridge to apolipoprotein-A [2]. Higher Lp(a) concentration is a significant independent risk factor for major atherosclerotic events and aortic calcification. In general, circulating Lp(a) concentrations increase with decreasing kidney function and are highest in dialysis patients. Given the structural similarity between Lp(a) and LDL-cholesterol most quantification of LDL-cholesterol either by formula or direct assay is the sum of both LDL-cholesterol and Lp(a) [2]. This might be very important in situations of low LDL-cholesterol and raised Lp(a) concentrations such as in dialysis patients.

6.2 Lipid-Lowering Therapy

6.2.1 Low Density Lipoprotein-Lowering Therapy

6.2.1.1 Statins

The beneficial effects of lowering circulating LDL-cholesterol concentrations with 3-hydroxy-3-methylglutaryl-coenyme A reductase inhibitors, commonly known as statins, has been well established in patients with normal kidney function. Statins conclusively lower cardiovascular risk in patients at increased cardiovascular risk as primary prevention, and in patients after an atherosclerotic cardiovascular event as secondary prevention. In these studies, a 1 mmol/L reduction in LDL-cholesterol is associated with a 22–23% reduction of major vascular events [1].

Several post-hoc analyses of large statin trials have shown a reduction in cardiovascular events in patients with CKD (eGFR<60 ml/min/1.73 m^2) [6]. However, two large RCTs in patients on dialysis, the Die Deutsche Diabetes Dialyse Studie (4D) [7] and A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [8] showed no benefit of statin therapy in patients with ESKD. The double-blind RCT SHARP tested the actions of LDL-cholesterol lowering with simvastatin plus ezetimibe for primary prevention of atherosclerotic events in 9270 patients with CKD [5]. At the start of the trial, 6270 of these patients has a serum creatinine level higher than 150 μmol/L for men or higher than 130 μmol/L for women. The remaining 3023 patients were already on dialysis treatment. Overall, there was a significant reduction (HR 0.83 95%CI 0.74–0.94) in major atherosclerotic events, defined as coronary death, myocardial infarction, non-haemorrhagic stroke, or any revascularisation. However, consistent with 4D and AURORA, LDL-cholesterol lowering was not associated with a reduction in atherosclerotic events in patients already on dialysis (HR 0.90, 95% CI 0.75–1.08).

Meta-analyses of LDL-lowering trials in patients with CKD/ESKD find a benefit of therapy in reducing major atherosclerotic events in patients with CKD with a trend towards smaller relative risk reductions as eGFR declines even after adjustment for smaller LDL-cholesterol lowering in patients with more severe CKD [9]. There is also little evidence that statin-based therapies prevent major atherosclerotic cardiovascular events in patients already on dialysis [9].

In the Assessment of Lescol in Renal Transplantation (ALERT) study, 2102 kidney transplant recipients on ciclosporin-based immunosuppression who had already had a myocardial infarction were randomised to either 40 mg fluvastatin or placebo and followed up for a mean of 5.1 years. Intervention with fluvastatin did not reduce the primary end-point defined as a reduction of cardiac death, non-fatal myocardial infarction or coronary intervention [10]. However, statin treatment was associated with a reduction in non-fatal myocardial infarction and cardiac deaths. In a complex extension study, all of the ALERT participants were offered open-label, longer-term high dose (80 mg) fluvastatin and followed for a total of 6.7 years [11]. This extension study confirmed that those initially randomised to receive fluvastatin had a sustained reduction in risk of suffering a non-fatal myocardial infarction or cardiac death.

6.2.1.2 Ezetimibe

Ezetimibe inhibits intestinal absorption of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. Ezetimibe is the most used non-statin agent, lowers LDL-

cholesterol by 13–20% and has a low incidence of side-effects [1]. It was used together with a statin in the SHARP trial [5].

6.2.1.3 Bile Acid Sequestrants

Bile acid sequestrants (anion exchange resins) bind gut bile acids reducing enterohepatic circulation and lead indirectly to lowering intestinal cholesterol absorption and reducing circulating LDL-cholesterol concentrations by 13–20% [1]. Although these medications are generally safe because they are not absorbed, they are associated with gastro-intestinal side-effects including constipation. They have not been well studied in RCTs in the general population. They also increase circulating triglycerides which may limit their utility in patients with hypertriglyceridaemia, including patients with CKD/ESKD, and very little evidence exists to support their use in these populations.

6.2.1.4 Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a secreted serine protease that binds to the extracellular domain of the LDL-receptor located on hepatocytes and promotes its lysosomal degradation preventing its recirculation to the cell surface and increasing circulating LDL-cholesterol [2]. Monoclonal antibodies against PCSK9 prevent LDL-receptor catabolism lowering circulating LDL-cholesterol concentrations. Treatment with statins increases PCSK9 and the increase is proportional to LDL-cholesterol reduction (Fig. 6.3) [2].

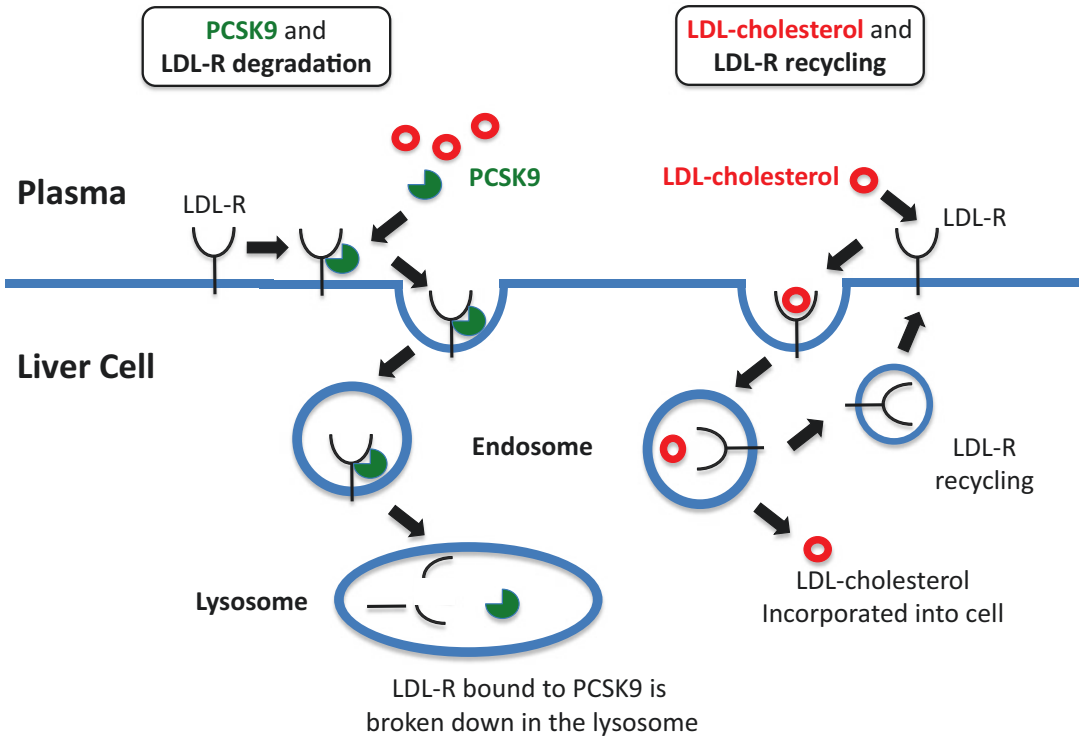

Fig. 6.3 Role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in low density lipoprotein cholesterol metabolism. LDL-cholesterol binds to LDL-receptors on the surface of cells to form a complex that is taken up by the cell. With falling pH, the LDL-receptor dissociates from the complex. The LDL is incorporated into the cell and the LDL-receptor recycles to the cell surface. PCSK9 is an extracellular protein that binds directly to the LDL-receptor and results in internalization and degradation of the receptor. Therapeutic agents targeting PCSK9 prevent degradation of the LDL-receptor resulting in more LDL-cholesterol being removed from the circulation and decreased LDL-cholesterol levels. LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low-density lipoprotein

Several strategies have been developed to lower PCSK9 concentrations. Monoclonal antibodies that act as PCSK9-inhibitors being the most studied so far, with two of them, alirocumab and evolocumab licensed for clinical use [1, 2]. Several RCTs have confirmed that these agents lower LDL-cholesterol levels by 36–65%, Lp(a) levels by approximately 25%, and lower the risk of major cardiovascular events in patients with familial hypercholesterolaemia, patients already optimised on statin therapy who have recently experienced an acute coronary syndrome, and patients with known atherosclerotic vascular disease [2]. From sub-analyses of these studies the safety profiles and LDL-cholesterol reducing properties of these antibodies do not appear to be affected by kidney function, although very few patients with CKD stages 3b or 4 were included in these trials [2]. To date, the efficacy and safety of these monoclonal antibodies in dialysis patients is scarce and have only been evaluated in case series. Therefore, although theoretically these agents may be of future use in lowering cardiovascular risk in patients with advanced CKD and those on dialysis, further information is needed before widespread adoption.

6.2.2 Triglyceride-Lowering Therapy

6.2.2.1 Fibrates

Fibrate monotherapy has been shown in RCTs to lower the risk of major cardiovascular events in the general population, although the benefit may be restricted to individuals with very high triglyceride and very low HDL-cholesterol circulating concentrations [1]. However, fibrates (although possibly not gemfibrozil) may increase serum creatinine concentrations especially in patients with an eGFR less than 30 ml/min/1.73 m^2. At present, there is very little evidence to recommend the use of fibrates in patients with CKD unless triglyceride concentrations are very high (>11.3 mmol/L; >1000 mg/dL). If used this should be done with caution after adjusting the dose for kidney function [1].

6.2.2.2 Omega-3 Fatty Acids

Pharmacological doses of omega-3 fatty acids (2–4 g/day) lower circulating triglyceride concentrations in a dose-dependent manner by mechanisms that remain unclear [1]. They have little effect on LDL-cholesterol and HDL-cholesterol in the general population nor in patients with CKD/ESKD. There is currently very little evidence to support their use in patients with CKD/ESKD to reduce cardiovascular risk [12].

6.2.3 Lipoprotein(a)

6.2.3.1 Inhibitors of Lipoprotein(a) Synthesis

Circulating concentrations of Lp(a) are resistant to life-style interventions and accumulating evidence indicates they are increased by statin treatment. Nicotinic acid and PCSK9 inhibitors lower Lp(a) concentrations [2]. A hepatocyte-directed antisense oligonucleotide targeting Lp(a) mRNA has been recently tested in phase 1 and 2 RCTs. However, patients with a GFR less than 60 ml/min/1.73 m^2 were excluded and patients with "significant kidney disease" will be excluded from a planned hard-endpoint RCT [2].

6.3 Management of Lipids in Patients with CKD and ESKD

6.3.1 Guidelines

Several guidelines have been produced over the last few years addressing the management of lipids in patients with CKD/ESKD [12–15]. Some of the more influential ones are listed in Box 6.2. In particular, the 2013 KDIGO Clinical Practice Guideline for Lipid Management is widely used at present, despite having caused extensive discussion and controversy when launched [13]. It should, however, be remembered that guidelines tend to be simplifications, which makes them easier to remember and

implement but can result in the misclassification of individual patients. Summary recommendations can be interpreted as being very rigid and should not be taken as a strict set of instructions. Guideline documents should be read as they will set any summary recommendations into context, often allowing for personalised treatment, especially when the supporting evidence is considered weak.

6.3.2 Assessment of Lipid Status at Baseline

The KDIGO Guideline recommends assessment of a lipid profile consisting of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. It does not recommend measurement of Lp(a), ApoB (the major apolipoprotein embedded in LDL- and VLDL-cholesterol), or other lipid markers that might have risk prediction utility in the general population but their usefulness in patients with CKD/ESKD remains to be established [13]. The American Heart Association 2018 Guideline suggests considering measuring Lp(a) concentrations if there is a strong family history of cardiovascular disease not explained by major risk factors and measuring Apo-B in hypertriglyceridaemia [14].

6.3.3 Assessment of Lipid Status After Starting Treatment

The KDIGO Guideline does not recommend follow-up measurement of lipid levels after starting treatment, although the evidence level for this is recommendation is "not graded." This "fire and forget" recommendation is based on the lack of data on treatment escalation to achieve specific LDL-cholesterol targets, and substantial variability in LDL-cholesterol measurements over time.

In contrast, the other major guidelines do recommend achieving both a target percentage lowering of LDL-cholesterol as well as achieving LDL-cholesterol concentrations below a certain level. These are summarised in Table 6.1. These recommendations are based on strong evidence of a linear relationship between the reduction of LDL-cholesterol concentrations and the observed reduction in cardiovascular risk.

6.3.4 Lipid-Lowering Treatment

All guidelines recommend life-style modification to lower LDL-cholesterol and triglycerides, as well as cardiovascular risk in general, and this is something that is often neglected in clinical practice.

The KDIGO Guideline recommends that patients older than 50 years with CKD stage 3–5 but not yet on dialysis should be treated with a statin or statin plus ezetimibe combination. This recommendation is based on the robust trial evidence already discussed and is consistent with other guidelines that do not recommend the use of risk assessment tools in this population given they already are at high cardiovascular risk. In patients aged 18–49 with CKD stages 3–5 not on dialysis, the KDIGO Guideline recommends treatment if they have known coronary artery disease, diabetes mellitus, previous ischaemic stroke or an estimated 10-year risk of coronary death or non-fatal myocardial infarction greater than 10%. The evidence for this recommendation is considered weak but is consistent with other guidelines (Table 6.1). The KDIGO guideline also recommends treatment for patients with CKD stages 1–2 more than 50 years old with significant albuminuria (>30 mg/g).

The KDIGO guideline and ESC 2019 Guideline recommend starting kidney transplant recipients with a statin (Table 6.1) [13]. The 2019 ESC Guidelines on lipid management are more nuanced advising that the benefits of statin treatment in kidney transplant recipients are uncertain but advising that these patients should be treated as if they were at high or very high risk of atherosclerotic cardiovascular disease with statins being considered as first line agents with the potential to use ezetimibe if statin intolerant or treatment targets not achieved [15]. The calcineurin inhibitor ciclosporin is metabolised by the CYP3A4 pathway and increases statin levels increasing the risk of myopathy. Fluvastatin,

Table 6.1 Summary of major guideline recommendations for starting lipid lowering therapy and targets

	KDIGO	2018 AHA guideline	2019 ESC guideline	2021 ESC guideline
CKD stages 1–2	Adults aged ≥50 years recommend treatment with a statin	No specific recommendation	No specific recommendation	Treat as high risk if ACR> 300 mg/mmol
CKD stages 3–5 not on dialysis	Adults aged ≥50 years recommend treatment with a statin or statin ezetimibe combination Adults aged 18–49 years suggest statin treatment if either: Known coronary disease Diabetes mellitus Prior ischaemic stroke Estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10%	Adults 40–75 with LDL-cholesterol 1.7–4.9 mmol/L and a 10-year ASCVD risk of >7.5% a moderate intensity statin ± ezetimibe might be useful In patients with known ASCVD lower LDL-cholesterol by >50% but if LDL-cholesterol remain above 1.8 mmol/L on maximally tolerated statin consider adding in ezetimibe. If despite this LDL-cholesterol remains above 1.8 mmol/L consider using a PCSK9-inhibitor if cost: benefit ratio is favourable	The use of statin or statin/ezetimibe combination is recommended For individuals at moderate risk, an LDL-cholesterol goal of <2.6 mmol/L should be considered For patients at high risk, an LDL-cholesterol reduction of >50% from baseline and an LDL-cholesterol goal of <1.8 mmol/L are recommended In very-high-risk patients, an LDL-cholesterol reduction of ≥50% from baseline and an LDL-cholesterol goal of <1.4 mmol/L are recommended	The use of statin or statin/ezetimibe combination is recommended LDL-cholesterol < 2.6 mmol/L (>50% reduction in LDL-cholesterol (<1.8 mmol/L in highrisk patients; <1.4 mmol/L in very high-risk patients)
CKD stage 5 (on dialysis)	If already on a statin or statin ezetimibe combination suggest agents continued Do not initiate statin or statin/ezetimibe combination	If already on a statin, it would be reasonable to continue If not already on a statin, do not start	If already on a statin or statin/ezetimibe combination continuation of these drugs should be considered, particularly in patients with ASCVD In patients on dialysis who are free of ASCVD starting a statin is not recommended	If already on hypolipidaemic therapy this may be maintained If not already on hypolipidaemic therapy do not start
Transplant	Recommend treatment with a statin	No recommendation	Statins should be considered first line agents. Initiation should be low dose with careful up titration. Ezetimibe can be considered for patients who are statin-intolerant or have significant dyslipidaemia despite maximally tolerated statin treatment Treat as if at high or very high risk	No recommendation

2021 ESC Guideline: High Risk = Moderate CKD (eGFR 30–44 ml/min/1.73 m^2 and ACR <30 mg/mmol or eGFR 45–59 ml/min/1.73 m^2 and ACR 30–300 mg/mmol or eGFR ≥60 mL/min/1.73 m^2 and ACR >300); Very high risk = Severe CKD (eGFR<30 ml/min/1.73 m^2 or eGFR 30–44 ml/min/1.73 m^2 and ACR >30 mg/mmol)
2019 ESC Guideline: High risk = eGFR 30–59 ml/min/1.73 m^2; Very High risk = eGFR <30 ml/min/1.73 m^2

Table 6.2 High-, moderate-, and low-intensity statin treatment with specific examples[a]

	Low intensity	Moderate intensity	High intensity
LDL-cholesterol reductions	<30%	30-49%	≥50%
Statins	Simvastatin 10 mg Pravastatin 10–20 mg Fluvastatin 20–40 mg	Simvastatin 20–40 mg Pravastatin 40 mg Fluvastatin 40 mg twice daily Atorvastatin 10–20 mg Rosuvastatin 5–10 mg	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg

[a] For atorvastatin, rosuvastatin, and simvastatin estimated from the VOYAGER database. For fluvastatin and pravastatin estimated from US Food and Drug Administration-approved product labelling

pravastatin, and rosuvastatin are metabolised through different CYP enzymes and have less potential for interaction. Tacrolimus, another calcineurin inhibitor, is also metabolised by CYP3A4 but appears to have less potential for harmful interaction with statins. Other drugs that interact with the CYP3A4 pathway should be avoided in patients on calcineurin inhibitors and statins if at all possible.

The KDIGO, AHA, and ESC Guidelines do not recommend starting a statin or combination therapy with statin and ezetimibe in patients already receiving dialysis therapy. However, they do suggest that patients that are already receiving a statin at the time of starting dialysis therapy should not have this discontinued. This recommendation is based on the SHARP trial in which 2141 patients with CKD started dialysis during the study period but were analysed in the non-dialysis group in which overall benefit was observed. Although these two explanations seem to be rather incongruous it reflects the very limited RCT evidence in this population. One possible explanation as to why patients on dialysis might only benefit from statin-based therapy if started before dialysis initiation might relate to the duration of treatment. All RCTs of statin treatment in dialysis patients have an approximately 5-year follow-up period. However, the exposure to risk is much longer. As such the Canadian Cardiovascular Society Guidelines for the Management of Dyslipidaemia suggest initiating treatment in patients on dialysis if they are likely to remain on dialysis for many years or likely to go on and receive a kidney transplant [16].

The KDIGO guideline advocates a rather cautious approach to statin dosing recommending reduction of the dose used if eGFR is <60 ml/min/1.73 m^2, based on the reduced renal excretion of some statins, high polypharmacy rates in patients with CKD and the doses of statins used in trials recruiting patients with CKD. This recommendation essentially means that high intensity statins (Table 6.2) should be avoided and is inconsistent with other guidelines that recommend large reductions in LDL-cholesterol of more than 50% in certain situations. Moderate intensity statin therapy is known to produce a mean reduction in LDL-cholesterol of about 30% (Table 6.2). Therefore, a significant proportion of patients will not experience a reduction in LDL-cholesterol of this magnitude, never mind the 50% reduction recommended in other guidelines. This is especially relevant in certain situations, including after an acute coronary syndrome. The TNT trial showed that after an acute coronary syndrome, patients with an eGFR 45–59 ml/min/1.73 m^2 gained substantial benefit from high dose atorvastatin treatment [17].

Before You Finish: Practice Pearls for the Clinician

- Patients with CKD are at high risk of cardiovascular disease with a high prevalence of both traditional and non-traditional cardiovascular risk factors.
- One of the traditional risk factors, dyslipidemia, is potentially modifiable. Abnormalities of lipid metabolism are evident even in the early stages of CKD and worsen with declining renal function.
- Statin and statin/ezetimibe combination treatment reduces the risk of atherosclerotic events in patients with CKD. The benefit lessens with declining kidney function and appears to be

lost in patients with ESKD on dialysis treatment.

- Several guidelines make important recommendations for treating dyslipidaemia in patients with CKD/ESKD and these are changing with the emergence of new evidence.
- Multiple novel lipid-lowering treatments are emerging, with PCSK9-inhibitors now being recommended for use by some guidelines when statin or statin/ezetimibe treatment are either not tolerated or unable to reach treatment goals.

Box 6.1 Conversion Factors

Variable	SI units	Conventional units	Conversion factor
Creatinine	μmol/L	mg/dL	88.4
Cholesterol	mmol/L	mg/dL	0.0259
Triglycerides	mmol/L	mg/dL	0.0113

Notes:

Conventional unit multiplied by conversion factor equals SI unit

Cholesterol includes total cholesterol, LDL-cholesterol, and HDL-cholesterol

Box 6.2 Relevant Guidelines

1. *KDIGO Guideline*

   Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:259-305.
2. *ACC/AHA Joint Guidelines*

   2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. Circulation 2019;139:e1082-e1143.
3. *ESC Guidelines*

   2019 ESC/EAS Guidelines for the management of dyslipidaemias;: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-188.

   2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-3337.
4. *Canadian Guideline*

   2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Can J Cardiol. 2016;32:1263-82.

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Hyperuricaemia and Chronic Kidney Disease

7

Julia Molly Jefferis, David Wayne Johnson, and Sunil Badve

Before You Start: Facts You Need to Know

- Urate is a by-product of purine metabolism and serum levels are increased in mammalian species, with proposed benefit as an anti-oxidant.
- Elevated serum urate concentrations (defined as >6.0 mg/dL [0.39 mmol/L]) are found in diabetes mellitus, hypertension, obesity, cardiovascular disease, and kidney disease.
- Urate-lowering treatment with xanthine oxidase inhibitors allopurinol and febuxostat have also been studied as potential protective effect in kidney disease.
- Several randomized control trials with small sample size, short duration of follow-up and inferior methodology, in populations with both normal and reduced kidney function found mixed results for and against urate-lowering therapy in preventing progressive decline in kidney function.
- Three large, well-designed randomized placebo-controlled trials with longer follow-up have provided moderate certainty evidence against the use of urate-lowering therapy to delay progression of kidney disease.

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- Patients with kidney disease are at greatly increased risk of cardiovascular disease, however, there is no clear evidence that urate-lowering therapy in chronic kidney disease improves cardiovascular outcomes.

7.1 Introduction

Urate is a by-product of human metabolic processes that has pathological roles in several disease processes including gout, tumour lysis syndrome, and uric acid urolithiasis. Multiple studies have linked elevated serum urate concentrations with chronic kidney disease (CKD), and urate-lowering therapy has been under investigation for some time as a possible intervention in CKD. This chapter will discuss normal urate metabolism, pathophysiological role of urate in humans, consider evidence from population level studies and randomized control trials (RCT) and management of hyperuricaemia in patients with CKD.

7.1.1 Normal Urate Metabolism

Liver, muscle and endothelial tissues catabolise purines, adenine and guanine to generate the end product of urate ($C_5H_4N_4O_3$). Catabolism involves complex enzymatic pathways with hydroxylation of hypoxanthine to xanthine and xanthine to urate by the enzyme, xanthine oxidase (XO), representing key steps in generating urate, as shown in Fig. 7.1 [1]. Urate is poorly water soluble, and conversion by uricase to allantoin enables easy excretion in the urine in non-mammalian species. Humans have lost the uricase enzyme during evolution, resulting in higher serum uric acid levels, although the evolutionary advantage of elevated urate is unclear. Proposed benefits of the loss of uricase activity include neutralising free radicals and protection from hypotension through its anti-natriuretic effect [2, 3]. In humans, excretion of urate is dependent on excretion by the gastrointestinal tract (30%) and kidney filtration (60–70%) [4]. Furthermore, purine intake is increased in Western diets and is proposed to contribute to elevated levels of serum urate levels in populations consuming more westernized diets [3]. At the level of the nephron, urate filters freely through the glomerulus to be reabsorbed by urate anion transporter 1 (URAT1) and the organic anion transporter (OAT) in the proximal tubule, with proximal tubular excretion also playing a role in urate balance [5]. Multiple transporters can use urate as a substrate, with URAT1 being the predominant apical transporter, and glucose transporter-like protein 9 (GLUT9) being the predominant basal transporter. Humans with the loss of function mutations in GLUT9 are hypouricaemic [6]. Urate levels are markedly elevated in kidney disease as a result of reduced clearance by the kidney due to lower levels of filtration and secretion.

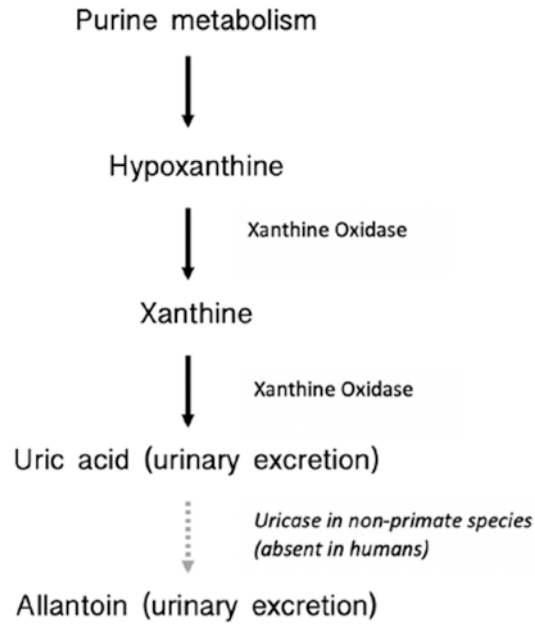

Fig. 7.1 Enzymatic pathways of uric acid metabolism: Purine metabolism with the enzyme xanthine oxidase generates uric acid, which is predominantly excreted in urine. Humans are deficient in uricase and are unable to generate water soluble allantoin, predisposing to hyperuricaemia [1]

7.1.2 Pathophysiology of Urate

There are many postulated mechanisms by which urate causes CKD including endothelial dysfunction, activation of the renin angiotensin system, activation of the inflammasome, oxidative stress, and crystal deposition and calculi formation as shown in Fig. 7.2 [7–10]. Preclinical studies show that uric acid may play a pathogenic role in kidney disease and cardiovascular disease. Rats fed with the uricase inhibitor, oxonic acid, became hyperuricaemic and their kidney exhibited arteriole thickening, renal cortical vasoconstriction, and glomerular hypertension. Treatment with allopurinol ameliorated these changes [8]. Other preclinical studies showed that experimentally-induced hyperuricaemia led to the development of hypertension with the loss of endothelial nitric oxide, rise in renin secretion from the juxtaglomerular apparatus and increased tubulointerstitial fibrosis. Treatment with allopurinol mitigated these effects [9]. Urate has been shown to upregulate inflammatory markers including IL-1β through the NALP3 inflammasome in vitro and increase NF-Kß signalling and increase in the levels of IL-1B, IL-18, MCP-1 [11–13]. Human studies show that uric acid stones are associated with an increased risk of CKD [14]. These studies suggest that urate may be a therapeutic target for slowing the progression of CKD.

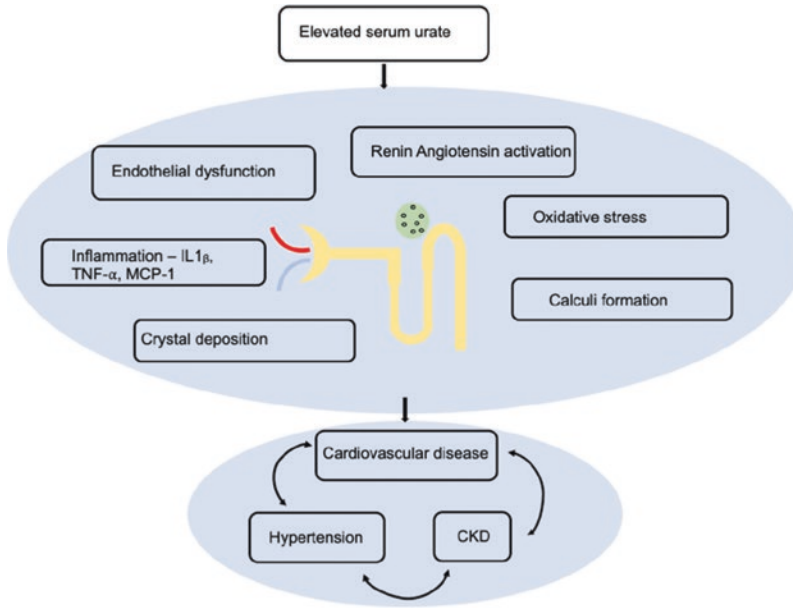

Fig. 7.2 Proposed mechanisms of hyperuricaemia in cardiovascular and chronic kidney disease: Elevated levels of serum urate have multiple postulated deleterious effects in the kidney, causing endothelial dysfunction, activation of the renin angiotensin system and ensuing glomerular hypertension, inflammation mediated by interleukin 1B (IL1β), tumour necrosis factor alpha, (TNF-α) and monocyte chemoattractant protein 1 (MCP-1), oxidative stress, crystal deposition and formation of uric acid stones [2, 7–10]. This damage to the kidney can drive hypertension and cardiovascular disease, which further promotes kidney dysfunction

7.2 Population Level Evidence Linking Serum Urate Levels to Disease in Humans

Population level studies have found relationships between elevated serum urate concentrations, considered when serum urate >6.0 g/dL [0.36 mmol/L] and a host of metabolic diseases including diabetes mellitus, hypertension, obesity, cardiovascular disease, and kidney disease [15, 16]. In a meta-analysis of 18 prospective cohort studies with 55,607 patients, elevated serum urate was associated with an increased risk (relative risk 1.41, 95% CI 1.23–1.58) of hypertension, with 1 g/dL increase in serum urate associated with a relative risk of 1.13 (95% CI 1.06–1.58) which was more pronounced in younger patients and females [17]. Another meta-analysis of 32,016 patients identified a relationship between hyperuricaemia and diabetes mellitus with a relative risk of 1.56 (95% CI 1.39–1.76) for those in the highest quartile of serum urate levels [18]. Meta-analysis of 13 studies with 190,718 patients found hyperuricaemia was an independent predictor of new diagnosis of CKD in men and women with an odds ratio of 2.35 (95% CI 1.59–3.46) for those in the highest quartile of serum urate [19]. Several studies have found that elevations in serum urate precede diagnosis of CKD, such that early intervention to lower urate has been proposed to modulate disease progression. Secondary analysis of the retrospective "Coronary Artery Calcification in Type 1 Diabetes" study found that, in patients with type 1 diabetes for an average duration of 23 years followed over a 6-year period, each 1 mg/dL rise in serum urate level was associated with an 80% increased risk of micro- or macroalbuminuria [20]. Another study which followed patients with type 1 diabetes over a median of 18 years found that elevated serum urate preceded development of albuminuria [21]. High-normal urate levels have also been associated with reduced estimated glomerular filtration rate (eGFR) prior to development of proteinuria in those with type 1 diabetes mellitus [22]. Multiple prospective studies have independently associated hyperuricaemia with disease progression in IgA nephropathy [23–25]. Taken together, these studies were hypothesis-generating and provided equipoise to evaluate the effect of urate-lowering treatment on slowing the progression of kidney disease.

7.3 Urate-Lowering Therapy to Modify CKD

Multiple, single centre randomized trials have investigated the effects of urate-lowering therapy on kidney function in a range of patient groups including healthy populations and patient groups with gout, type 1 diabetes mellitus or immunoglobulin A (IgA) nephropathy summarized in Table 7.1. In one study, 72 healthy hyperuricaemic patients with elevated serum urate levels and preserved kidney function (eGFR 84.3–92.8 mL/min per 1.73 m^2) with minimal proteinuria (urine protein:creatinine ratio [PCR] 0.11–0.12 mg/mmol) were randomized to either 300 mg allopurinol daily or no study medication for 16 weeks. Compared with hyperuricaemic controls who maintained stable eGFR, allopurinol resulted in lower serum urate, improved eGFR, improved diastolic blood pressure, and reduced endothelial dysfunction, but no change in proteinuria. These patients had minimal medical comorbidities, normal blood pressure, and a low risk of progressive kidney disease [26]. These patient characteristics, together with the short follow-up duration and open labelled design, limited the strength of conclusions that could be drawn. Another randomized study in 59 patients with gout, 98% male, compared colchicine 0.5 mg twice daily only, or with 200 mg of allopurinol for 2 years, found that eGFR was maintained in the allopurinol group, but declined in the colchicine group. These patients had preserved kidney function with initial eGFR was >90 mL/min per 1.73 m^2 and minimal proteinuria, and as such did not progress to CKD (eGFR <60 mL/min per 1.73 m^2) [27]. A RCT with 54 hyperuricaemic patients with CKD comparing 100–300 mg daily allopurinol in addition to standard care found that improvement in urate levels was associated with preserved kidney function at 12 months, with no effect on serum creatinine or blood pressures

Table 7.1 Summary of single centre randomized controlled trials investigating the effect of urate-lowering therapy on kidney function

Study	Number of patients	Population	Baseline serum urate (mg/dL)	Baseline eGFR mL/min per 1.73 m^2	Control	Intervention	Follow up duration (months)	Kidney outcome	Limitations
Kanbay et al. 2011 [16]	72	Asymptomatic hyperuricaemia with no history of gout	Control: 7.9 ± 0.7 Allopurinol: 8.3 ± 1.1	Control: 84.3 ± 16.7 allopurinol: 86.3 ± 19.4	No study medication	Allopurinol 300 mg daily	4	Increase in eGFR in allopurinol group, stable eGFR in control ($p = 0.001$)	Lack of blinding, no placebo, short follow up duration, preserved kidney function
Gibson et al. 1982 [27]	59	Gout with at least one flare of arthritis in past 12 months	Colchicine: 6.39 ± 0.01 Colchicine and allopurinol: 6.72 ± 0.12	Colchicine: 98 ± 17 Colchicine and allopurinol: 90 ± 24	Colchicine 0.5 mg twice daily alone	Colchicine 0.5 mg twice daily with allopurinol 20 0 mg daily	24	Allopurinol reduced decline in eGFR: 37% colchicine only group had >10% decline in eGFR at 24 months compared to 9% of allopurinol and colchicine treated groups	Small sample size, preserved eGFR
Siu et al. 2005 [28]	54	Hyperuricaemic patients with CKD	Control: 9.92 ± 1.68 Allopurinol: 9.75 ± 1.18	Mean serum creatinine control:145 µmol/L Mean serum creatinine allopurinol: 164 µmol/L	No study medication	100 to 300 mg allopurinol	12	Kidney outcome of 40% increase in creatinine or dialysis dependence 46.1% of control group and 16% of allopurinol treated group ($p = 0.015$)	Small sample size, use of creatinine rather than eGFR

(continued)

Table 7.1 (continued)

Study	Number of patients	Population	Baseline serum urate (mg/dL)	Baseline eGFR mL/min per 1.73 m^2	Control	Intervention	Follow up duration (months)	Kidney outcome	Limitations
Goicoechea et al. 2010 [29]	113	Chronic kidney disease with eGFR <60 mL/min per 1.73 m^2	Control: 7.3 ± 1.6 Allopurinol: 7.9 ± 2.1	Control: 39.5 ± 12.4 Allopurinol: 40.6 ± 11.3	No study medication	Allopurinol 100 mg daily	24	Kidney function at 24 months found that control group eGFR decreased 3.3 ± 1.2 mL/min per 1.73 m^2, where allopurinol treated eGFR increased 1.3 ± 1.3 mL/min per 1.73 m^2 ($P = 0.018$)	Lack of placebo, not double blinded
Momeni et al. 2010 [30]	40	Type 2 diabetes mellitus with diabetic nephropathy (proteinuria of 500 mg/24 h and creatinine <265.25 μmol/L)	Placebo: 5.96 ± 1.21 Allopurinol: 6.50 ± 2.20	Serum creatinine: Placebo: 1.3 ± 0.45 mg/dL Allopurinol: 1.5 ± 0.6 mg/dL	Placebo	Allopurinol 100 mg daily	4	No difference in creatinine between groups at 4 months, however allopurinol treated group had significant lower urine protein compared with control ($P = 0.049$)	Short follow up duration, small population
Shi et al. 2012 [25]	40	Hyperuricaemic patients (uric acid >6 mg/dL in women and > 7 mg/dL in men) with IgA nephropathy and proteinuria between 0.15–2 g in 24 h	Placebo: 7.98 ± 1.1 Allopurinol: 7.88 ± 1.1	Control: 69.5 ± 26.5 Allopurinol: 63.8 ± 27.5	No medication therapy	Allopurinol 100–300 mg daily	6	Kidney outcomes of eGFR and proteinuria were no different between groups, noted reduction in anti-hypertensive dosage in those treated with allopurinol	Small population, short follow up duration
Beddhu et al. 2016 [32]	80	Type 2 diabetes mellitus with hyperuricaemia, eGFR 30–60 and proteinuria (1+ dipstick or urine albumin/creatinine ratio > 3.4 mg/mmol)	7.16 ± 1.4	53.5 ± 17.2	Placebo	Febuxostat 80 mg daily	6	Both placebo and intervention had mean eGFR declined by ~3 mL/min/1.73 m^2 over 6 months	Short follow up duration

Mukri et al. 2018 [33]	93	CKD stage 3 and 4 patients with diabetic nephropathy and asymptomatic hyperuricaemia	Control: 9.03 ± 1.19 Febuxostat: 9.07 ± 1.75	Control: 26.2 ± 14.3 Febuxostat: 28.2 ± 19.8	No medication therapy	Febuxostat 40 mg daily	6	The eGFR was stable over 6 months in Febuxostat treated group (26.2 mL/min/1.73 m^2 at baseline to 26.3 mL/min/1.73 m^2) but declined in the control group eGFR 28.2 mL/min/1.73 m^2 to 27.6 mL/min/1.73 m^2 (p value <0.01). There was no difference in eGFR between control and febuxostat at 6 months	Short follow up duration, open label
Yu et al. 2018 [34]	73	Hyperuricaemia with CKD (eGFR 20–60 mL/min/1.73 m^2)	Benzbromarone 8.87 (8.17–9.94) Febuxostat: 9.61 ± 1.86	Median eGFR benzbromarone: 41.2 (29.9–49.1) Febuxostat: 38.5 ± 13.1	Benzbromarone started at 25 mg daily, uptitrated to 100 mg daily	Febuxostat 20 mg daily uptitrated to 80 mg daily	12	No difference in eGFR after 12 months of treatment between groups	Open label, not blinded

Data are expressed as mean ± SD or median with 95% confidence interval

between the two groups [28]. Another randomized study in 113 CKD patients with eGFR <60 mL/min per 1.73 m^2 compared 100 mg daily allopurinol with no study medication. Allopurinol therapy stabilized kidney function, whereas standard care alone resulted in a decline in eGFR, independent of blood pressure, diabetes status, and use of RAS blockade. Cardiovascular outcomes, combined outcome of ischemic heart disease, congestive cardiac failure, cerebrovascular disease, and peripheral arterial disease, were reduced in those treated with allopurinol therapy. There was no difference in blood pressure after treatment between the two groups [29]. An Iranian study compared allopurinol (100 mg daily) with placebo in 40 patients at high risk of progressive CKD with type 2 diabetes, 24-h urine protein >500 mg and evidence of diabetic retinopathy on RAS blockade. After 4 months, treatment with allopurinol significantly reduced proteinuria compared with the placebo group but did not significantly alter kidney function or blood pressure [30]. On the other hand, a randomized controlled trial of 100–300 mg daily allopurinol versus no treatment over 5 years in 40 hyperuricaemic patients with IgA nephropathy not on RAS blockade did not observe improvements in either eGFR or proteinuria, although those treated with allopurinol required reduced dosage of anti-hypertensive medications [25]. A systematic review and meta-analysis of these trials published in 2014 was unable to determine a clear relationship between improvement in serum urate levels and clinically relevant outcomes including progression of CKD, hypertension, and cardiovascular outcomes [31]. Overall, these earlier studies across a heterogenous spectrum of kidney disease identified that allopurinol treatment significantly lowered serum urate but could neither support nor refute a role for this agent in preventing CKD progression due to study imprecision, inconsistency and high or unclear risks of bias. Limitations of these randomized studies included small sample size, short follow-up periods, lack of blinding, and patient populations at low risk of progressive kidney disease.

Several subsequent RCTs have also investigated the role of febuxostat, a xanthine oxidase inhibitor, in CKD progression. One RCT involving 80 patients with type 2 diabetes mellitus and an eGFR between 30 and 60 mL/min per 1.73 m^2 compared 80 mg daily febuxostat with placebo and found febuxostat lowered serum urate but did not significantly alter urinary biomarkers of kidney fibrosis, eGFR or blood pressure [32]. A single centre open label trial comparing 40 mg daily febuxostat with placebo in people with stage 3 or 4 diabetic kidney disease and well controlled diabetes (HbA1c <8%) showed no difference in eGFR or proteinuria at 6 months of therapy, though notably the febuxostat group had a higher baseline HbA1c, and this paradoxically increased at the end of the study period [33]. A small trial involving 66 patients with CKD found that eGFR was sustained after 12 months of 20 mg titrated up to 80 mg daily febuxostat therapy [34]. Together, these trials found that use of febuxostat in patients with CKD lowered serum urate levels with no significant clinical impact on CKD.

Publication of three large, multi-centre RCTs has greatly helped to clarify the role of urate-lowering therapy in patients with CKD, summarized in Table 7.2. The first of these was the FEbuxostat versus placebo rAndomized controlled trial regarding reduced renal function in patients with hyperuricaemia complicated by chronic kidney disease stage 3 (FEATHER) [35]. This was a multi-centre, double-blind RCT of febuxostat (10 mg daily increasing at monthly intervals up to 40 mg daily) versus placebo in 443 adults with stage 3 CKD treated in 55 Japanese centres over 108 weeks. Inclusion criteria were patients aged over 20 years with hyperuricaemia (serum urate concentration > 7.0–10.0 mg/dL), stage 3 CKD, and no history of gout. Patients with poorly controlled diabetes mellitus (HbA1c >8.4%) or hypertension (systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg), elevated alanine or aspartate aminotransferase enzyme levels, >50% variation in creatinine 12 weeks preceding the study and kidney failure or kidney transplant were excluded. Baseline characteristics of the placebo group were aged 65.4 year, 77% male, 30.6% with diabetes mellitus, 73.4% on ACE inhibitor or angiotensin receptor blocker [ARB], mean serum urate

Table 7.2 Summary of multi-centre randomized controlled trials investigating the effect of urate-lowering therapy on kidney function

Study	Kimura et al. 2018 (FEATHER investigators) [35]	Doria et al. 2020 (PERL investigators) [36]	Badve et al. 2020 (CKD-FIX investigators) [37]
Number of patients	467	530	369
Location	Japan	The United States, Canada and Denmark	Australia and New Zealand
Population	Stage 3 CKD and asymptomatic hyperuricaemia in Japan	Type 1 diabetes mellitus an eGFR value between 40 and 99 mL/min per 1.73 m^2, with either albuminuria (urinary albumin excretion rate, 20 to 3333 μg per min) or a decline in the GFR of >3 mL per min per 1.73 m^2 per year in the previous 3 to 5 years, and a serum urate level of at least 4.5 mg/dL	Stage 3 or 4 CKD without gout, ACR > 265 mg/g or 3 mL/min per 1.73 m^2
History of gout	Excluded	Excluded	Excluded
Baseline serum urate (mg/dL)	Placebo: 7.8 ± 0.9 Febuxostat: 7.8 ± 0.9	6.1 ± 1.5	8.2 ± 1.8
Baseline eGFR mL/min per 1.73 m^2	Placebo: 44.9 ± 9.7 Febuxostat: 45.2 ± 9.5	74.7 ± 19.1	31.7 ± 12.0
Baseline albuminuria μg/min	Placebo: 120.5 (17.2–517.0) Febuxostat: 124.0 (19.1–525.0)	41.6 (8.5–207.5)	716.9 (244.3–1857)
Control	Placebo	Placebo	Placebo
Intervention	Febuxostat 10 mg uptitrated to 40 mg daily	Allopurinol 100–300 mg daily	Allopurinol 100–300 mg daily
Follow up duration (months)	27	36	26
Kidney outcomes	No difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m^2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; $P = 0.1$)	No difference for primary outcome of mean iohexol-based GFR adjusted for baseline values (mean between-group difference 0.001 mL/min per 1.73m^2, 95% CI -1.9–1.9)	No difference between groups in primary outcome of slope of eGFR decline ($P = 0.85$)
Limitations	Stable kidney function in both groups, low risk of progression	Higher baseline eGFR and lower serum urate levels	Did not meet target recruitment

Data are expressed as mean ± SD or median with 95% confidence interval, or median and interquartile range for non-normally distributed data

7.8 mg/dL, eGFR of 44.9 mL/min per 1.73 m^2 with median urinary albumin-to-creatinine ratio [UACR] 120.5 mg/g. The febuxostat treatment group were similar with mean age 65.3 years, 77.6% male, 29.2% with diabetes mellitus, 82.6% on ACE or ARB, serum urate 7.8 mg/dL, eGFR 45.2 mL/min per 1.73 m^2 and median UACR 124 mg/g. Patients were followed for 108 weeks. Mean serum urate level in the febuxostat group decreased significantly by 12 weeks to 4.2 mg/dL and remained at that level thereafter. Compared with placebo, febuxostat did not significantly affect the primary outcome of mean difference in slope of eGFR (0.70 mL/min per 1.73 m^2/year, 95% CI -0.21–1.62), estimated according to the *Japanese Society of Nephrology*

Chronic Kidney Disease Initiative (JSN-CKDI eGFR) equation. Subgroup analysis identified that those without proteinuria and those with serum creatinine concentrations below the median population value had significantly lower slopes of eGFR decline, although in the absence of a convincing explanation for physiological differences for response to urate-lowering therapy, subgroup analysis should not be overinterpreted. A key limitation of FEATHER was the stability of kidney function in this Japanese population over 2 years, with a decline in eGFR of only 0.47 ± 4.48 mL/min per 1.73 m^2 in the placebo group, indicating inclusion of a cohort at low risk of CKD progression [35].

The Preventing Early Renal Loss in diabetes (PERL) trial [36], included 530 patients with type 1 diabetes for more than 8 years, aged 18–70 years with an eGFR value between 40 and 99 mL/min per 1.73 m^2, with either albuminuria (urinary albumin excretion rate, 20 to 3333 μg/min) or a decline in the GFR of >3 mL per min per 1.73 m^2 per year in the previous 3–5 years, and a serum urate level of at least 4.5 mg/dL. Exclusion criteria included a history of gout, recurrent kidneys stones, prior treatment with urate-lowering therapy, kidney transplantation, use of medications which interact with allopurinol, HLA-B*5801 positivity, non-diabetic kidney disease or poorly controlled hypertension. Patients were randomly assigned to either allopurinol (100–300 mg daily) or placebo for 3 years. This trial included a run-in phase with optimization of blood pressure targeting <140/90 mmHg and implementation and optimization of renin angiotensin system (RAS) blockade. Baseline characteristics were similar between the two groups with mean age 51.1 years, 66.2% male, a mean creatinine-based eGFR of 74.7 mL/min per 1.73 m^2, UACR 41.6 μg/min, mean HbA1c of 8.2%, mean blood pressure of 126/71 mmHg, 90% use of RAS blockade and a mean duration of diabetes of 34.6 years. Compared with placebo, allopurinol significantly reduced serum urate from 6.1 mg/dL to 3.9 mg/dL but did not significantly affect the primary outcome of mean iohexol-based GFR adjusted for baseline values (mean between-group difference 0.001 mL/min per 1.73 m^2, 95% CI -1.9–1.9). PERL was powered to detect a 1 mL/min per 1.73 m^2 per year decline in eGFR. No differences were observed in pre-specified subgroup analyses for age, race, serum urate, HbA1c, and proteinuria. Serious adverse events were similar between the placebo and allopurinol groups, with 33% of patients reporting adverse events with 1.4% skin and subcutaneous disorders.

The Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase (CKD-FIX) investigated the effect of allopurinol (100–300 mg daily) versus placebo in 369 adult patients with stage 3 or 4 CKD with no history of gout who were at risk of CKD progression (urinary albumin:creatinine ratio [UACR] >265 mg/g or eGFR decrease ≥3 mL/min per 1.73 m^2 in the preceding 12 months) [37]. Exclusion criteria included a history of gout, allopurinol hypersensitivity, clinical indication for allopurinol, and unresolved acute kidney injury in preceding 3 months. The baseline population had an eGFR of 31.7 mL mL/min per 1.73 m^2, serum urate of 8.2 mg/dL, UACR of 716.9 mg/g, mean age of 62.4 years, blood pressure 139.3/76.1 mmHg, 45% diabetic kidney disease, 58% diabetics with 76% on ACE inhibitor or ARB therapy. Allopurinol was up titrated in increments of 100 mg daily each month to a maximum daily dose of 300 mg, independent of serum urate levels. Despite a sustained mean reduction in serum urate levels of 35% over the 2-year study period, allopurinol did not significantly affect the primary outcome of change in eGFR slope (mean difference − 0.10 mL/min/1.73 m^2, 95% CI -1.18–0.97, $p = 0.85$). No subgroups were identified in which allopurinol had a beneficial effect on the primary outcome, and the effect of allopurinol did not differ between tertiles of serum urate concentration. The secondary outcome of 40% decrease in eGFR, kidney failure or death occurred in 35% of the allopurinol treated group and 28% of the placebo group, which was not statistically different. There was no difference in UACR, systolic blood pressure, diastolic blood pressure or health related quality of life. Serious adverse events 0ccured in 45% of patients, with no difference between the groups, including rash. Only 17% of

person-years of treatment time was lost during the study. Although the trial did not meet its original recruitment target of 620 patients, a posthoc futility analysis demonstrated that, had the target been met, the conditional power to detect the prespecified clinically meaningful difference of 0.6 mL/min/1.73 m^2 would have only been 1 in 1000.

A systematic review and meta-analysis of 28 RCTs (including FEATHER, PERL, and CKD-FIX) involving 266 kidney failure events in 3087 patients found that urate-lowering therapy did not reduce the incidence of kidney failure (RR 0.97, 95% CI 0.61–1.54) [38]. However, urate-lowering therapy did attenuate the slope of eGFR decline compared with control by 1.18 mL/min per 1.73 m^2 (95% CI 0.44–1.91), which was primarily driven by trials with short follow-up and low quality [38].

In summary, when one considers the evidence collectively and particularly focuses on the three large, well-designed RCTs (FEATHER, PERL, and CKD-FIX), there is moderate certainty evidence that urate-lowering therapy does not prevent progression of CKD to kidney failure [35–37]. In all three trials, treatment with urate-lowering therapy resulted in large and sustained reductions in serum urate levels, suggesting that lowering urate across a spectrum of baseline serum urate levels does not impact decline in kidney function. These studies included patients with a wide range of kidney function, with baseline eGFR between 15 and 99.9 mL/min per 1.73 m^2, and a wide range of proteinuria, with no benefit of urate-lowering therapy on kidney function across this spectrum of kidney disease. The risk of progression of CKD was highest in CKD-FIX, followed by PERL, with moderate risk of progression in FEATHER, suggesting that urate-lowering therapy was ineffective in patients with moderate to very high risk of disease progression. The proportion of patients with diabetes varied across the studies: the PERL population included only high risk type 1 diabetics, the CKD-FIX population included 58% with diabetes, and the FEATHER population included 30% with diabetes. Urate-lowering therapy had no effect on kidney function in patients with diabetic kidney disease. All three trials excluded patients with preexisting history of gout, such that these results cannot be extrapolated to those with CKD and gout. A lower incidence of gout was seen with use of Febuxostat 0.9% compared to placebo 5.9% in FEATHER ($P = 0.007$), but this trend was not seen in PERL or CKD-FIX, which had low incidences of gout in both placebo and control groups. The finding that febuxostat treatment reduced gout was only seen in FEATHER, is limited by the small number of events as this study was under powered for this outcome. Importantly, combined analysis of CKD-FIX and PERL suggested higher mortality associated with allopurinol (4.7%) compared to placebo (2.2%), with a relative risk of 2.07 (95% CI 0.98–4.34, $P = 0.06$) although numbers in this exploratory analysis are small and should be interpreted with caution [39]. Urate-lowering therapy is therefore not recommended to treat elevated serum urate levels in asymptomatic patients with CKD. These studies have changed clinical practice and have been incorporated into the Caring for Australians and new zealandeRs with kIdney disease (CARI) living guidelines (Box 7.1) [40].

Box 7.1 Relevant Clinical Guidelines

1. Caring for Australians and New Zealanders with Kidney Impairment (CARI) Guidelines. Urate-lowering therapy for people with chronic kidney disease. Available at: https://app.magicapp.org/#/guideline/LqR80n
2. 2020 American College of Rheumatology Guideline for the Management of Gout. Available at: https://pubmed.ncbi.nlm.nih.gov/32391934/

Targeting serum urate levels with the xanthine oxidase inhibitors, febuxostat, and allopurinol, has proved ineffective in CKD, although lowering urate through other mechanisms may be beneficial in CKD. A posthoc analysis of the "Canagliflozin Cardiovascular Assessment Study Program" (CANVAS) noted a 6.7% reduction in serum urate and lower incidence of gout in the canagliflozin treatment group, with evidence from

in vitro studies showing sodium-glucose cotransporter-2 (SGLT2) inhibitors altered glucose handling in the nephron with increased glucose increasing urate transport [41, 42]. The clinical significance of urate-lowering therapy on CKD in the era of SGTL2 therapy warrants further investigation. Verinurad, a novel GLUT1 inhibitor, which mediates urate reabsorption in the nephron, is being investigated in conjunction with febuxostat for effects on kidney function. A pilot randomized control trial in 60 patient with type 2 diabetes, eGFR >30 mL/min per 1.73 m^2, hyperuricaemia (urate >6.0 mg/dL) and albuminuria (UACR 50–3500 mg/g) compared 80 mg febuxostat and 9 mg verinurad with placebo, and found that after 12 weeks there was improvement in albuminuria, with no effect on kidney function [43]. A small-randomized crossover trial in adults with asymptomatic hyperuricaemia and eGFR >45 mL/min per 1.73 m^2 compared 80 mg febuxostat, 9 mg verinurad and placebo to 80 mg febuxostat, 9 mg verinurad, and 10 mg dapagliflozin for 1 week, and found that dapagliflozin lowered urate levels with a tolerable safety profile [44]. Currently, a randomized placebo-controlled Study of verinurAd and alloPurinol in Patients with cHronic kIdney disease and hyperuRicaEmia (SAPPHIRED) has recruited 860 patients with eGFR >25 mL/min per 1.73 m^2, hyperuricaemia (urate >6.0 mg/dL) and albuminuria (UACR 30–5000 mg/g), comparing dosing regimens of verinurad and allopurinol with allopurinol and placebo with the primary end point of change in albuminuria at 6 months [45]. Furthermore, large-scale trials are required to understand the role of these novel urate-lowering agents in CKD.

Key Practice recommendations

1. Recommendation against use of urate-lowering therapy in people with chronic kidney disease (not receiving dialysis) and asymptomatic hyperuricaemia (strong recommendation).
2. Patient with chronic kidney disease and gout should receive appropriate urate-lowering therapy.

7.4 Cardiovascular Risk, CKD, and Urate-Lowering Therapy

CKD is associated with both elevated serum urate concentrations and a greatly increased risk of cardiovascular disease [46]. In a meta-analysis of 11,050 patients with CKD, those with the higher serum urate were increased risk of cardiovascular mortality with a hazard ratio of 1.47 (95% CI 1.11–1.96) [47]. There is some evidence that higher serum urate levels may independently contribute to heightened cardiovascular risk as a result of endothelial dysfunction, renin angiotensin activation, inflammation, and oxidative stress [16]. Although there are no large-scale randomized trials specifically investigating the effect of urate-lowering therapy on cardiovascular outcomes in CKD populations, a systematic review and meta-analysis of 15 RCTs involving 5327 patients and 506 major adverse cardiovascular events (MACE) reported that urate-lowering therapy did not reduce the risk of MACE compared with no treatment or placebo (RR 0.93, 95% CI 0.74–1.18, I^2 = 33%) [38].

Studies of urate-lowering therapy in high cardiovascular risk groups have also generally not shown a reduction in cardiovascular events. In the "Cardiovascular Safety of Febuxostat and Allopurinol in the patients with gout and Cardiovascular co-morbidities" (CARES) trial, 6190 patients with gout and cardiovascular disease, of whom 46% had stage 3 CKD, were randomly allocated to febuxostat (40–80 mg daily) or allopurinol (300–600 mg daily if eGFR >60 mL/min/1.73 m^2; 200–400 mg daily if eGFR 30–60 mL/min/1.73 m^2) for a median period of 32 months [48]. This study demonstrated that febuxostat was non-inferior to allopurinol for the primary composite end point of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or unstable angina with urgent revascularization (hazard ratio [HR] 1.03, upper 95% limit 1.23 with pre-specified non-inferiority margin of 1.3, p = 0.002) but did increase the risks of the secondary end points of cardiovascular mortality (HR 1.34, 95% CI 1.03–1.73). Subgroup analysis noted an interaction between non-steroidal anti-inflammatory drug (NSAID) use and absence of

aspirin with increased cardiovascular mortality. Further analysis in the stage 3 CKD population showed that 93 patients treated with febuxostat and 78 treated with allopurinol experienced cardiovascular mortality, although this may have represented higher pre-existing cardiovascular comorbidity [49].

The "Febuxostat for Cerebral and Cardiorenovascular events prevention study" (FREED) trial was a large multi-centre RCT of 1084 people in Japan, comparing the effects of febuxostat versus allopurinol on the combined primary end point of fatal, non-fatal cerebral, cardiovascular and kidney events. The population was aged over 65 years with elevated serum urate and at least one other risk factor for cardiovascular disease; 37% had diabetes mellitus and 66% of the population had underlying kidney disease, with a mean eGFR of 55 mL/min per 1.73 m^2. After 3 years of treatment, the combined primary end point was lower in the febuxostat treated group with a hazard ratio of 0.75 (95% CI 0.59–0.95). The secondary end points of death due to cerebral, cardiovascular or kidney disease, non-fatal coronary artery disease, heart failure requiring hospitalizations, atherosclerotic disease requiring treatment and atrial fibrillation were no different between groups. "Kidney impairment," defined as development of microalbuminuria, mild proteinuria, progression to overt albuminuria (>300 mg/g) or worsening of over albuminuria, doubling of serum creatinine or progression to kidney failure, was significantly less in the febuxostat lowering group with a hazard ratio of 0.75 (95% CI 0.56–0.99). The FREED study was unable to inform on the effect of febuxostat on progression of CKD, as measured by eGFR. In this population, 66% of which had underlying CKD, there was no difference in cardiovascular mortality between allopurinol and febuxostat [50].

The "long term cardiovascular safety of febuxostat compared with allopurinol in patients with gout" (FAST) trial investigated the use of allopurinol vs. febuxostat on cardiovascular outcomes in patients with gout and at least one cardiovascular risk factor. Median age in the study was 71 years, with a predominantly male (85.3%) population, of whom only 16.1% had kidney disease, 22.5% had diabetes mellitus and 40.2% received RAS blockade. The study reported no difference in the primary outcome of hospitalization for non-fatal myocardial infarction or biomarker positive acute coronary syndrome, non-fatal stroke (in hospital or occurring during hospitalization), or death due to a cardiovascular event. In the intention to treat analysis, all-cause death was non-inferior in the febuxostat group compared with the allopurinol group [51]. In contrast to the CARES study, FAST did not find an increased hazard of cardiovascular mortality with febuxostat, which may have been explained by the fact that CARES specifically included patients with pre-existing cardiovascular morbidity and differences in methodology including initial run-in phase with allopurinol. The low level of kidney disease, and relatively low uptake of RAS blockade limited its generalisability to the CKD population.

In summary, there are no adequately powered, randomized placebo-controlled trials assessing cardiovascular outcomes in specifically targeting patients with CKD treated with urate-lowering therapy. Combined analysis of CKD-FIX and PERL suggests Allopurinol therapy may be associated with increased mortality. Extrapolation from FREED, CARES and FAST does not reveal any difference in major adverse cardiovascular events between allopurinol and febuxostat in populations of patients at heightened cardiovascular risk that included reasonable numbers of patients with CKD. Based on the secondary findings of the CARES study, febuxostat should be avoided in patients with pre-existing cardiovascular disease and CKD because it may be associated with increased cardiovascular mortality.

7.5 Urate-Lowering Therapy in Gout and CKD

Gout is highly prevalent in patients with CKD and treatment with urate-lowering therapies has been shown to reduce the incidence of gout in CKD. In the FEATHER trial, febuxostat significantly reduced the incidence of gouty arthritis

compared with placebo over 108 weeks (0.9% vs. 5.9%, respectively, $p = 0.007$). Whilst urate-lowering therapy is not indicated in patients with CKD and asymptomatic hyperuricaemia, the American College of Rheumatology 2020 guidelines recommend initiating urate-lowering therapy after the first flare of gouty arthritis in patients with CKD, due to high risk for recurrence and development of tophi [52]. Urate-lowering therapy is also recommended for patients with urolithiasis to reduce stone events. The Hande guidelines from 1984 recommended lower starting doses of allopurinol in patients with reduced kidney function to reduce the risk of toxicity syndromes [53]. This has led to suboptimal control of hyperuricaemia in patients with CKD. Further studies have shown that starting allopurinol at a low dose (50–100 mg daily) with subsequent up titration by 50–100 mg each month to achieve serum urate targets, resulted in better control of serum urate, without a significant increase in adverse effects [54, 55]. CKD-FIX demonstrated that patients with stage 3 and 4 CKD could tolerate up to 300 mg allopurinol daily with reduction in serum urate and tolerable safety profile [37]. Strict adherence to the Hande guidelines results in suboptimal control of hyperuricemia, with data supporting use of higher dosing to achieve effective urate levels safely. For allopurinol, the risk of adverse reactions is reduced by initiating therapy at a low dose (100 mg daily or less) and up-titrating the dose by 100 mg daily every 4 weeks or more to achieve a target serum urate level of 0.36 mmol/L or less (or 0.30 mmol/L or less if tophi are present) [56]. HLA-B*5801 screening should be considered in Asian (particularly Han Chinese) patients prior to initiating allopurinol therapy as the allele is a genetic marker for patients at greatly increased risk of severe hypersensitivity syndromes. Alternatively, febuxostat can be initiated at a dose of 40 mg daily or less and uptitrated as necessary up to 80 mg daily. Febuxostat should be avoided in patients who have a history of cardiovascular disease or who develop cardiovascular disease. As there is an increased risk of precipitating gout following initiation of urate-lowering therapy, consideration should be given to co-prescribing anti-inflammatory prophylaxis (colchicine or prednisolone) in the early period following initiation of urate-lowering therapy.

The angiotensin receptor blocker, losartan, has a unique ability to induce uricosuria by blockade of URAT1 in hypertensive patients and can be a useful adjunct to urate-lowering therapy, although has not been formally tested in clinical trials as a urate-lowering therapy [57].

7.6 Conclusions

Elevated urate levels are associated with CKD onset and progression in multiple observational cohort studies. However, moderate certainty evidence from well-designed randomized control trials has found that urate-lowering therapy does not prevent CKD progression. Therefore, asymptomatic hyperuricaemia does not require urate-lowering treatment in people with CKD. Currently, there is insufficient evidence to inform whether urate-lowering therapy affects cardiovascular risk in people CKD, although febuxostat should be avoided in those with pre-existing cardiovascular disease. Patients with urate crystal disease, including nephropathy and gout, should receive urate-lowering treatment. Generally, allopurinol is well tolerated in CKD groups if dosing is started low and gradually up titrated.

Before You Finish: Practice Points for the Busy Clinician

- Elevated urate is associated with gout and urate nephropathy, and the use of urate-lowering therapy such as allopurinol is appropriate for these indications.
- Urate-lowering therapy should be started after the first episode of gout in patients with CKD due to high risk of recurrence.
- Observational studies associated elevated urate levels with risk of chronic kidney disease, hypertension, and cardiovascular disease.
- Three RCTs CKD-FIX, PERL, and FEATHER found that urate-lowering therapy with allopu-

rinol or febuxostat does not delay progression of kidney disease.

- There is no evidence to support urate-lowering therapy improves cardiovascular outcomes in patients with kidney disease, and febuxostat should be avoided in those with pre-existing cardiovascular disease.

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Acute Kidney Injury in Chronic Kidney Disease

8

Bethany C. Birkelo, Sharidan K. Parr, Yuang Chen, and Edward D. Siew

Before You Start: Facts You Need to Know

- The incidence of AKI has grown rapidly in recent years.
- CKD and proteinuria are common risk factors for developing AKI.
- Patients with a rapid course to ESKD often have non-linear decline in kidney function marked by AKI.
- Diagnostic tests such as fractional excretion of sodium (FeNa) may be less reliable in patients with CKD.
- After an episode of moderate to severe AKI or those where recovery to baseline has not occurred, patients should be evaluated within 3 months to resolution and for new onset or worsening of pre-existing CKD.
- Ideally, long-term goals of care (including whether to initiate dialysis) should be discussed *before hospitalization*, particularly among frail and elderly patients with CKD.

8.1 Introduction: The Growing Impact of AKI

8.1.1 Occurrence and Definition

The Centers for Disease Control and Prevention estimate that kidney disease is the eighth leading cause of death in the United States (US) and consumes 23% of total Medicare expenditures. It is projected that by the year 2030, 16.7% of adults in the US over the age of 30 will have CKD [1]. AKI, particularly when severe, has been recognized as an increasingly common risk factor for CKD progression [2]. AKI is characterized by an abrupt decline in glomerular filtration rate (GFR). The Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guideline for Acute Kidney Injury suggests that a minimal threshold for defining AKI should include an increase in serum creatinine of at least 0.3 mg/dL (26.5 μmol/L) within 48 h or 1.5 times the baseline value within 7 days, or urine volume less than 0.5 mL/kg/h for at least 6 h (Table 8.1), with increasing severity denoted by incrementally

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Table 8.1 Staging of AKI. Kidney disease improving global outcomes [3]

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dL (≥ 26.5 μmol/L) increase	˂0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	˂0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥ 353.6 μmol/L) OR Initiation of renal replacement therapy OR, in patients ˂ 18 years, decrease in eGFR to ˂ 35 mL/min per 1.73 m^2	˂0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

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larger increases in serum creatinine values or the persistence or worsening of oliguria [3]. This change in paradigm has been largely driven by observations showing that even in the absence of overt kidney failure, smaller changes in serum creatinine independently associate with poor clinical outcomes (Fig. 8.1) [4]. Within hospitalized populations, incidence rates for AKI vary by setting, ranging up to 18% in hospitalized patients and up to 57% in ICU patients [5, 6]. Population-based studies within industrialized countries estimate incidence rates for AKI of between 2147 and 5000 cases/million population/year [7].

While AKI can be associated with exacerbations of intrinsic kidney disease or systemic diseases that target the kidney (e.g., lupus), the majority of AKI in developing countries occurs as a consequence of an acute illness or procedures that either compromise perfusion (e.g., volume-depleting illnesses, acute blood loss,

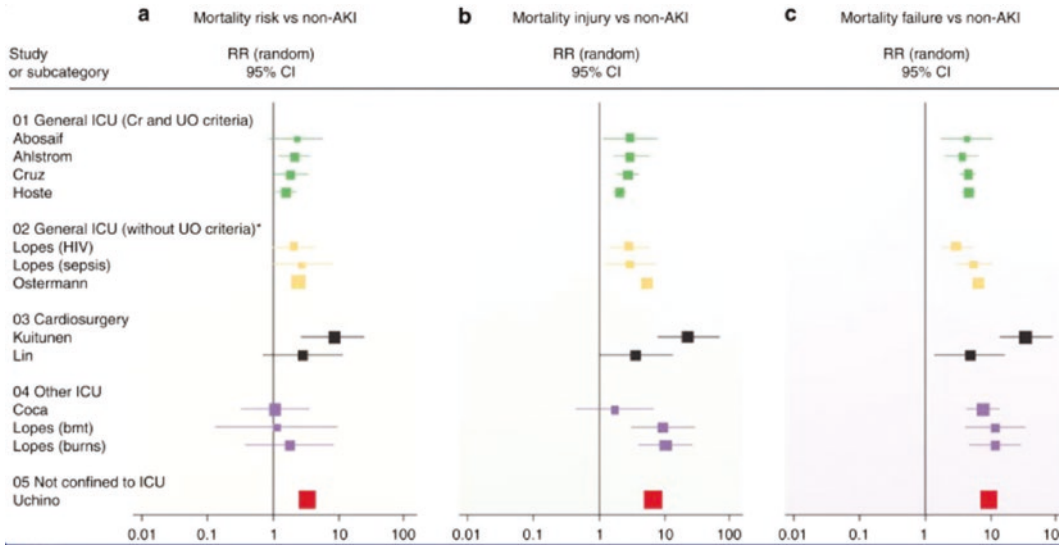

Fig. 8.1 Increased mortality risk associated with AKI extends to milder injury. Systematic review showing consistent increases in mortality risk associated with incrementally larger acute changes in serum creatinine in different acute care settings illustrated by Forrest plot. (**a**) Risk category denoted by a 50% increase in baseline serum creatinine/25% decrease in baseline GFR/urine output <0.5 mg/kg/h × 6 h (Relative Risk = 2.4), (**b**) Injury denoted by a doubling in baseline serum creatinine/50% decrease in GFR/urine output <0.5 mL/kg/h × 12 h (Relative Risk = 4.15), and (**c**) Failure denoted by a tripling of baseline serum creatinine/GFR decrease of >75%/acute increase in serum creatinine to >4 mg/dL with and acute rise of 0.5 mg/dL/urine output <0.3 mL/kg/h × 24 h/anuriax12 h (Relative Risk = 6.37). (Reprinted from *Kidney International*; volume 73, issue 5; Ricci Z, Cruz D, Ronco C; The RIFLE criteria and mortality in acute kidney injury: a systematic review; March 2008; pages 538–546, with permission from Elsevier)

Table 8.2 Urinalysis findings in AKI

Normal or hyaline casts	Pre-renal azotemia Post-renal/obstruction
Dysmorphic RBC's/ RBC casts	Glomerulonephritis Malignant hypertension Thrombotic microangiopathy Vasculitis
WBC's/WBC casts	Glomerulonephritis Acute interstitial nephritis (AIN) Pyelonephritis
"Muddy-brown casts" or pigmented casts	Acute tubular necrosis (ATN) Myoglobinuria Hemoglobinuria
Eosinophiluria	AIN Atheroembolic disease
Crystals	Uric acid Calcium oxalate (can be seen in ethylene glycol ingestion) Calcium phosphate Triple phosphate Cystine Crystal caused by drugs or toxins (indinavir, acyclovir, amoxicillin)

major vascular surgery) and/or stimulate a profound inflammatory response (e.g., sepsis) (Table 8.2). Medications directly toxic to the kidney (e.g., non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast) may also contribute to up to 1/5 of cases [8]. Recent advances in cancer chemotherapies, including immune checkpoint inhibitors and tyrosine kinase inhibitors, have been also associated with AKI. In developing countries, where disease surveillance is not widely implemented, a higher prevalence of diarrheal and infectious-related causes of AKI exist, particularly among children.

8.1.2 Prognosis

AKI is strongly associated with devastating short-term complications with mortality rates up to 56.8% among critically ill patients with severe AKI [5, 8, 9]. Of greater concern are signals arising from both administrative and laboratory databases that the incidence of AKI is expanding rapidly (Fig. 8.2) [7]. Similar growth in nondialysis-requiring AKI, which constitute most cases, has also been observed. There are numerous possible reasons for these increases, including increasing prevalence of comorbidities including CKD, parallel rises in known precipitants including sepsis, increasing use of medications or invasive procedures that place patients at increased risk for developing AKI, and aging populations throughout the world [10]. The latter was illustrated in a study showing that the observed increases in population-based incidences of AKI among a rural United States community from 2006 to 2014 were no longer present after adjusting for age and sex, suggesting that observed increases may be largely related to an increasingly elder population [11].

Recent attention focused on the long-term impact of this disease indicates that AKI strongly associates with CKD progression, particularly in severe cases or when superimposed on underlying CKD, as well as with cardiovascular complications such as heart failure. When taken together with ongoing increases in disease incidence, important implications emerge including a growing population of AKI survivors at risk for the development or acceleration of CKD and its complications.

In this chapter, we will examine the bidirectional nature of the interaction between AKI and CKD. Specifically, we will detail how the growing population of patients with CKD may be especially vulnerable to developing AKI and its complications. In addition, we will discuss literature suggesting that AKI is an important contributor to both the development and progression of CKD. Lastly, we will review recent practice guidelines to the diagnostic approach and management of this disease.

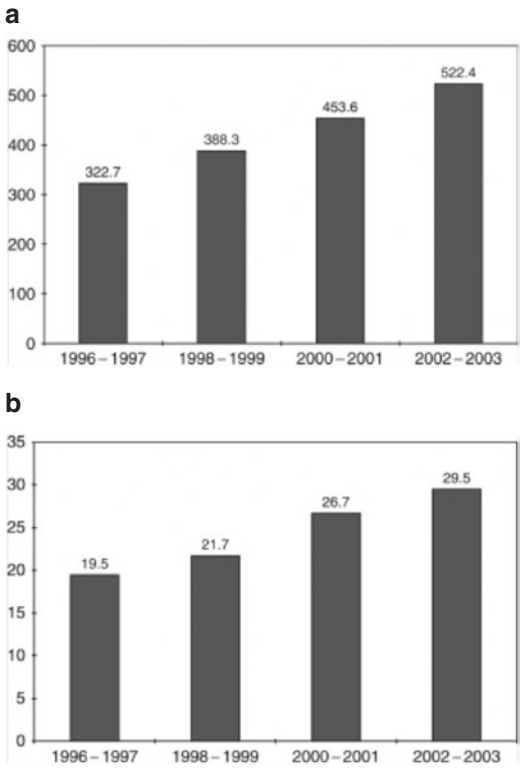

Fig. 8.2 The population incidence of dialysis and non-dialysis requiring AKI in the USA is increasing. (**a**) Community-based incidence rates (per 100,000 person-years) of non-dialysis requiring AKI per year. (**b**) Community-based incidence rates (per 100,000 person-years) of dialysis requiring AKI per year. (Reprinted from Kidney International; volume 72, issue 2; Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM; Community-based incidence of acute renal failure; July 2007; pages 208–212, with permission from Elsevier)

8.2 CKD as a Risk Factor for AKI

Administrative data have identified CKD as a risk factor for AKI. However, as many early studies used diagnostic coding to identify AKI, concerns over potential biases in detection (e.g., AKI is more likely to be recognized in patients with underlying CKD) prompted additional studies using serum creatinine to define AKI. A population-based study in Northern California observed an adjusted odds of developing dialysis-requiring AKI of up to 20- to 30- fold higher in those with advanced Stage III and Stage IV CKD compared to non-CKD patients (Fig. 8.3) [12]. Subsequent studies have demonstrated a graded relationship between the severity of CKD and the risk for AKI, indicating that the increase in observed risk begins at even earlier stages of CKD [13]. Despite the consistency of this data, some concern exists over whether biases in ascertainment may be partially responsible for these observations. Among these include the notion that patients with CKD are more likely to have serum creatinine checked, which increases the likelihood of detecting AKI. In studies that use serum creatinine to define AKI, the same absolute increase in serum creatinine in a patient with CKD represents a smaller overall change in kidney function compared to a patient without CKD, making it easier for patients with CKD to meet diagnostic criteria.

Other markers of kidney disease, such as proteinuria, have also been shown to associate with an increased risk for AKI independent of eGFR. In the Atherosclerosis Risk in Communities (ARIC) cohort, which prospectively followed 11,200 patients, a stepwise increase in risk for AKI was observed with increasing degrees of albuminuria. After adjusting for age, gender, race, cardiovascular risk factors, and categories of eGFR, the ORs for AKI were 1.9 (95% CI, 1.4–2.6), 2.2 (95% CI, 1.6–3.0), and 4.8 (95% CI, 3.2–7.2) for urine albumin-to-creatinine ratio groups of 11 to 29 mg/g, 30 to 299 mg/g, and ≥ 300 mg/g, respectively [13]. Another population-based cohort of nearly one million patients in Canada also confirmed an independent association between proteinuria and the risk for hospitalization with AKI, death, and the composite endpoint of doubling of serum creatinine or ESKD. Across all stages of CKD, increasing levels of proteinuria measured by urine dipstick carried an increased adjusted risk for hospitalized AKI. Even among those with preserved eGFR, mild to heavy proteinuria carried a graded 2.5 (95% CI, 2.3–2.7) to 4.4 (95% CI, 3.7–5.2) fold-risk of hospitalization for AKI (Fig. 8.4) [14]. More recently, one study examined the association between proteinuria and post-operative AKI among patients undergoing non-cardiac surgery. After adjustment for kidney function, comorbid conditions, medication use, and intraoperative

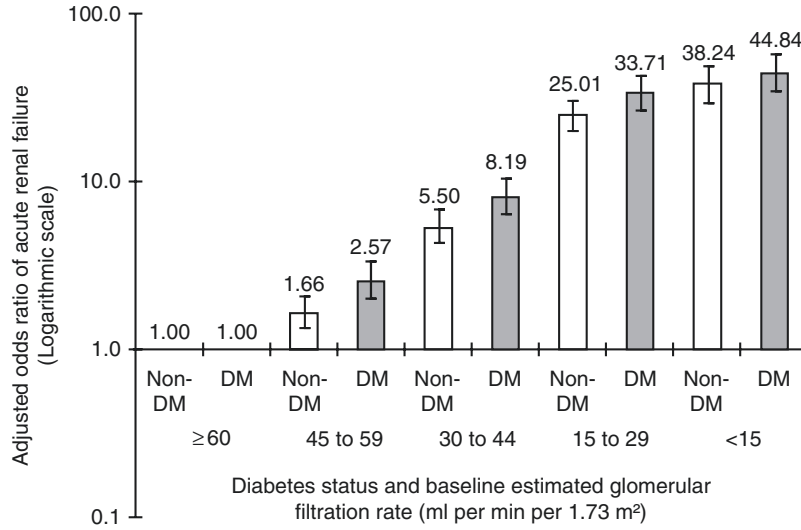

Fig. 8.3 Multivariable association of baseline estimated GFR and dialysis-requiring ARF stratified by the presence or absence of diabetes mellitus (DM). Each model adjusted for age, sex, race/ethnicity, diagnosed hypertension, and documented proteinuria. (Reprinted from Kidney International; volume 72, issue 2; Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM; Community-based incidence of acute renal failure; July 2007; pages 208–212, with permission from Elsevier)

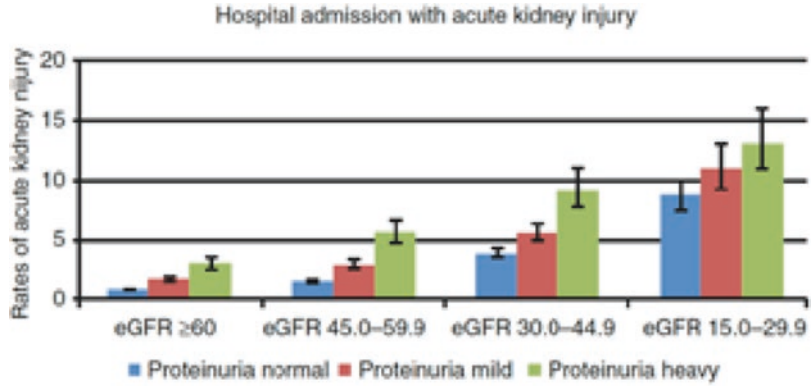

Fig. 8.4 Estimated glomerular filtration rate and proteinuria independently associate with acute kidney injury. Adjusted for means (and frequencies) of covariates for: age, sex, aboriginal status, low income, social assistance, comorbidities (HIV/AIDS, history of cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, diabetes mellitus, hypertension, metastatic solid tumor, mild liver disease, moderate or severe liver disease, myocardial infarction, paralysis, peptic ulcer disease, peripheral vascular disease, rheumatic disease). In this analysis, dipstick urinalysis was used to classify participants with respect to proteinuria: normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick ≥2+). The tests for linear trend across eGFR categories and across proteinuria categories were all significant at the $p < 0{\cdot}0001$ level. (Data from Lancet 2010 Dec 18;376(9758):2096–103)

hemodynamics, they observed ORs for AKI of 1.14 (95% CI, 0.75–1.73), 1.24 (95% CI, 0.79–1.95), 2.75 (95% CI, 1.74–4.35), and 3.95 (95% CI, 1.62–9.62) for trace, 1+, 2+ and 3+ proteinuria, respectively [15]. A similar trend was observed in a study of United States Veterans undergoing elective inpatient surgery [16].

Chronic kidney disease often co-exists with other comorbid diseases that themselves increase the risk for AKI in this population. Patients with

congestive heart failure, for example, are at risk for AKI that occurs during acute decompensations of the disease itself (i.e., acute cardiorenal syndrome) or exacerbated by its therapy (i.e., diuretics or RAAS inhibitor medications that are used in guideline-directed medical therapy). Cardiovascular disease, including coronary artery disease (CAD), is another common comorbidity that tracks with CKD and is associated with AKI. Patients with CAD are at particular risk of AKI due to contrast exposure (e.g., heart catheterization procedures) and, less commonly, due to atheroembolic disease.

In summary, these studies reinforce the link between both underlying structural or functional impairment of the kidney and the risk for AKI, as well as the susceptibilities conferred by common comorbid conditions and their therapies. Whether reducing proteinuria modifies the risk for AKI remains an important question that remains to be tested. While the intuitive notion that lower functional reserve in any organ might lower the threshold for injury, the presence of CKD and/or proteinuria can help clinicians identify patients at highest risk for developing AKI. Therefore, we recommend measuring proteinuria and serum creatinine prior to procedures or drug exposures carrying intrinsic risk for AKI (e.g., iodinated contrast procedures) to aid in risk stratification.

8.3 AKI as a Risk Factor for CKD

Early studies more than a half-century ago suggested that patients with normal kidney function before a severe AKI event were often able to return to active lives independent of dialysis. However, small but detailed physiologic studies revealed "subclinical" decreases in clearance, as well as an inability to concentrate and dilute urine when measured directly, refuting the notion of AKI being a self-limited event. The potential outcomes of AKI are illustrated in Fig. 8.5. For some patients, there appears to be a complete or near-complete recovery. In others, an incomplete recovery of AKI may occur resulting in the development of incident CKD. Lastly, among those with previous CKD, AKI may serve to accelerate the progressive loss of kidney function over time, although the mechanisms that lead to decline and potential interventions to attenuate disease progression have not been fully established.

Animal studies have demonstrated that beyond the initial tubular injury and nephron loss, ischemic insults to the kidney also result in endothelial damage to the microvasculature, which have less regenerative capacity than tubules. The loss of vascularity may lead to chronic regional ischemia that promotes downstream hypoxic signaling, inflammation, and fibrosis (Fig. 8.6) [17]. Even after apparent recovery, affected animals can develop proteinuria and are less able to excrete sodium in the urine leading to salt-sensitive hypertension, which may contribute to further loss of kidney function. Furthermore, nephron loss in other experimental models of CKD has also been observed to lead to compensatory adaptations including hyperfiltration in the "remnant kidney" that result in glomerular hypertension and cellular proliferation. Whether the latter also occurs following AKI is not clear.

Prospective studies of children who recover from AKI associated with the hemolytic uremic syndrome (HUS) found that survivors were more likely to develop microalbuminuria and lower eGFR values using cystatin C levels relative to a group of control patients during 5 years of follow-up [18]. The extension of these findings to adults has been noted in multiple observational studies [2]. One such study used administrative data for 233,803 hospitalized Medicare beneficiaries and found that among those with a discharge diagnosis of AKI, there was a 7% chance of initiating treatment for ESKD within 2 years of follow-up, with a nearly two-fold increase in adjusted risk compared with CKD patients hospitalized without AKI. The likelihood of a patient with CKD experiencing AKI to need treatment for ESKD was 14%, with an over four-fold adjusted risk compared to CKD patients without an AKI diagnosis. The latter is particularly compelling given literature identifying CKD as the *predominant* risk factor for AKI [19].

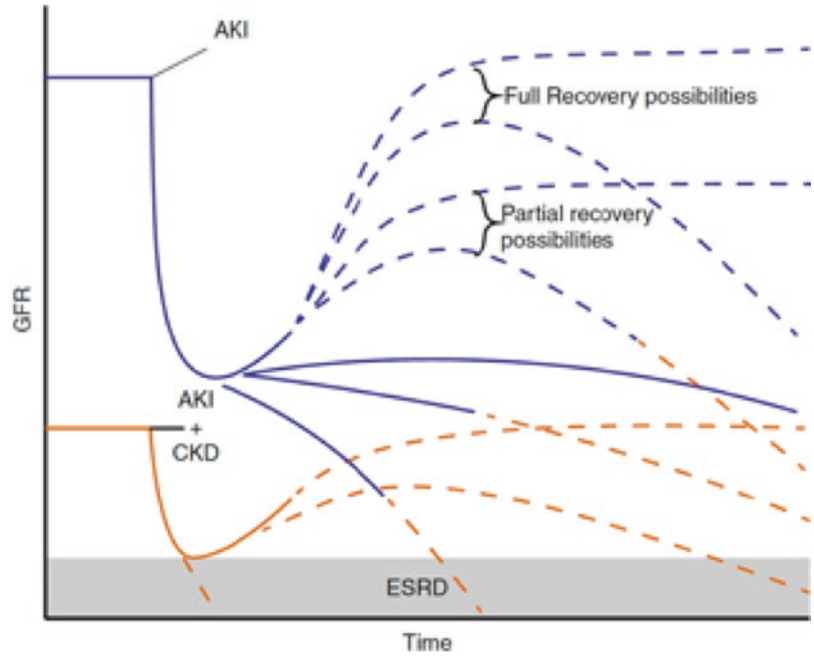

Fig. 8.5 Potential kidney outcomes following AKI

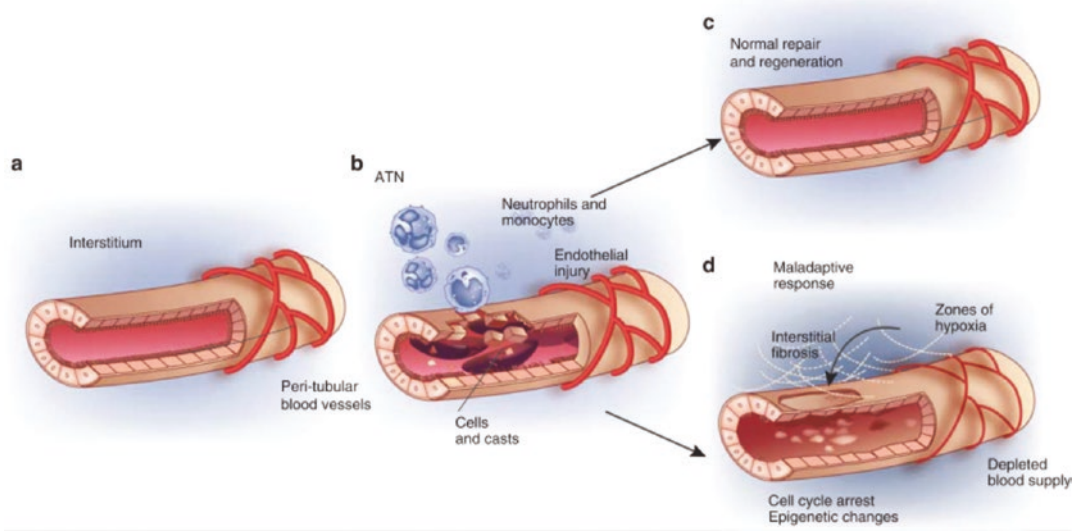

Fig. 8.6 Potential mechanisms of how AKI can lead to irreversible loss of kidney function. Tubule cross-section. (**a**) Cross section of normal renal tubule with intact epithelial cells, renal interstitium, and peri-tubular blood vessels. (**b**) Cross section of renal tubule with acute tubular necrosis (ATN) with epithelial cell necrosis, intra-tubular cast formation, endothelial injury of peri-tubular blood vessels, and migration of monocytes and macrophages into renal interstitium. (**c**) Cross section of renal tubule after normal repair and regeneration showing restoration of normal renal architecture. (**d**) Cross section of renal tubule after severe episode of AKI, resulting in maladaptive repair. Epithelial cells have evidence of cell cycle arrest and epigenetic changes that favor a fibrosis phenotype. Renal interstitium shows evidence of fibrosis. Post-injury vascular supply is less dense than baseline. The combination of decreased blood supply and fibrosis leads to zones of hypoxia wherein the combination of decreased vascular supply and fibrosis can initiate a vicious cycle leading to ongoing fibrosis. (Reprinted from *Kidney International*; volume 82, issue 5; Lakhmir CS, Kimmel PL; Acute kidney injury and chronic kidney disease: an integrated clinical syndrome; September 2012; pages 516–524, with permission from Elsevier)

Subsequent studies anchored by baseline kidney function have found similar results. In a population-based study in Northern California in patients whose eGFR before hospitalization was >45 mL/min/1.73m^2, patients experiencing dialysis-requiring AKI were 28 times more likely to develop advanced CKD compared to other hospitalized patients without AKI after adjustment and matching for potential confounders (Fig. 8.7) [20]. The risk for incident CKD appears to be increased 1.9-fold even among patients with reversible AKI in whom eGFR returns to within 10% of their pre-hospitalization baseline [21]. Enough data has accumulated to perform meaningful meta-analyses which estimate pooled adjusted hazard ratios for CKD, ESKD, and mortality following AKI of 8.8 (95% CI, 3.1–25.5), 3.1 (95% CI, 1.9–5.0), and 2.0 (95% CI, 1.3–3.1), respectively, compared to hospitalized patients without AKI [2]. More recently, the largest multicenter prospective cohort study examined long-term outcomes including kidney disease progression following an episode of AKI among patients who survived at least 3 months after a hospitalization. Among 769 adults with AKI and 769 adults without AKI who were matched on center, baseline CKD status and eGFR, age, comorbidities (diabetes mellitus and cardiovascular disease), and treatment in the ICU, AKI was associated with an increased risk of both incident CKD and progressive CKD (adjusted hazard ratio for incident CKD 3.98, 95% CI 2.51–6.31; aHR for CKD progression 2.37, 95% CI 1.28–4.39) [22].

Building upon this literature, recent efforts have focused on identifying patients at highest risk for developing CKD following AKI. Several studies have demonstrated a graded relationship between AKI severity (as measured by change in serum creatinine) and the risk for incident and progressive CKD [23]. Another potential harbinger of poor outcomes includes the duration of injury. Studies in surgical patients found that higher long-term mortality rates among those with injury that persists for multiple days, even among those with mild

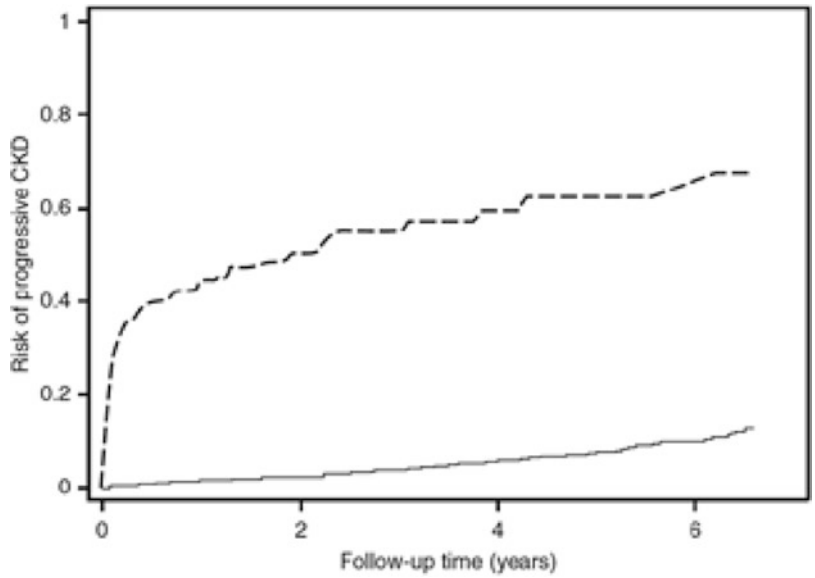

Fig. 8.7 Severe AKI increases the risk of developing advanced kidney disease. Kaplan-Meier Curves showing the long-term risk of KDOQI Stage 4 or worse kidney disease among patients with well-preserved kidney function who did (dashed line) or did not (solid line) suffer and recovered at least partially from dialysis-requiring AKI. (Reprinted from *Kidney International*; volume 76, issue 8; Lo LJ, Go AS, Chertow GM, et al.; Dialysis-required acute renal failure increases the risk of progressive chronic kidney disease; October 2009; pages 893–899, with permission from Elsevier)

injury, and were more prognostic than injury severity alone [24]. More recent studies in hospitalized and cardiac surgery patients have shown similar findings. A large retrospective study of hospitalized patients showed a dose-dependent association between duration of AKI with incident CKD at 1 year [25], while a study of patients undergoing elective cardiac surgery found that duration of AKI lasting >3 days had an adjusted odds ratio of 13.5 (95% CI 4.2–43.7) for incident CKD at 1 year [26]. Non-recovery from AKI may also be predictive of CKD progression. In a multivariable model predicting risk of progression to advanced CKD among survivors of AKI, serum creatinine at hospital discharge and AKI severity were major drivers of risk (C statistic for full model 0.81, 95% CI 0.75–0.86) [27]. Other risk factors for long-term loss of kidney function following AKI include advancing age, African American race, baseline kidney function, comorbidity burden including the presence of diabetes, HTN, or CHF, and serum albumin levels during hospitalization [28]. Proteinuria following AKI has also been shown to be a predictor of long-term kidney disease. In a study of patients with AKI sustained during a hospitalization, higher levels of albuminuria measured at 3 months after hospital discharge were associated with increased risk of progressive chronic kidney disease, defined as a halving of estimated GFR or end-stage kidney disease [29].

Lastly, the majority of studies have characterized the impact of a discrete episode of AKI on disease progression. However, recent attempts have also begun to examine the impact of subsequent AKI events on long-term loss of kidney function. Thakar et al. [30] followed a high-risk cohort of 3679 diabetic patients, 62% with baseline proteinuria, within an integrated health care system for the development of stage IV CKD over a mean of 5 years. Despite overall preserved baseline kidney function (mean eGFR 81 +/− 26 mL/min/1.73 m^2), 14% of the population experienced an AKI event, with nearly one-third of this group experiencing multiple events. Patients experiencing an AKI event were twice as likely to reach stage IV CKD as those who did not (24.6% vs. 12.9%, $p < 0.01$). Multivariate Cox regression analysis identified the presence of any AKI to be associated with an adjusted Hazard Ratio of 3.5 (95% CI, 2.7–4.6) with each subsequent episode of AKI further doubling that risk (HR 2.02; 95% CI, 1.78–2.30). Retrospective studies have identified factors that may increase an individual's risk for recurrent AKI, including demographics (older age, black race, Hispanic ethnicity), comorbid conditions (congestive heart failure, diabetes, liver disease, and cancer), acute events (decompensated liver disease, acute coronary syndrome, volume-depleting events), and more severe illness at index hospitalization [31, 32]. Renal functional reserve (RFR), which refers to the kidney's ability to increase its filtration rate in response to a stimulus, is a topic of ongoing investigation and a factor that appears to be associated with risk of AKI. RFR is measured as the difference between baseline GFR and GFR measured after a protein load. Assessment of RFR may more accurately capture the degree of structural injury following AKI in patients with normal GFR (i.e., subclinical injury). Diminished RFR has also been observed in patients with CKD. Recent studies have demonstrated that lower RFR are associated with risk of AKI, as was shown in a study of patients undergoing cardiac surgery who had RFR measured pre-operatively; in that study, pre-operative RFR predicted post-operative AKI with an area under the receiver operator curve of 0.83 (95% CI, 0.70–0.96), and patients with a RFR $\leq$ 15 mL/min/1.73m^2 were 11.8 times more likely to experience AKI [33]. RFR measurement is not used in routine clinical practice at present, and remains an area of active investigation.

With biological and epidemiologic evidence supporting an independent association between AKI and incident CKD, research efforts over the past decade have explored potential mechanisms by which AKI may lead to new or progressive CKD. Preclinical studies have implicated maladaptive repair processes after AKI which may promote interstitial fibrosis through a number of mechanisms. Tubular injury can result in interstitial fibrosis through secretion of profibrotic fac-

tors and tubular mitochondrial dysfunction [34]. AKI can also cause a reduction in capillary density in affected tissue (microvascular rarefaction) which may promote interstitial fibrosis through renal hypoxia [35]. Identification of these biochemical pathways of progression holds promise for possible targets of therapy, however this work remains nascent [36]. Regardless, it is clear that AKI is an important marker for long-term loss of kidney function, particularly among those with pre-existing CKD. Therefore, we recommend that an episode of AKI be documented in the medical history portion of the electronic medical record, and that the routine evaluation of all patients with CKD include inquiring about past history of AKI.

8.4 Prevention and Management of AKI in CKD

8.4.1 Before and Early During Hospitalization: Recognizing High-Risk Patients and Situations

As the interaction between AKI and CKD becomes clearer, improved understanding of how to optimally care for this growing population will be needed. An important first step is for clinicians to recognize the patients and situations that combine to increase the risk for developing AKI in patients with CKD. In addition to patients with CKD, other patients at risk of developing AKI include patients with diabetes, hypertension, heart failure, and African American race. Among the fastest growing populations experiencing AKI include the elderly, who like those with CKD are also less likely to recover and more likely to progress to ESKD following AKI. Age-related changes in both structure and function of the kidneys in this population and a higher comorbidity burden combine to reduce the threshold for injury in response to abrupt changes in renal perfusion. Additionally, these patients are at increased risk for inappropriate drug dosing and polypharmacy that increase the risk of drug interactions and/or nephrotoxicity.

Certain medication classes of proven benefit in the chronic setting can also lower the threshold for AKI during acute illness. For example, the normal response to decreases in kidney perfusion include increases in postglomerular (i.e., efferent arteriolar) vascular tone, which helps to maintain glomerular perfusion pressure and adequate filtration. However, the increased use of medications in the CKD population, including angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs), blunts the compensatory response that maintains glomerular perfusion pressure. When coupled with diuretics or antihypertensive agents that decrease effective circulating volume or reduce perfusion pressure, the threshold for kidney injury can be lowered. This risk is particularly relevant in patients with heart failure, for whom increasingly potent blockade of the renin-angiotensin system coupled with aggressive diuresis as part of evolving guideline-directed medical therapy may lower the threshould for AKI. Careful stepwise initation and titration of these medications may be warranted in patients with underlying CKD. Furthermore, temporary suspension of these medications during AKI or when the risk for AKI is high (such as during acute illness) may be prudent. In these so-called sick-day protocols patients are instructed to withhold ACE-I, ARBs, and diuretics during volume-depleting illnesses such as diarrhea or vomiting. The evidence to support the widespread adoption of such protocols has been mixed. A pooled analysis of three randomized clinical trials that examined similar protocols in which specific medications are temporarily withheld during illness or a radiologic or surgical procedure found a nearly 50% increased risk of AKI among those who continued the meds compared with those who held them as part of the sick-day protocol, however the observed effect was not statistically significant (RR

1.48, 95% CI 0.84–2.60) [37]. The effectiveness of sick-day protocols in reducing AKI may also be limited by insufficient understanding by patients. Illustrating this point, a small study of 20 volunteers with stage 3–5 CKD assessed the usability of the sick-day protocol used by the National Health System in Scotland. The volunteers were educated about the protocol and provided mock medication bottles, and were then asked which (if any) medications should be held in four different clinical scenarios. Of the 20 study participants, only one individual was able to identify the correct medications to hold in each of the four scenarios [38]. An ongoing clinical trial examining this topic is being completed at the time of this writing and may provide better guidance. We do recommend that patients with CKD be cautioned to avoid NSAIDs in combination with the aforementioned antihypertensives and/or diuretics as the latter compromise prostaglandin-mediated dilation of the afferent arterioles during decreased perfusion, which may make patients with CKD more vulnearable. Healthcare providers should have a low threshold for suspending these medications when the risk for AKI is more dynamic such as during hospitalization or before anticipated procedures known to increase risk for AKI including major surgery or contrast exposure. Communication with procedural teams should be pursued to ensure that risk is minimized (i.e., minimizing contrast loads) and that adequate prophylaxis is given (see Chap. 3 for contrast-induced nephropathy).

Finally, facilitating communication with patients or their surrogates regarding the long-term goals of care *before hospitalization* is a much-needed area for improvement, particularly among frail and elderly patients with CKD. Studies have demonstrated that among patients with diminished functional status, such as nursing home residents, nearly two-thirds of patients die within a year of initiating chronic dialysis and premorbid functional status is maintained only in 13% of patients [39]. Therefore, attempts to ascertain patient goals of care in the context of chronic disease and functional status should occur prior to hospitalization. This will enable patients and physicians with an established relationship to develop a plan of action should hospitalization with AKI occur (e.g., advance directive) and help patients better balance the risk of potential AKI with the benefit of procedures that carry an intrinsic risk for AKI (e.g., major vascular surgery). The possibility of a more conservative approach to care should be presented as a viable option early in the course of conversation and the joint input of both the patient's primary provider and nephrologist should be sought.

8.4.2 Determining the Time Course and Diagnosis of AKI

A simplified algorithm of the evaluation and treatment of AKI is depicted in Fig. 8.8. In evaluating a patient with suspected AKI, effort should be made to determine whether the pattern of kidney injury is acute, acute on chronic, or chronic. This discrimination is important, as some forms of AKI are reversible if the inciting event is removed. Clinicians should elicit a history of CKD including obtaining pre-hospitalization serum creatinine values, if available. Baseline serum creatinine obtained during chronic steady state can provide insight into the acuity of change in kidney function, more accurately gauge the severity of AKI, and provide prognostic information. Any abrupt rise from the baseline creatinine in patients with CKD should prompt evaluation for AKI. Radiographic evidence of small, scarred kidneys would suggest underlying CKD. However, in some cases of CKD the kidney size may be normal or increased such as in diabetic nephropathy, HIV-associated nephropathy, polycystic kidney disease, or infiltrative diseases such as amyloidosis. Additional findings that may suggest underlying CKD include anemia, hyperphosphatemia, hypocalcemia, hyperparathyroidism, and neuropathy.

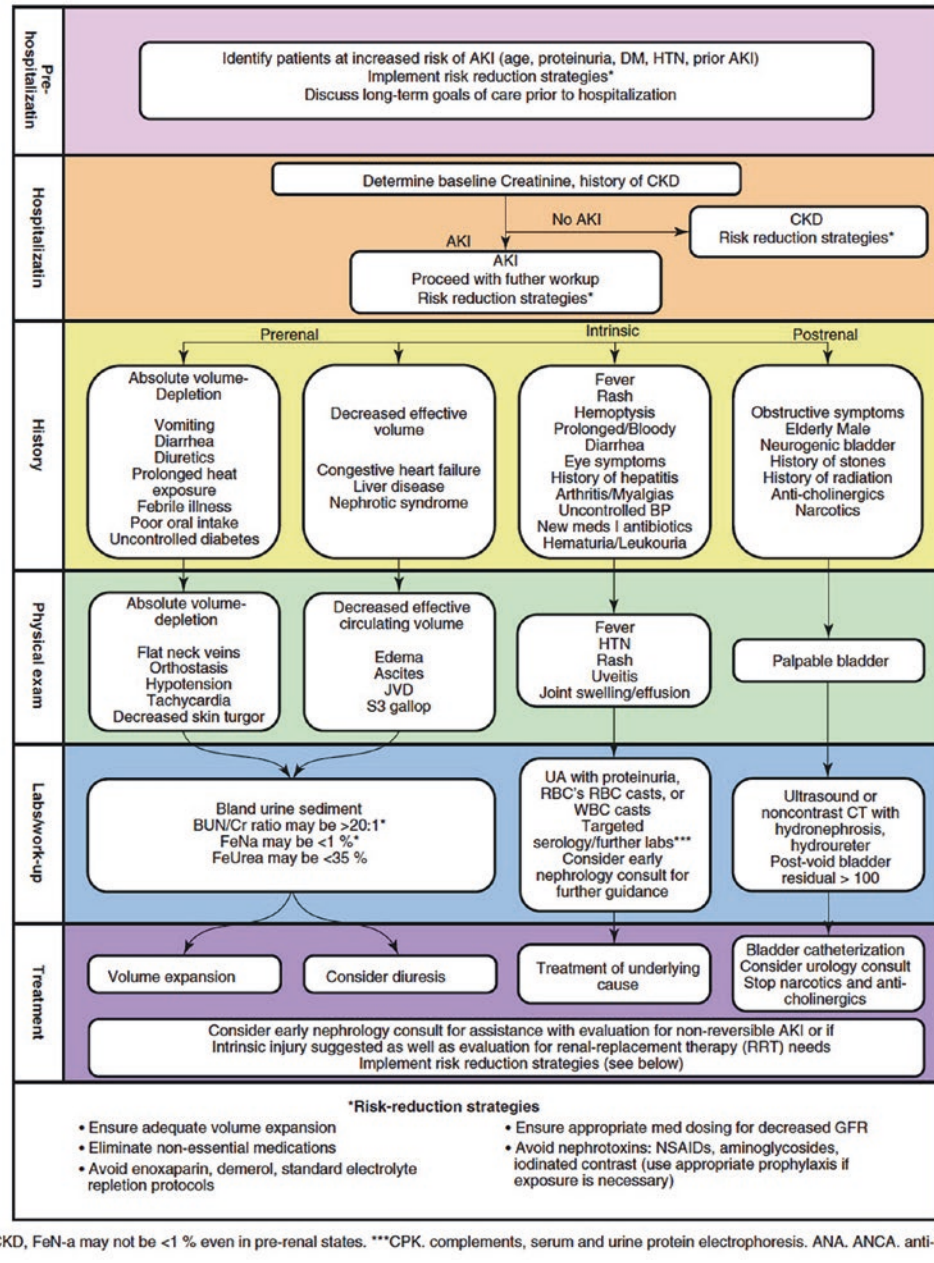

Fig. 8.8 Algorithm for evaluation and treatment of AKI

8.4.3 History, Physical Exam, and the Differential Diagnosis of AKI

Once a diagnosis of AKI has been made, steps should be taken to determine the etiology. Classically, underlying causes are grouped into pre-renal, intrinsic, or post-renal categories (Table 8.2). However, many cases of AKI are multifactorial and multiple contributors should be considered.

Pre-renal AKI most often results from impaired perfusion to the kidney and is the most common cause of community-acquired AKI. Early in the course of injury, net filtration is diminished. However, compensatory hemodynamic and hormonal adaptations occur within the kidney that increase the efficiency of filtration and promote sodium and water retention that maintain blood volume and minimize the development of tissue injury *if adequate perfusion can be restored quickly*. Therefore, the diagnosis of pre-renal AKI is made after a successful intervention is applied (e.g., creatinine decreases with IV fluid resuscitation). However, deciding which intervention to apply can be challenging as pre-renal physiology can be seen in both states of *absolute* volume depletion (e.g., diarrhea, vomiting, overdiuresis, dehydration, bleeding) and diseases with decreased *effective* circulating volume (e.g., nephrotic syndrome, liver disease, congestive heart failure) which often present with signs of fluid accumulation (i.e., edema). In patients with underlying CKD, diminished renal reserve and blunted ability to adapt to decreased perfusion may lower the threshold for progression to true parenchymal injury, underscoring the importance of a timely diagnosis.

A rapid historical assessment for volume-depleting illness including bleeding, vomiting, diarrhea, febrile illness, infection, or prolonged heat exposure should be elicited. Information on comorbid disease states including poorly controlled diabetes (osmotic diuresis), or those associated with effective arterial volume depletion including congestive heart failure or cirrhosis should also be sought. Additionally, contributing medications should be identified, paying particular attention to recent changes or addition of antihypertensives, diuretics, cathartics, NSAIDs/COX-2 inhibitors, and ACE/ARB use. Physical exam should prioritize determining volume status. In patients with absolute depletion of circulating volume, patients may have orthostatic hypotension, flat neck veins, decreased skin turgor, hypotension or tachycardia. In contrast, patients with decreased effective circulating volume such as patients with cirrhosis or CHF may have evidence of volume overload including jugular venous distension, S3 gallop, edema, or ascites.

Several laboratory tools have traditionally been used to reflect appropriate tubular response to diminished perfusion, supporting the diagnosis of pre-renal azotemia rather than intrinsic causes of AKI during oliguric kidney injury. Among these include a BUN/Cr ratio of >20:1, a fractional excretion of sodium (FeNa) of less than 1%, or a fractional excretion of urea (FeUrea) of less than 35% in patients exposed to diuretics. However, the predictive value of these tools in the patient with underlying CKD may be diminished. For example, a lower filtered of sodium and impaired tubular function may result in a higher FeNa at baseline. Therefore, the predictive value of FeNa levels >1% for indicating the presence of tubular dysfunction may be less reliable, although a low FeNa of <1% in the oliguric CKD patient still suggests pre-renal azotemia. These caveats place a greater emphasis on history and physical exam findings and other supplemental laboratory data to establish the diagnosis and nature of pre-renal AKI listed in Text Box 8.1.

A diagnosis of intrinsic renal injury is made when tissue damage to one or more portions of the kidney (glomerulus, vasculature, tubules, or interstitium) has occurred. While a discussion of the vast etiologies of intrinsic AKI is beyond the scope of this chapter, ATN is considered to be among the most common injuries in hospitalized patients. Kidney perfusion is estimated to account for 25% of cardiac output with portions of the tubular epithelium being particularly vulnerable to decreases in perfusion due to high metabolic activity and relative low tissue oxygen content. For this reason,

Box 8.1 AKI: Pre-Renal, Intrinsic, and Post-Renal Causes

Pre-Renal Causes

Intravascular Volume Depletion
- Hemorrhage
- Renal losses—aggressive diuresis, osmotic diuresis (hyperglycemia)
- Increased insensible losses—sweating, burns
- GI losses
- "Third-spacing"—pancreatitis, rhabdomyolysis
- Hypercalcemia (also causes renal vasoconstriction)

Decreased Perfusion
- Congestive heart failure
- Sepsis
- Liver failure
- Systemic vasodilation/anaphylaxis

Drugs
- Antihypertensives
- Diuretics
- Anesthetics
- Vasopressors
- Ergotamine
- ACE-I or ARB's—in renal artery stenosis or other causes of hypoperfusion
- NSAID's—during kidney hypoperfusion

Vascular
- Renal Artery Stenosis

Intrinsic

Acute Tubular Necrosis

Acute Interstitial Nephritis
- Medications
- Infections

Small-vessel disease
- Thrombotic microangiopathy, vasculitis, atheroemboli

Glomerular disease
- Lupus
- Anti-GBM disease
- Membranoproliferative glomerulonephritis (GN)
- Post-infectious GN
- Infective endocarditis
- IgA nephropathy/Henoch-Schonlein purpura

Tubular obstruction
- Cast nephropathy (multiple myeloma)
- Stones or crystals

Post-Renal
- Bladder outlet obstruction
- Calculi
- Tumors
- Retroperitoneal fibrosis

many consider ATN and pre-renal azotemia to represent different points on the same spectrum of response to acute ischemia within the kidneys. However, in addition to diminished perfusion, direct tubular injury can result from inflammation from sepsis or nephrotoxic medications including iodinated contrast, NSAIDs, aminoglycosides, and amphotericin (Table 8.3). Novel anticancer therapies developed over the past two decades, including molecularly targeted agents (small molecule tyrosine kinase inhibitors and monoclonal antibodies) and immune checkpoint inhibitors (ICIs), have also been associated with kidney complications including electrolyte abnormalities and AKI. The incidence of AKI associated with these therapies ranges from 2 to 7% depending on the agent [40–43]. Direct nephrotoxicity from these agents can occur by a number of mechanisms. Intraglomerular thrombotic microangiopathy (TMA) is a rare but serious complication that is seen with agents targeting vascular endothelial growth factor (e.g., bevacizumab and lenvatinib). Patients with AKI caused by TMA typically present with proteinuria and hypertension. Drug withdrawal or dose reduction is often adequate therapy, though some patients may require eculizumab, plasmapheresis, or rituximab to restore renal function [44, 45]. Biopsy series suggest acute tubulointerstitial nephritis (ATIN) is a common form of kidney injury in patients treated with an ICI [41]. Risk factors for ATIN include eGFR <60 and concurrent proton-pump inhibitor use [46]. Various case series and case reports suggest that treatment

Table 8.3 Drugs associated with AKI

ATN	**Antibiotics/antivirals**
	Aminoglycosides
	Amphotericin B
	Acyclovir (can also cause crystal formation)
	Indinavir (can also cause crystal formation), tenofovir, cidofovir, adefovir
	Foscarnet
	Pentamidine
	Anti-Inflammatory agents
	NSAIDs (including COX-2 inhibitors)
	Immunosuppressive agents
	Cyclosporine
	Tacrolimus
	Chemotherapeutic agents
	Ifosfamide
	Cisplatin
	Organic solvents
	Ethylene glycol (can also cause crystal formation)
	Toluene
	Radiocontrast agents
	Other
	Herbal remedies, acetaminophen
AIN	**Antibiotics**
	Penicillins
	Cephalosporins
	Sulfamethoxazole
	Ciprofloxacin
	NSAIDs/COX-2 inhibitors
	Chemotherapeutic agents (cause acute tubulointerstitial nephritis)
	Tyrosine kinase inhibitors
	Immune checkpoint inhibitors
	Loop and thiazide diuretics
	Allopurinol
	Omeprazole
	Phenytoin

with glucocorticoids and drug discontinuation are effective in achieving at least partial kidney recovery, with a recurrence rate after therapy reinitiation of 16% [46, 47]. Glomerular diseases (most commonly minimal change disease, focal-segmental glomerulonephritis, and membranous nephropathy) have also been associated with these novel agents and typically present with nephrotic syndrome. Glucocorticoids and drug discontinuation generally lead to at least partial recovery in most patients [48–51].

Certain diseases can also contribute directly to tubular injury. For example, in some patients with multiple myeloma, monoclonal urinary immunoglobulin light chains (Bence Jones proteins) that are freely filtered can precipitate in the tubular lumen causing intraluminal cast formation and incite a strong inflammatory reaction that injures tubular epithelia. Clinically, this can mimic ATN, especially since conditions that result in volume depletion can predispose to cast formation. Urinalysis typically shows bland urine sediment and standard urine dipsticks, which typically detect albumin and not light chains. Features that may increase suspicion of myeloma cast nephropathy include ATN without a clear precipitant or out of proportion to the presumed insult in a middle-aged or elderly patient. Accompanying hypercalcemia or anemia, back pain, and/or a history of unexplained CKD should raise suspicion. In these patients, further testing including serum/urine protein electrophoresis, immunofixation, and free light chain assays should be considered. Rhabdomyolysis and gross hemolysis can also cause direct tubular injury due to the release of contents of damaged muscle or red blood cells into the circulation, resulting from trauma, overexertion, autoimmune disease, or associated with medications (e.g., statins). Heme-pigments including myoglobin or hemoglobin are filtered by the glomerulus and degraded with the subsequent release of heme pigment that can cause direct tubular injury, tubular obstruction, and vasoconstriction. Concurrent volume depletion is an important risk factor in both cases with clinical and laboratory manifestations including decreased urine output, dark urine, elevated creatinine kinase levels (rhadomyolysis), elevated LDH, low haptoglobin levels (hemolysis), and a urine dipstick that is positive for blood but without obvious red blood cells on microscopy.

Acute interstitial nephritis (AIN) is another subclass of intrinsic kidney injury. AIN is an inflammatory reaction that involves the interstitium of the kidney, the tissue that resides between the tubules. The inflammatory infiltrates generally consist of lymphocytes and monocytes, but plasma cells, eosinophils, and neutrophils may also be present. There is also interstitial edema in sites of inflammatory infiltrate. Medications account for the vast majority of cases of AIN (Table 8.3), with

NSAIDs, penicillin antibiotics, and proton-pump inhibitors being common offenders. Rarely, AIN can be seen as a consequence of infection or systemic disease such as sarcoidosis or Sjögren's syndrome. Physical and laboratory findings consistent with AIN include rash, fever, leukouria, and/or the presence of eosinophils in the blood or urine, though estimates of their relative and combined diagnostic performance are highly variable. The main treatment of AIN is removal of the offending medication, though steroids may have a limited role when initiated early.

Though less common, processes that cause rapid and severe injury to the glomerulus can result progressive loss of kidney function over days to weeks and constitute a nephrologic emergency. Acute glomerulonephritis (GN) can be caused by numerous etiologies including autoimmune diseases and infections (Table 8.2). History should focus on symptoms of vasculitis including arthritis, rash, hemoptysis, serositis or risk factors for blood-borne viral infections like hepatitis B, C, and human immunodeficiency virus, or endocarditis. Exam findings of uveitis, arthritis, rash, or embolic phenomenon should increase suspicion for potential for glomerulonephritis. On urinalysis, hematuria and/or proteinuria should prompt examination of the urine sediment for dysmorphic red blood cells or red cell casts (Table 8.4), which suggest glomerulonephritis. If proteinuria is detected, a urine spot protein-to-creatinine ratio (PCR) or 24-h excretion should be directly quantified. In general, proteinuria >3.5 g/24 h is considered "nephrotic." If a diagnosis of acute GN is being considered, early nephrology consultation should be considered to guide further serologic testing and to facilitate timely tissue diagnosis and treatment.

Table 8.4 Drugs with potentially toxic accumulation in AKI or CKD

Drug	Clinical manifestations of accumulation
Allopurinol	Leukopenia, increased risk for immune-mediated hypersensitivity reaction
Codeine Morphine	Respiratory depression, CNS depression
Propoxyphene	Dysrhythmia
Midazolam	Drowsiness, sedation, apnea
Meperidine	Tremor, agitation, anxiety, myoclonus, seizure
Enoxaparin	Increased risk of bleeding
Succinylcholine	Hyperkalemia

The constellation of thrombocytopenia, anemia, and kidney dysfunction, with or without fever and central nervous system (CNS) manifestations, should prompt consideration of thrombotic microangiopathy (TMA). TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia, with other end-organ manifestations such as kidney dysfunction and CNS symptoms being variable depending on the degree of platelet thrombosis in the microcirculation. Thrombocytopenia occurs from platelet aggregation in microcirculation. Hemolytic anemia occurs from mechanical stress and fragmentation of RBC's during transit through narrowed vessels. In addition to thrombocytopenia and anemia, other lab findings include elevated bilirubin, elevated LDH, reticulocytosis, and low haptoglobin. Schistocytes are seen on peripheral smear. Hemolytic uremic syndrome (HUS) predominantly affects children and is characterized by AKI, often associated with diarrheal illness and usually with minimal or no CNS symptoms. Thrombotic thrombocytopenic purpura (TTP) does occur in adults and generally has CNS involvement with variable kidney involvement. Scleroderma and malignant hypertension can also present with TMA.

Lastly, post-renal AKI refers to obstruction to urine flow within the collecting system (kidney, ureters, bladder, or urethra). Obstruction to urine flow can occur via intraluminal (stones, crystals, urethral stricture) or extraluminal (prostate, retroperitoneal fibrosis) causes. Common causes of post-renal AKI in patients with CKD are prostatic obstruction and defects of bladder emptying such as in neurogenic bladder in patients with long-standing diabetes. Additionally, the use of narcotics or anti-histamines (which impair bladder emptying), can be particularly problematic in the elderly. In addition to inquiring about symptoms of urinary difficulty (type and duration) and history of uri-

nary tract infections or nephrolithiasis, providers should also consider recent exposure to medications that can cause urine crystal formation (intravenous acyclovir or indinavir). In patients with a known history of malignancy, a history of prior radiation to the abdomen or pelvis might suggest the possibility of retroperitoneal fibrosis. It is important to note that the absence of oliguria does NOT rule out significant obstruction. Furthermore, bilateral obstruction is not necessary to have significant worsening of kidney function in patients with CKD, as unilateral obstruction can cause significant decline in kidney function when there is underlying parenchymal disease in the contralateral kidney. In addition to physical exam findings of a distended or palpable bladder, non-invasive renal imaging including ultrasound or non-contrasted CT may reveal a dilated collecting system (i.e., hydronephrosis). Imaging should be obtained whenever there is suspicion of obstruction or if AKI is worsening without an obvious cause. However, imaging may not show evidence of obstruction early in the course of obstruction in patients with concomitant volume depletion or retroperitoneal fibrosis. A simple measure that can be conducted at the bedside is a bladder scan or post-void urine residual. Urine volume greater than 400 mL on a routine bladder scan or a post-void residual volume of greater than 100 mL should prompt work-up and management for outflow obstruction. Prompt relief of outflow obstruction can result in rapid improvement in kidney function if addressed early.

8.4.4 General Management Principles

An abbreviated summary of AKI treatment guidelines is provided in Text Box 10.2. An exhaustive discussion of specific management strategies across the broad spectrum of AKI is beyond the scope of this chapter. However, once the diagnosis of AKI is made, the search for the underlying cause(s) should be accompanied by a simultaneous assessment for evolving complications. Among these include electrolyte abnormalities (e.g., hyperkalemia, hyperphosphatemia, hypocalcemia), acidosis, volume overload, and signs or symptoms of uremia, such as decline in mental status or pericarditis. We recommend early consultation with a nephrologist in patients with evidence of evolving complications of AKI or progressively worsening AKI, as dialytic therapy may be required. Concomitantly, interventions to address potentially reversible causes should be applied. In the absence of obvious volume overload, a trial of volume expansion is often reasonable. While both crystalloid and colloid solutions can be used, isotonic crystalloids are recommended except in cases of hemorrhagic shock [3]. Balanced crystalloid solutions (e.g., lactated ringers) may be superior to non-balanced crystalloids (e.g., normal saline), as data from recent randomized clinical trials of patients in emergency department and ICU settings have observed improved outcomes (including lower mortality, less renal replacement therapy and persistent kidney dysfunction, and hospital-free days) with use of balanced crystalloids compared with normal saline [52]. Starch-based solutions should be avoided given evolving evidence that they may be associated with the development of AKI. There is no established role for the use of diuretics in *prevention* of AKI. However, if volume overload is thought to be contributing to or complicating the AKI (e.g., congestive heart failure), loop diuretics can be used and are preferred over monotherapy with thiazide diuretics, as the latter are less efficacious in patients with diminished GFR. KDIGO proposes a stage-based approach to the management of AKI, shown in Fig. 8.9. However, we would add that consideration for dose adjustment of drugs and assessment of the need for renal replacement therapy (RRT) should occur at all stages of AKI and be individualized to each patient. Furthermore, as the optimal care of patients following AKI has not been established, we feel that greater attention for follow-up of patients with AKI shortly after discharge should focus on patients with persistent injury or among those with moderate to severe injury (KDIGO Stages II and III).

Box 8.2 Abbreviated Summary of Guidelines for Treatment of AKI [3]

What the Guidelines Say You Should Do in AKI

- The cause of AKI should be determined whenever possible, paying special attention to reversible causes
- Patients should be risk stratified for AKI according to their susceptibilities and exposures
- Test patients at increased risk for AKI with measurements of SCr and urine output to detect AKI, with frequency and duration of monitoring based on patient risk and clinical course
- In the absence of hemorrhagic shock, use isotonic crystalloids rather than colloids as initial management for expansion of intravascular volume
- Avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT
- Diuretics should not be used to prevent AKI
- Diuretics should not be used to treat AKI, except in the management of volume overload
- Low-dose dopamine should not be used to prevent or treat AKI

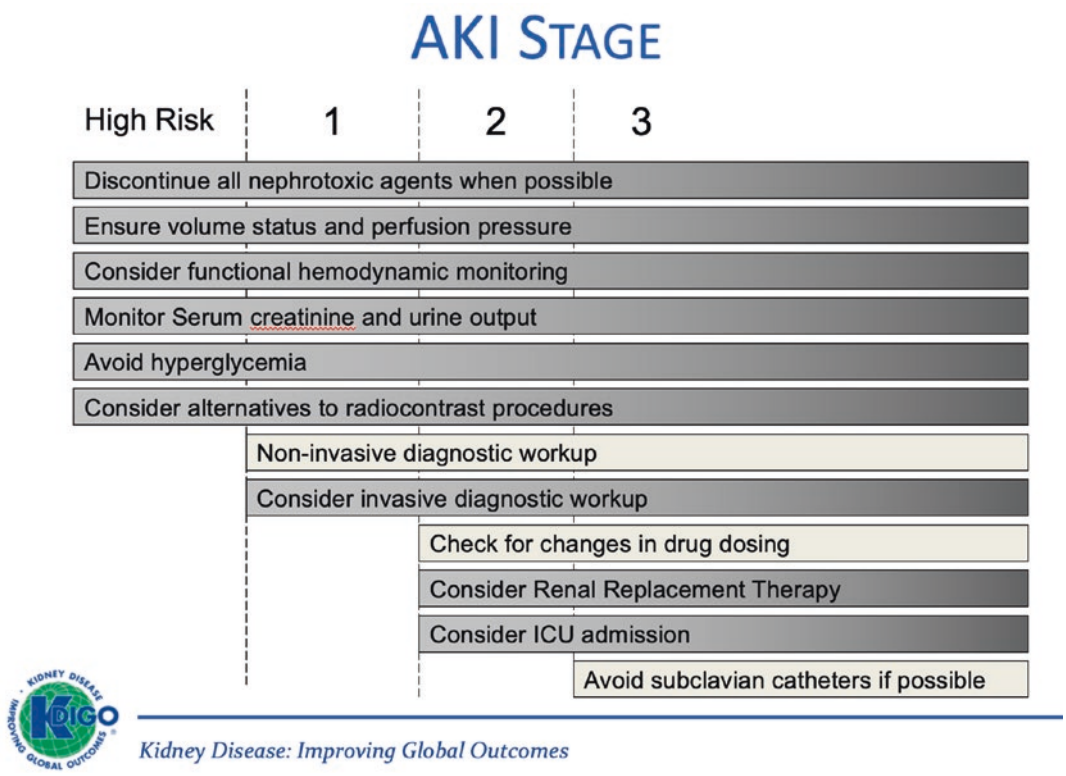

Fig. 8.9 Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. *AKI* acute kidney injury, *ICU* intensive-care unit. (Reprinted from *Kidney International Supplements*; Volume 2, Issue 1; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group; KDIGO Clinical Practice Guideline for Acute Kidney Injury; 2012; pages 1–138; with permission from Elsevier)

It is important to note that the estimation eGFR assumes a "steady state" of glomerular filtration. However, elevation of creatinine lags behind the initial decrease in GFR and the calculated eGFR is not necessarily an accurate reflection of true GFR in patients with AKI and dynamic changes in kidney function. The trend in creatinine should be considered when interpreting GFR, and if the creatinine trend is increasing, there should be an understanding that the actual GFR is less than the calculated GFR. This is important to keep in mind with medication dosing, particularly with potentially nephrotoxic medications such as vancomycin and aminoglycosides. We would recommend conservative dosing of potentially nephrotoxic medications, cautious use of scheduled dosing in drugs with a narrow therapeutic window, and more frequent evaluation of measurable drug levels to guide additional dosing. Some common medications that accumulate with compromised kidney function are listed in Table 8.4.

8.4.5 Renal Replacement Therapy (RRT)

Patients whose injury appears progressive or not readily reversible may require dialysis. The decision to initiate RRT is generally based on averting or treating complications of AKI including azotemia, hyperkalemia, metabolic acidosis, and volume overload. Despite its critical role in managing severe AKI, RRT is not devoid of risk. The process of dialysis itself carries the risk of hypotension and arrhythmia. The anticoagulation process for RRT with heparinization carries bleeding risk, and anticoagulation with regional citrate introduces risk of significant electrolyte abnormalities. Temporary vascular access via catheter for RRT carries risk of bleeding, infection, pneumothorax (with internal jugular catheters), and risk of subsequent central venous stenosis. There is also a concern that the effects of RRT may delay recovery of renal function and contribute to the progression of CKD, though this has yet to be proven. Given these considerations, the optimal timing to initiate dialysis has been unclear. Over the past decade this topic has been studied in multiple randomized clinical trials comparing early versus delayed dialysis initation strategies. The earliest of these included two RCTs (AKIKI and ELAIN), which compared overall survival in critically ill patients with severe AKI who were randomized to early versus delayed dialysis initiation strategies. The two studies had conflicting findings, with AKIKI observing no survival benefit at 60 days with the early initiation strategy, while ELAIN observed a reduced mortality at 90 days with early initiation [53, 54]. Notably, nearly half of patients in the delayed arm of the AKIKI trial did not start RRT, and there were twice the rate of catheter-associated bloodstream infections in the early arm.

Given the discrepant findings of AKIKI and ELAIN, the IDEAL-ICU study similarly compared early and delayed initiation of RRT in patients septic shock and severe AKI. IDEAL-ICU was stopped early for futility after showing no significant difference in 90-day mortality. Most recently, STARRT-AKI, a large multinational trial randomized over 3000 patients with severe AKI (defined as KDIGO stage 2 or 3 AKI) to an accelerated (within 12 h of meeting eligibility criteria) or standard strategy (dialysis for specific indication or if AKI duration exceeding 72 h). Consistent with the findings of AKIKI and IDEAL-ICU, STARRT-AKI found no significant difference in 90 day mortality observed with early initiation [55]. With the benefit of early initiation of dialysis not having been consistently demonstrated, we generally favor a delayed approach in initiating RRT for AKI that is guided by specific clinical indications.

8.4.6 Special Considerations for the Hospitalized Patient with AKI or CKD

There are some special considerations that should be given to patients with CKD who experience AKI. It is preferable to avoid nephrotoxic exposures including IV contrast dye (e.g., CT with

iodinated contrast) in patients with CKD. Additionally, in patients with significantly impaired kidney function (GFR < 30 mL/min/1.73 m^2), MRI with gadolinium contrast should be avoided when possible due to the rare but serious potential consequence of nephrogenic systemic fibrosis (NSF). Newer gadolinium agents may have a better safety profile, though it is unclear if the lower incidence of NSF observed since these agents have come into use is due to lower risk of the agents itself or the more judicious use of the agents in individuals with kidney disease [56]. Standard electrolyte repletion protocols should be avoided in patients with CKD and with AKI in CKD, as the "standard repletion" protocols for potassium, magnesium and phosphorus can result in overcorrection in patients with impaired excretion. In patients with advanced CKD who may need permanent vascular access for dialysis in the near future, an assessment of the patient's dominant arm should be ascertained, and the non-dominant arm should be avoided for blood pressure measurement, blood draws, and peripherally inserted central venous catheters. Additionally, subclavian central catheters should be avoided due to the risk for subsequent central venous stenosis, which can hinder successful creation of arterioveneous fistula or graft placement on the ipsilateral side. Lastly, transfusion of blood products, while often necessary, should be carefully considered in patients who may be eligible for renal transplantation in the future, as exposure to and development of preformed antibodies targeting human leukocyte antigen may hinder future organ matching.

8.4.7 Following AKI: At the Time of Discharge and Beyond

As data accumulate indicating that AKI is an important risk factor for both subsequent AKI and accelerated progression of CKD, determining how to best care for these patients will depend on identifying potential care processes that can reduce the risk for further injury. Per the KDIGO Clinical Practice Guidelines for Acute Kidney Injury, "patients should be evaluated 3 months after AKI for resolution, new onset or worsening of pre-existing CKD" [3]. However, studies have indicated that patients with persistent kidney dysfunction following an AKI event are infrequently seen by nephrologists in the year following AKI and may even be unaware of having had AKI. A recent study finding that among survivors of stage 2–3 AKI, a majority were unaware of that diagnosis at hospital discharge [57]. Whether this results in lack of receipt of established standards of care such as timely vascular access for dialysis or transplant referral or risk factor management is unknown. We recommend that patients who survive an episode of AKI, particularly if severe, be followed regularly to assess for early evidence of CKD (i.e., development of hypertension, proteinuria, or reduced GFR). Post-AKI proteinuria in particular has been shown to be a valuable predictor of CKD progression among patients who survive AKI, with a prospective study of AKI survivors found that the risk of kidney disease progression increased by over 50% for every doubling of post-AKI urine albumin-creatinine ratio (HR 1.53 for each doubling, 95% CI 1.45–1.62) [58]. Follow-up care after AKI also provides the opportunity for a careful appraisal of a patient's medications to ensure appropriate dosing, assess nephrotoxin exposures, and consider resuming nephro- and cardioprotective medications such as ACE-I and ARB. The importance of medication reconciliation after an episode of AKI was illustrated in a recent study that found an increased risk of hypoglycemia after hospital discharge in diabetic patients with AKI compared with matched diabetic patients who did not have AKI (HR 1.27, 95% CI 1.22–1.33); the risk was even higher among patients with non-recovery of kidney function after AKI (HR 1.48, 95% CI 1.36–1.60) [59]. Finally, survivors of AKI appear to be at increased risk of cardiovascular disease. In a systematic review and meta-analysis of cohort studies of adults with and without AKI, individuals with AKI had an 86% and 38% increased risk of cardiovascular mortality and major cardiovascular events, respectively (RR 1.86; 95% CI, 1.72–2.01 and RR 1.38; 95%

CI, 1.23–1.55) [60]. A subsequent prospective cohort study that examined outcomes among survivors of AKI compared with matched patients without AKI found that AKI was associated with increased risk of heart failure events, which was attenuated after adjusting for residual kidney function and proteinuria at 3 months following hospital discharge [22]. As cardioprotective medications are often suspended around the time of AKI, and with CKD a potent cardiovascular risk factor, it is important that careful reinitiation of these medications be considered after AKI has resolved.

8.4.8 Novel Biomarkers in the Diagnosis of AKI

The current gold standard for diagnosis of AKI relies on changes in serum creatinine, which provides a retrospective surrogate measure of GFR, but provides little to no additional phenotyping. Creatinine alone does not distinguish between pre-renal azotemia and true parenchymal damage, nor does it characterize the critical aspects of injury—type of injury, onset, or etiology. These limitations prompted the American Society of Nephrology (ASN) to deem the discovery and standardization of AKI biomarkers with early diagnostic and prognostic potential a *top-priority* research area [61]. In the time since, several urine and serum candidate biomarkers have shown promise in specified patient populations with defined use cases. The rationale for their use derives from preclinical identification of candidate markers serving a functional (i.e., enzymatic or inflammatory) and/or structural role within renal tubular epithelia, or as low molecular weight proteins normally filtered through by the glomerulus and/or metabolized by healthy tubular epithelia. The native functions of these markers indicate their various locations (i.e., intracellular or on the plasma membrane). In commonly used animal models of AKI including ischemia-reperfusion or nephrotoxic injury, active release or shedding of these markers in either free or membrane bound form (exosomes) into the urine following tubular damage has prompted testing in analogous settings of human injury such as cardiopulmonary bypass. Serum/plasma markers, particularly low molecular weight proteins normally filtered by the kidney have also been studied. Early applications of novel biomarkers have included clinical trials, where they have been used in enrollment criteria to enrich study populations, as well as AKI phenotyping studies, though validation of their strength as indicators of specific injury types remains ongoing. Recently, the acute dialysis quality initiative (ADQI) suggesed a potential role of novel biomarkers in combination with serum creatinine to differentiate types of AKI by distinguishing functional changes (elevation in serum creatinine) from evidence of structural damage (biomarker elevation) [62]. These AKI categories provide substages of KDIGO stages of AKI, including stage 1S (“subclinical” AKI: creatinine negative, biomarker positive), stage 1A: (“pre-renal azotemia”: creatinine positive, biomarker negative), and stage 1B (“intrinsic AKI”: creatinine positive, biomarker positive). The strength of this recommendation was condional, indicating that further research is needed to improve confidence.

8.5 Conclusion

In summary, the incidence of AKI is increasing and associated with increased morbidity and mortality. AKI is now recognized as a risk factor for progressive CKD. Additionally, patients with CKD are at increased risk for development of AKI due to structural and functional abnormalities, comorbidities, need for invasive procedures, and multiple medications. Patients with rapid progression to ESKD often have courses marked by decline in kidney function due to one or more episodes of AKI. It is important to identify and counsel patients at risk for AKI and to employ risk reduction measures prior to the development of AKI. A rapid assessment for reversible causes of AKI should occur, especially in patients with CKD, and treatment aimed at rapid optimization of volume and hemodynamic status should be pursued. Early

consultation with a nephrologist is indicated if the cause is not immediately clear, evidence of progressive AKI or the complications emerge, or if a tissue diagnosis is required. Finally, patient who experience AKI should be followed for the resolution of AKI and to evaluate for development or progression of CKD.

Before You Finish: Practice Pearls for the Clinician

- Check eGFR and proteinuria before exposures to nephrotoxins and high-risk procedures to better identify patients at risk for AKI in whom risk reduction strategies may be helpful.
- Discuss long-term goals of care (including whether to initiate dialysis) *before hospitalization.*
- Obtain pre-hospitalization "baseline" serum creatinine to better define kidney function.
- As the rise in creatinine tends to lag behind the inciting injury, focus your search for the underlying cause in the hours to days before creatinine starts to rise.
- The trend in eGFR during evolving or recovering AKI will be more useful for guiding drug dosing than a single eGFR value.
- A high FeNa may not exclude pre-renal azotemia in the patient with CKD and AKI.
- Starch-based crystalloid solutions, phosphate-containing cathartics, and meperedine should be avoided in patients with CKD or AKI.
- Avoid subclavian lines to preserve future dialysis access in hospitalized patients with CKD or severe AKI.
- As patients with CKD who experience AKI may be at high risk for progression to ESKD, prior episodes of AKI in the patient's medical history should be documented.

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9 Preventing Progression of Chronic Kidney Disease: Diet and Lifestyle

Merlin C. Thomas

Before You Start: Facts You Need to Know

- Patients with chronic kidney disease are often recommended to undergo a comprehensive assessment of their diet and lifestyle as part of their overall management strategy.
- Diet and lifestyle modifications are considered to be the cornerstone for the prevention and management of diabetes and hypertension.
- Most patients believe that changes in their diet and lifestyle are among the most important interventions for the management of their kidney disease.
- Most nephrologists are not trained in diet and lifestyle management and are unfamiliar with techniques to institute sustained and effective changes and the potential for adverse outcomes.

9.1 Diet and Lifestyle in the Management of Chronic Kidney Disease

All the major forms of chronic kidney disease (CKD) contain elements of diet and lifestyle in their pathogenesis and progression. Many of these actions are indirect, determined by the effects of diet and lifestyle on the common pathogenic mediators of CKD, including hyperglycemia, hypertension, hyperfiltration, oxidative stress, hyperphosphatemia, systemic inflammation, and activation of the renin angiotensin aldosterone system (RAAS), as well as modulation of the microbiome and the immune system. In addition, exposure to environmental toxins may also play a direct role in damaging the kidneys and accelerating the chronic progression of kidney disease in some patients. Equally, it is now widely recognized that most patients with CKD can benefit from changes in their diet and lifestyle, and current CKD management protocols are based on a foundation of dietary and lifestyle modifications. For the most part, these interventions are directed towards reducing the risk of comorbidities and complications of CKD, including bone demineralization, hyperkalemia, salt and water overload, cardiovascular disease, vascular calcification, and anemia. However, there is now evidence that diet and lifestyle can also significantly influence the progression of CKD and the decline of kidney function towards slowing the march towards end-stage kidney disease (ESKD). In the first instance, all patients with early CKD should be recommended to follow standard dietary recommendations for the general population. Collectively this means that most individuals with early CKD will be asked to moderate their energy, fat, and carbohydrate intake and an

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increase in their intake of fruit and vegetables. However, some patients with CKD will require additional dietary changes or more aggressive dietary restrictions to support failing kidney function and prolong their time before kidney failure. This chapter will review the dietary and lifestyle management of non-dialysis patients with established CKD, including its implementation, potential benefits, safety, and challenges for adherence. The specific dietary management of patients on dialysis and those with kidney stone disease is beyond the scope of this chapter.

9.2 Should Patients with CKD Restrict Their Intake of Protein?

Protein restriction is often the first thing that comes to mind, when considering implementing a dietary change in their non-dialysis patients with CKD. Most people with moderate to severe kidney impairment will already have spontaneously reduced their protein intake (to around 1.0–1.2 g/kg/day), due to the action of CKD on central appetite control centers. However, even this lower amount may still be more dietary protein than is probably optimal. It remains widely recommended in global guidelines that daily protein intake should be further restricted to <0.8 g/kg (i.e., a low protein diet) in most patients with an eGFR<60 mL/min/1.73 m^2, with the exception of patients with heavy proteinuria (>1 g/day) in whom protein losses must be compensated to avoid protein malnutrition [1]. A dietary protein intake of intake <0.8 g/kg is roughly half the amount of protein contained in a standard Western diet. Although this has become known as a "low protein diet," in fact, the globally recommended daily intake (RDI) of protein for the general population also targets this level of dietary intake, meaning that, in reality the nutritional goal is achieve a healthy protein intake, rather than continue a potentially unhealthy protein intake associated with over-nutrition that has become new baseline in most societies.

Dietary protein has a range of actions on healthy kidney function. In particular, a high protein intake induces pre-glomerular (afferent) arteriolar vasodilatation and hyperfiltration, possibly by activating tubulo-glomerular feedback as a result of increased proximal tubular sodium reabsorption. By restricting protein intake, it is hoped to increase afferent arteriolar tone and protect the remnant glomeruli from unnecessary hemodynamic stresses. Other benefits of a low protein diet may include modification of intestinal microbiota and a reduction in phosphate levels. Fifty years ago, when there was little or no effective RAAS blockade available and other antihypertensive therapies were suboptimal, dietary protein restriction was perceived as the best way to safety target kidney hemodynamics and their role in progressive glomerular damage, particularly in disease states where hyperfiltration was a pathogenetic important (e.g., diabetes, focal segmental glomerulosclerosis).

The renoprotective effects of aggressive protein restriction are clearly observed in experiential models of kidney disease [2]. However, its benefits in real-world patients with CKD remain controversial. A recent meta-analysis of ten clinical trials concluded that dietary protein restriction is not beneficial in slowing progressive kidney disease or reducing mortality when compared to standard dietary protein intake [3]. However, most of these studies were small and short term. The best-known clinical trial to test the utility of protein restriction was the Modification of Diet in Renal Disease (MDRD) study, that followed 585 non-diabetic participants with an eGFR<55 mL/min/1.73 m^2 (average 39 mL/min/1.73 m^2). Participants were randomly assigned to a "normal diet" (targeting 1.3 g/kg/day but achieving 1.1 g/kg/day) or a low protein diet (0.58 g/kg/day but achieving 0.77 g/kg/day). Similar to the hemodynamic response with an SGLT2 inhibitor or RAAS inhibitor, there was an initial greater fall in eGFR in those receiving with a low protein diet, followed by a slower rate of decline in eGFR (2.8 vs. 3.9 mL/min/1.73 m^2; i.e., a slowing of 28%). Although ESKD was similar in both arms of the trial, a 6-year follow-up of participants also suggested that this slowing translated into lower rates of ESKD and mortality in those receiving a low protein diet [4]. Although

small, this delay could be advantageous in providing additional time for comprehensive preparation for ESKD management, and which is strongly associated with improved outcomes when commencing dialysis.

Hyperfiltration and increased intra-glomerular pressure is also an important mediator of progressive nephron loss in diabetes. In so far as reducing protein intake may also reduce intra-glomerular pressures, there may be particular benefits of reducing protein intake in people with diabetes. However, the utility of protein restriction in patients with diabetes and CKD also remains problematic [5]. Early studies in patients with type 1 diabetes and CKD have suggested a modest but significant effect of protein restriction on slowing of the rate of decline in kidney function [6], as well a reduction in all-cause mortality [7]. In contrast, studies in people with type 2 diabetes have not shown the same benefits. Moreover, whether these data are equally applicable to modern patients with CKD that are already optimally treated with RAASi and SGLT2 inhibitor is unclear, as the proposed mechanisms of action may be similar to those induced following initiation of a low protein diet.

It has also been argued that conventional protein restriction does not go far enough, and that very low protein diets (<0.3 g/kg/day) may be required to slow kidney function decline in patients with CKD. Consistent with this hypothesis, a recent meta-analysis of ten trials suggested that a very low protein diet (targeting 0.3–0.4 g/kg/day) likely reduces the number of participants reaching ESKD when compared to a low protein diet (targeting ~0.6 g/kg/day) or unrestricted protein intake [3]. However, the challenges of achieving and maintaining a very low protein diet are real. Keto supplements and essential amino acids may need to supplemented, to maintain adequate nutrition. Moreover, in the long-term follow-up of the MDRD study, mortality increased in participants randomized to a very low-protein diet (0.28 g/kg/day + supplements) when compared to a low-protein diet (0.58 g/kg/day) [8].

Overall, the long-term adherence to a low-protein diet can be difficult outside of an intensive trial setting, especially if fat content is also restricted (see below), meaning that such low-protein diets must therefore be high in carbohydrate (which has its own challenges especially in patients with diabetes). Alternatively, all dietary elements must be reduced to achieve these targets, which increases the risk of malnutrition, especially in catabolic patients with uremia. Ultimately, the intensive and restrictive nature of protein restriction means that, although recommended, it is seldom rigorously implemented outside of specialist centers.

9.3 Should Patients with CKD Become Vegetarian or Vegan?

There is a widely held belief that eating vegetable 'protein' may be better for patients with CKD than a regular intake animal 'protein'. Of course, vegetarianism or stricter veganism have a number of potential advantages, including dietary changes in the amount and composition of fat, fiber, minerals and vitamins which impact on health and well-being, and likely convey the benefits of vegetable protein. Recommended diets, such as the Mediterranean diet and the DASH diet, have a regular intake of vegetables as a key component, while minimizing intake on meat, butter, and cheese.

A vegetarian-based diet is safe for CKD patients and may be a practical way to achieve dietary protein restriction goals by avoiding dairy and meat (i.e., animal protein). In addition, some small studies have supported the hypothesis that a vegetarian diet may also slow the decline in kidney function in some individuals and therein delay the initiation of kidney replacement therapy in patients with advanced CKD. For example, one crossover study suggested that the addition of vegetable protein was not associated with eGFR decline, while animal protein intake was associated with progressive decline in kidney function [9]. Benefits on blood pressure, phosphate, and lipid control have also been reported. However, at the same time fruits and vegetables can be high in potassium, meaning every diet must be carefully individualized and

some patients at risk of hyperkalemia will need to be directed away from these foods.

One critical component of a healthy diet is the regular intake of dietary fiber. Increasing the intake of vegetables while total protein intake declines is one way to ensure adequate fiber intake of at least 30 g/day, which is the same as for the general population. Most people will get half of this amount from their diet. Observational studies in patients with CKD have suggested a positive association between fiber intake and survival in patients with CKD. Some small studies have also reported improvements in kidney function [10].

9.4 Should Patients with CKD Restrict Their Intake of Calcium and Phosphorus?

Disturbances of mineral metabolism are common-place in patients with CKD, including increased renal phosphorus retention and hyperphosphatemia, especially in advanced CKD as the GFR falls below 30 mL/min/1.73 m^2. That it seldom occurs before this, is due to the activation of compensatory pathways that promote phosphate loss, including secondary hyperparathyroidism and activation of fibroblast growth factor 23 (FGF23). Restriction of dietary phosphate in proportion to the reduction in eGFR in patients with CKD can prevent the development of excessive parathyroid hormone (PTH) levels. Phosphate restriction (to less than 0.8–1.0 g/day) is often recommended to patients with CKD when serum phosphate or PTH levels are found to be elevated (i.e., in individuals with hyperphosphatemia or hyperparathyroidism) [1]. Again, this target corresponds to the recommended dietary intake for phosphate for healthy adults, so should not be considered a 'low phosphate diet'. However, the amount of phosphate regularly taken each day by most Americans is almost twice the recommended dietary intake. The rationale for treating/preventing hyperphosphatemia or hyperparathyroidism related to its deleterious effects on vascular calcification/stiffness, calciphylaxis, and cardiovascular risk. Phosphate restriction is usually achieved by restriction of dairy products and animal protein intake (Box 9.1), which may already be being undertaken for their respective benefits. However, it is possible to restrict protein without fully restricting phosphorus, so careful selection of protein sources must also be undertaken. Processed foods may also contain higher amounts of processed phosphate with much higher bioavailability compared with organic phosphate from unprocessed sources.

Box 9.1 Foods Naturally High in Phosphate (Which Should Be Avoided or Eaten in Small Amounts in Patients with CKD When Serum Phosphate or PTH Levels Are Elevated)

- Drinks: beer, milk, cocoa, cola
- Dairy products: cheese, custard, yogurt, ice cream
- High-protein foods: meat, liver, shellfish, legumes (beans and peas), nuts and seeds, whole-grain products

To reduce the calcium-phosphate product, alongside dietary phosphate restriction, some kidney dieticians also recommend limiting total calcium intake to <1 g/day, consistent with healthy intake guidelines. Certainly, limiting intake to below the usual 2 g/day may reduce the risk a positive calcium balance and ectopic calcification. The major calcium source in most diets is dairy products, which are also restricted when attempting to reduce potassium intake, addressing both targets simultaneously.

9.5 Should Patients with CKD Restrict Their Intake of Potassium?

Hyperkalemia is a common finding in patients with CKD, especially in those with diabetes and those using beta blockers, RAAS blockers, mineralocorticoid receptor antagonists (MRA), alone

or in combination. Excessive levels of potassium may contribute to bradycardia, severe muscle weakness, paralysis or even sudden death in some patients. In patients with CKD, hyperkalemia is a common reason for hospitalization and (emergency) initiation of dialysis that may be associated with poor outcomes when compared to a timely staged introduction of kidney replacement therapy. The advent of effective oral potassium binders can substantially reduce the risk of hyperkalemia in some settings. However, these do not eliminate the need for dietary potassium restriction.

Most patients with advanced CKD (eGFR <30 mL/min/1.73 m^2) and those with CKD at risk of hyperkalemia (e.g., those on high potassium levels, on RAAS blockers or MRA) are often recommended to reduce their dietary intake of foods that are rich in potassium (Box 9.2) and aim to eat between 2 and 4 g of potassium per day as a means to reduce the risk of dangerous hyperkalemia. This is usually achieved by choosing lower-potassium fruit and vegetables and their juices (Box 9.3) and limiting the intake of milk, legumes, nuts, tomatoes, and stone fruit. Many products now provide potassium content as part of their nutritional information, allowing patients to choose the lower-potassium alternatives.

At the same time, diets naturally rich in potassium (e.g., the Mediterranean diet) may be associated with improved outcomes, including lower blood pressure, and slower decline in eGFR. For example, in the MDRD cohort higher potassium consumption was associated with improved survival. In addition, some studies suggest that patients with a potassium in mild to moderate hyperkalemia (5–5.5 mol/L) may have a lower risk of dying than those with low or even low-normal potassium levels (<4 mmol/L) [11], partly due to actions on cardiac arrhythmogenicity. Outside of the setting of individuals at risk for hyperkalemia, most patients with CKD should not restrict their potassium intake, although potassium levels should be carefully monitored, especially when starting new agents or during intercurrent illness when potassium levels can risk due to an acute fall in eGFR.

Box 9.2 Foods Naturally High in Potassium (Which Should Be Avoided or Eaten in Small Amounts in Patients with CKD at Risk of Hyperkalemia?)

- Grains
  - Whole-grain breads, wheat bran, granola, and granola bars
- Dairy products
  - Milk and milk products
- Drinks
  - Sports drinks, energy drinks, vegetable juices, soy milk
- Snack foods/sweets
  - Peanut butter, nuts or seeds, chocolate, dried fruit
- Fruits
  - Stone fruit (e.g., apricots, avocado, dates, prunes, mango, papaya, cherries), bananas, kiwifruit, coconut, melon, nectarines, oranges, pears, pomegranate
- Vegetables
  - Tomatoes and tomato products, raw brassica (e.g., broccoli, Brussels sprouts, cabbage greens), carrots, olives, legumes (e.g., pinto beans, kidney beans, black beans, baked beans, peas) potatoes, pumpkins, parsnips
- Seafood
  - Shellfish, lobster, whitefish, salmon
- Beef
  - Ground beef, sirloin steak (and most other beef products)

Box 9.3 Foods Naturally Low in Potassium (Which Should Be Preferred in Patients with CKD at Risk of Hyperkalemia?)

- Foods prepared with white flour (e.g., pasta, bread)
- White rice
- Fruits: apples, watermelon, berries (e.g., blackberries, blueberries, cranberries, raspberries, strawberries)
- Vegetables: cauliflower, asparagus, zucchini, spinach, corn, onions
- Meat: chicken, turkey, tuna, eggs
- Dairy products: Cheddar, Swiss or cottage cheese

9.6 Should Obese Patients with CKD Lose Weight?

The majority of adults are now overweight or obese. This is also the case in most patients with CKD. The accumulation of fat, and subsequently deposition of ectopic fat in the development of diabetes, hypertension, and atherosclerotic vascular disease, the major causes of CKD. But even outside these obvious settings, more and more of our patients with glomerular diseases and other kidney pathology are overweight or obese. This may be considered part of a global trend for all adults to progressively gain weight over their lifetime, amplified by the reduced physical activity associated with chronic illness. Put together, obesity is now an everyday companion for the nephrologist. But should we be doing something about it?

Certainly, obesity in patients with CKD is associated with the increased incidence and severity of CVD, hypertension, dyslipidemia, diabetes, and reduced survival. Obesity itself may be associated with focal and segmental glomerulosclerosis, possibly due to changes in intraglomerular hemodynamics induced by obesity. In observational studies, weight gain is independently associated with incident CKD, even after adjusting for blood pressure and incident diabetes [12]. In addition, excess body fat is associated with faster rate of decline in kidney function and increased incidence of end-stage kidney disease (ESKD) in patients with CKD [13].

In clinical trials, weight loss clearly results in reduction in blood pressure, especially in patients already taking antihypertensive drug treatment like many of those with CKD. Moreover, amongst overweight patients with chronic kidney disease, weight loss interventions may be associated with a decrease in albuminuria. For example, in a cohort of Dutch patients from the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, weight loss was associated with a reduction in urinary albumin excretion [14]. Significant weight loss associated with bariatric surgery and its effects of kidney function [15] further exemplifies the potential of benefits of weight loss that are seldom realized by diet alone, but never achieved without it. Moreover, the broad effects of obesity on cardiovascular health, sleep, cancer, mood, wound healing, self-image and a myriad of other areas means that most obese patients with CKD should be encouraged to lose weight, chiefly through dieting.

Fundamentally, weight loss diets aim to provide less food energy (measured as calories or kilojoules) than is required for metabolism and daily energy expenditure (known as a negative energy balance). The daily energy requirement can be roughly calculated (Box 9.3). To lose weight, the energy intake must be less than that of the daily energy requirement. Most weight loss diets start at an energy deficit of about 500 kcal/day. For example, if you calculate your patient's energy requirement as 8000 kJ a day, to slowly lose weight, they can target 7500 kJ/day. This will generally achieve a weight loss rate of approximately 1 lb (~0.5 kg) per week.

Reducing the amount of energy obtained from the diet can be achieved in any number of different ways. There is no 'one size fits all' approach, which means a comprehensive diet and lifestyle assessment by a trained dietician is an important first step. Sometimes only minor changes are required to reduce the energy content of a diet. For example, the energy in a can of Coke is around 500 kJ. So to lose weight, subtrating all the additional calories contained in soft drink and other calorie rich foods by omitting them from your diet, may be enough for may patients with CKD to acheive a negative calorie balance and lose weight.

The most common way to reduce energy intake is to go on a diet. This means regulating some or all of food intake according to a formula, recipe book or strategy. Whether the composition of a diet affects how well it produces weight loss remains highly contentious. Rigorous head-to-head studies of different diets have failed to show any superiority of one over another. On average they all achieve about the same amount of weight loss of 2–4 kg. It may be that what they are eating is probably not as important as the fact that they are adhering to some sort of plan for what they eat. It is likely that the mere process of embracing any dietary restrictions, thinking about and coordinating the foods they eat, makes them tend to eat less (energy) and eat better.

Diets that promote weight loss can be broadly divided into four categories, which chiefly restrict one element (for the sake of simplicity and compliance):

Low- fat diets—(e.g., STEP, Pritikin and Ornish diets) reduce energy from fat, without reducing meals. Reducing the fat in the diet can also improve lipid levels (see below). However, reducing fat often means increasing the content of carbohydrate and/or protein in the diet which may have drawbacks in insulin-resistant patients with CKD.

Low- carbohydrate diets (e.g., Atkins diet)—are popular for the management of type 2 diabetes, because of their beneficial effects on glucose control as well as caloric intake. There are a range of other diets that share roughly the same principles with respect to carbohydrate but vary in regard to other nutrients (e.g., fat or protein). For example, the Atkins diet does not restrict the (animal) fat you eat, while the CSIRO Total Wellbeing Diet and the 'Zone diet' reduce both fat and carbohydrate in your diet, so the relative proportion of energy from protein goes up. While this can have the added effect of suppressing hunger and promoting your sense of fullness earlier in the meal, it may also have adverse effects in the kidney and is therefore not generally recommended to patients with CKD.

Low- energy/calorie diets (e.g., DASH diet and Weight Watchers)—specifically target the problem of too much energy in the diet, by focusing on reducing the intake of processed 'energy-dense' foods exchanging them for low-calorie substitutes without focusing on diet composition. This strategy is generally preferred in obese patients with CKD and can be readily achieved by calorie counting, meal substitutes or following recipe plans.

Low- GI diets—(e.g., New Glucose Revolution, South Beach diet) have also become popular as a means to both slow the delivery of carbohydrate for meals and induce weight loss. High-GI (>70) foods such as white bread, potatoes or corn flakes break down their sugars quickly during digestion requiring insulin to surge in response to the extra demand. Over and above the extra energy they contain, a diet rich in high-GI foods is strongly associated with weight gain. By contrast, low-GI (<55) foods deliver their sugar load more slowly, so the demands on the pancreas are not so steep and fat accumulation is reduced. It is thought that low-GI diets may assist weight control by improving satiety and hunger between meals as slow sugars continue to be absorbed well after a meal.

9.7 Should All Patients with CKD Be on a Low-Fat Diet?

There is strong evidence that the presence and severity of dyslipidemia is associated with the risk of progressive kidney function decline in both diabetic and non-diabetic kidney diseases. Whether dyslipidemia is simply a marker of kidney dysfunction or a mediator of progressive damage remains to be firmly established. Certainly, a kidney phenotype is not seen in familial hypercholesterolemia or familial mixed dyslipidemia that would suggest its primary role in kidney injury. However, treatment with statins may reduce urinary albumin excretion and has been shown to modestly slow the rate of decline of GFR [16]. In each case, these kidney benefits were not correlated with improvements in lipid levels leading to the argument that any kidney actions are pleiotropic effects of statins rather than the result of lipid lowering. Yet, because of the high cardiovascular risk and clear benefits of

lipid lowering on cardiovascular outcomes in patients with CKD (not on dialysis), most patients will be recommended to reduce their lipid levels. This usually takes the form of statin therapy in combination with reduction in dietary fat intake, whether or not patients are overweight.

There is some observational data to suggest dietary fat is associated with progressive kidney disease. For example, in one study the nutritional pattern of patients with diabetes progressing from normo-albuminuria from micro-albuminuria was characterized by greater intake of saturated fat and a reduced intake of polyunsaturated and monounsaturated fat [17]. These lipid differences are also characteristic of diets associated with hypertension, weight gain and insulin resistance, all of which may contribute to progressive kidney disease.

Limited intake of intake of saturated fat (to <10% of total energy) and total fat (to <30% of daily energy intake is recommended for all healthy adults, and is also recommended for all patients with CKD. The broader utility of this strategy is exemplified by the Mediterranean diet and the DASH diet) that are associated with a lower risk for CKD progression and all-cause mortality among people with CKD [18].

9.8 Should Patients with CKD Restrict Their Intake of Salt?

Urinary sodium retention is a major contributor to hypertension and volume overload in patients with chronic kidney disease. Consequently, limiting the dietary intake of sodium appears a logical and appealing intervention for the prevention and management of hypertension in patients with CKD. Most guidelines suggest patients with CKD should target an intake of <60 mmol/day, equivalent to about one-third of the salt consumed by the general public. However, this target remains controversial. The dietary intake of sodium represents only a small fraction of the filtered sodium load (<1%), so its effects on kidney load are minimal. Any reduction in sodium intake is also associated with activation of sodium retention pathways including the RAAS and sympathetic nervous system, which may be counterproductive in the setting of CKD. The anticipated reduction in blood pressure from sodium restriction (1–3 mmHg in a trial setting) is also much lower and more variable than that achieved by antihypertensive therapy, and if blood pressure control is desired, it may be more effectively achieved by medications. Finally, the long-term benefits of sodium restriction in patients with CKD remain unclear. One study in patients with type 1 diabetes and macroalbuminuria suggested that a low sodium intake was associated with an increased risk of progression to ESKD [19]. By contrast, short-term studies have suggested additive benefits on both blood pressure and albuminuria when sodium restriction is added to patients with CKD already on RAAS blockers [20]. This may be because the RAAS is the chief counter-regulatory response to sodium restriction, and blocking it prevents escape. Consequently, it is reasonable to consider that RAAS blockade should be given to any patients adhering to a low-salt diet and a low-salt diet be considered for any patient on RAAS blockade, because of this synergism. As the majority of patients with CKD struggle to control their blood pressure and prevent volume overload, in practice this means a low-sodium diet is appropriate for most patients with CKD.

The major sources of dietary sodium are processed foods and condiments, rather than salt that is added onto meals by patients. Switching to low-salt version of products and using fresh ingredients where possible are the simplest ways to reduce sodium intake for most patients with CKD.

9.9 Should Patients with CKD Be Undertaking Regular Physical Activity?

Inactive people have an increased risk of developing kidney disease compared with very active people. Most patients with CKD are sedentary, undertaking little physical activity on a regular basis [21]. Although physical activity can improve blood pressure, lipid, glucose, and weight control and alleviate their mood status, it

is seldom stressed as an intervention in patients with CKD. This is mostly because of reduced exercise tolerance and comorbidity, such as hypoglycemia, anemia, postural dizziness, foot disease, and cardiovascular disease. Indeed so many patients with CKD have established CVD or risk factors for it that vigorous activity is usually contraindicated. However, this does not mean that moderate activity is inappropriate or unhelpful. Indeed, even in patients with established CVD, a program of regular moderate physical activity is associated with improved clinical outcomes.

There is a robust association between kidney function decline in patients with established CKD and physical activity [18]. Only limited research has been undertaken on the effects of exercise in the management of patients with CKD. Some trials have reported improvement in albuminuria following initiation of exercise programs [22], implying kidney benefits, although this could reflect better hemodynamic control. However, taken together, physical activity and exercise interventions have not been associated with slower kidney function decline in patients with established CKD [23].

9.10 Should Patients with CKD Give Up Drinking Alcohol?

Many patients believe that excessive alcohol intake is a common cause of chronic kidney disease (because of its obvious polyuric effects). Indeed, many patients believe that moderating or giving up their drinking is the most important way to protect their kidney function. Certainly, a high intake of alcohol (>5 units per day in men) is associated with an increased risk of cardiovascular disease, hypertension, cancer, and other health problems including chronic kidney disease. Whether this association is confounded by the adverse lifestyle of heavy drinkers remains to be fully established. Overall, a J-shaped association between alcohol intake and adverse health outcomes (such that abstainers have an increased risk of some health problems compared to those who regularly drink 1–3 units every day) appears to exist in patients with CKD [18]. This means that abstinence need not be recommended to most patients with CKD. Where patients can maintain control of their drinking, a healthy habit should not be discouraged. However, binge drinking may be potentially more dangerous in patients with CKD [24] and abstinence may be appropriate in heavy drinkers with CKD.

9.11 All Smokers with CKD Should Be Encouraged to Stop Smoking

There is clear evidence that smoking is a risk factor for progressive kidney disease. Inhaled toxins and generated reactive oxygen species pass to the kidney as well as to other parts of the body where they are both directly injurious and amplify injurious processes including inflammation and fibrosis in the kidney. Smoking also results in neurohormonal surges that may be particularly injuries to stiff vascular architecture that characterizes patients with CKD. There is some data to suggest that smoking cessation reduces the rate of loss of kidney function amongst patients with progressive kidney disease [18]. At the same time, some studies have reported acute increases in urinary albumin excretion 6 months after quitting [25]. This may be similar to the increase in diabetes and weight gain also observed with smoking cessation, which abates and ultimately leads to reduction in the long term. The long-term effects of smoking cessation on kidney function remain to be established but appear to be positive [26]. By contrast, smoking cessation should be reiterated for cardio-protection and cancer risk as these remain the major causes of death in patients with CKD [1].

9.12 Does Diet and Lifestyle Really Matter in Patients with CKD?

More evidence is needed regarding the best approach to diet and lifestyle in non-dialysis patients with established CKD. This cannot be

simply extrapolated from patients without CKD, as the complex effects of comorbid illness, polypharmacy, and the uremic milieu itself each present their own challenges. Overall there is limited data that initiating comprehensive changes in diet and lifestyle is able to protect kidney function (Box 9.4). At the same time, dietary change exposes patients to significant culinary restrictions. Many of these patients can anticipate very poor clinical outcomes, so quality of life is also often an important consideration. A 'healthy' diet can be safely recommended in most patients with CKD as a baseline, consistent with general population recommendations, with additional restrictions only added on an as required basis, as appropriate in patients with or high risk of specific complications, such as hypertension, volumeoverload,hyperkalemia,hyperparathyroidism (Boxes 9.5 and 9.6).

Box 9.4 Estimating Energy Intake in Adults

Women:

[655.1 + (9.56 × weight in kg) + (1.85 × height in cm) − (4.68 × age in years)] × 4.2 × activity factor

Men:

[664.7 + (13.75 × weight in kg) + (5 × height in cm) − (6.76 × age in years)] × 4.2 × activity factor

The activity factor in each equation (which adjusts for how active you are) is:

- For those who do little or no exercise each day, multiply by 1.2
- For those who do light exercise on 1–3 days a week, multiply by 1.375
- For those who do moderate exercise on 3–5 days a week, multiply by 1.55
- For those who do hard exercise on 6–7 days a week, multiply by 1.725
- For those who do daily exercise, a physical job or hard training, multiply by 1.9

Box 9.5 What the KDIGO Guidelines Say You Should Do [1]

We recommend that individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated

Restriction of Dietary Salt Intake in Patients with CKD

We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated

Restriction of Dietary Protein Intake in Patients with CKD

We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes or without diabetes and GFR <30 mL/min/1.73 m^2 with appropriate education. We suggest avoiding high protein intake (41.3 g/kg/day) in adults with CKD at risk of progression

Lifestyle in Patients with CKD

We recommend that people with CKD be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 min 5 times per week), achieve a healthy weight (BMI 20–25, according to country-specific demographics) and stop smoking

Box 9.6 Relevant Guidelines

1. KDOQI Guideline 2020

Ikizler TA, Burrowes JD, Byham-Gray LD, et al.; KDOQI Nutrition in CKD Guideline Work Group. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis. 2020;76(3)(suppl 1):S1–S107. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/

2. National Institute for Diabetes, Digestive and Kidney Diseases
Nutrition for Advanced Chronic Kidney Disease in Adults. https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/eating-nutrition/nutrition-advanced-chronic-kidney-disease-adults

3. National Institute for Health and Clinical Excellence (NICE) Guideline [NG203] 2021
Chronic kidney disease: assessment and management. https://www.nice.org.uk/guidance/ng203/chapter/Recommendations

4. SIN-ANDID-ANED: Italian Society of Nephrology-Association of Dieticians-Italian Association of Hemodialysis, Dialysis and Transplantation 2018
Nutritional treatment of advanced CKD: twenty consensus statements https://link.springer.com/article/10.1007/s40620-018-0497-z

5. Renal Association (UK)
Wright, M.; Southcott, E.; MacLaughlin, H.; Wineberg, S. Clinical practice guideline on undernutrition in chronic kidney disease. BMC Nephrol. 2019, 20, 370. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6796390/

6. Andalusian Group for Nutrition Reflection and Investigation (GARIN) Group
Alhambra-Expósito, M.-R.; Molina-Puerta, M.-J.; Olveira, G.; Arraiza-Irigoyen, C.; Fernández-Soto, M.; García-Almeida, J.-M.; García-Luna, P.-P.; Gómez-Pérez, A.-M.; Irles-Rocamora, J.-A.; Molina-Soria, J.-B.; et al. Recomendaciones del grupo GARIN para el tratamiento dietético de los pacientes con enfermedad renal crónica. Nutr. Hosp. 2019, 36, 183–217. https://www.nutricionhospitalaria.org/articles/01823/show

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Before You Finish: Practice Pearls for the Clinician

- All patients with CKD should be encouraged to adopt a healthy diet, consistent with nutritional guidelines for all adults.
- There is limited evidence that additional dietary restrictions or lifestyle modifications significantly improves kidney outcomes in patients with chronic kidney disease.
- A more liberal approach to diet and lifestyle should be considered in patients with advanced CKD in keeping with their poor prognosis and comorbidity and the overall goal of palliation.
- Targeted interventions can be highly appropriate for some patients, such as those with bone-mineral disorder, poorly controlled hypertension or hyperkalemia.
- In severely obese patients, significant weight loss may improve cardiovascular health, mood, healing, sleep and a myriad of other outcomes and should be encouraged.
- Nephrologists should engage in their patients' diet plans to ensure that their safety is not compromised and its potential for success is reinforced.

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10 Preventing Progression of Chronic Kidney Disease: Renin–Angiotensin–Aldosterone System Blockade Beyond Blood Pressure

Merlin C. Thomas

Before You Start: Facts You Need to Know

- Activation of the renin–angiotensin–aldosterone system (RAAS) contributes to the progressive decline in kidney function of patients with chronic kidney disease.
- RAAS inhibitors are a first-line therapy for most patients with CKD, for the control of blood pressure, reduction in cardiovascular and heart failure risks.
- Blockade of the RAAS is also the most widely used strategy to prevent progression of chronic kidney disease, both in the presence and absence of diabetes.
- Blockade of the RAAS has pleiotropic effects in the kidney beyond blood pressure lowering, consistent with the role of the RAAS in kidney pathophysiology.
- Clinical trials have demonstrated slowing in kidney function decline in patients with chronic kidney disease following treatment with RAAS inhibitors, beyond that seen with other antihypertensive classes despite comparable efficacy with respect to blood pressure lowering.

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10.1 The Renin–Angiotensin–Aldosterone System (RAAS)

The renin–angiotensin–aldosterone system (RAAS) is a fundamental regulator of kidney homeostasis, mediated through its myriad effects on kidney structure/function, sodium and water handling, glomerular filtration pressure, blood flow, cellular growth, and differentiation. The RAAS has important systemic (endocrine) actions, local (paracrine) actions, and cellular (autocrine) functions. Indeed, there is also evidence of an intracrine function with an active RAAS within kidney cells. Increased activation of the RAAS is a common element in all forms of kidney disease. It serves to adaptively maintain kidney function in the acute setting, but in the chronic setting RAAS activation drives maladaptive change, progressive nephron loss, and fibrogenesis, as well as the development of common complications associated with CKD including volume overload, hypertension, endothelial dysfunction, electrolyte disturbances, adverse cardiac remodeling, and accelerated atherosclerosis.

The RAAS is a complex multi-enzymatic hormonal cascade (Fig. 10.1). RAAS activity is regulated on many levels, with both positive and negative feedback pathways that ensure optimal responsiveness to both physiological

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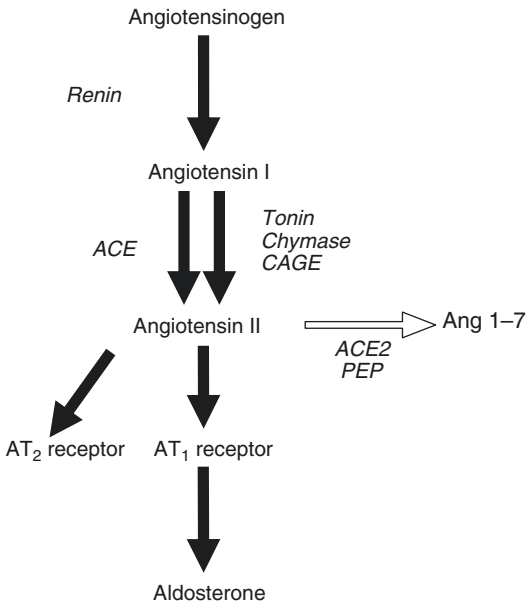

Fig. 10.1 The renin–angiotensin system

and pathogenic stimuli. At its most simplistic, angiotensinogen, the major peptide substrate, is processed in a two-step proteolytic reaction involving renin and angiotensin-converting enzyme (ACE), resulting in the generation of angiotensin (Ang) II, the major effector molecule of the RAAS. Other enzymes can also generate Ang II via different enzymatic processing of angiotensinogen (so-called non-ACE pathways) which are more or less important in different tissues and in different states. Ang II has potent vasoconstrictor actions on the renal efferent arterioles that increase kidney vascular resistance and elevate intraglomerular hydraulic pressures. In addition, Ang II has many non-hemodynamic actions on the kidney function and structure (Box 10.1). Ang II also triggers the release of aldosterone from the adrenal cortex and mediates vasoconstriction via activation of type 1 angiotensin (AT_1) receptors.

Ang II is degraded predominantly by angiotensin-converting enzyme 2 (ACE2) and prolyl-endopeptidase to generate smaller peptides including Ang 1–7 which have vascular and kidney actions antagonistic to those of Ang II. The coordinated actions of these opposing pathways provide exquisite control of Ang II levels and its downstream metabolites, allowing for the dynamic responsiveness required to ensure a rapid return to homeostasis.

Box 10.1 Some of the Non-Haemodynamic Actions of Angiotensin II in the Kidney

- Increased sodium/water reabsorption.
- Tubular hypertrophy and atrophy.
- Epithelial to mesenchymal transition.
- Myofibroblast accumulation.
- Mesangial contraction.
- Foot process effacement (dedifferentiation).
- Fibrogenesis.
- Renal tubular acidosis.
- Potassium secretion.
- NADPH-dependent generation of reactive oxygen species.
- Mitochondrial dysfunction.
- Proinflammatory signaling and inflammatory cell recruitment.
- Inhibition of renin release (short feedback loop).

The systemic RAAS is regulated by angiotensinogen secreted by the liver, renin released from the kidneys, and ACE activity in the lungs. However, except for renin that is kidney specific, each tissue and many cells contain other functional elements of the RAAS to a greater or lesser extent. In particular, the levels of Ang II and other angiotensin peptides are higher in the kidney than in any other tissue in the body, reflecting the key role of the intrarenal RAAS in dynamically maintaining healthy kidney function. For example, the concentration of Ang II in the kidney interstitial fluid has been reported to be over a 1000-fold higher than in the systemic circulation [1]. In patients with chronic kidney disease (CKD), the activity of the intrarenal RAAS is often inappropriately elevated for the elevated volume status of most patients, which under normal circumstances should see suppres-

sion of the RAAS and augment natriuresis. It is thought that this compensation is an adaptation in attempt to maintain kidney function in times of acute stress. However, in the long term, chronic activation of the RAAS is ultimately maladaptive. Some patients (especially those with diabetes) may manifest no apparent increase or even suppression of the systemic RAAS, possibly because of excessive local activation of the RAAS in the kidney. Indeed, the action of RAAS blockers even in low renin hypertension suggest that kidney (tissue) RAAS may be as or more important than the systemic RAAS. Indeed, an infusion of angiotensin II, even in sub-pressor doses, still results in tubular hypertrophy, apoptosis, and progressive glomerulosclerosis.

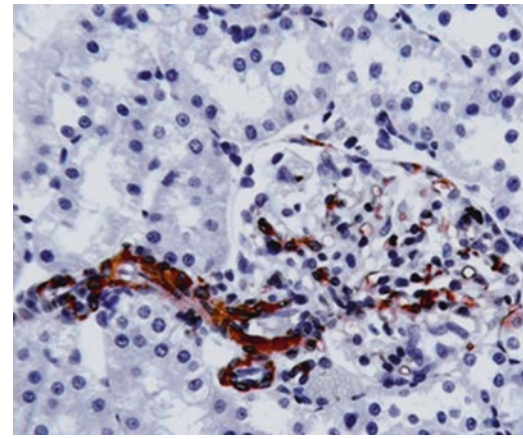

Fig. 10.2 Localization of AT_1-receptor expression in the kidney with dense staining in the juxtaglomerular apparatus, glomerular capillaries and along the efferent glomerular arteriole

10.2 How Do You Block the RAAS?

The discovery agents to inhibit signaling through the RAAS blockade was one of the most important medical breakthroughs of the twentieth century, particularly for the management of CKD. Although β-blockers have actions to inhibit kidney renin release, the development of agents that inhibit ACE to reduce the synthesis of Ang II (known as ACE inhibitors) and agents that antagonize the actions of Ang II at type 1 angiotensin (AT_1) receptors (known as angiotensin II receptor blockers or ARBs; Fig. 10.2) enabled significant inhibition of the pathogenic effects of the RAAS for the first time.

Although very different in their target activities, both ACE and ARBs block the actions of Ang II and also increase production of Ang 1–7, by reducing its degradation or increasing circulating levels of Ang II, respectively. In addition, both strategies also produce a reactive rise in the production of renin and aldosterone to partly overcome their actions. As a result, both ACE inhibitors and ARBs produce broadly similar effects on blood pressure [2], although individual responses may vary. Similarly, the antiproteinuric and cardiac responses appear to be broadly equivalent [3, 4]. For example, in the head-to-head Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, the ACE inhibitor, enalapril and the ARB, telmisartan had similar renoprotective actions in patients with type 2 diabetes and early kidney disease [5]. Although some meta-analyses have suggested that while ACE inhibitors have kidney advantages over ARBs in trials, more recent studies suggest very similar effects on kidney failure, heart failure cardiovascular outcomes, and CV death in patients with CKD [6].

Oral antagonists of the mineralocorticoid receptor (MRA) that competitively antagonize its activation by the adrenal steroidal hormone, aldosterone, have been available since spironolactone was originally developed in the 1950s using structural elements of the sex hormone, progesterone. MRA are able to induce renal natriuresis and therein lower systemic blood pressure levels. However, the antihypertensive effects of steroidal MRAs are generally modest compared to ACE inhibitors or ARBs and are more in line with other diuretic agents. Dosing with spironolactone is also often limited by side effects (e.g., hyperkalaemia, acute kidney injury), partial agonism at the MR, and lack of selectivity leading to off-target activity at other steroid hormone receptors. More recently, nonsteroidal MRAs with far greater affinity, selectivity, and potency have been developed, including finerenone and esaxerenone. Not only does there

appear to be a lower risk of limiting hyperkalaemia with these nonsteroidal agents, but recent clinical trials have demonstrated important effects on kidney and cardiac outcomes in patients with CKD (see below).

10.3 What Is the Evidence That RAAS Blockade Protects the Kidneys in CKD?

Many studies have been undertaken to explore the effects of RAAS blockade in patients with progressive CKD. The first was undertaken by the Collaborative study group in early 1990s in participants with type 1 diabetes with severely elevated urinary albumin excretion (>500 mg per day). Over a median follow-up of 3 years, and despite aiming for the same BP targets, participants randomized to receive captopril were significantly less likely to experience doubling of their serum creatinine (25/207) when compared to placebo (43/202; $P = 0.007$) and the overall rate of decline in kidney function was 35% slower in participants receiving captopril ($P = 0.03$) [7]. Similar findings were reported in patients with type 2 diabetes and proteinuria (>1 g/day) in the RENAAL and IDNT trials [8, 9]. Similar studies in nondiabetic CKD in patients with proteinuria have also reported similar benefits [10]. For example, the HKVIN study in patients with IgA nephropathy reported a 33% reduction in proteinuria, as well as a modest slowing in kidney function decline [11]. Current kidney guidelines strongly recommend the use of RAAS blocker in all forms of proteinuric kidney disease, to slow progression to end-stage kidney disease (ESKD) (Boxes 10.2, 10.3, and 10.4) and as well as antagonize the effects of RAAS on hypertension, heart failure, and CVD outcomes. Importantly, these renoprotective benefits in the response to RAAS blockade in proteinuric patients appears to be independent on systemic blood pressure levels such that observed renoprotective efficacy is similar in hypertensive and normotensive patients.

By contrast, the potential utility of RAAS blockade in non-proteinuric kidney disease, beyond blood pressure lowering, remains controversial. In patients with diabetes, there is evidence that RAAS blockade reduce the risk of progression from microalbuminuria to macroalbuminuria by at least one third and increased likelihood of regression from microalbuminuria to normoalbuminuria by two- to threefold when compared to standard (non-RAAS) antihypertensive therapy [12]. However, in the Benazapril trial and REIN trials, although benefits were seen in nondiabetic patients with proteinuria, little or no benefit was observed in individuals with (non-nephrotic range) protein excretion 500–1000 mg/day. Although there remain useful antihypertensive, cardiovascular, and heart failure benefits in this setting that mean that most patients with non-proteinuric CKD will still be using RAAS inhibitors, it may not be sufficient to protect their kidneys.

Nonsteroidal MRAs have also recently remonstrated useful renoprotective effect in patients with diabetes and elevated albuminuria, over and above standard of care with an ARB or ACE inhibitor. For example, in the FIDELIO-DKD trial the use of finerenone was associated with an 18% lower incidence of primary composite outcome (kidney failure, sustained decrease of 40% decline in eGFR, or death from kidney causes). In the FIGARO-DKD trial, despite cardiovascular/heart failure benefits being observed, the effect on the same kidney outcome was not significantly different between finerenone and placebo (HR 0.87, 95% CI 0.76 to 1.01). Taken together the effect appears to be consistent, though potentially more modest than observed with SGLT2 inhibitors in the same setting. In addition, serious hyperkalaemia remains a concern with these nonsteroidal MRA, outside of the carefully considered inclusion criteria and monitoring in a trial setting.

10.4 Does RAAS Blockade Only Protect the Kidneys by Improving Blood Pressure Control?

Most people (>90%) with CKD have hypertension requiring antihypertensive therapy. Blood pressure control is important to slow progression of kidney damage in CKD (see Chap. 5).

It is well established that the activation of the RAAS promotes the development and maintenance of hypertension in CKD. This is partly mediated by the direct vasoconstrictor actions of Ang II on smooth muscle to increase peripheral vascular resistance. However, salt and water retention, tubular hypertrophy, augmented activation of the sympathetic nervous system, and sensitivity to the effects of noradrenaline in the kidney also play a role [13]. In addition, T-cell activation also appears to be an important driver of angiotensin-dependent hypertension, as the induction of hypertension in mice is prevented by removing the AT_1 receptor from T cells.

The key role played by the RAAS in the development of hypertension in CKD has meant that blockade of the RAAS has become the most widely used antihypertensive strategy in patients with progressive kidney disease (see Chap. 5). But while the RAAS plays a key role in the pathogenesis of hypertension, it is also recognized that inappropriate or persistent activation can lead to kidney damage over and above its effects on blood pressure. Moreover, it is often suggested that RAAS blockade offers unique renoprotective benefits in patients with CKD, beyond blood pressure lowering.

There is no doubt that drugs that block the RAAS are effective antihypertensive agents. However, in addition, RAAS blockers may also have actions on different aspects of blood pressure control compared to other agents, even for the same achieved reduction in mean or systolic blood pressure levels. For example, some researchers have argued that the antiproteinuric benefits of RAAS blockade observed in the micro-HOPE study may simply have reflected the better 24-h and/or night-time control of blood pressure achieved with ramipril rather than any pleiotropic effects arising from RAAS blockade [14]. Another key difference between blood pressure lowering strategies may be their effects on blood pressure variability, beyond simply lowering of mean blood pressure levels. For example, it is known that visit-to-visit variability in blood pressure is independently associated with the risk of progressive kidney disease, over and above mean blood pressure control. Indeed, in the DCCT study, visit-to-visit variability in blood pressure explained as much of the variability in incident nephropathy as differences in mean blood pressure [15]. Notably, some antihypertensive combinations, including some that contain RAAS blockers, result in the lower blood pressure variability than other combinations. These findings may partly explain why additional renoprotective advantages of RAAS blockade have been largely reported in the studies of hypertensive patients, where RAAS blockade is one of usually three or four different antihypertensive agents. Indeed, it may be that the better, more sustained and less variable effects of RAAS blockade on blood pressure may partly or largely explain the so-called independent benefits with respect to kidney disease.

Another consideration are the effects of RAAS blockade in normotensive individuals with CKD. Although it is rare for patients with CKD to have perfectly "normal" blood pressure levels, studies in normotensive salt replete individuals show only limited utility. For example, the ACE inhibitor ramipril (10 mg/day) did not reduce the incidence of new onset microalbuminuria in normotensive patients with type 2 diabetes from the micro-HOPE study [16]. Similarly, in type 2 diabetic patients enrolled in the DIRECT study, the ARB, candesartan (16 mg/day), failed to reduce the development of microalbuminuria, despite lower blood pressure levels in the candesartan-treated group [17].

Although there is a strong physiological rationale for early blockade of the RAAS in patients at risk of kidney disease, the utility of RAAS blockade for primary prevention beyond blood pressure lowering continues to be debated. Certainly, lowering blood pressure is effective in preventing diabetic kidney disease (see Chap. 6) and many trials have demonstrated kidney benefits using RAAS blockers in hypertensive patients while at the same time lowering blood pressure levels.

A number of trials have attempted to specifically explore the unique renoprotective utility of RAAS blockade beyond blood pressure lowering in patients with diabetes. However, with few exceptions these studies have largely failed to demonstrate a clear and independent efficacy for the primary prevention of microalbuminuria. Put

together with observational findings in a meta-analysis, Casas et al. controversially concluded that ACE or ARBs provided no renoprotective effect beyond BP control [18]. This study has been widely criticized because of "methodological flaws" and, in particular, the inclusion of posthoc kidney data from the ALLHAT study, which because of its size, dominated the outcome analysis. This study included a large proportion of black patients in whom RAAS blockade is often considered to be less effective, and patients in the RAAS treatment arm were limited in their access to diuretics.

Although some subsequent clinical studies have observed some renoprotective effects from RAAS blockade, many of these studies deliberately included hypertensive patients and/or achieved greater blood pressure lowering with the RAAS blocker. Consequently, whether RAAS blockade truly offers additional benefits for primary prevention over and above blood pressure control remains contentious. At best, any "independent effects" on primary prevention achieved by RAAS blockers beyond blood pressure lowering are modest, and certainly not the panacea envisaged by many practitioners.

10.5 Does RAAS Blockade Only Protect the Kidneys by Reducing Proteinuria?

In controlled trials in patients with CKD, ACE inhibitors and ARBs reduce urinary protein excretion by approximately 35–40%, which is greater than other antihypertensive agents, even when the effect of blood pressure reduction on urinary protein excretion has been taken into account. This effect is partly mediated through effects on kidney hemodynamics. Indeed, the reduction in albuminuria with RAAS blockade correlates with the change in intra-glomerular pressure in animal models. Other actions may include antagonizing the direct effects of Ang II on glomerular perm-selectivity, podocyte structure and function tubular protein handling and the contraction of mesangial cells to decrease the glomerular capillary ultrafiltration coefficient. Proteinuria is not only a marker of kidney injury but may also a mediator of progressive kidney damage as reabsorption of filtered proteins can injure the tubulo-interstitium of the kidney by activating intracellular events leading to the release of vasoactive, pro-fibrotic, and proinflammatory mediators. Posthoc analyses from the RENAAL and IDNT trials showed that the ARB-induced reduction in albuminuria explained most of the long-term kidney and cardio-protective effects of ARBs in patients with type 2 diabetes and advanced nephropathy [19].

10.6 Does RAAS Blockade Have Independent Hemodynamic Effects on the Kidney to Slow Progressive Functional Decline?

Among the earliest changes in the injured kidney is an increase in efferent arteriolar tone leading to an increase in intra-capillary pressure and a loss of auto-regulation. Activation of the RAAS increases the filtration fraction as Ang II constricts the post-glomerular (efferent) arterioles to a greater extent than at the afferent arteriole resulting in an increase intra-glomerular pressure (Fig. 10.3). By contrast, blockade of the RAAS with ACE inhibitors or AT_1-receptor blockers alleviates hydrostatic "stress" on the glomerulus by causing preferential vasodilatation of the same (post-glomerular) efferent arterioles. This effect on glomerular hemodynamics is most often used to explain why RAAS blockade appears to be more efficacious in preventing proteinuria and kidney injury when compared to similar blood pressure reduction using other agents. Moreover, the finding that the slight drop in GFR observed in some patients following the commencement of RAAS blockade (see below) is also associated with a slower decline in kidney function suggests that a reduction in intra-glomerular pressure plays a key role in both phenomena.

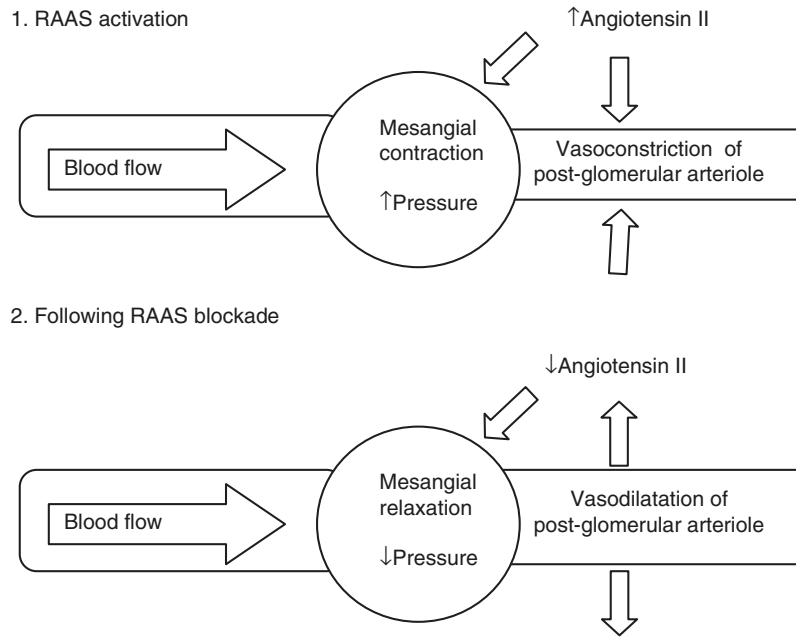

Fig. 10.3 The actions of angiotensin II and RAAS blockade on intra-glomerular pressure

10.7 Does RAAS Blockade Have Direct Effects on Pathogenic Pathways to Slow Progressive Functional Decline?

Ang II is also an important stimulus for inflammation, oxidative stress, and fibrogenesis in the kidney (Box 10.1). Each of these represents important pathogenic pathways involved in the development and progression of CKD. For example, the formation of reactive oxygen species (ROS) as a result of oxidative stress is recognized as a key component in the progression of chronic kidney disease. ROS are directly cytotoxic and upregulate inflammation and fibrosis. The expression and activity of NADPH oxidase represents the major source of ROS in the kidney and NADPH oxidase is directly stimulated by Ang II via activation of the AT_1 receptor. This pro-oxidant action may independently contribute to the kidney consequences of activation of the AT_1 receptor and therein the benefits arising from its blockade in the setting of kidney disease. Ang II is also able to modulate immune responses relevant to scarring, inflammation, and hypertension in progressive kidney disease. Indeed, immunosuppression during Ang II-induced hypertension can reduce albuminuria, inflammatory cell infiltration, and structural damage in the kidney, suggesting that changes in immune functioning play a vital role in determining the actions of RAAS activation.

10.8 Does RAAS Blockade Protect the Kidneys by Improving Adherence?

The other key advantage of conventional RAAS blockade is its tolerability and compliance over other antihypertensive classes [20]. In particular, ARBs are generally the best tolerated of all antihypertensive agents. Discontinuation rates are modestly higher for ACE inhibitors and a dry cough from may be troublesome for some individuals. However, adherence with ACE inhibitors is more favorable than calcium channel blockers, beta-blockers, and diuretics. RAAS blockers are generally long acting, taken once a day and can be easily combined with other agents in fixed dose formulations with other antihypertensive

agents, with which there is considerable synergy. Taken together, these effects mean that patients prescribed RAAS blockers are generally more likely to be taking them [20]. This does not explain benefits in clinical trials where adherence is strictly enforced. But in the real world it ultimately translates into better blood pressure control on an intention to treat basis and potentially better kidney outcomes as well.

Box 10.2 KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease [21]

We recommend starting renin–angiotensin system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and moderate to severely increased albuminuria (G1–G4, A3) with or without diabetes.

It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASi (ACEi or ARB).

RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

Box 10.3 KDIGO Guidelines for the Management of Diabetic Kidney Disease 2022 [22]

We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated.

For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAS inhibitor.

Nonsteroidal MRAs are most appropriate for patients with T2D who are at high risks of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard of care therapies.

Box 10.4 KDIGO 2012 Clinical Practice Guideline for CKD Evaluation and Management [23]

We suggest that an ARB or ACEI be used in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 h (or equivalent).

We recommend that an ARB or ACEI be used in both diabetic and nondiabetic adults with CKD and urine albumin excretion >300 mg/24 h (or equivalent).

10.9 Is the Effect of RAAS Blockade on the Kidneys Sustained?

Although RAAS inhibition can be effective in patients with CKD, most of the apparent benefit in outcomes between patients on RAAS blockers and those receiving standard therapy occurs early, within the first 18 months. After this time, the (time-to-event) lines appear to run in parallel. Moreover, if or when RAAS blocking agents are discontinued, albuminuria often rebounds to former levels. These observations call into question the potential durability of the treatment effect on the RAAS and/or the underlying disease processes. This may be because the RAAS relies on feedback regulation to achieve and sus-

tain the delicate balance required for vascular function and this feedback regulation is intrinsically antagonistic to the therapeutic goal of blocking the RAAS (Fig. 10.3). The blockade achieved by ACE inhibitors and ARBs may only be partial and short lived, even when used in combination [24]. In fact, in a third to a half of all patients treated with ACE inhibitors, there is a paradoxical overshoot in aldosterone concentrations after years of treatment (known as *aldosterone escape*). This escape phenomenon also occurs with ARBs possibly due to the activation of the AT_2 receptor [24]. Indeed, equal rates of elevated aldosterone levels are observed among subjects on ACE inhibitors, ARBs, or a combination of both [24], which may explain the lack of additive effect observed in some clinical studies.

10.10 What Is the Best Dose to Use to Protect the Kidneys in CKD?

When initiating RAAS inhibitors, therapy should always be initiated at a low dose to reduce the risk of side effects (see below). However, the best effects of ACE inhibitors and ARBs on albuminuria (as a surrogate for kidney protection) appear to be achieved with maximum approved dose, even without additional blood pressure lowering efficacy. Most CKD guidelines recommend that RAAS inhibitors should be titrated up to the to the highest approved dose that is tolerated by the patient.

There also is evidence that "mega-doses" of ACE inhibitors or ARBs can exceed the effectiveness of conventional doses in experimental models of chronic kidney disease. Some clinical observations have suggested that supramaximal doses can be exceeded if proteinuria remains substantial. However, this paradigm remains to be formally tested clinical trials. Moreover, there are also regulatory limits that appropriate restrict dosing of RAAS inhibitors that can be used in the clinical setting, which need to be followed for safe practice.

10.11 What Are the Potential Drawbacks of RAAS Blockade?

Although RAAS blockers have many potential benefits, treatment with ACE inhibitors and ARBs may also result in adverse effects, which are more common in patients with CKD (Box 10.5). Apart from cough caused by ACE inhibitors, the most common side effects leading to dose modification or discontinuation of therapy are early decrease in eGFR, hypotension, and hyperkalemia.

Having prioritized the protection of kidney function in patients with CKD, many clinicians are justifiably cautious about risking any further reduction in eGFR particularly associated with titration. This means that many patients are treated with submaximal doses, potentially to the detriment of optimal kidney protection. Indeed, a fall in eGFR is a common dose-related functional effect. An acute fall in estimated eGFR of more than 15% occurs in approximately 10% of patients following initiation of RAAS blockade. However, it is a functional effect related to reduce efferent arterial tone following blockade of the RAAS, and is reversible upon discontinuation of therapy, unlike the eGFR decline associated with progressive kidney disease. Indeed, the fall in eGFR upon initiation of RAAS inhibitors may correlated to the antiproteinuric effects of these agents and an acute fall in eGFR that stabilizes within the first 2 months actually predicts a slower decrease in long-term kidney function.

The absolute change in eGFR upon initiation of RAAS inhibitors is correlated with volume status, dose at initiation, and (intra-glomerular) pressure dependence of kidney function in any one individual. This risk of declining kidney function should be reduced by optimizing the volume status prior to initiation (e.g., reducing diuretics, controlling hyperglycemia or heart failure), starting with a low dose and undertaking slow dose titration.

In all patients starting RAAS blockers, kidney function should be checked within 2–4 weeks of initiation and subsequently following any

increase in dose. If eGFR decreases by more than 30% over baseline, the dose of ACE inhibitor or ARB should be reduced, and the eGFR reassessed frequently until kidney function has stabilized. In many cases, the ACE inhibitor or ARB can be managed without discontinuation.

It is well known that RAAS blockade may precipitate acute kidney failure in patients with bilateral critical kidney renovascular disease, as eGFR is maintained in this state by heightened activity of the intrarenal RAAS. However, such events are uncommon and reversible (if detected early). Most patients with established renovascular disease do not experience acute kidney failure when treated with a RAAS blocker. Even among patients with known kidney renovascular disease, the use of RAAS blockade is actually associated with an improved kidney and cardiovascular outcomes.

Box 10.5 Side Effects Arising from Blockade of the RAAS

Related to RAAS Blocking Activities

- Hypotension.
- Acute decline in GFR/kidney failure.
- Hypokalemia.
- Fetal toxicity.

Unrelated to RAAS Blocking Activity

- Cough (10–20% of those taking ACE inhibitors, minimal with ARBs).
- Rash/urticaria/itch (especially with captopril).
- Angioedema.
- Neutropenia/agranulocytosis.
- Dysgeusia (abnormal taste sensation; especially with captopril).

Hyperkalemia may also be induced following initiation or up-titration of RAAS inhibitors in patients with CKD, due to inhibition of aldosterone production and kaliuresis. It may be modestly more common with ACE inhibitors than with ARBs. Increases in serum potassium with RAAS inhibitors are more common in CKD patients with a low eGFR or with diabetes, interstitial nephritis, heart failure and acidosis as well as those taking NSAIDs, beta-blockers, potassium-sparing diuretics or potassium supplements. Hyperkalemia is also more common following the use of combination RAAS blockade, such as an ACE inhibitor/ARBs with an MRA.

In all patients starting RAAS blockers, potassium levels should first be documented. Caution should be taken when initiating RAS blockers individuals with $K > 5$ mEq and efforts to reduce K are usually appropriate before starting. Potassium levels should be checked within 2–4 weeks of initiation and subsequently following any increase in dose. If serum potassium levels rise to 5.5 (nominally hyperkalemia) is usually be managed by initiating a "low-potassium diet" (see Chap. 9), potassium binders (e.g., sodium zirconium cyclosilicate, patiromer), loop diuretics, and/or alkali replacement (if metabolic acidosis, serum bicarbonate concentration <21 mEq/L) as appropriate. However, decreasing the dose or stopping RAAS inhibitor may be necessary in some unresponsive cases.

ACE inhibitors or ARB can also sometimes cause symptomatic hypotension upon initiation of up-titration. Monitoring of blood pressure as well as electrolytes and kidney function is therefore warranted. As the utility of RAAS blockade is questionable in non-proteinuria non-hypertensive individuals, the risk of hypotension sometimes outweigh the benefit in starting RAAS inhibition in these individuals.

10.12 Is There Any Advantage for Combined RAAS Blockade?

10.12.1 Combined ACE Inhibition and Angiotensin Receptor Blockade

One potential strategy to achieve better inhibition of RAAS has been to combine ACE inhibition with angiotensin receptor blockade in the so-called dual therapy. A number of studies have

reported additive antiproteinuric effects of combination therapy, although this may partly reflect the suboptimal doses used of either or both components when used on their own. For example, the ONTARGET trial, which used high doses of one or both ramipril and/or telmisartan, did demonstrate that albuminuria fell more from baseline with dual therapy when compared with monotherapy with either agent alone. Whether this was due to blood pressure lowering or better RAAS blockade is uncertain. However, combination therapy was associated with an increased risk of hyperkalemia and kidney failure, and is generally not recommended in patients with CKD.

10.12.2 Mineralocorticoid Receptor Blockade

The addition of a MRA to an ACE inhibitor or ARB has also been studied as a potential means to achieve better RAAS blockade. Many studies have suggested additive antiproteinuric effects. Recent studies with the nonsteroidal MRA, finerenone have also demonstrated benefits for slowing kidney function decline in diabetic patients with CKD when used on top of conventional RAAS blockade. It is unclear whether the benefits of combination therapy are specifically enhanced in patients with aldosterone escape, or simply because of better blood pressure control with enhanced natriuresis. However, hyperkalemia is a significant risk with this strategy in patients with CKD.

10.13 Shouldn't Everyone with CKD Receive a RAAS Inhibitor If Tolerated?

Although it is widely publicized that RAAS blockade has unique renoprotective benefits for patients with CKD, in modern clinical practice such arguments are largely moot. Given the better tolerability, efficacy and side-effect profile of RAAS blockers over other antihypertensive agents [20], as well as added beneficial effects on retinal and cardiovascular disease [25], heart failure, and other end-organ damage [26], most patients with or at risk of CKD currently receive RAAS blockers as first-line antihypertensive agents. Indeed, most patients will initially or ultimately need combination antihypertensive therapy to control their blood pressure, in which case RAAS blockade will almost always be utilized in routine clinical practice. In recent guidelines (Box 10.2) RAAS inhibitors are recommended as part of multifactorial first-line therapy in all patients with CKD, with subsequent goal directed therapy added onto the baseline formed by RAAS blockade.

Patients with CKD without hypertension or proteinuria generally have a low risk of adverse kidney outcomes. Even if there was renoprotective effect in these patients the number need to treat would be large to afford sufficient benefit while at the same time exposing patients to unnecessary treatment.

Finally, it is important to note that despite its benefits, RAAS blockade even in optimal combination with other interventions is not enough to prevent progressive kidney disease. At its best it achieves a modest and temporary slowing of kidney decline in some patients. Therefore, while it is important to use RAAS blockade in our patients, it is also important to acknowledge that more must be done to preserve kidney function and health in our patients with CKD (Box 10.4).

10.14 Should I Keep Using a RAAS Inhibitor in Advanced CKD If Tolerated?

The utility of continuing RAAS inhibition into advanced CKD is controversial. Some clinicians prefer to discontinue RAAS inhibition to raise the eGFR and reduce the risk of hyperkalemia and hypotension. Others prefer to continue these agents to draw out the time until kidney replacement therapy is required. Although observational data supports the continued use of RAAS inhibitors in this setting [27], such studies are often confounded by indication, as healthier and more stable patients are more likely to continue RAAS blockade. Even with adjustment using propensity scores, the potential for bias remains. Certainly, reducing dosing or discontinuing RAAS inhibi-

tion in patients with advanced CKD in the setting of either hypotension or hyperkalemia is appropriate, and close monitoring ensured in those individuals continuing therapy. Temporary discontinuation of RAAS blockade on "sick days" associated with dehydration, poor oral intake, significant illness or before major procedures is also appropriate.

Box 10.6 Relevant Guidelines

1. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease [21]

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.

https://kdigo.org/guidelines/blood-pressure-in-ckd/

2. KDIGO Guidelines for the management of diabetic kidney disease 2022 [22]

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.

https://kdigo.org/guidelines/diabetes-ckd/

3. KDIGO 2012 Clinical Practice Guideline for CKD Evaluation and Management [23]

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(Suppl):1–150.

https://kdigo.org/guidelines/ckd-evaluation-and-management/

4. The National Kidney Foundation

High Blood Pressure and Chronic Kidney Disease.

https://www.kidney.org/sites/default/files/docs/hbpandckd.pdf

5. Joint National Commission on Prevention, Detection, Assessment and Treatment of Hypertension (JNC-VIII)

James, P.A.; Oparil, S.; Carter, B.L.; Cushman, W.C.; Dennison-Himmelfarb, C.; Handler, J.; Lackland, D.T.; LeFevre, M.L.; MacKenzie, T.D.; Ogedegbe, O.; et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014, 311, 507–520.

https://jamanetwork.com/journals/jama/fullarticle/1791497

6. National Institute for Health and Clinical Excellence (NICE) Guideline

Chronic Kidney Disease: Assessment and Management. 2021 Royal College of Physicians.

https://www.nice.org.uk/guidance/ng203/resources/chronic-kidney-disease-assessment-and-management-pdf-661437

7. American College of Cardiology

ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J. Am. Coll. Cardiol. 2018, 71, e127–e248.

https://www.sciencedirect.com/science/article/pii/S0735109717415191?via%3Dihub

Before You Finish: Practice Pearls for the Clinician

- Blockade of the RAAS is an effective strategy to reduce blood pressure in patients with CKD, but no more so than other antihypertensive strategies.
- RAAS blockers have a more favorable side-effect profile than other antihypertensive agents, meaning that patients are generally more likely to be taking them.

- There are clear benefits for optimal RAAS inhibition in patients with CKD and elevated urinary albumin excretion for slowing kidney function decline.
- Most patients can tolerate some RAAS inhibition with the assistance of their physician and their care team.

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11 Chronic Kidney Disease and the Cardiovascular Connection

Nuri Baris Hasbal and Ozkan Gungor

Before You Start: The Facts You Need to Know

- The heart and kidneys are linked via hemodynamic, neurohormonal, and cell signaling systems.
- Chronic kidney disease bone and mineral disorder results in acceleration in calcification of atherosclerosis, particularly in the vascular media.
- Heart failure is the most common symptomatic manifestation of cardiovascular disease requiring hospitalization in patients with chronic kidney disease.
- Myocardial disease, electrolyte imbalance, and acid-base disturbances can lead to arrhythmias in patients with renal failure.

11.1 Introduction

The complex relationship between the kidney and the heart has been known and studied from the beginning of the nineteenth century. At first, it caught attention with structural changes of the heart in patients with advanced chronic kidney disease (CKD); then observational, clinical, and pathophysiological evidence revealed that these two organ systems are inextricably linked via vascular, neurological, hormonal, and cellular signaling systems. The kidneys are the most vascular organs in the body receiving a quarter of cardiac output at rest. Thus, it is no surprise as we explore the extent of the cardiovascular system that kidney disease is strongly associated with cardiovascular disease and, in fact, may reflect the state of vascular health or disease at any time. Additionally, when either organ has acute or chronic injury, there appears to be a sequential acute or chronic effect on the other organ in either an adaptive or maladaptive response, which we now recognize as a "cardiorenal syndrome" [1]. This chapter will review the connections between the heart and the kidneys from epidemiological, biological, and clinical perspectives with the aim of gaining greater appreciation for this important interface in both acute and chronic care.

11.2 Why Does Chronic Kidney Disease Convey Increased Cardiovascular Risk?

Data from the US Renal Data System (USRDS) 2022 revealed that the prevalence of any CVD was higher in individuals with CKD than in patients

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https://doi.org/10.1007/978-3-031-42045-0_11

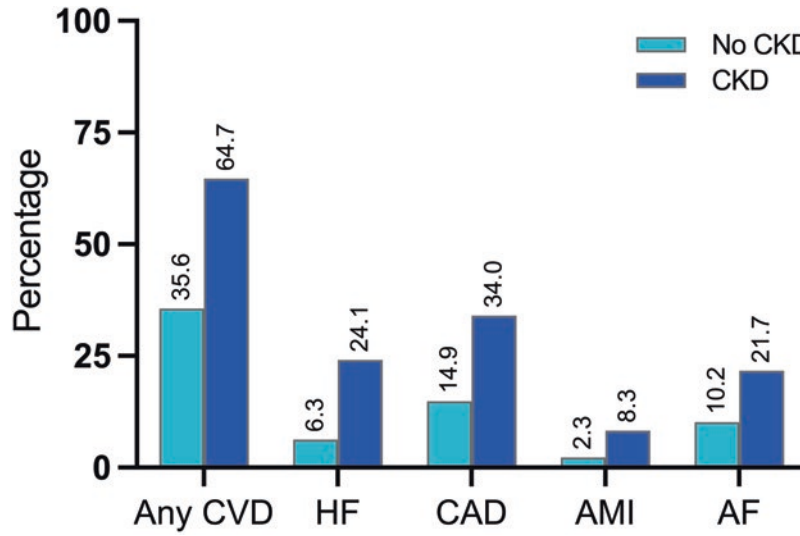

Fig. 11.1 Prevalence of common cardiovascular diseases in older adults with CKD

without CKD [2]. Prevalence of common cardiovascular diseases in older adults with CKD at 2020 were shown at Fig. 11.1 [2]. The Chronic Kidney Disease Prognosis Consortium (CKD-PC) was established in 2009 by Kidney Disease Improving Global Outcomes (KDIGO) organization to understand the risks of declining renal filtration function represented by the estimated glomerular filtration rate (eGFR) and the presence of albumin in the urine indexed to the filtered creatinine concentration (urine albumin/creatinine ratio [ACR]). In a series of manuscripts, this group demonstrated a milestone data that changed all guidelines, in a very large, pooled database (1,555,332 in 45 cohorts) that the severity of chronic kidney disease (CKD) was related to the risks of all-cause mortality, cardiovascular death, acute kidney injury, progressive CKD, and end-stage kidney disease (ESKD) as shown in Fig. 11.2 [3]. These relationships can also be shown in a colored "heat map" of risk as demonstrated in Fig. 11.3. It is important to understand that when both reduced eGFR and elevated ACR overlap, there appears to be magnified risks for all outcomes. The addition of eGFR and ACR significantly predicted the cardiovascular outcomes rather than traditional risk factors in general populations. But ACR may be a more appropriate marker than eGFR, and more evident for heart failure and cardiovascular outcome than for stroke and coronary artery disease coronary disease [4]. The commonly-measured clinical characteristics including eGFR and ACR, can predict the timing and occurrence of clinical outcomes in patients with severely decreased GFR [5]. Furthermore Matsushita et al. developed three Add-ons [eGFR only, eGFR +ACR, and eGFR + dipstick proteinuria] for systemic coronary risk estimation 2 (SCORE2) and systemic coronary risk estimation 2 in older persons (SCORE2-OP) and validated in 3,054,840 participants from 34 datasets to predict CVD risk more accurately [6]. They found that Add-ons with CKD measures improved CVD risk prediction beyond SCORE2 and SCORE2-OP. Importantly, the overlap between the two markers is less common than one alone in these large populations. However, when both reduced eGFR and albuminuria are present in the same patient, the predicted and observed rates of cardiovascular events are markedly increased over a relatively short (<5 years) duration. Thus, it is critical that, in every patient, both the eGFR be calculated from the age, gender, race, and serum creatinine using standardized equations and the urine ACR be checked using the first morning-voided specimen. Structural kidney disease detected by imaging studies including polycystic kidney disease are also characterized as CKD in the absence of eGFR and ACR abnormalities.

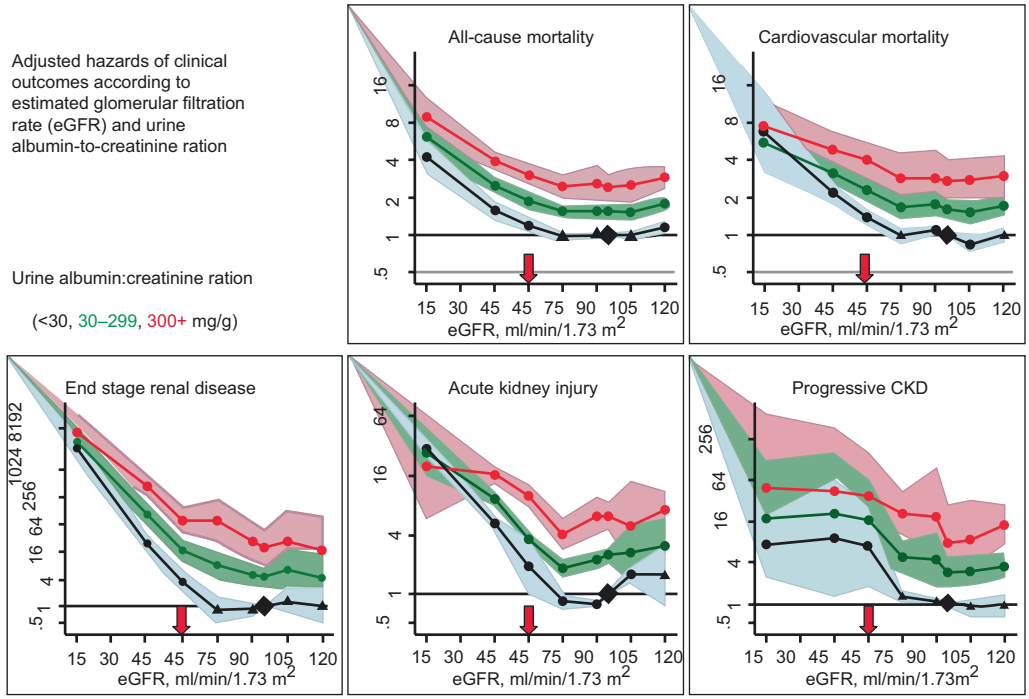

Fig. 11.2 Risks of fatal and nonfatal kidney outcomes from the Chronic Kidney Disease Prognosis Consortium (CKD-PC). (Adapted by permission from Macmillan Publishers Ltd: Levey et al. [3] Available from: http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html)

Adjusted hazards of clinical outcomes according to estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR)

eGFR in ml/min/1.73 m^2
ACR in mg/g

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1,044	1,056	2,286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	Ref	Ref	0.4	3.0
eGFR 90–105	Ref	Ref	0.9	3.3
eGFR 75–90	Ref	Ref	1.9	5.0
eGFR 60–75	Ref	Ref	3.2	8.1
eGFR 45–60	3.1	4.0	9.4	57
eGFR 30–45	3.0	19	15	22
eGFR 15–30	4.0	12	21	7.7

Fig. 11.3 Adjusted risk of outcomes according to eGFR and urine ACR. (Adapted with permission from Macmillan Publishers Ltd: Levey et al. [3] Available from: http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html)

11.3 Does Kidney Disease Promote Coronary Atherosclerosis Calcification?

Data from many studies suggests that the CKD milieu promotes the early initiation and accelerated course of coronary atherosclerosis. Because CKD is strongly associated with traditional coronary risk factors including hypertension, diabetes, dyslipidemia, and smoking, the combination of these factors may be reflected by CKD, and thus its relationship is amplified by positive confounding. However, when adjusting for these factors, CKD has been consistently associated with nonfatal myocardial infarction and cardiovascular death [7]. Although there are some conflicting results in the literature, some authors and older guidelines consider CKD as a CVD risk equivalent [8]. A prominent feature of coronary atherosclerosis in patients with CKD and ESKD is accelerated calcification which occurs in all cases of atherosclerosis. However, the progression of atherosclerosis involves a multitude of local and systemic factors which stimulate vascular smooth muscle cells to undergo osteoblastic transformation into osteocyte-like cells which deposit calcium hydroxyapatite crystals into both the subendothelial and medial compartments of blood vessels. Many factors have been implicated in CKD to accelerate this process including low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol, vascular calcification factor, osteoprotegerin, and most notably phosphorus [9]. As eGFR falls, there is retention of phosphate, which can stimulate the Pit-1 receptor on vascular smooth muscle cells thereby facilitating the osteoblastic transformation. Of note, neither the local calcium concentration nor the blood levels of calcium have been independently associated with atherosclerotic calcification in the coronary arteries. As CKD progresses, coronary artery disease is commonly identified on a variety of clinical studies, frequently as longer lesions and in more proximal vessels [10]. Fortunately, more extensive calcification, while it is related to the burden of coronary disease, is also associated with more stable lesions; thus, CKD patients often have stable but extensive CAD leading to episodes of both silent and symptomatic coronary ischemia.

It has been suggested that there are both traditional and nontraditional risk factors that may contribute to more accelerated atherosclerosis in persons with CKD. The traditional risk factors that are highly prevalent in patients with CKD include metabolic syndrome, older age, dyslipidemia, hypertension, diabetes mellitus, smoking, and family history of premature coronary disease (first-degree relative female before age 55 and male before age 45 years). Nontraditional risk factors in CKD have been variously mentioned in the literature and include blood markers of mineral and bone disorder (hyperphosphatemia, elevated calcium-phosphorus product, osteopontin, hyperparathyroidism), C-reactive protein, uremia, asymmetric dimethylarginine and reduced nitric oxide availability, anemia, increased unbound iron (catalytic or poorly liganded iron), homocysteine, fibrinogen, and increased coagulation proteins. It should also be kept in mind that there are some contradictory evidences about nontraditional risk factors in CKD in the literature.

11.4 Why Does the Heart Fail as a Pump in Kidney Patients?

Increased afterload, increased preload, and some intrinsic factors not associated with afterload or preload may result in CKD-associated cardiac changes as also known as CKD-associated cardiomyopathy [7]. These pathophysiological alterations may induce increased left ventricular (LV) mass and left ventricular hypertrophy (LVH), diastolic and systolic LV dysfunction, profound myocardial fibrosis on histology and/or imaging studies. Although these features are predominantly stated in advanced stages of CKD, some functional and anatomic changes begin to be seen in very early stages of CKD. Salt and water retention result in chronic volume overload. Nephrotic syndrome and loss of oncotic forces results in worsened fluid retention and edema. Uremia and retention of many other ure-

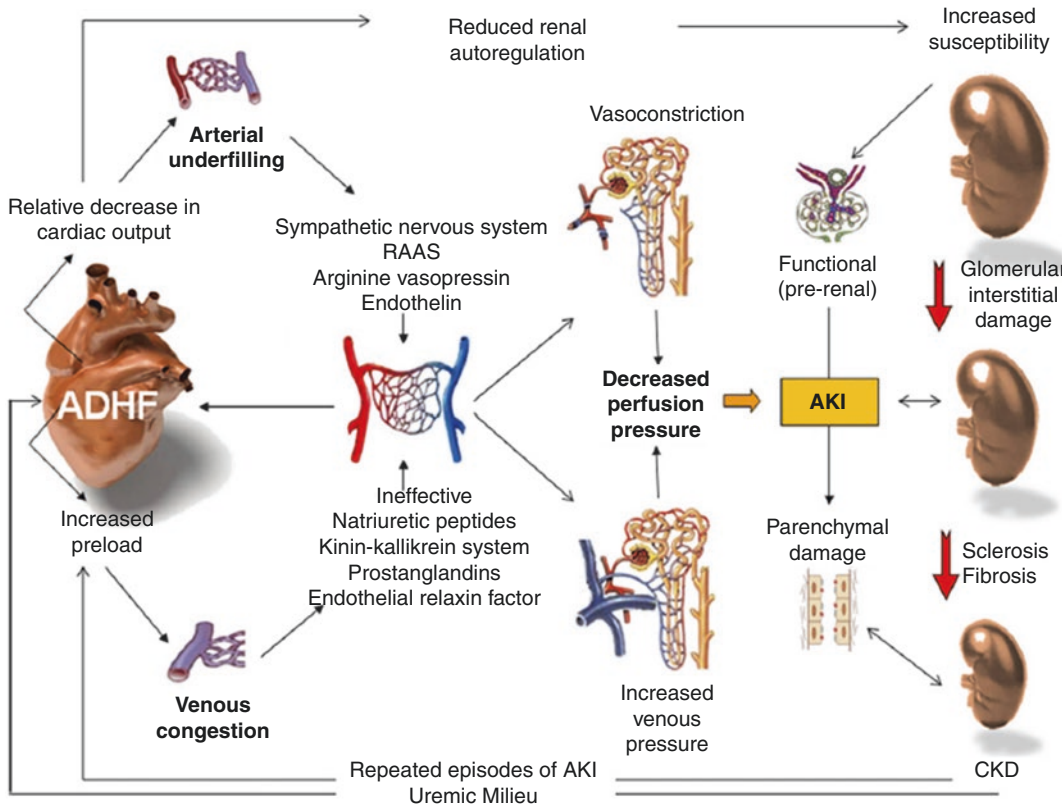

Fig. 11.4 Pathophysiology of cardiorenal syndrome type 1. ADHF acutely decompensated heart failure. AKI acute kidney injury. (Reproduced with permission from Ronco et al. [13]. Copyright 2012, with permission from Elsevier)

mic toxins results in impaired myocyte function in both systole and diastole. The production of fibroblast growth factor-23 from bone in response to CKD phosphate retention has off-target effects on the left ventricular myocardium resulting in increased left ventricular mass and cardiac fibrosis. The resultant myocardial tissue has a reduced capillary density compared to that of persons with normal kidney function. Considerable evidence is accumulating that CKD-associated cardiomyopathy is manifest by impaired systole and diastole with biomarker and imaging evidences of cardiac fibrosis. T1 and T2 mapping on cardiac magnetic resonance imaging (MRI) has been used to understand the extent of the cardiac involvement in patients with CKD. While T1 mapping diagnoses the myocardial fibrosis, T2 mapping gives extra information about myocardial oedema. Although more extensive studies are awaited, T1 and T2 mappings thought to be associated with BNP, myocardial injury and worse clinical status [11]. The observation that galectin-3 levels correlate with type III amino-terminal propeptide of procollagen, matrix metalloproteinase-2, and tissue inhibitor of metalloproteinase-1 suggests that myocardial macrophage infiltration enhances turnover of extracellular matrix proteins in patients with CKD [12]. Thus, patients with CKD are at very high risk for the development of heart failure associated with markedly impaired cardiorespiratory function and the cardinal features of fatigue, effort intolerance, edema, and clinical findings including pulmonary congestion and elevation of B-type natriuretic peptides. When acutely decompensated heart failure is present, then a vicious cycle of worsened renal filtration function, venous and renal congestion, and further retention of salt and water can occur. This is commonly termed as cardiorenal syndrome type 1 (Fig. 11.4) [3].

11.5 Should I Hear a Murmur?

Accelerated aortic valvular and mitral annular calcification and fibrosis is common in patients with CKD and nearly universally present in patients with ESKD. The murmur of aortic valve sclerosis is found in most patients, while the mitral annular disease is usually silent and detected only by echocardiography or other forms of imaging. The aortic valve sclerosis and calcification can progress to symptomatic aortic stenosis, while the mitral annular disease can result in very mild functional stenoses or regurgitation by Doppler but rarely requires surgical attention. Both valvular lesions can be the substrate for acute infective endocarditis in ESKD patients with temporary dialysis catheters. In a recent meta-analysis including 18 studies and 45,799 patients revealed a high prevalence (%2.7–3.1) of infective endocarditis and a high mortality rate (in-hospital and long-term death-rates; 29.5% and 45.6%, respectively) [13]. Most patients with CKD should undergo echocardiography at some point in their care to evaluate not only for the extent of valve disease but also to assess left ventricular systolic and diastolic function.

11.6 Why Are There More Arrhythmias?

Patients with CKD have the myocardial and hemodynamic determinants of all forms of arrhythmias. In the United States Renal Data System database, arrhythmia/cardiac arrest accounted for 33.1% of deaths; 40.0% of deaths which were cardiovascular in nature [2]. Atrial fibrillation occurs at an elevated rate in patients with CKD and is associated with an increased risk of cardioembolic stroke compared to those with normal renal function. Because of accelerated myocardial fibrosis and the presence of macrovascular and microvascular disease, reentrant ventricular arrhythmias occur at increased rates and are believed to be the inciting event in sudden death. Increased premature atrial and ventricular beats when seen on monitoring can be harbingers of atrial fibrillation and ventricular tachycardia, respectively. Electrolyte shifts and imbalance that occur in CKD and is accentuated with forms of dialysis are also believed to play a role in ventricular arrhythmias and sudden death, most likely due to ventricular fibrillation. The roles of anticoagulation for stroke prevention in atrial fibrillation, atrial and ventricular antiarrhythmic medications, and the use of implantable cardio defibrillators are still all controversial. Thus, therapy must be individualized, and very frequent monitoring is required.

11.7 Summary

The connection between kidney and heart disease can be viewed in four domains: coronary atherosclerosis, myocardial disease, valvular abnormalities, and arrhythmias. Chronic kidney disease plays a role in the pathogenesis, presentation, outcomes, and management of each manifestation of CVD. Future research is needed to better understand the unique mechanisms at work in patients with CKD that promotes and worsens CVD outcomes. Practical strategies are needed to guide clinicians in the most appropriate management of this high-risk population.

Before You Finish: Practice Pearls for the Clinician

- Osteoblastic transformation of vascular smooth muscle cells is responsible for the calcification of atherosclerosis and the vascular media in patients with kidney disease.
- Both myocyte hypertrophy and increases in the interstitial matrix account for the phenotypic changes seen in the myocardium.
- Valvular thickening and calcification result in murmurs and risk for endocarditis, particularly in dialysis patients.
- Increased premature atrial contractions and premature ventricular beats can be harbingers for atrial fibrillation and ventricular tachycardia.
- Sudden death is the greatest cardiovascular concern among end-stage renal disease patients.

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12 Screening and Diagnosing Cardiovascular Disease in Chronic Kidney Disease

Ali Veysel Kara and Ozkan Gungor

Before You Start: Facts You Need to Know

- Cardiovascular disease is a leading cause of morbidity and mortality in patients with chronic kidney disease as determined by reduced estimated glomerular filtration rate and/or albuminuria.
- Patients with chronic kidney disease are known to have increased risk of coronary artery disease, heart failure, arrhythmia, valvulopathies, and sudden cardiac death.
- Atherosclerosis is both accelerated in development and in calcification in patients with chronic kidney disease.
- Heart failure is the most common symptomatic manifestation of cardiovascular disease requiring hospitalization in patients with chronic kidney disease.
- Blood B-type natriuretic peptide, N-terminal pro B-type natriuretic peptide, galectin-3, and soluble ST-2 are approved tests as these aid in the diagnosis, prognosis, and management of heart failure; however, caution should be exercised in the interpretation of these markers in the setting of chronic kidney disease.
- Aortic valve sclerosis and mitral annular calcification are common valve pathologies associated with chronic kidney disease.
- All forms of arrhythmias are more common in chronic kidney disease, especially sudden death which is markedly increased in risk in dialysis patients.

12.1 Why Screening for Cardiovascular Disease Is Important in Chronic Kidney Disease

Screening is a strategy which help us to identify people who have risk factors (primary prevention) or occult pathologies (secondary prevention) so that early intervention and treatment can be offered, the natural history of a disease process can be altered, and disease outcomes can be improved. Cardiovascular disease (CVD) is leading cause of morbidity and mortality in the world and accounts one third of all deaths. CVD is also a leading cause of morbidity and mortality in chronic kidney disease (CKD) patients. Patients with CKD are known to have increased risk of coronary artery disease (CAD), heart failure, arrhythmia, valvulopathies, and sudden cardiac death [1]. According to The United States Renal Data System (USRDS) 2022 annual report, CVD of any type was present in 75.8% of patients receiving hemodialysis, 65.4% of patients

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receiving peritoneal dialysis, and 52% of patients with a kidney transplant. Again, according to the same report, CVD was found to be responsible for more than half of the deaths in both hemodialysis and peritoneal dialysis patients [2]. In end stage renal disease (ESRD) population, mortality due to CVD is 20–30 times higher than general population. This increased risk is not limited to ESRD population, but it is seen in all stages of CKD. In a population based study including 1,120,295 adults, it is shown that cardiovascular events increased inversely with estimated glomerular filtration rate (eGFR) [3]. In a meta-analysis reviewing 39 studies involving 1,371,990 non-dialysis dependent CKD patients, it was shown that non-dialysis dependent CKD was associated with increased risk of cardiovascular death [4]. In the light of above information, screening and early diagnosing of CVD is very important in CKD population.

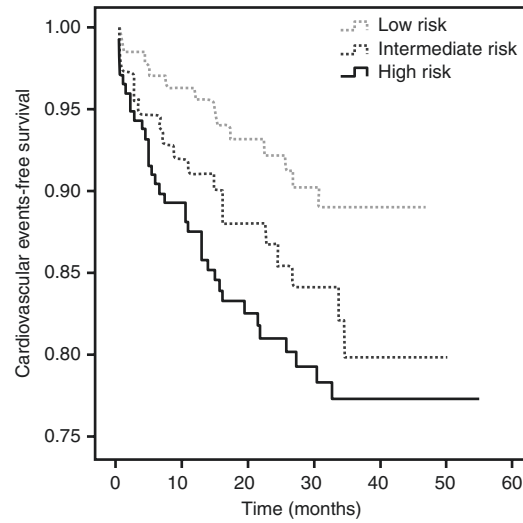

Fig. 12.1 Event-free survival from major cardiac events according to the Framingham risk score applied to a population of patients with chronic kidney disease

12.2 What Are the Approaches to Screen for Coronary Artery Disease?

Chronic kidney disease itself is an independent risk factor for the development of CAD and CAD is the leading cause of morbidity and mortality in this patient group. All adult patients including those with CKD should undergo an assessment for CAD risk using a standard risk assessment such as that proposed by the Framingham investigators [5]. Variables in the Framingham risk calculation include age, total or low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, and systolic blood pressure [6]. A 20% 10-year risk (2% annual risk) of nonfatal myocardial infarction or cardiovascular death is considered high risk and is a call for full prevention measures in the general population. Most patients with CKD (67%) will be in Framingham moderate- or high-risk groups; however, as shown in Fig. 12.1, patients with Stages 3–5 CKD in these groups will have a 10–20% annual risk of cardiovascular events (tenfold that of subjects in Framingham) [5]. Therefore; traditional prognostic tools such as the Framingham score have limited prognostic power as traditional risk factors fail to fully explain the increased risk in CKD patients [7]. Also, classical signs and symptoms of CAD may not be observed in CKD and especially in ESRD patients and it is more difficult to correctly diagnose the acute coronary syndrome in these patient groups than normal population. There are several reasons that can explain this situation such as lower sensitivity to chest pain (angina), specific electrocardiogram (ECG) changes are seen in a relatively small proportion of patients with angina, CAD symptoms may be incorrectly attributed to other CKD complications and serum biomarkers related to CAD might be chronically elevated in the absence of acute coronary syndrome (ACS). Serum biomarkers especially troponin assays (both high-sensitivity troponin I and troponin T) may be used for risk stratification and may be helpful for detecting asymptomatic CAD. Although elevated values are less definitive, dynamic change in troponin levels may be useful for myocardial infarction (MI) diagnosis and a normal troponin assay may be sufficient to rule out infarction. But we need more data to interpret troponin levels for management decisions [8].

We can use exercise stress testing for exercise prescription and prognosis in high-risk individu-

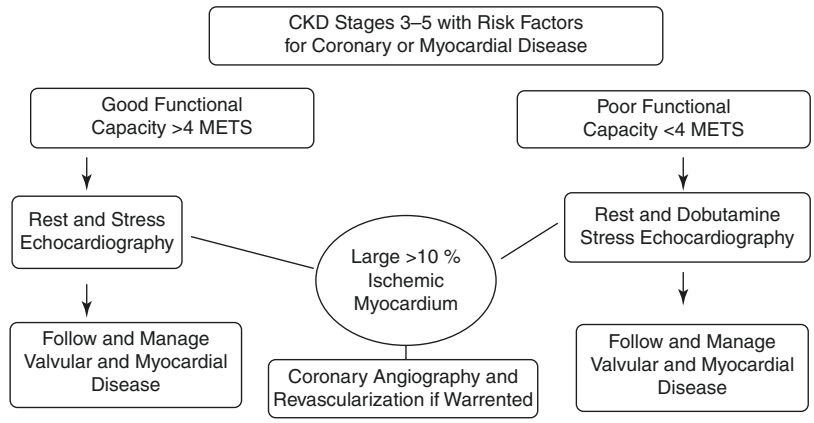

Fig. 12.2 Coronary artery disease screening algorithm (METS metabolic equivalents of functional capacity)

als. Exercise ECG has limited role due to high rates of abnormal baseline ECG, left ventricular hypertrophy, and conduction abnormalities. The other factor limiting the role of exercise ECG is the reduced exercise capacity commonly seen in CKD and especially ESRD patients [9]. Therefore, exercise stress testing combined with either echocardiographic imaging or nuclear scintigraphy is reasonable.

For those who cannot exercise, both dobutamine and dipyridamole/adenosine/regadenoson can be used as pharmacological means of achieving myocardial perfusion imaging. Large areas of ischemia (>10% of the left ventricular myocardium) usually call for invasive assessment of coronary lesions and consideration for revascularization. In the setting of diabetes and multivessel disease, coronary artery bypass surgery is the preferred method of revascularization [10]. Coronary computed tomography angiography in patients with CKD is not advised given the very high rates of coronary calcification which causes "bloom" artifact which works to make lesion severity difficult to assess [11]. However, if vascular calcification is detected incidentally on computed tomography or roentgenography, it is indicative of advanced atherosclerosis, and attention should be paid to both atherosclerosis risk factors and the elements of CKD mineral and bone disorder (phosphate retention, hyperparathyroidism, and relative hypocalcemia) (Fig. 12.2) [12, 13].

12.3 Should Patients with Chronic Kidney Disease Undergo Routine Echocardiography?

According to 2022 cardiology guidelines; heart failure (HF) is defined as a complex clinical syndrome with symptoms and signs due to any structural and/or functional disorder [14]. In CKD patients, it is difficult to distinguish classic HF symptoms and signs such as fatigue, edema, effort intolerance from symptoms related to volume overload [15]. We also know the very high incidence of left ventricular hypertrophy, risk for Stage A and Stage B heart failure in CKD patients and the associations between CKD and valvular heart disease. Therefore; all patients with CKD should be considered for echocardiography at the time CKD is diagnosed by the presence of reduced estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or evidence of kidney damage manifest by an increased urine albumin: creatinine ratio or imaging evidence of kidney disease such as polycystic kidneys by ultrasound [16]. Importantly, cardiovascular disease including coronary disease and heart failure occurs at much earlier ages than in the general population [17]. The presence of combined heart and kidney failure is considered as "cardiorenal syndrome" and should be considered in the context of the more antecedent abnormality with respect to both diagnosis and management [18]. Five subtypes of cardiorenal syndromes are dis-

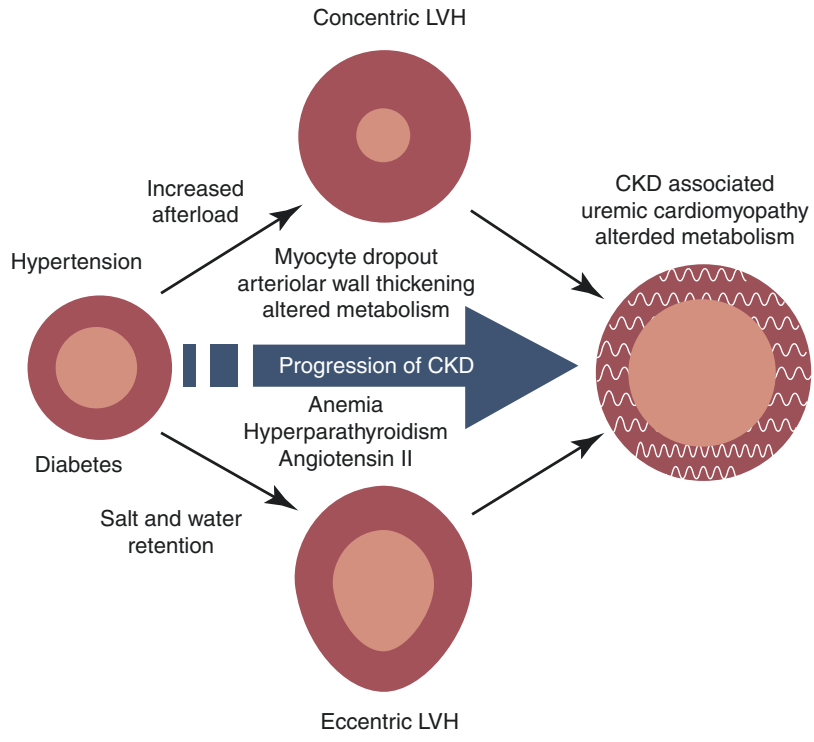

Fig. 12.3 Hypertension, diabetes mellitus, and the development of chronic kidney disease cardiomyopathy

played in (Box 12.1). The current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend echocardiograms for all CKD 5D patients 1–3 months after renal replacement therapy initiation and at 3-year intervals thereafter [19]. Serial echocardiographic examination at closer intervals such as 12 months may provide additional benefits in terms of prognosis. (Boxes 12.2 and 12.3). Echocardiography with complete Doppler assessment reliably estimated left ventricular ejection fraction (normal 55–75%), left ventricular hypertrophy (left ventricular mass index >115 and >95 g/m^2), and assesses both the morphology and flow characteristics of all four cardiac valves. According to recent studies; left ventricular hypertrophy and diastolic dysfunction are the most common structural and functional defects in hemodialysis patients, respectively [20]. Findings suggesting reduced ejection fraction, diastolic dysfunction, or regional wall motion abnormalities may prompt an evaluation for chronic cardiac ischemia as discussed above [21]. Echocardiographic evaluation of left ventricular diastolic dysfunction (LVDD) can be complicated. Especially six parameters are basically used for diagnosis and grading of LVDD. These are E wave, E/A ratio, septal or lateral è, average E/è, left atrial volume index, and peak tricuspid regurgitation velocity [22]. E and A represent velocities of the rapid early and late transmitral diastolic flow, while è is a measurement of mitral annulus recoil velocity. Diastolic dysfunction is ideally graded according to the European Association of Cardiovascular Imaging/American Society of Echocardiography criteria as normal, Grade I (impaired relaxation and decreased suction of the LV), Grade II (pseudonormalization, increased stiffness of the LV, and possible elevated filling pressure), and Grade III (most severe form) with restrictive filling with elevated filling pressure and noncompliant LV [23]. Chronic kidney disease is associated with a form of uremic or CKD cardiomyopathy as shown in Fig. 12.3. The cardiomyopathy associated with CKD is characterized by the presence of left ventricular hypertrophy, evidence of diastolic dysfunction, and, in more severe cases, superimposed systolic dysfunction with reduced

ejection fraction. The structural remodeling of the heart due to diffuse interstitial fibrosis and cardiac hypertrophy can cause electromechanical dysfunction and an increased risk of sudden cardiac death [24]. Cardiac magnetic resonance imaging (MRI) is the gold standard for LV mass quantification, chamber size and volume. But the use of contrast enhanced MRI in advanced CKD patients is limited due to the potential increased risk of gadolinium retention and nephrogenic systemic fibrosis. This risk can be decreased with the use of macrocyclic MRI contrast agents or using non-contrast tissue characterization techniques [25].

Box 12.1 Five Cardiorenal Syndromes and Their Common Clinical Scenarios

Cardiorenal Syndrome (CRS) *General Definition*

A pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

CRS Type I (Acute *Cardiorenal Syndrome*).

Abrupt worsening of cardiac function (e.g., acutely decompensated congestive heart failure) leading to acute kidney injury.

CRS Type II (Chronic *Cardiorenal Syndrome*).

Chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease.

CRS Type III (Acute Renocardiac *Syndrome*).

Abrupt worsening of kidney function (e.g., acute kidney injury) causing acute cardiac disorder (acute heart failure).

CRS Type IV (Chronic Renocardiac *Syndrome*).

Chronic kidney disease (e.g., diabetic nephropathy) contributing to decreased cardiac function and cardiac hypertrophy and fibrosis and/or increased risk of adverse cardiovascular events.

CRS Type V (Secondary *Cardiorenal Syndrome*).

Systemic conditions (e.g., sepsis) causing both acute cardiac and renal injury and dysfunction.

Box 12.2 What the Guidelines Say You Should Do

- Patients with chest pain should receive a complete history and physical examination to assess the probability of coronary disease before additional testing.
- A resting ECG is recommended in patients without an obvious, noncardiac cause of chest pain.
- Assessment of resting left ventricular function and evaluation for abnormalities of myocardium, heart valves, or pericardium are recommended with the use of Doppler echocardiography in patients with known or suspected coronary disease and a prior MI, pathological Q waves, symptoms, or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur.
- Standard exercise stress testing is recommended for risk assessment in patients with stable coronary disease who have an interpretable ECG and no disabling comorbidity. Pharmacological stress with nuclear myocardial perfusion imaging or echocardiography is an alternative in those who are incapable of exercising to an accepted workload.
- Echocardiograms should be performed in all patients at the initiation of dialysis, once patients have achieved dry weight (ideally within 1–3 months of dialysis initiation), and at 3-yearly intervals thereafter.
- In asymptomatic patients with stable coronary artery disease and chronic kidney disease, routine angiography and revascularization are not recommended.

- An initial invasive strategy did not demonstrate a reduced risk of clinical outcomes or improved quality of life measures compared with an initial conservative strategy in stable patients with moderate CKD and at least moderate ischemia.
- Coronary computed tomography angiography is reasonable for patients with a low to intermediate pretest probability of ischemic heart disease who have a disabling comorbidity.

Source: Data from Refs. [1, 26–28].

Box 12.3 Relevant Guidelines

1. American Heart Association Guidelines:
   (a) 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012; 126:3097–137 [26].
   (b) 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines J Am Coll Cardiol. 2021 Nov, 78 (22) e187–e285 [27].
   (c) 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines Circulation. 2022;145: e18–e114 [28].
2. National Kidney Foundation Guidelines:
   (a) National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 Suppl 3:S1–154 [1] [18].

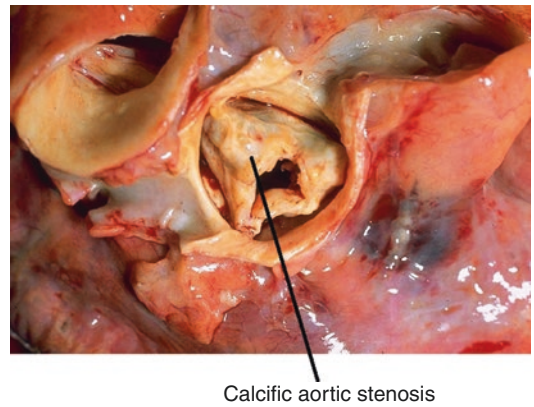

Fig. 12.4 Calcific aortic stenosis

A finding of significant valvular or pericardial disease warrants clinical correlation and follow-up. Most patients with moderate or more aortic stenosis/regurgitation or mitral regurgitation will require annual echocardiography and cardiology consultation for surveillance. In general, severe symptomatic aortic stenosis (Fig. 12.4) and/or regurgitation is an indication for valve replacement [12].

Pericardial disease may develop in kidney failure as pericarditis, pericardial effusion, or chronic constrictive pericarditis. BUN elevations over 60 mg/dL may lead to inflammation in the pericardial membranes causing uremic pericarditis. Fluid overload can also lead to pericardial

inflammation without uremia. Typical symptoms include fever and pleuritic chest pain that is relieved by sitting up or bending forward. Platelet function impairment may cause a hemorrhagic pericardial effusion and possibly tamponade depending on the rate of fluid accumulation. Typical diffuse ST elevations observed with acute pericarditis are generally not shown when uremia is the cause [29]. Echocardiography can exclude silent effusions and useful in determining associated myocarditis and altered ventricular function. Early echocardiography at the time of initiation of dialysis can also be beneficial for pericardial disease.

12.4 What Blood Biomarkers Are Useful in Heart Failure?

The role of biomarkers has consistently increased in the current medical practice due to their contribution to diagnosis, prognosis, and treatment. An ideal biomarker should be easily available and interpretable, cheap, rapid, accurate and specific for a particular situation [30]. There are many potential biomarkers for heart failure. The natriuretic peptides are the most extensively studied and used biomarkers for heart failure.

Both blood B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) have been approved, recommended by guidelines, and are commercially available for several years. When measured in blood, they are indicated as diagnostic aids for the evaluation of patients with acute shortness of breath, prognostic indicators for death and heart failure hospitalization, and aids in the management of patients particularly with respect to the titration of chronic medications. In general, when BNP >200 pg/mL and NT-proBNP>2000 pg/mL, there is increased myocardial production even in the presence of reduced clearance by the kidneys. The higher the levels, the greater the positive predictive value for heart failure and the worse the prognosis for hospitalization or death. Chronic use of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, aldosterone receptor blockers, and beta-adrenergic receptor antagonists and use of biventricular pacing have been shown to reduce BNP/NT-proBNP over time. In approximately 25% of patients with preserved kidney function, natriuretic peptides can be normalized (BNP <100 pg/mL, NT-proBNP<150 pg/mL) with therapy for heart failure. In the setting of CKD, it is rare for natriuretic peptides to normalize; however, relatively lower levels (~50% reduction from prior levels) are associated with a favorable prognosis. Conversely, a doubling of levels over a time frame of 6 weeks or more portends a high rate of future hospitalization and death, both from pump failure and arrhythmias.

Mid-regional proatrial natriuretic peptide (MR-proANP) is a new marker and it can be useful for diagnosis and prognosis of heart failure in CKD patients. Cut-off values for the diagnosis of heart failure increased with the decreased glomerular filtration rate. However, there is no large-scale study in CKD patients to identify the threshold more precisely [31].

Galectin-3 is a paracrine substance produced by macrophages that are participating in myocardial fibrosis. Increased levels of galectin-3 (>25.9 ng/mL) are strongly prognostic for short-term death and hospitalization in patients with either diastolic or systolic dysfunction. There have been very limited number of studies evaluating the clinical value of galectin-3 in patients with CKD; however, many subjects in the heart failure studies where it was measured met the criteria for CKD according to eGFR <60 mL/min [32]. A recent study which included asymptomatic hemodialysis patients showed that galectin-3 was associated with cardiovascular mortality [33]. Another study which also includes hemodialysis patients also showed the association between galectin-3 and cardiac mortality [34]. A suggested algorithm for the management of heart failure using galectin-3 is shown in Fig. 12.5.

Soluble ST2 (sST2) and interleukin-33 compete for the transmembrane protein ligand (ST2L) and induce production of T helper type 2 cytokines. In heart failure, serum ST2 is elevated and indicates increased abnormal immune cell signaling related to myocardial dysfunction. ST2 aids in prognostication in patients with acute and

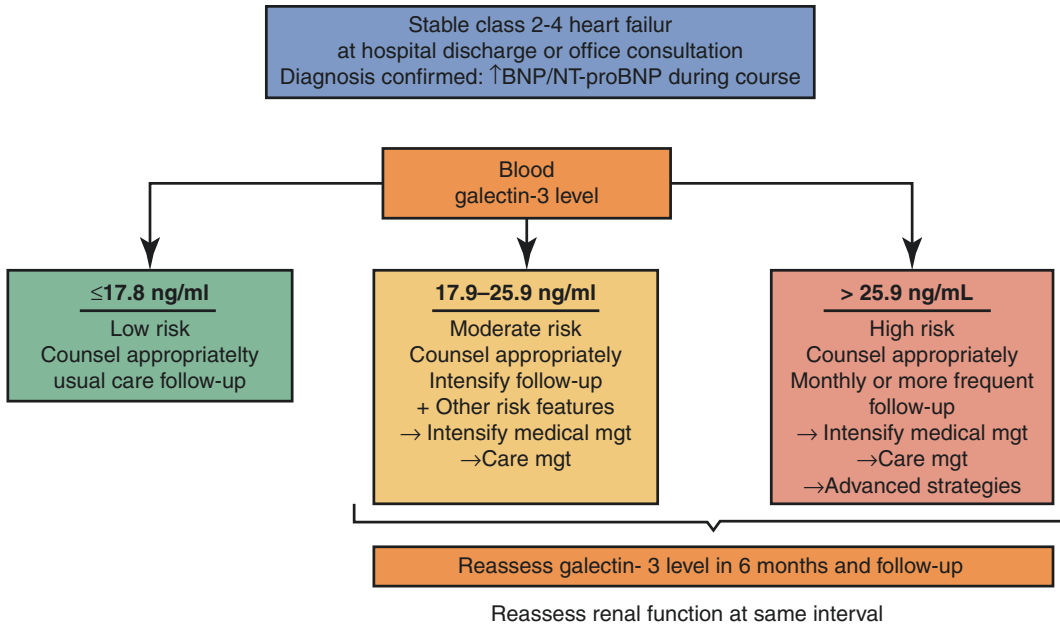

Fig. 12.5 Suggested algorithm for the management of heart failure patients using galectin-3 levels measured in blood

chronic heart failure, particularly when at very high levels (sST2 > 36.3 ng/mL). However, an elevated concentration of serum sST2 is found in CKD patients and correlates with progression of CKD [35]. Serum sST2 may be also associated with secondary hyperparathyroidism. The sST2 may have an important role in the development of CKD or as a marker of disease severity, particularly in those with incipient heart failure. Future research in this area is warranted.

Growth differentiation factor-15 (gdf-15) is a member of transforming growth factor β superfadf-15 secreted by myocardial cells due to ischemia, inflammation, and oxidative stress and it helps myocardial repair. Serum gdf-15 gradually increases with the decrease of glomerular filtration rate. Its cut-off level in CKD patients was found as 1646 ng/L. It can help the diagnosis of diastolic dysfunction and heart failure in CKD patients. It was also shown that higher serum levels of gdf-15 were associated with cardiovascular events in CKD patients [31]. Combined use with other markers may increase its prognostic role. However, more extensive studies are needed to confirm its usefulness. High-sensitivity troponin T (hs-TnT) may also be used as a predictive factor for heart failure in CKD patients. In a recent study including old patients, most of whom had renal dysfunction, patients with hs-TnT < 5 ng/L had lower heart failure risk [36]. There is also need for further studies for the use of this biomarker. Heart-type fatty acid-binding protein (H-FABP) is another promising marker with very limited number of studies in CKD patients. Higher serum level of H-FABP is associated with adverse cardiovascular events in heart failure patients [37].

12.5 Should Patients with Renal Dysfunction Have Arrhythmia Surveillance?

Maintenance of normal sinus rhythm can become progressively more difficult in patients with CKD who develop left ventricular hypertrophy, left atrial dilatation, right ventricular strain and hypertrophy, and right atrial dilatation. With activation of factors that promote cardiac fibrosis, the conduction system of the heart can show signs of failure at all levels. Thus, at the minimum in an asymptomatic patient with CKD, a 12-lead electrocardiogram should be obtained on an annual basis and with any change in cardiac symptoms.

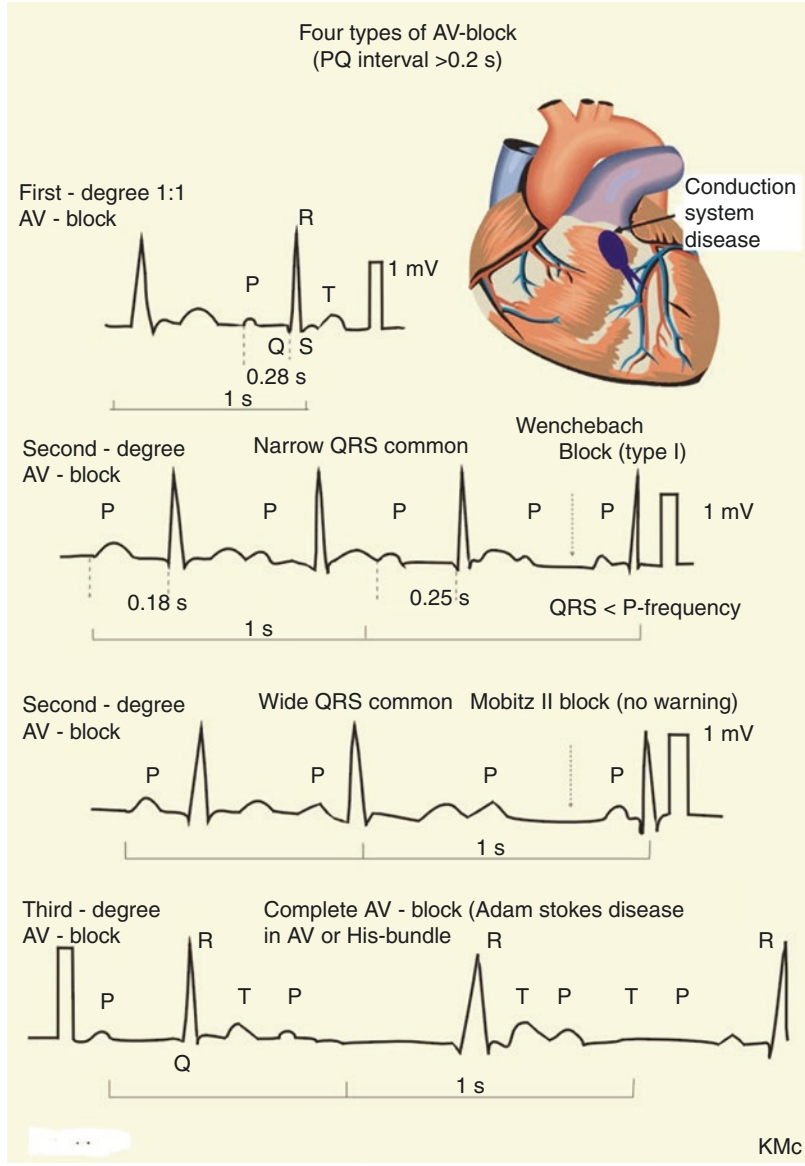

Fig. 12.6 Types of atrioventricular block as identified by electrocardiography

Failure of conduction at the level of the sinus node can lead to sick sinus syndrome (episodes of sinus pauses and tachycardia), atrioventricular node block (Mobitz Type II second degree and complete heart block (Fig. 12.6), and bundle branch blocks. These lesions in symptomatic patients are indications for permanent pacemaker implantation.

Right atrial dilatation can create a macro reentrant circuit which facilitates atrial flutter. This rhythm is recognized by sawtooth atrial depolarization waves and ventricular conduction typically in a 2:1 or 3:1 ratio (Fig. 12.7). Atrial flutter is easily managed by radio-frequency ablation and deserves electrophysiology referral. Left atrial dilatation and left ventricular hypertrophy as well as advanced age and hypertension are strong determinants for the development of atrial fibrillation (AF). Atrial fibrillation is the most common dysrhythmia among general and CKD populations. The prevalence of AF is approximately 15–20% in CKD patients not on dialysis and 15–40% in patients on dialysis [38]. Because the disorganized rhythm leads

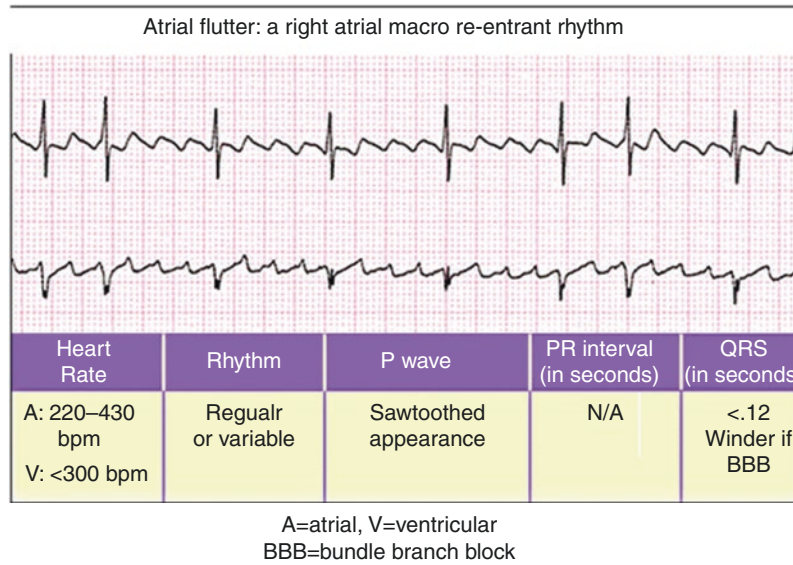

Fig. 12.7 Atrial flutter

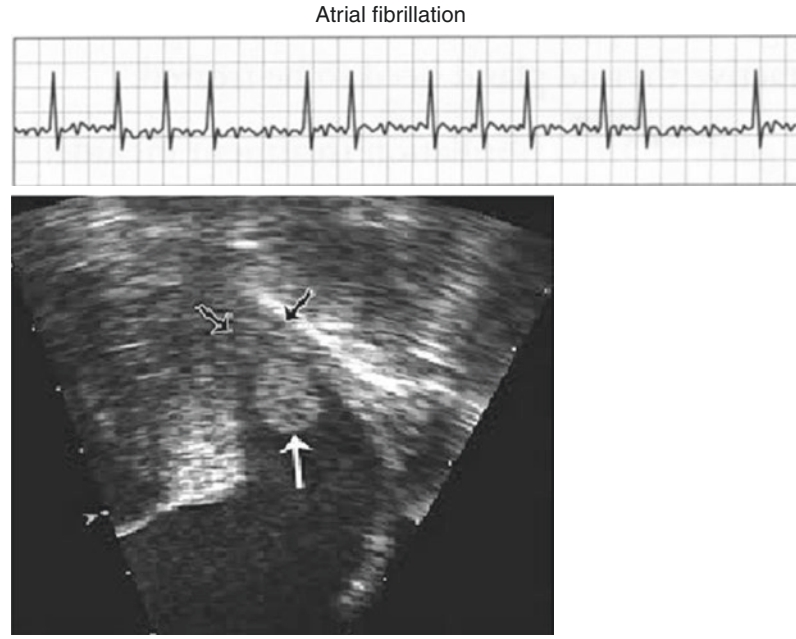

Fig. 12.8 Atrial fibrillation on electrocardiography and a left atrial appendage identified by transesophageal echocardiography

to stasis of blood in the left atrial appendage, thrombi can form and be ejected into the left circulation resulting in stroke and systemic cardioembolism (Fig. 12.8). Thus, AF presents multiple management dilemmas including rhythm versus rate control, anticoagulation, and heart failure prevention. Any patient who presents with palpitations, tachycardia, or stroke symptoms should be assessed for AF with inpatient monitoring, 24- or 48-h outpatient Holter monitoring, or patient-triggered event monitoring. For difficult cases, an implantable loop recorder can be placed subcutaneously in the infraclavicular region and give information about cardiac rhythm for several years using noninvasive computer interrogation. In the setting of cryptogenic stroke, use of intensive rhythm monitoring has shown that approxi-

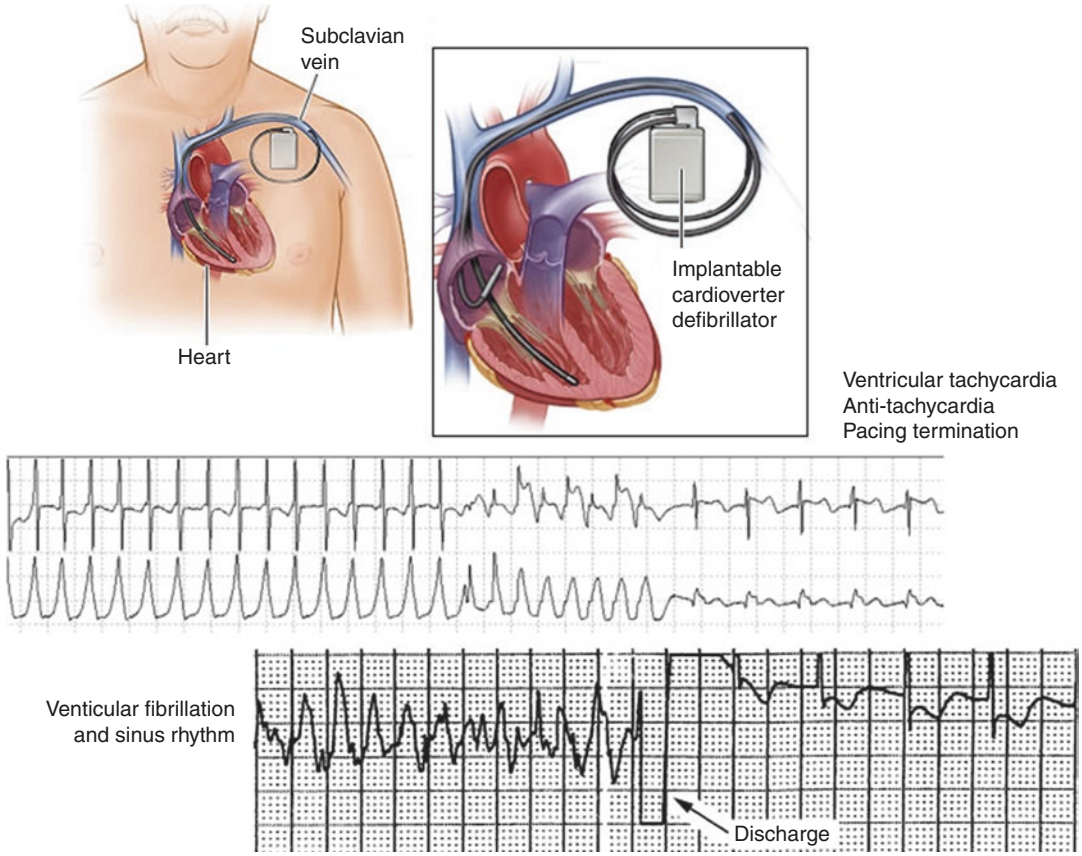

Fig. 12.9 Implantable cardio-defibrillator and demonstration of its two major forms of therapy: (1) anti-tachycardia pacing termination of ventricular tachycardia and (2) defibrillation for ventricular fibrillation

mately one third of cases can have the stroke be attributable to paroxysmal AF that was previously unrecognized.

Approximately 35–45% of CKD patients have also ventricular arrhythmias in the form of ventricular extrasystole, non-sustained and sustained ventricular tachycardia, and ventricular fibrillation. Ventricular arrhythmias may manifest as palpitation, syncope, and chest pain. If not recognized, sudden cardiac death may occur as first manifestation. ECG and 24 h ECG monitoring are important for diagnosis and risk assessment. Echocardiography and cardiac MRI can also help for detection of structural heart disease which is one of the underlying causes of arrhythmias [39].

Sudden cardiac death is typical sudden natural death, thought to be of cardiac origin, occurring within 1 h of onset of symptoms in witnessed cases, and within 24 hour of last being seen alive without witnessing [40]. Sudden cardiac death is the leading cause of death in CKD and ESRD. The details surrounding these cases are often difficult to pull together since many occur in the home and out of hospital. Presumably heart block, electromechanical dissociation, pump failure, or ventricular fibrillation is the terminal scenario. The implantable cardioverter-defibrillator has no role for primary prevention but patients with left ventricular ejection fractions <35%, those with a history of a prior resuscitated cardiac arrest, and spontaneous sustained ventricular tachycardia on monitoring should all be considered for implantable cardioverter-defibrillators. These devices reduce cardiac mortality in the general population but have not definitively been shown to prolong survival in patients with CKD or ESRD. The two major therapies delivered by implantable cardio-defibrillators are anti-tachycardia pacing and defibrillation as shown in Fig. 12.9. Because of increased myocardial

interstitial matrix in CKD and left ventricular hypertrophy, CKD and ESRD patients can be expected to have higher defibrillation thresholds and should undergo more frequent monitoring by the electrophysiologist using noninvasive programmed stimulation [41].

12.6 Summary

High rates of serious cardiovascular disease in patients with CKD and ESRD call for a more attentive approach to both routine and responsive testing in patients at risk or with potential cardiac symptoms [42]. The nephrologist needs a basic understanding of electrocardiographic interpretation both on routine single-lead monitoring and with 12-lead electrocardiography. Use of stress imaging, echocardiography, and continuous forms of rhythm monitoring provide an approach for the diagnosis and management of cardiovascular disease. Early detection and prompt management offer the hope for prevention of myocardial infarction, heart failure, valvular-induced structural damage and fatal arrhythmias.

Before You Finish: Practice Pearls for the Clinician

- Assess atherosclerosis risk factors on all patients and work to manage them to optimal levels.
- Serum biomarkers especially troponin assays may be used for risk stratification and may be helpful for detecting asymptomatic CAD. Although elevated values are less definitive, dynamic change in troponin levels may be useful for myocardial infarction (MI) diagnosis and a normal troponin assay may be sufficient to rule out infarction.
- Exercise stress testing combined with either echocardiographic imaging or nuclear scintigraphy is reasonable due to limitation of exercise stress testing in CKD patients.
- Diagnose significant cardiac ischemia with stress imaging. Large amounts of ischemia (>10% of the left ventricle) deserve coronary angiography and consideration of revascularization.
- Obtain routine 12-lead electrocardiography and have a low threshold to obtain more advanced forms of monitoring in patients with palpitations, near syncope, syncope, and stroke.
- Consider echocardiography for all patients with CKD and ESRD for assessment of myocardial function and valvular disease. Echocardiography is recommended for all CKD 5D patients 1–3 months after renal replacement therapy initiation and at 3-year intervals thereafter. We also recommended serial echocardiographic examination at closer intervals such as 12 months may increase prognostic value. All patients with considerable abnormalities need cardiology consultation and surveillance.
- In acute or chronic dyspnea, or when heart failure is suspected, elevated levels of BNP, NT-proBNP are recommended to support the diagnosis of heart failure and can portend decompensation and death. New markers such as galectin-3, ST2, MR-proANP, gdf-15 may also be used for these purposes if there is access to them.
- Patients with left ventricular ejection fractions <35%, a history of a prior resuscitated cardiac arrest, and spontaneous sustained ventricular tachycardia on monitoring should all be considered for implantable cardioverter-defibrillators.

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13 Management of Cardiovascular Disease in Chronic Kidney Disease

Sena Ulu and Engin Onan

Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) is a major risk factor for cardiovascular mortality and patients should be assessed regularly for signs and symptoms of coronary heart disease.
- Atherosclerosis, heart failure, valvular heart disease, and arrhythmias are the most common causes of morbidity and mortality in CKD patients and may exacerbate kidney dysfunction.
- Treating risk factors for atherosclerosis provides an amplified benefit for CKD patients.
- Management of heart failure is chellenging in the context of CKD.
- CKD predisposes patients to various arrhythmias, especially atrial fibrillation.
- Valvular heart disease commonly accompanies ESRD due to accelerated rate of calcification.

13.1 Coronary Atherosclerosis

Atherosclerosis begins with fatty streaks in young adult life. The lipoproteins then accumulate in the subendothelial space, inducing inflammation by cytokines and oxidative stress. Attracted macrophages to the site promote foam cell formation by lipid phagocytosis. Vascular smooth muscle cells migrate and interact with plaque as well as the vascular environment, taking on properties similar to osteoblasts. These cells respond to a variety of lipid, inflammatory, and mineral stimuli to deposit calcium hydroxyapatite crystals in the plaque and vascular environment. A fibrous plaque is gradually formed by smooth muscle migration and proliferation. This process takes many years and is usually asymptomatic [1]. When the lesion fills more than 60% of the arterial lumen, chronic stable heart disease develops [2].

During the COVID-19 pandemic, as in the normal patient population, the risk of atherosclerosis and acute myocardial infarction increased in patients with CKD, and therefore more sudden cardiac deaths had been seen [3].

13.1.1 Dyslipidemia Management: Should Patients with Kidney Disease Receive Statins?

Chronic kidney disease is a major risk factor for cardiovascular mortality. It is recommended that CKD should be treated as a coronary heart disease equivalent. Dyslipidemia, vascular stiffness, and elevated inflammatory markers are common findings in CKD patients and are associated with

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a more rapid decline in kidney function, especially if proteinuria is present. Although dyslipidemia is common in people with CKD, it is not absolute. The main determinants of dyslipidemia in CKD are glomerular filtration rate (GFR), presence of diabetes mellitus, severity of proteinuria, use of immunosuppressive agents, modality of renal replacement therapy (RRT: treatment with HD, peritoneal dialysis or transplantation), comorbidity, and nutritional status [4]. Statins are among the most potent cholesterol-lowering agents. They inhibit HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase), a rate-limiting enzyme involved in cholesterol formation and have been studied in both pre-dialysis and dialysis patients.

The best data supporting the use of statins for primary prevention of cardiovascular events in patients with non-dialysis CKD, come from the Heart and Renal Protection Study (SHARP) study and meta-analyses of statin studies involving subgroups of patients with CKD. These data demonstrate a reduction in cardiovascular risk with statin therapy in patients with CKD non-dialysis [5]. The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines agree with the AHA/ACC (American Heart Association/American College of Cardiology) guidelines in many areas. LDL (low density lipoprotein) values and titrating treatment to certain levels are no longer indicated. In fact, association between LDL and coronary heart disease gets weaker with the glomerular filtration rate (eGFR) potentially misleading clinicians since this population is still at very high risk. But if a triglyceride level is >1000 mg/dL or an LDL level is >190 mg/dL, the lipid profile should be evaluated in all CKD patients to evaluate those who would benefit from investigating secondary causes. Statins or a statin/ezetimibe combination is the best pharmacological approach. Cardiovascular risk in CKD patients is age-related, with a cardiovascular death rate >10 per 1000 patient years in individuals over 50 years of age. Therefore, statins are indicated in all CKD patients ≥50 years of age who are not on dialysis treatment. Because of higher toxicity rates, lower doses should be initiated when the eGFR is <60 mL/min/1.73 m^2. However, since higher doses reduce cardiovascular events more than lower doses, the dose can be increased if patients tolerate it well. Statin therapy is indicated in patients with CKD who are not dialysis treatment when they have coronary heart disease, a history of ischemic stroke, diabetes, and an estimated 10-year risk >10% between the age of 18 and 49 years. These patients may also be considered for treatment according to ACC/AHA guidelines. In this age group, treatment should be individualized according to the presence of high-risk factors.

There is no direct evidence that statin therapy is beneficial in dialysis patients. It was shown that atorvastatin in the 4D (The Deutsche Diabetes Dialysis Study) study and rosuvastatin in the AURORA study had no effect on cardiovascular mortality and total mortality in the dialysis patient group [6, 7].

Kidney transplant recipients have a significantly higher risk of cardiovascular events. Data from the placebo arm of the ALERT study show that the rate of cardiovascular death or non-fatal MI was approximately 21.5 per 1000 patient years. The ALERT study examined the effect of statin therapy on reducing cardiovascular risk for 5–6 years in 2102 patients aged 30–75 years with kidney transplants. Fluvastatin treatment given at a dose of 40–80 mg/day resulted in a nonsignificant 17% reduction in coronary death or non-fatal MI compared to placebo. (RR 0.83; 95% CI 0.64–1.06) [8]. The age at initiation of statin therapy in kidney transplant recipients is uncertain: the risk of coronary events is age-related, and ALERT did not enroll participants younger than 30 years. Even in the presence of optimal graft function, cardiovascular risk is expected to increase over time.

The risk of statin toxicity in CKD patients is similar to general population. Routine liver function monitoring is not recommended because hepatic failure due to statins is rare. Control of basal transaminase levels before initial treatment and control liver function test evaluation in the situation of hepatotoxicity is sufficient. Statins should be prescribed in patients with chronic liver disease and elevated aminotransferase levels with no progressive liver failure. Statin-related

Table 13.1 Statin therapy with dose, pharmacology data for CKD patients and recent studies

Medication/Dose/Pharmacology	Data for CKD patients
Simvastatin Cardiovascular protection dose: 20 mg p.o. once daily Maximum dose: 40 mg p.o. given at hour of sleep Metabolism: liver, CYP450 Excretion: bile primarily, urine <2%	Consider starting dose at 5 mg in the evening in patients with CKD In SHARP, lipid lowering with simvastatin + ezetimibe was beneficial in patients with CKD
Atorvastatin Cardiovascular protection dose: 10 mg p.o. once daily Metabolism: liver, CYP450 Excretion: bile primarily, urine <2%	No specific dose adjustments for patients with CKD Atorvastatin 10 mg in patients with CKD revealed a significantly lower risk of the primary end point (non-fatal MI or cardiac death) when compared with placebo With the TNT and GREACE studies, atorvastatin showed improvement in kidney function in patients with CKD In CARDS study, atorvastatin 10 mg daily is safe and effective in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes whose LDL cholesterol is in the normal range [9]
Fluvastatin Cardiovascular event protection: 40 mg p.o. twice daily Extended release: 80 mg p.o. once daily Excretion: feces 90%, urine 5%	No specific dose adjustments for patients with CKD In a meta-analysis, fluvastatin use was associated with a reduction in major adverse cardiac events among kidney transplant patients [10]
Pravastatin Cardiovascular event protection start: 40 mg p.o. once daily, may adjust dose every 4 weeks Maximum dose: 80 mg p.o. once daily Excretion: feces 70%, urine 20%	Start at 10 mg p.o. once daily in patients with CKD Treatment with a low dose of pravastatin reduces the risk of coronary heart disease in MEGA study [11]
Rosuvastatin Cardiovascular event protection: 20 mg p.o. once daily Metabolism: ~10% by hepatic CYP2C9 Maximum dose: 40 mg Excretion: feces 90%, urine 10%	Mild or moderate (CrCl ≥30 mL/min/1.73m^2): No dosage adjustment necessary. Severe (CrCl <30 mL/min/1.73m^2) and not on hemodialysis: Decrease starting dose to 5 mg PO qDay; not to exceed 10 mg/day In JUPITER study results showed that rosuvastatin was associated with a significant reduction in first major cardiovascular events [12]

ACS acute coronary syndrome, *CKD* chronic kidney disease, *CYP 450* cytochrome p 450, *MI* myocardial infarction, *P.o.* per oral. The table was inspired from Mohammad Nasser, Peter A. McCullough and recreated with recent studies.

myopathies are frequently observed in clinical practice. Pravastatin, fluvastatin, and rosuvastatin have a lower risk of myopathy and can be used safely in patients with chronic kidney disease. Atorvastatin and fluvastatin do not require dose adjustment in CKD. Other statins are more dependent on the CYP3A4 enzyme; therefore, they have the potential to accumulate in slow metabolisers or with CYP3A4 inhibitor administration (Table 13.1). Once the myopathy has resolved, the same treatment can be restarted with lower doses. If myotoxicity still exists, switch to safer statins is recommended. Reducing the dose every other day may also be a possible approach. Coenzyme Q10 and vitamin D have not been shown to be effective in preventing statin-induced myopathy therefore they are not recommended in current guidelines. New guidelines recommend the evaluation of newly diagnosed diabetes mellitus patients on statin therapy. New diabetic patients should be advised to follow a healthy diet and participate in an exercise program.

Hypertriglyceridemia is a prominent abnormality that often accompanies renal impairment. Diminished elimination of lipids and impaired lipoprotein lipase activity are the primary causes of hypertriglyceridemia. The non-pharmacological management of hypertriglyceridemia in CKD patients is similar to the general

population. Therapeutic lifestyle changes should include diet change, weight loss in case of overweight, increased physical activity, and reduced alcohol intake. Dietary changes may include a low-fat diet, reduction of monosaccharides and disaccharides, reduction of carbohydrates, and use of fish oils. Fibrates, which have an increased potential for side effects, especially when prescribed together with statins, are not recommended for treatment (KDIGO 2013). Despite non-pharmacological interventions CKD patients with serum total triglycerides >10 mmol/L (886 mg/dL) may need specific triglyceride therapy to prevent pancreatitis and to reduce cardiovascular risk. For these patients, fibrates are the most effective treatment for lowering serum triglyceride levels [13].

Niacin therapy is also effective in reducing serum triglyceride levels, and niacin therapy additionally increases serum high density lipoprotein C (HDL-C) levels. However, in a study conducted in CKD patients, the addition of niacin to the statin did not reduce cardiovascular events [14]. Niacin also has side effects such as flushing and gastrointestinal intolerance. And it is no longer available in many countries.

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) evaluated the effect of gemfibrozil in patients with CHD and HDL-C < 40 mg/dL (1.03 mmol/L). In this cohort of 2531 patient, there were 1044 men with impaired creatinine clearance, including 638 and 406 patients with creatinine clearance of 60–75 and 30–59.9 mL/min, respectively [15]. Among these patients with impaired creatinine clearance, gemfibrozil reduced the risk of coronary death and the primary endpoint of non-fatal myocardial infarction (18.2% vs. 24.3%), odds ratio [HR] 0.73, 95% CI 0.56–0.96). However, treatment with gemfibrozil had no effect on total mortality (HR 1.03) and a significant decrease in kidney function was observed. In the study, 5.9% and 2.8% of patients treated with gemfibrozil and placebo, respectively, experienced a sustained increase in creatinine values that remained 0.5 mg/dL higher than baseline for the remainder of follow-up ($p = 0.02$).

Box 13.1 What the Guidelines Say You Should Do

- Statin therapy is recommended for all CKD patients which have an eGFR level above 60 mL/min and over 50 years old or eGFR level below 60 mL/min or eGFR above 60 mL/min but with concomitant risk factors such as diabetes mellitus, hypertension, smoking, low HDL cholesterol, and high lipoprotein a level. Targeting LDL levels is not recommended.
- Lifestyle changes such as reducing salt intake, maintaining a healthy weight, and being on an exercise program should be offered to all patients.
- Statins are not indicated in patients on dialysis due to the lack of high level of scientific evidence.
- Lifestyle changes, such as reducing monosaccharide and disaccharide intake, reducing total dietary carbohydrate intake, and replacing long-chain triglycerides and fish oils, are indicated in dialysis patients with CKD or hypertriglyceridemia ≥500 mg/dL.
- Fibrates should be offered to patients with triglyceride ≥500 mg/dL and patients with triglyceride ≥200 mg/dL and non-HDL levels ≥130 mg/dL who cannot tolerate statins.
- Antiplatelet agents should be recommended in patients with CKD unless contraindicated.
- In the case of heart failure, acute clinical decompensation and additional or increase in therapy should require close eGFR and potassium monitoring [16].

13.1.2 Antiplatelet Therapy: Which Agents for What Syndromes?

Platelets play an important role in the pathogenesis of acute coronary artery syndrome and atherosclerosis. Endothelial damage induces platelet

activation, aggregation, and adhesion to the subendothelium. Antagonizing the early phases of activation is the main mechanism of action of many antiplatelet agents such as aspirin and thienopyridines. Aspirin is the most commonly used agent, inhibits thromboxane A2 with irreversible COX-1 acetylation, resulting in weakening of platelet activation. Long-term aspirin therapy reduces the risk of subsequent myocardial infarction (MI), stroke, and vascular death in patients without CKD but with a wide range of preexisting cardiovascular disease manifestations.

There is less data on the efficacy and safety of antiplatelet therapy in CKD patients. The best data came from a meta-analysis of 27,139 CKD patients who participated in 50 randomized trials evaluating the efficacy of antiplatelet agents (mostly aspirin) for the prevention of cardiovascular disease [17]. Antiplatelet therapy significantly reduced the incidence of fatal or non-fatal myocardial infarction compared to placebo or no treatment (6.7% vs. 7.0%, or 3 myocardial infarctions per 1000 treated patients were prevented). However, antiplatelet therapy also significantly increased the rate of major bleeding (2.9% vs. 4.4%, or 15 additional major bleeding events per 1000 treated patients). Antiplatelets had no effect on stroke or mortality. Results were similar in patients of all CKD stages [18]. This recommendation is largely consistent with the KDIGO CKD (12) management guidelines. In addition to cardiovascular disease, aspirin therapy can reduce the risk of cancer incidence. This should be taken into account when deciding whether to use aspirin in patients with chronic kidney disease.

Thienopyridines also improve cardiovascular outcomes when used as monotherapy. They act by inhibiting platelet aggregation caused by adenosine diphosphate (ADP). These drugs are preferred in patients with severe vascular disease, previous MI or stroke, as well as when allergy to aspirin is present. Dual antiplatelet therapy does not provide additional benefit in patients with stable atherosclerotic disease, but increases the augmented risk of bleeding compared to monotherapy. Adding a thienopyridine to aspirin should be reserved for certain conditions, such as acute ischemia or stent implantation [19].

13.1.3 Angina Relief

Commonly used antianginal drugs include nitrates, beta-blockers, calcium channel blockers, and ranolazine. These agents exhibit different properties and actions.

13.1.3.1 Nitrates

The antianginal efficacy associated with nitrates is a result of venodilation, reduced cardiac preload, and oxygen demand, as well as improved collateral coronary flow in a more relaxed myocardium. Sublingual forms have the fastest onset of action; however, their effects only last 30–60 min. They are useful in the acute period. In contrast, isosorbide 5-mononitrate is a long-acting agent with effects lasting up to 12 h. It is an active metabolite of the dinitrate form. This medication should be used once a day, allowing for a 12-h drug-free period that helps avoiding tolerance. Side effects of nitrates include flushing, headache, and hypotension. No dose adjustment is required in patients with CKD [2].

13.1.3.2 Beta-Blockers

Beta receptor activation triggers a reaction that increases inotrophy and chronotrophy. Beta adrenergic receptor blockers are the competitive antagonists of noradrenaline and adrenaline. Beta-blockers (β-blockers) diminish exercise endurance due to antagonizing the sympathetic nervous system. In healthy individuals, β-blockers reduce exercise endurance by antagonizing the sympathetic nervous system. This is not the case in patients with coronary artery disease. β-blockers cause an increase in exercise capacity in patients with angina. The relief of angina by beta-blockade is due to increased diastolic duration and reduced oxygen demand. Unlike patients who have not had a prior MI, β-blockers reduce mortality when used after an acute event, which is why the ACC/AHA committee recommended β-blockers as first-line therapy for chronic stable angina. Reducing heart rate to 50–60 beats/min and exercise tolerance determine effectiveness. Adverse effects include bronchoconstriction, weight gain, insulin resistance (except carvedilol), bradycardia, hypotension, sexual dysfunction,

Table 13.2 β-blocker therapies for CKD patients in acute coronary seyndrome

Medication/Dose/Pharmacology	Data for CKD patients
Metoprolol Acute MI: Metoprolol tartrate: 2.5–5 mg rapid IV every 2–5 min, up to 15 mg over 10–15 min, then 15 min after last IV and receiving 15 mg IV or 50 mg p.o. every 6 h for 48 h, then 50–100 mg p.o. twice daily Angina: Metoprolol tartrate: initially 50 mg p.o. twice daily then titrated to 200 mg p.o. twice daily, metoprolol succinate: 100 mg p.o. once daily, no more than 400 mg per day Dialysable: Yes Metabolism: hepatic CYP2D6 Metabolites: inactive Excretion: urine 95%	No specific dose adjustments for patients with CKD Recommend close monitoring for adverse effects Metoprolol increases uric acid and risk of gout in African Americans with chronic kidney disease attributed to hypertension [20]
Esmolol Immediate control For intraoperative treatment give an 80 mg (approximately 1 mg/kg) bolus dose over 30 s followed by a 150 μg/kg per min infusion, if needed For postoperative treatment, give loading dosage infusion of 500 μg/kg per min over 1 min followed by a 4 min infusion of 50 μg/kg per min. If no effect within 5 min, repeat loading dose and follow with infusion increased to 100 μg/kg per min Maximum infusion rate: 300 μg/kg per min Metabolism: extensively metabolized by esterase in cytosol of red blood cells Metabolites: major acid metabolite (ASL8123), methanol (inactive) Excretion: urine <1–2%	No specific dose adjustments for patients with CKD
Carvedilol Hypertension and post-MI protection: 6.25–25 mg p.o. twice daily start at 6.25 mg p.o. twice daily, then increase every 3–14 days to 12.5 mg p.o. twice daily, then 25 mg p.o. twice daily Elimination: mainly biliary Excretion: primarily via feces	No specific dose adjustments for patients with CKD In a small study of patients on dialysis with dilated cardiomyopathies, carvedilol improved left ventricular function and decreased hospitalization, cardiovascular deaths, and total mortality Studies with carvedilol demonstrate attenuated increases in albuminuria as well as reduction in cardiovascular events in CKD patients with hypertension [21]

ACS acute coronary syndrome, *CKD* chronic kidney disease, *CYP 450* cytochrome p 450, *MI* myocardial infarction, *P.o.* per oral. The table was inspired from Mohammad Nasser, Peter A. McCullough and recreated with recent studies.

and fatigue. These agents have no effect on kidney function. Hydrophilic β-blockers (e.g., atenolol, nadolol, and sotalol) are not well metabolized by the liver and are usually excreted unchanged in the urine. Hydrophobic agents (eg propranolol, metoprolol) are well tolerated in case of kidney disease.

There are two main types of beta (β) receptors; these are β1 and β2 adrenergic receptors. Most of the β-blockers used in clinical therapy show equally high affinity for β1 and β2 receptors and block both to the same degree, which are called "non-selective β-blockers." On the other hand, especially bisoprolol, atenolol, acebutolol, betaxolol, metoprolol, celiprolol, and esmolol show higher affinity for β1 receptors than β2. β-blockers that act selectively on β1 receptors are called "cardioselective beta-blockers" and they can be used in the treatment of chronic kidney disease. β-adrenergic receptor blockers for ACS in patients with CKD are given in Table 13.2.

13.1.3.3 Calcium Channel Blockers

Calcium channel blockers (CCBs) work by antagonizing calcium channels in vascular smooth muscle cells and myocytes, thereby reducing cytoplasmic calcium influx. The net effect is vasodilation, improved coronary blood flow, and reduced contractility. When combined with β-blockers, CCBs are more effective than either drug in the treatment of angina. There are two main classes in this drug group: Non-dihydropyridines (diltiazem, verapamil) and dihydropyridines. CCBs have varying individual pharmacological and therapeutic properties, but as a group, they are effective antihypertensive agents in patients with kidney disease. Their effect on the kidneys may go beyond lowering blood pressure alone.

Existing studies suggest that CCB do not worsen the progression of kidney disease, but may benefit when systemic BP is firmly returned to normal. Non-dihydropyridine calcium channel blockers (NDHP), diltiazem, and verapamil slow down the progression of type 2 diabetic kidney disease with overt proteinuria to an extent almost similar to that observed with ACE-I. Dihydropyridine calcium channel blockers (DHP) have a variable effect on proteinuria. CCBs may have an advantage in combination with ACE-I and/or ARB [22]. Several studies have shown that short-acting nifedipine can exacerbate ischemia and worsen heart failure, making its use a major concern [23]. Longer-acting dihydropyridines appear to be safer and better tolerated. Amlodipine reduced cardiovascular events in clinical studies. It is eliminated by the liver and used safely in CKD patients. In contrast, non-dihydropyridines have greater potential in reducing contractility with less profound vasodilatory effects. Verapamil has more cardiodepressive effects and therefore more side effects than diltiazem. In view of the negative ionotropic effects of NDHP, caution should be exercised in patients with atrioventricular node disease and heart failure.

13.1.3.4 Ranolazine

Ranolazine works by inhibiting late inward sodium channels, thereby reducing calcium concentration and diastolic tension. Because this sodium channel is often not inactivated in some major myocardial disease states, such as ischemia and hypertrophy, excess influx of sodium ions leads to activation of the sodium/calcium exchanger, raising the calcium concentration [24]. Given the normal rapid inactivation of the late inward sodium channel in normal myocytes, the drug does not exert a significant effect on normal myocardium at normal doses. This potentially increases its therapeutic window. The starting dose of ranolazine is 500 mg twice daily. In patients who remain symptomatic, 1000 mg twice daily can be used. Long-term treatment with ranolazine is not thought to cause progressive renal dysfunction. It is recommended to reduce the dose to 500 mg twice daily in patients with chronic renal failure [25].

13.1.4 Management of Acute Coronary Syndrome

Patients with end-stage renal disease and CKD may have silent ischemia more frequently. Suspicion of acute coronary syndrome (ACS) should be high when ECG changes and abnormal cardiac enzyme levels are present. Standard ACS pharmacotherapy provides an enhanced benefit in kidney patients. Treatment includes dual antiplatelet therapy, statins, β-blockers, ACEIs, low-molecular-weight heparin, and glycoprotein IIb/IIa antagonists [26]. Dose adjustments are recommended for these agents (Tables 13.4, 13.5, and 13.6).

ACEIs provide a survival advantage after an acute event and should be continued thereafter. While several studies have demonstrated the superiority of early intravenous β-blocker use in acute MI, other studies have not been consistent with such benefit. In the "Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries" (GUSTO) and "Clopidogrel and Metoprolol in Myocardial Infarction" (COMMIT) trials, early beta-blockade resulted in an increased risk of cardiogenic shock and even death [34, 35]. Therefore, caution should be exercised when initiating β-blockers early in acute ST elevation MI during hemodynamic instability. Higher loading

Table 13.3 Antiplatelet therapies for CKD patients in acute coronary syndrome

Medication/Dose/Pharmacology	Data for CKD patients
Aspirin Acute MI: 160–325 mg p.o. as soon as possible MI prophylaxis: 81–162 mg p.o. once daily PCI: 325 mg p.o. 2 h pre-surgery, then 160–325 mg p.o. maintenance UA: 75–162 mg by mouth once daily Renal clearance: 80–100% 24–72 h Excretion: principally in urine (80–100%). Sweat, saliva, and feces	Meta-analysis involving patients on dialysis demonstrated a benefit of aspirin therapy on cardiovascular outcomes Low-dose aspirin was associated with an increased risk of cardiovascular events in patients with chronic kidney disease and low bodyweight. Prescribing low-dose aspirin for the prevention of cardiovascular events in patients with chronic kidney disease, particularly patients with low bodyweight (<60 kg) needs to be individualized [37]
Clopidogrel UA/NSTEMI: 300–600 mg initial loading dose, followed by 75 mg p.o. once daily with aspirin STEMI: 75 mg p.o. once daily with aspirin 75–162 mg per day Recent MI: 75 mg p.o. once daily Metabolism: CYP3A4, CYP2C19 (predominantly) and others to generate active metabolite; also by esterase to an inactive metabolite Excretion: urine and feces	No specific dose for patients with CKD CYP2C19 genotypes and clinical risk factors can be integrated by ABCD-GENE score to estimate the efficacy of clopidogrel-aspirin therapy [38]
Prasugrel ACS: Loading dose- 60 mg p.o. once Maintenance dose: 10 mg p.o. once daily with aspirin 81–325 my per day; bleeding risk may increase if weight < 60 kg, consider 5 mg p.o. once daily (efficacy/safety not established) Metabolism: liver; CYP450, CYP2B6, CYP2C9/CYP2C19 (minor). CYP3A4 substrate; CYP2B6 (weak) inhibitör Excretion: urine (68%) and feces (27%)	No specific dose for patients with CKD In one study results show that among patients with ACS, reduction of eGFR is associated with increased risk for ischemic and bleeding events but has no significant impact on the relative efficacy and safety of ticagrelor versus prasugrel [39]
Ticagrelor ACS with PCI and stent: Starting dose: 180 mg p.o. once Maintenance dose: 90 mg p.o. twice daily To be given for 1 year with aspirin as an alternative option for dual antiplatelet therapy Metabolism: hepatic CYP450 Excretion: bile primarily, urine <1%	No specific dose for patients with CKD

CAD coronary artery disease, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST elevation myocardial infarction, p.o. per oral, *UA* unstable angına, *NSTEMI* non-ST elevation myocardial infarction. The table was inspired from Mohammad Nasser, Peter A. McCullough and recreated with recent studies.

doses of clopidogrel produce a reduction in death, MI, and stroke compared to lower doses. The duration of dual antiplatelet therapy should be adjusted for each patient. Although it seems reasonable to continue aspirin plus clopidogrel for more than 1 year in patients with severe vascular disease, further studies are needed in this regard [36]. Antiplatelet therapies for CKD patients in acute coronary syndrome are given in Table 13.3. Acute and chronic treatments for ACS in patients with CKD are given in Table 13.4.

13.1.5 Revascularization Therapy

Patients with CKD and acute coronary syndrome should be treated in the same way as patients with acute coronary syndrome without kidney disease. The benefit of revascularization in patients with advanced kidney disease and coronary artery disease (CAD) is unknown. Observational studies suggest that revascularization may provide a survival benefit compared to medical treatment alone. There is little evidence from randomized trials regarding the efficacy of revascularization

Table 13.4 Acute and chronic treatments for ACS in patients with CKD

Medication/Dose/Pharmacology	Data for CKD patients
Captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, fosinopril Indicated for the treatment of hypertension, prevention of cardiovascular events including heart failure in those at risk, reduction in the progression of type 1 diabetic nephropathy, and reduction in cardiovascular events in patients post MI with left ventricular dysfunction or heart failure Also indicated for the treatment of heart failure Elimination: mainly renal with an elimination half-life of 12.6 h in healthy individuals In patients with impaired renal function (CrCl ≤30 mL/min) a longer half-life and accumulation have been observed without clinical consequences	Dosing may need to be individualized for each dialysis session to avoid intradialytic hypotension
Losartan, irbesartan, olmesartan, candesartan, valsartan, telmisartan Indicated for treatment of hypertension, to reduce the progression of type 2 diabetic nephropathy, and reduce cardiovascular events in patients post-MI with left ventricular dysfunction or heart failure Indicated for heart failure in those intolerant to ACE inhibitors Losartan has 88% hepatic and 12% renal clearance	Both ACE inhibitors and ARBs have been shown to reduce LVH in most patients with CKD Levels of ARBs do not change significantly during hemodialysis
CCBs Dihydropyridines; amlodipine, nimodipine, nitrendipine, felodipine, nicardipine, nifedipine; non-dihyrdropyridines: diltiazem, verapamil In UA/NSTEMI, if B-blockers are contraindicated, a non-dihydropyridine CCB should be chosen in the absence of clinically significant left ventricular dysfunction or other contraindications Diltiazem undergoes primary liver metabolism	No specific dose adjustments for patients with CKD Management of chronic CAD in dialysis patients should follow that of the general population and use of CCBs The hemodynamic and electrophysiological effects of CCBs differ markedly from each other. Therefore, each agent should be carefully selected
Nitroglycerin Angina: 0.5–2 in. applied in morning and 6 h later to truncal skin Heart failure: 1.5 in., increase by 0.5–1 in. up to 4 in., every 4 h Sublingual: 0.4 mg for relief of chest pain in ACS every 5 min Maximum: 3 doses within 15 min Metabolism: Mainly in liver, extrahepatic sites such as vascular wall, red blood cells Excretion: urine	No specific dose for patients with CKD Care must he used to avoid hypotension in low volume states such as dialysis sessions
Ranolazine 500–1.000 mg p.o. twice daily Max: 2000 mg per day Excretion: urine 73–75%, feces 25%	No specific dose adjustments for patients with CKD Prolongs QTc interval Recommend close monitoring

ACE angiotensin-converting enzyme, *ACS* acute coronary syndromes, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *LVH* left ventricular hypertrophy, *MI* myocardial infarction, *NSTEMI* Non-ST elevation myocardial infarction: *PCI* percutaneous coronary intervention, p.o. per oral, *STEMI* ST elevation myocardial infarction, *UA* unstable angına. The table was inspired from Mohammad Nasser, Peter A. McCullough and recreated with recent studies.

by coronary artery bypass grafting or percutaneous coronary intervention in patients with CAD versus medical therapy alone in patients with CKD [40]. The risk of contrast-induced nephropathy is a major source of concern when percutaneous coronary intervention is performed in patients with CKD. Strict rehydration protocols and techniques to minimize the use of contrast are essential to reduce this risk. Finally, non-invasive or invasive CAD screening approach should be used in CKD patients awaiting kidney transplantation, based on their cardiovascular risk profile. Revascularization should be performed in candidates with critical stenosis [41].

13.1.5.1 Percutanous Coronary Intervention

Percutanous coronary intervention (PCI) can be selected as the revascularization method in patients who are suitable candidates. It does not prolong life compared to medical treatment [42]. It is indicated for the treatment of symptomatic single or double vessel disease. There are concerns about data on the association between CKD and increased rates of restenosis. Patients with chronic total occlusion of an infarct-related artery should not undergo PCI because of the excessive risk of reinfarction and no clinical benefit for death or heart failure. Drug-eluting stents are known to have lower rates of in-stent restenosis than normal metal stents [43].

Post-PCI pharmacotherapy should include dual antiplatelet targeting with aspirin and a thienopyridine. Prasugrel inhibits platelet aggregation to a greater extent,with a faster onset of action than clopidogrel. Compared with clopidogrel in patients after PCI, prasugrel is more effective in reducing the incidence of cardiovascular death, MI, stroke, and stent thrombosis. But prasugrel has higher rates of life-threatening and fatal bleeding in comparison with clopidogrel [44]. The risk of bleeding was particularly higher in patients with a history of transient ischemic attack and stroke, and in elderly patients. Prasugrel is therefore contraindicated in these patients. It is recommended that the treatment period should maintain at least 1 year after intracoronary stent implantation [45]. Intravenous glycoprotein IIb/IIIa inhibitors for unstable angina/NSTEMI and STEMI are given in Table 13.5. Antithrombotic agents for unstable angina/NSTEMI and STEMI are given in Table 13.6.

Table 13.5 Intravenous glycoprotein IIb/IIIa inhibitors for unstable angina/NSTEMI and STEMI

Medication/Dose/Pharmacology	Data for CKD patients
Abciximab Adjunct to PCI: 0.25 mg/kg IV bolus over at least 1 min, 10–60 min before start of PCI, then 0.125 μg/kg per min (not to exceed 10 μg per min) continuous IV infusion for 12 h Unstable angina with PCI planned within 24 h: 0.25 mg/kg IV bolus over at least 1 min, then 0.125 μg/kg per min (not to exceed 10 μg per min) IV infusion for 18–24 h concluding 1 h after PCI Metabolism: unknown, but likely by the reticuloendothelial system Excretion: urine	No specific dose adjustments for patients with CKD Because the potential risk of bleeding is increased in patients with stage 4 CKD, the use of abciximab in CKD patients should be considered only after careful appraisal of the risks and benefits [27]
Eptifibatidc ACS: 180 μg/kg IV bolus, then 2 μg/kg per min IV for up to 72 h PCI: 180 μg/kg IV, then a continuous infusion at 2 μg/kg per min with another 180 μg/kg IV bolus 10 min after first bolus Continue infusion for at least 12 h Metabolism: other, minimal Excretion: urine 50%	In patients with stage 3 to 4 CKD, the clearance of eptifibatide is reduced by ≈50%, and steady-state plasma levels are approximately doubled. The maintenance dose of eptifibatide should therefore be reduced from 2.0 to 1.0 μg/kg/min in patients with creatinine clearance ≥30 to <50 mL/min [28]
Tirofiban In patients undergoing PCI, tirofiban is not recommended as an alternative to abciximab ACS: 0.4 μg/kg per min IV for 30 min, then 0.1 μg/kg per min IV for 48–108 h PCI: Continue 0.1 μg/kg per min IV through procedure and for 12–24 h after Excretion: urine 65% (primarily unchanged), feces 25% (primarily unchanged)	Creatinine clearance <30 mL/min and ACS: reduce dose to 50% of normal rate Safety and use during hemodialysis not established Among patients with stage 2 to 3 CKD in the platelet receptor inhibition in ischemic syndrome Management in Patients Limited by unstable signs and symptoms (PRISM-PLUS), tirofiban was well tolerated and effective in reducing ischemic ACS complications, with no evidence of treatment-by–creatinine-clearance interaction [29]

ACS acute coronary syndromes, *CKD* chronic kidney disease, *IV* intravenous, *NSTEMI* non-ST elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST elevation myocardial infarction. The table was inspired from Mohammad Nasser, Peter A. McCullough and recreated with recent studies.

Table 13.6 Antithrombotic agents for unstable angina/NSTEMI and STEMI

Medication/Dose/Pharmacology	Data for CKD patients
Unfractionated heparin Recommended dosage and desired aPTT values as per institutional protocol PCI: 60–100 units/kg IV given once Target ACT 250–350 s In patients receiving glycoprotein IIb/IIIa inhibitor. Give 50–70 units/kg IV to target ACT 200 s STEMI, adjunct treatment, streptokinase use: 800 units/h when <80 kg body weight or 1000 units per h when >80 kg body weight Start: 5000 units IV, adjust dose to target aPTT 50–75 s NSTEMI: 1215 units/kg per h IV Start: 60–70 units/kg IV; Max 5000 units bolus, max rate 1000 units per h Adjust dose to target aPTT 50–75 s Metabolism: liver (partial) Metabolites; none Excretion: urine	In patients with CKD. Suggested starting dose of heparin is 50 IU/kg bolus, then 1S IU/kg per h Monitor aPTT level and adjust accordingly as per institutional protocol
Low-molecular-weight heparin (e.g., enoxaparin) Unstable angina, nonQ-wave myocardial infarction: 1 mg/kg subcutaneously twice daily, CrCl <30 mL/min STEMI, aged <75 years: 30 nig IV bolus plus 1 mg/kg subcutaneously, then 1 mg/kg subcutaneously every 12 h PCI: additional 0.3 mg/kg IV bolus it last subcutaneous administration given >8 h before balloon inflation STEMI, aged >75 years: 0.75 mg/kg subcutaneously every 12 h (no IV bolus) Excretion: urine 40%	STEMI, aged <75 years: 30 mg IV bolus plus 1 mg/kg subcutaneously. Then 1 mg/kg subcutaneously once a day STEMI, aged >75 years: 1 mg/kg subcutaneously once a day
Fondaparinux Unstable angina/NSTEMI Conservative strategy: 2.5 mg subcutaneously once daily During PCI: add unfractionated heparin 50–60 units/kg IV bolus for prophylaxis of catheter thrombosis Excretion: urine (primarily unchanged)	CrCl 30–50 mL/min: use with caution CrCl <30 mL/min: not indicated A meta-analysis showed that the safety and efficacy of fondaparinux in renally impaired patients is limited and does not support its use in such population [30]
Bivalirudin Intended for use with aspirin 300–325 mg per day 0.75 mg/kg TV bolus initially, followed by continuous infusion at rate of 1.75 mg/kg per h for duration of procedure Perform ACT 5 min after bolus dose Administer additional 0.3 mg/kg bolus if necessary May continue infusion following PCI beyond 4 h (optional post-PCI, at discretion of treating healthcare provider) initiated at rate of 0.2 mg/kg per h for up to 20 h as needed Dialysable: with 25% reduction in levels Dialysable: with 25% reduction in levels Excretion: urine	CrCl 10–29 mL/min: usual bolus dose, then initial infusion of 1 mg/kg per h IV up to 4 h Hemodialysis: usual bolus dose, then initial infusion of 0.25 mg/kg per h IV up to 4 h Bivalirudin is a direct thrombin inhibitor with specific dosing adjustments for patients on dialysis and should be preferentially considered In one recent study bivalirudin is safer than and as effective as heparin plus GPIs in CAD patients with CKD. Impaired renal function does not affect the safety benefits of bivalirudin. Similar efficacy profiles were identified between the two groups after both short- and long-term follow-up in the CAD patients with CKD [31]

(continued)

Table 13.6 (continued)

Medication/Dose/Pharmacology	Data for CKD patients
Dabigatran Indicated for the prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation Excretion: urine 7%, feces 86%	CrCl 15–30 mL/min: 75 mg p.o. twice daily CrCl >30 mL/min: 150 mg p.o. twice daily CrCl <15 mL/min or hemodialysis: not indicated For patients currently taking dabigatran, wait 12 h (CrCl ≥30 mL/min) or 24 h (CrCl <30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant If possible, discontinue dabigatran 1–2 days (CrCl ≥50 mL/min) or 3–5 days (CrCl <50 mL/min) before invasive or surgical procedures because of increased risk of bleeding
Rivaroxaban Indicated for prevention of stroke and thromboembolism associated with nonvalvular atrial fibrillation Metabolism: liver CYP450 Excretion: urine 66%, feces 28% Half life: 5–9 h or 11–13 h in elderly	CrCl 15–50 mL/min: 15 mg p.o. CrCl >50 mL/min: 20 mg p.o. CrCl <15 mL/min: not indicated Among patients with nonvalvular atrial fibrillation and stage 4 or 5 chronic kidney disease or undergoing hemodialysis, rivaroxaban appears associated with significantly less major bleeding compared to warfarin [32]
Apixaban Indicated for prophylaxis against stroke with atrial fibrillation and as postoperative prophylaxis of deep vein thrombosis (DVT) and to prevent pulmonary embolism (PE) The recommended dose of Apixaban for most patients is 5 mg taken orally twice daily Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4	Serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose of Apixaban is 2.5 mg twice daily Patients with advanced CKD taking apixaban had similar bleeding rates at 3 months compared with those taking warfarin. However, those who continued therapy had higher major bleeding rates with warfarin between 6 and 12 months [33]

ACT activated clotting time, *aPTT* activated partial thromboplastin time, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *IV* intravenous, *NSTEMI* non-ST elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST elevation myocardial infarction. The table was inspired from Mohammad Nasser, Peter A. McCullough and recreated with recent studies.

13.1.5.2 Coronary Artery Bypass Greft

There is increasing evidence from recent studies that coronary artery bypass greft (CABG) has lower long-term adverse outcomes and requires less revascularization in HD patients [46]. CABG appears to be superior to PCI in reducing mortality and MI rates in diabetic patients with multivessel disease [47]. It is supported as the treatment of choice in HD patients with severe CAD. CKD patients with a creatinine value greater than 2.5 mg/dL are at risk of needing dialysis after surgery. Using data from the National Adult Cardiac Society of Thoracic Surgeons Database (United States), Cooper et al. showed that perioperative mortality, ranging from 9.3% in patients with severe CKD to 1.3% in patients with normal kidney function, was inversely associated with decreased kidney function [48]. In the same study, the use of internal mammarian artery grafts in patients with eGFR <30 mL/min/1.73 m^2 was significantly protective compared to the use of venous grafts. Larger studies are needed to further elucidate the role of PCI versus CABG in the CKD population.

13.2 Heart Failure

Heart failure (HF) is diagnosed in approximately 30% of kidney patients undergoing hemodialysis [49]. Concomitant kidney dysfunction makes HF management more challenging and complex. The correlated functioning of the kidney and heart in a patient with heart failure and chronic kidney disease is shown in Fig. 13.1. Correction of

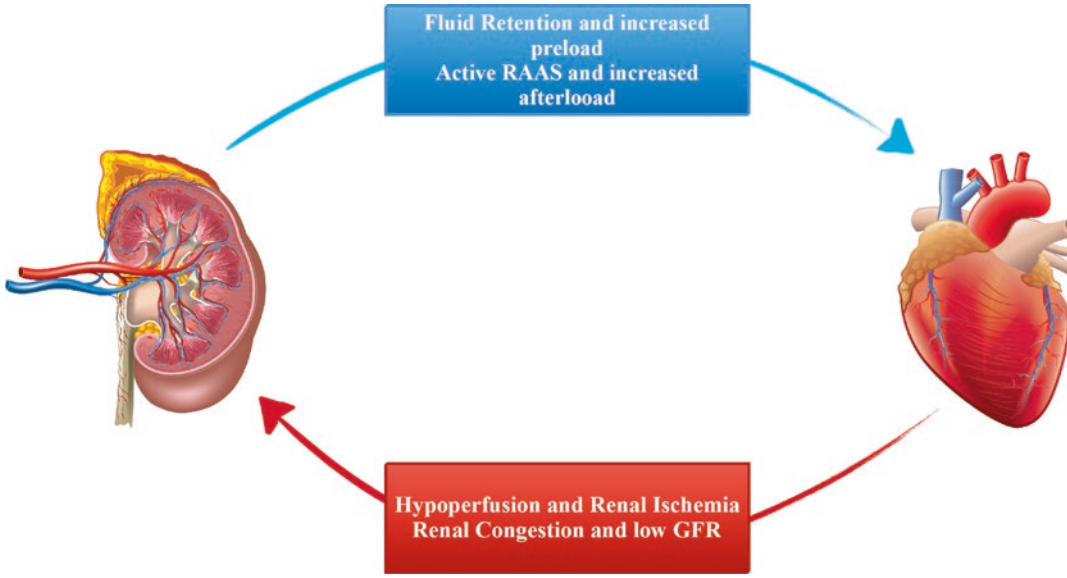

Fig. 13.1 The correlated functioning of the kidney and heart in a patient with heart failure and chronic kidney disease, *RAAS* renin angiotensin aldosteron system

hemodynamic abnormalities remains the main goal of HF treatment. Reversible causes and triggering factors should be identified and targeted in treatment. The correlated functioning of the kidney and heart in a patient with heart failure and chronic kidney disease is shown in Fig. 13.1.

Chronic kidney disease is common, occurring in 49% of patients with HF and is associated with a high mortality and increased frequency of hospitalizations [50]. New evidence of improvement in cardiovascular death and HF hospitalizations has emerged with angiotensin receptor neprilysin inhibitor, ivabradine, and more recently sodium glucose cotransporter inhibitors in heart failure with reduced ejection fraction (HFrEF) in patients with CKD Stage 1–3. However, these studies excluded CKD Stage 4 and 5 patients. There is evidence for β-blocker therapy in CKD Stage 1–3 and separately in hemodialysis patients. Cardiac resynchronization therapy reduces hospital admissions and mortality due to HF. It also reduces mortality in CKD Stage 1–3 patients, but has not been shown to do so in Stage 4 and 5 CKD or dialysis patients. In HFrEF patients, internal cardioverter and defibrillator therapy has been shown to be beneficial in CKD 3 patients, but not in dialysis patients, as it is associated with high infection rates. Treatment for HFpEF patients with CKD is symptomatic because there is no treatment proven to improve survival or hospitalizations [51]. Treatment recommendations for patients with HFrEF Stages C and D medications may be started simultaneously at initial (low) doses recommended for HFrEF [52].

13.2.1 Prognosis of HF Patients with CKD

Clinically important adverse outcomes to be considered in patients with HF include the number and duration of hospitalizations due to symptoms, mortality and poor quality of life, and functional status. The prognosis of HF has improved over time but remains poor compared to other chronic conditions. In the recently completed Empagliflozin Outcome Study in Patients with Chronic Heart Failure and Low Ejection Fraction (EMPEROR-Reduced) in New York Heart Association (NYHA) Class II-IV, HF, and low ejection fraction (HFrEF) patients treated with placebo [age 66 ± 11 years, EF 27 ± 6%, diabetes 50%, angiotensin converting enzyme inhibitor

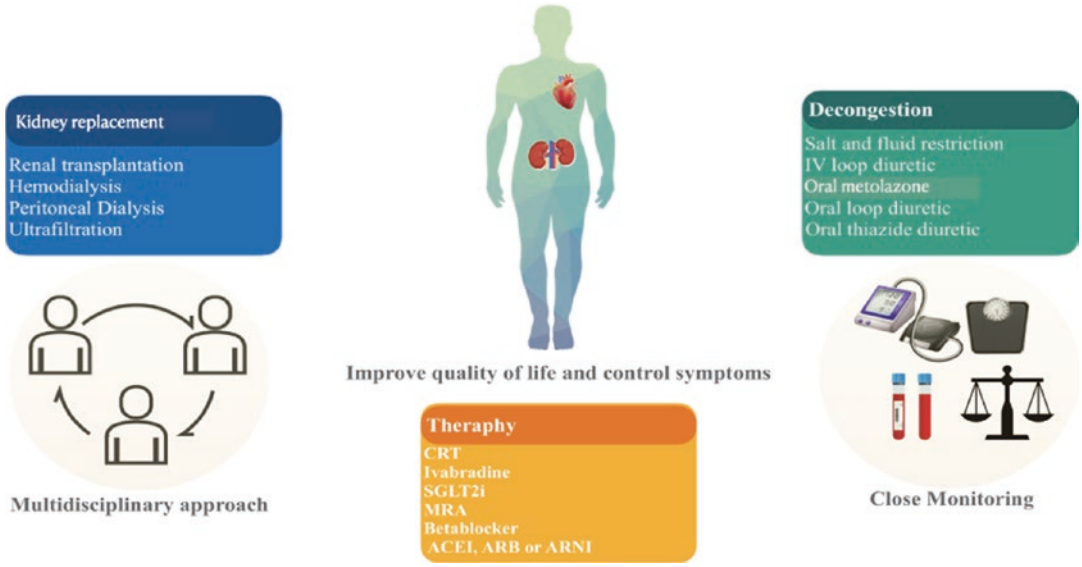

Fig. 13.2 Treatment options in patients with heart failure and chronic kidney disease. *CRT* cardiac resynchronization therapy, *SGLT2$_i$* sodium glucose cotransporter 2 inhibitor, *MRA* mineralocorticoid receptor antagonist, *ACEI ACE* angiotensin-converting enzyme, *ARB ARB* angiotensin receptor blocker, *ARNI* Angiotensin receptor neprilysin inhibitor

(ACEi) or angiotensin receptor blocker (ARB) 70%, 73% mineralocorticoid receptor antagonist (MRA), 95% β-blocker, 44% device therapy], all-cause related mortality was 10.7%/year and hospitalizations were 71%/year [53].

In a meta-analysis of patients with acute and chronic HF, co-existing CKD was associated with a higher risk of death. Mortality was found 2.34 times higher in patients with CKD than in patients without CKD; The mean surveillance for acute HF patients was 361 ± 333 days and for chronic HF patients 942 ± 802 days [54].

13.2.1.1 Principles of Management of HF Patients with CKD

The goal of treatment in HF patients is not only to improve survival, but also to improve functional status and quality of life. Better symptom control and quality of life may often have a higher priority over long-term survival in multimorbid HF-CKD patients. Recurrent hospitalizations are undesirable as they affect patients' life goals and quality of life, and therefore prevention of hospitalizations is an important treatment outcome. A common indication for hospitalization is dyspnea and edema, which usually require carefully managed diuretic therapy. Treatment options in patients with heart failure and chronic kidney disease are shown in Fig. 13.2.

13.2.1.2 Challenges in the Management of HF Patients with CKD

There are several challenges in the management of HF in the presence of kidney disease, including abnormalities of drug pharmacokinetics, altered drug pharmacodynamics, biochemical abnormalities of electrolytes, and infections with device therapy. Abnormalities in drug pharmacokinetics due to poor kidney function are numerous. The blood concentrations of some drugs are increased in CKD due to decreased renal elimination. In addition, CKD causes abnormalities in glycoprotein function, which increases the bioavailability of digoxin, and cytochrome P450 enzyme function, which decreases the clearance of carvedilol and verapamil. Generally, available evidence for the definitive effect of CKD on drug pharmacokinetics is limited and dose adjustments are difficult.

Diuretic Resistance

The effects of diuretic therapy diminish with worsening kidney function, but the term diuretic resistance is not well defined. Thiazide diuretics are generally ineffective in CKD Stages 4 and 5. Loop diuretics are more effective at lower estimated glomerular filtration rate (eGFR); however, higher doses are required at lower GFRs. Loop diuretics work by acting on sodium-potassium co-transporters on the luminal side of tubular cells in the ascending limb of the loop of Henle. Decreased function of organic anion transporters inhibits the secretion of loop diuretics into the tubular lumen, counteracting their effects [55].

13.2.2 Lifestyle Changes for Management of HF Patients with CKD

Exercise improves quality of life in patients with HFrEF, as demonstrated in a randomized clinical trial (RCT) of 2332 patients who performed 36 sessions of exercise over 3 months [56]. These patients had a mean creatinine of 1.2 mg/dL, so they had a significant proportion of CKD. Salt restriction is recommended, especially in patients with fluid overload, but there is no evidence from randomized controlled trials.

13.2.2.1 Drug Therapy for HF with Reduced EF and CKD

ACEI or ARB

General population studies such as the SOLVD and Survival and Ventricular Enlargement (SAVE) have positive evidence for mortality and hospitalizations in CKD Stage 1–3 patients in CKD and HF. The SAVE trial randomized 2231 patients with creatinine levels up to 221 mmol/L and showed an improvement in all-cause mortality with captopril compared to placebo [57]. The SOLVD study randomized 2569 patients with creatinine values up to 177 mmol/L and showed an improvement in all-cause mortality with enalapril compared to placebo [58]. These drugs caused a decrease in kidney function that was not associated with an adverse outcome. Hyperkalemia is a rare side effect and its incidence increases with worsening kidney function. However, these trials did not include patients with advanced CKD.

The effects of ACEi/ARB in dialysis patients remain controversial; one randomized trial suggested that the β-blocker atenolol was better than the ACEi lisinopril [59], while another study [Fosinopril on Dialysis (FOSIDIAL)] showed no difference in survival between fosinopril and ACEI treatment and placebo during the 3-year follow-up period [60].

SGLT2 Inhibitors

SGLT2i (sodium glucose cotransporter 2 inhibitor) act by preventing glucose reabsorption in the proximal tubule where 90% of glucose is reabsorbed and cause osmotic diuresis by increasing sodium excretion together. This diuretic effect causes a decrease in extravascular and intravascular volume, resulting in a reduction in blood pressure and body weight. Unlike diuretics, it has no adverse effects on kidney functions and significantly improve outcomes related to kidney. Besides their renoprotective effects, SGLT2 inhibitors have been shown to be an effective treatment in HF independent of diabetes.

Patients with HFrEF and CKD with eGFR >20 mL/min/1.73 m^2 were included in the EMPEROR-Reduced study. A total of 1799 (48%) of 3730 patients had CKD with eGFR<60 mL/min/1.73 m^2. Cardiovascular death and hospitalizations for HF were reduced by 25% [HR 0.75 (95% CI 0.65–0.86); $P < 0.001$], 50% of whom were diabetic and 73% had ejection fraction [EF] < 30%. eGFR decline was slower with empagliflozin compared to placebo (−0.55 vs. –2.28 mL/min/1.73 m^2/year), 1.7 mL/min/1.73 m^2/year between groups (95% CI 1 0.10–2.37; $P < 0.001$). The primary endpoint was reached with empagliflozin in 202/893, compared with 237/906 with placebo in patients with eGFR <60 mL/min/1.73 m^2. There was a 50% (95% CI 32–77) reduction in the incidence of renal replacement therapy or sustained loss of eGFR [52].

The Dapagliflozin [DAPA-HF] study in Patients with Heart Failure and Low Ejection Fraction included patients with eGFR>30 mL/min/1.73 m^2 and EF <40%. The primary endpoint (worsening HF or cardiovascular death) was reduced by 26% (95% CI 65–85) and eGFR <60 mL/min/1.73 m^2 in 40.6% (1926/4744) of patients. The reduction in the primary endpoint was observed similarly in patients with and without CKD [HR 0.72 (95% CI 0.59–0.86) and HR . 0.76 (95% CI 0.63–0.92), respectively]. Serious renal adverse events occurred in 38 patients (1.6%) in the dapagliflozin group and 65 patients (2.7%) in the placebo group (*P* 0.009) [61].

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure recommends for heart failure Stages C and D patients that therapy should include an **angiotensin receptor neprilysin inhibitor** (ARNI) in NYHA (Newyork Heart Association)II- III; ACEI or ARB in NYHA II-IV, a B-blocker, a MRA, a SGLT2i and diuretic as needed [62].

Initial Increase in Serum Creatinine with Initiation of ACEi/ARB and SGLT2 Inhibitor Therapy

When initiating ACEi/ARB therapy, both HF and non-HF patients may initially experience a slight decrease in kidney function. In the Studies of Left Ventricular Dysfunction [SOLVD], 606 patients (9.5%) experienced worsening kidney function between baseline and 14 days after randomization; There was a mean reduction in eGFR of 29.2 ± 9.8% in the enalapril group and 28.9 ± 9.3% in the placebo group. Patients who experienced premature worsening kidney function at 14 days had a significant improvement in kidney function at 1 year ($P < 0.0001$), and the degree of improvement was similar between those given enalapril or placebo (16.0 ± 34.1% vs. 18.2 ± 38.0% in the placebo group).); $P = 0.52$). However, patients with rapidly deteriorating kidney function with enalapril had not increased mortality compared to patients with placebo [HR 1.0 (95% CI 0.78–1.3); $P = 1.0$] [HR 1.3 (95% CI 1.1–1.7); $P = 0.012$] [63].

More recently, a reanalysis of the SOLVD study found that up to 10% reduction in eGFR with enalapril was associated with a survival benefit [HR 0.87 (95% CI 0.77–0.99)] compared with a 0% eGFR reduction in the placebo arm as a reference.)]] A reduction in eGFR of up to 35% was associated with a reduced risk of hospitalization for HF [HR 0.78 (95% CI 0.61–0.98)] [61].

Early worsening of kidney function is associated with efferent arteriolar vasodilation and reduction in filtration pressure in each nephron. Low intraglomerular pressure prevents hyperfiltration in each nephron and protects the glomerulus in the long term. A similar observation has been noted in SGLT2 inhibitor trials. In a study of 4744 HF patients randomized to dapagliflozin or placebo, there was a higher baseline reduction in eGFR in the dapagliflozin group compared to the placebo group (−3.97 ± 0.15 vs. –0.82 ± 0.15 mL/min/1.73 m^2) [60]. After that, however, the annual change in mean eGFR was smaller with dapagliflozin than with placebo (−1.67 ± 0.11 and −3.59 ± 0.11 mL/min/1.73 m^2, respectively), 1.92 mL/min/1.73 m^2/for an intergroup difference of years (95% CI 1.61–2.24).

Early worsening of kidney function at 2 weeks is consistent in all different SGLT2 inhibitor groups. This is likely due to tubuloglomerular feedback, in which increased salt and water delivery to the periglomerular distal tubule causes afferent arteriolar vasoconstriction and a decrease in filtration pressure in each glomerulus. Low intraglomerular pressure protects the glomerulus from hyperfiltration. In the latest "KDIGO Clinical Practice Guideline For Diabetes Management In Chronic Kidney Dısease," attention has been drawn to the reversible decrease in the eGFR with commencement of SGLT2i treatment and has been suggested not to discontinue therapy [64].

B-Blockers

Subgroup analysis of general population studies demonstrates survival benefits from the use of β-blockers in patients with HFrEF and CKD. Carvedilol treatment has been shown to

improve mortality in HFrEF patients on hemodialysis [65]. The American Heart Association recommends targeting blood pressure to a level below 120/80 mmHg for those with HF plus an LVEF below 40%. It should be emphasized to uptitrate the dose of B-blockers over weeks to avoid worsening of volume overload (1).

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRAs), often called aldosterone antagonists, are an important component of evidence-based therapy for patients with heart failure. Renin-angiotensin-aldosterone system activation is pathological, especially in HFrEF patients. Treatment strategies are based on normalizing and inhibiting the end product of this system; the excessive effects of aldosterone. Benefits of MRAs on mortality and hospitalization in CKD Stage 1–3 patients from general population have been shown in studies such as Randomized Aldactone Evaluation Study (RALES) and Eplerenone in the Mild Patient Hospitalization and Heart Failure Survival Study (EMPHASIS-HF). In RALES, 48% of 1658 patients had eGFR <60 mL/min/1.73 m^2, and subjects with eGFR <60 or >60 mL/min/1.73 m^2 had a similar reduction in risk of death and hospitalization for HF [66]. Hyperkalemia occurred more frequently in patients with eGFR <60 mL/min/1.73 m^2 than in patients with eGFR >60 mL/min/1.73 m^2 [67]. Impaired kidney function was a problem, as evidenced by a >30% decrease in eGFR in 14% of EMPHASIS-HF patients [68]. In two recent small RCTs in hemodialysis patients, there was a higher incidence of hyperkalemia (>6.5 mmol/L) with spironolactone, and more so with a dose of 50 mg (e.g., 8 of 32 patients) than 25 mg daily (e.g., 4 of 26 patients) [69, 70]. In 154 hemodialysis patients, the incidence of hyperkalemia (>6.5 mmol/L) was also higher (11%) with eplerenone compared to placebo (2%) [71].

Diuretics

Diuretic therapy is an essential element in restoring volume status and symptom relief. Renal venous congestion and consequent renal dysfunction due to increased right heart pressure is poorly understood and difficult to manage; volume status, body weight, and creatinine require close monitoring of diuretic doses [72].

Loop diuretics are first-line therapy and can be given as intravenous infusions or boluses. Edema of the gastrointestinal tract may delay oral drug absorption. For this reason, intravenous diuretics should be initiated, given their potency and efficacy compared to oral therapy. In patients not taking diuretics, intravenous furosemide can be initiated at 20–40 mg. In chronic users, the starting dose should be at least twice the daily dose. Higher doses of furosemide are associated with more significant relief of dyspnea, net fluid loss, and weight loss than lower doses. Thiazides work synergistically with loop diuretics and can be added for more effective diuresis. Commonly used thiazide diuretics are ineffective in advanced CKD, and loop diuretics are often used with metolazone when necessary for adequate diuresis. In patients with acute HF, spironolactone can be a natriuretic and help relieve congestion without significant adverse effects on serum potassium levels [73]. In a study in CKD Stage 3 and 4 patients with decompensated HF with a high urine volume of 8425 mL [interquartile range (IQR) 6.341–10.528] for 72 h, furosemide 560 mg (IQR 300–815) and serum creatinine were not associated with markers of tubular injury despite a slight increase [74].

Diuretic therapy may adversely affect blood concentrations of urea, creatinine, sodium, and potassium in HF patients with CKD. Changes in creatinine during diuretic therapy depend on the degree of cardiac and renal dysfunction offset by diuresis. Lowering renal venous pressure and improving cardiac output with diuretics may help maintain or improve GFR. However, excessive intravascular depletion can cause acute kidney injury, especially in patients with low left ventricular ejection fraction (LVEF). The first manifestation of renal perfusion deprivation is an increase in BUN. Diuresis should be reduced to prevent kidney damage in stable patients with mild congestive symptoms and elevation in BUN. If symptoms persist and severe diuresis needs to be continued, inotropes may be added as adjunctive therapy.

Angiotensin Receptor Neprilysin Inhibitor

Studies from the general population have demonstrated benefits in mortality and hospitalization with confirmed safety in CKD patients with an eGFR of 30 mL/min/1.73 m^2. Clinical benefits of angiotensin receptor neprilysin inhibitor (ARNI) was shown with first reduction in cardiovascular death and HF hospitalization in a large RCT involving 8842 HFrEF patients (eGFR >30 m/min/1.73 m^2) [HR 0.80 (95%)]. CI 0.73–0.87]; $P < 0.001$] [75]. There is evidence that ARNIs can slow CKD progression compared to ACEIs alone. Side effects such as hyperkalemia are less common compared to ACEIs or ARBs. A meta-analysis demonstrated that ARNI had a lower incidence of severe hyperkalaemia (defined as K > 6.0 mmol/L) and worsening kidney function in comparison with enalapril or valsartan [RR 0.79 (95% CI 0.67–0.95)]; $P < 0.010$] [76].

Ivabradin

Ivabradine, an I(f) current inhibitor, improved cardiac death and hospitalizations for HF when used in 6658 clinically stable, on β-blockage HFrEF patients with creatinine <220 mmol/L [77]. This study included a significant number of Stage 3 CKD patients who benefited with a risk reduction ratio of 0.82 (95% CI 0.75–0.90; $P < 0.0001$).The safety and efficacy of ivabradine in CKD Stage 4 and 5 patients are unknown.

Digitalis

Digitalis inhibits the Na-K-ATPase pump and thus increases intracellular calcium and contractility. Additionally, it increases vagal tone, which antagonizes the sympathetic pathway. Digitalis is indicated in patients with heart failure and atrial fibrillation. The symptomatic and functional benefit seen with this drug is offset by the increase in mortality observed in female and patients with trough levels above 1.0 ng/mL [78]. Target serum levels are between 0.5 and 0.8 ng/mL. It is often combined with a B-blocker or CCB to control the ventricular rate in atrial fibrillation. Digitalis is excreted by the kidneys and patients with low eGFR are at increased risk of toxicity. Electrolyte abnormalities, particularly hypokalemia, are common in patients taking diuretics, which may precipitate acute digitalis toxicity. This drug is eliminated unchanged in the urine; therefore, loading and maintenance doses should be reduced in CKD. The dose should be reduced by 50% when eGFR is below 60 mL/min/1.73 m^2 and by 75% when eGFR is below 30 mL/min/1.73 m^2. Patients should be aware of the early symptoms of digital intoxication such as nausea, vomiting and confusion. Both digitalis and its antidote, digoxin-specific antibody, have long-term elimination in kidney failure. Hemodialysis has not been shown to be effective in this setting and recurrence of symptoms is common [79].

13.2.2.2 Ultrafiltration

Trials have shown that greater fluid can be removed by ultrafiltration compared to diuretics. Ultrafiltration or dialysis can be used as alternative therapy in patients with progressive deterioration of renal function but clinical trials are not compatible. The multicenter "Ultrafiltration Versus Intravenous (IV) Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD)" study showed that the use of ultrafiltration before the development of AKI improved decongestion and reduced hospitalizations without any effect on kidney function [80]. In the more recent "Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF)" study, ultrafiltration therapy was associated with increased creatinine and more adverse events when started before the development of AKI. Therefore, this method may be a reasonable choice in patients whose symptoms persist despite medical treatment [81].

13.3 Arrhythmias

In the atrial and ventricular myocardium, anomalies in the structure or function of the heart's conduction system accumulate with age, causing atrial and ventricular tachyarrhythmias and

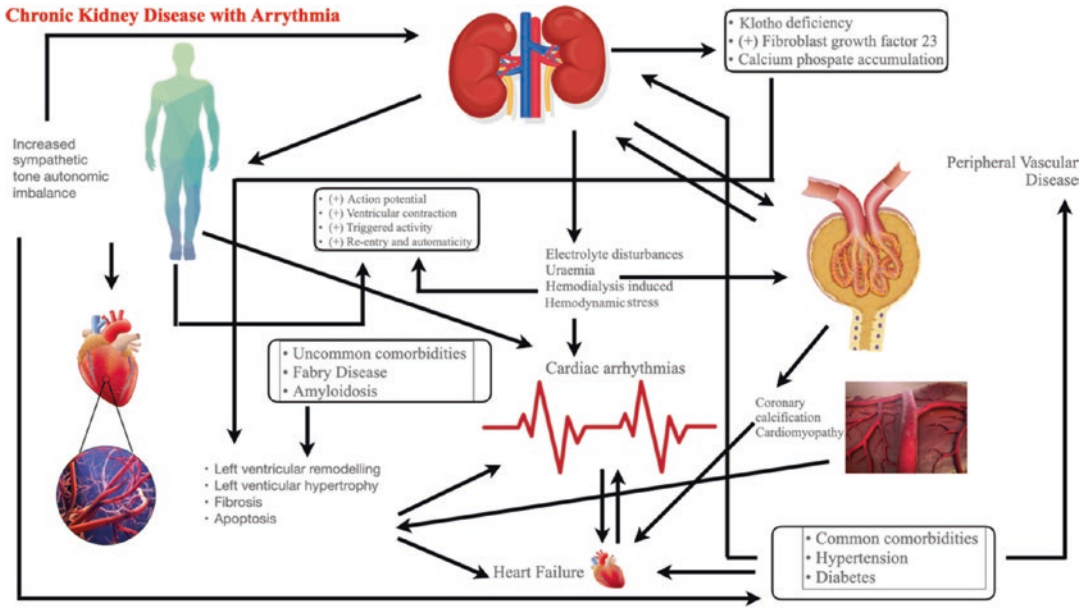

Fig. 13.3 Mechanisms of arrhythmia formation in chronic kidney disease

bradyarrhythmias. In CKD patients, the frequency is higher than in the normal population, due to both the myocardiotoxic effect of uremia and microvascular calcification. Atrial fibrillation (AF) is by far the most common sustained arrhythmia; increases sharply with age and affects 1.5% of the general population aged 55–59 years and 27% aged >85 years [82]. Persistent and recurrent ventricular arrhythmias are less common, but important as sudden death is often due to ventricular tachyarrhythmia. Complete atrioventricular block and other forms of bradyarrhythmia are common and increase sharply with age. CKD is even more common than sustained arrhythmia and is associated with multiple types of acquired arrhythmia, particularly in AF [83]. Sudden death is also more common in CKD and is responsible for about a quarter of deaths in dialysis patients [84]. Ventricular tachycardia (30.2%) and AF (7.4%) are present in CKD patients, and more than 90% of patients have ectopia [85].

Diabetes and hypertension are responsible for the majority of arrhythmias in the general population, especially AF. Both conditions are responsible for the majority of cases of end-stage kidney disease. In both cases, CKD and AF are often late effects of the underlying condition, but the underlying condition is often not diagnosed until the results are available. Mechanisms of arrhythmia formation in chronic kidney disease are shown in Fig. 13.3. In Table 13.7 antiarrhythmic agents are shown.

All patients with atrial fibrillation are at risk for embolic events, since kidney disease increases the risk, which can be attributed to higher blood stasis levels. Antithrombotic therapy is an accepted treatment to reduce the risk of embolization. Also, this patient population is prone to bleeding complications associated with antithrombotics. Before administering thromboprophylaxis, patients should be carefully evaluated about the risks weighed against the benefits. The CHAD-VASC scoring system is used to classify the risk of clotting. A score of 2 or higher is considered as “high risk” and such patients require antithrombotic therapy (Box 13.2).

Table 13.7 Antiarrhythmic agents

Medication/Dose/ Pharmacology	Data for CKD patients
Flecainide 100 mg BID. Maximum of 400 mg/day Half-life: 11–12 h Excretion: 80–90% in urine	CrCl <50 mL/min: Decrease dose by 50% Monitor serum levels
Procainamide IV: Loading dose of 15–18 mg/kg. Maintenance dose of 1–4 mg/min Oral: 50 mg/kg/24 h QID Half-life: 2.5–4.7 h Excretion: urine	CrCl <50 mL/min: Administer BID HD: Administer QD
Dofetilide Oral: 500 μg BID Half-life: 10 h Excretion: urine	CrCl 40–60 mL/min: 250 μg BID CrCl 20–39 mL/min: 125 μg BID CrCl <20 mL/min: Contraindicated
Amiodarone Oral: 200–400 mg/day IV: Loading dose of 150 mg, then 1 mg/min for 6 h, followed by 0.5 mg/min infusion Half-life: 40–55 days Excretion: feces	No dosage adjustment. Not dialyzable

The table is inspired from Mohammad Nasser, Peter A. McCullough. and recreated with recent studies. Copyright © Springer - Verlag Berlin Heidelberg 2014. With permission from Springer

Box 13.2 CHAD-VASC Scoring System

Condition	Score	
C	Congestive heart failure or left ventricular dysfunction	1
H	Hypertension	1
A_2	Age ≥ 75	2
D	Diabetes mellitus	1
S_2	Prior stroke or TIA	2
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic disease)	1
A	Age 65–74	1
SC	Sex category (female gender)	1

EHRA/EACT/ESC Committee for Practice Guidelines [86]. The table is inspired from Mohammad Nasser, Peter A. McCullough. Copyright © Springer - Verlag Berlin Heidelberg 2014. With permission from Springer

13.4 Valvular and Pericardial Heart Disease

Chronic kidney disease (CKD) is an important risk factor for heart valve disease. Mitral annular and aortic valve calcifications are very common in CKD patients and often lead to complications such as valve stenosis and regurgitation as well as conduction system abnormalities and endocarditis. Valvular heart disease (VHD), particularly mitral regurgitation and aortic stenosis, are associated with significantly reduced survival in CKD patients. Information regarding valvular heart disease in the general population is not always relevant for patients with CKD, as the pathophysiology may be different in patients with CKD and there is a high prevalence of comorbid conditions and a high risk of periprocedural complications and mortality [87].

Administrative data from the US Renal Data System in 2017 showed the prevalence of VHD diagnoses in patients with CKD to be 14%, compared to 7% in the Medicare survey of patients over 65 years of age [88]. More specifically, functional evidence of aortic stenosis (as opposed to aortic calcification) was present in 9.5% of patients with CKD compared to 3.5% of the general population. The same was found for mitral regurgitation with similar patterns in 43% vs. 24%, mitral stenosis 2% vs. 1%, and aortic regurgitation 19% vs. 10%. Even taking into account age, echocardiogram year, race, gender, history of hyperlipidemia, hypertension, congestive heart failure, diabetes mellitus, and previous coronary revascularization, the probability of aortic stenosis in patients with CKD is 1.2 to 1.3 times and the probability of mitral regurgitation is 1.3 to 1.8 times higher [89]. The prevalence was found to increase in parallel with progression to advanced kidney disease.

With regard to valve replacement surgery, this patient population is at risk for endocarditis, which increases surgical mortality, whether a bioprosthesis or mechanical valve is used. The most important preventive technique is maintaining oral health. Both tissue and mechanical valves carry the same survival in patients undergoing surgical intervention for valvular regurgitation after endocarditis. Mechanical covers are

more resistant to calcification and last longer; however, tissue valves are preferred in cases where anticoagulant therapy is contraindicated and in ESRD patients where survival is shortened by factors other than valvular heart disease.

Despite modern antimicrobial and surgical treatment, infective endocarditis is still fatal if untreated and continues to cause substantial morbidity and mortality [90]. Therefore, prevention is a priority [91]. Prophylactic antimicrobial therapy is now limited to those considered at high risk of developing infective endocarditis. Dental procedures are considered high risk for causing bacteremia, especially when it comes to gingival manipulation. Genitourinary and gastrointestinal procedures usually do not cause significant bacteremia, and the AHA does not recommend the use of prophylactic therapy in high-risk patients undergoing such procedures [92]. However, it is recommended that infective endocarditis prophylaxis be used prior to invasive airway procedures involving incision of the respiratory mucosa. High-risk patients are defined as those who have one of the following:

- Prosthetic heart valve (bioprosthetic or homograft valve).
- Prosthetic material used for valve repair.
- Previous history of infective endocarditis.
- Persistent cyanotic congenital heart disease.
- Congenital heart disease that has been fully/incompletely repaired with prosthetic material.
- Heart valve leaflet pathology or insufficiency in heart transplant recipients.

Many patients with kidney disease are at high risk for cardiac surgery (open or limited thoracotomy) and may be considered for transcatheter aortic valve replacement (TAVR). This procedure can be performed using a femoral, aortic arch or direct left ventricular percutaneous catheter insertion approach and a porcine cap loaded on a balloon expandable stent. Severe symptomatic mitral regurgitation and asymptomatic severe mitral regurgitation with left ventricular dilation/low ejection fraction are indications for mitral valve repair or replacement. Both procedures require a thoracotomy.

Kidney failure is associated with uremic or fluid overload pericarditis. The development of this disease is often due to inadequate or missed dialysis session. However, dialysis is the main treatment for these two forms of pericarditis. Dialysis can also help reduce the size of the effusion. Uremic patients may respond more quickly to treatment. Systemic anticoagulation may increase the risk of developing hemorrhagic effusion, especially when uremia is present and should be avoided if possible. Ineffective dialysis can lead to large effusions that can cause hemodynamic instability or diastolic compromise. Pericardiocentesis is recommended in these high-risk patients. Anti-inflammatory drugs can also be used in resistant cases. Colchicine is associated with the lowest recurrence rates. Surgical pericardiectomy is reserved for persistent or recurrent effusions.

Box 13.3 Relevant Guidelines

1. *Kidney Disease: Improving Global Outcomes Guidelines.*
   (a) Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:259–305.
   (b) Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019 Oct;96 (4):836–849.
2. *American Heart Association Guidelines.*
   (a) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145 (18):e876-e894.

(b) 2019 ACC/AHA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139 (25):e1082-e1143.
(c) 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2012;126:1784–800.
(d) ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458–73.
(e) 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143:72–227.

3. *European Society of Cardiology Guideline*.
(a) 2010 EHRA/EACT/ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010;12 (10):1360–420. doi: https://doi.org/10.1093/europace/euq350.
(b) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC
(c) 2009 ESC Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for infection and Cancer. Eur Heart J. 2009;30 (19):2369.
(d) 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36 (44):3075–3128. doi: 10.1093/eurheartj/ehv319.

Before You Finish: Practice Pearls for the Clinician

- Chronic kidney disease has been shown to be a risk factor for cardiovascular mortality and kidney disease patients should be assessed for signs and symptoms of coronary heart disease. Statins are the primary prevention of cardiovascular events in these patients with proven effects.
- CKD patients have silent ischemia and also ACS more frequently, Treatment includes dual antiplatelet therapy, statins, B-blockers, ACEIs, low-molecular-weight heparin, and glycoprotein IIb/IIa antagonists.
- Heart failure therapy in CKD patients should include ACEI or ARB + SGLT2i due to the survival benefits they provide.
- Fluid balance should be assessed carefully to be protected from decompensated heart failure.
- Heart failure Stages C and D therapy should include a ARNI in NYHA II- III; ACEI or ARB in NYHA II-IV, a B-blocker, a MRA, a SGLT2i and diuretic as needed.
- To recommend oral hygiene and prophylaxis when needed is pivotal to prevent infective endocarditis.

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14 Cerebrovascular Disease and Chronic Kidney Disease

Dearbhail Ni Cathain and Dearbhla M. Kelly

Before You Start: Facts You Need to Know

- Patients with low glomerular filtration rate (GFR) and/or albuminuria are at risk for both ischaemic and haemorrhagic stroke subtypes. Patients are at particularly high risk of cardioembolic and large artery stroke.
- Hypertension, diabetes mellitus, atrial fibrillation, and accelerated atherosclerosis are major contributing risk factors but chronic inflammation and genetic factors are also beginning to emerge as important mechanisms.
- Due to their bleeding diathesis, patients with CKD tend to have a higher rate of complications with acute stroke therapies including thrombolysis and mechanical thrombectomy.
- Patients with CKD derive similar benefits from standard stroke preventative therapies including antiplatelet, lipid-lowering, antihypertensive therapies, and anticoagulation but their benefit is attenuated or unclear for dialysis-dependent patients.

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14.1 Introduction

Chronic kidney disease (CKD) is predicted to be the fifth leading cause of death worldwide by 2040 [1]. The rise in the prevalence of CKD can be partly attributed to the rise in risk factors such as obesity and diabetes but also as a result of our increasingly elderly population with one third of people over the age of 75 being affected by CKD [2]. CKD has been established as a risk factor for cardiovascular disease [3] and in particular cerebrovascular disease (CVD), encompassing stroke and its various subsets, as well as vascular cognitive impairment and dementia [4, 5]. Compared to the general population, those with CKD have a higher incidence of the risk factors that we traditionally associate with stroke, including hypertension, diabetes mellitus, and atrial fibrillation [6]. However, there are other non-traditional risk factors purported to be as a result of kidney dysfunction including endothelial dysfunction, chronic inflammation, uraemic toxins, anaemia, mineral-bone abnormalities, and dialysis related risk factors that are associated with an increased risk of CVD [5, 7]. This chapter aims to explore the relationship between CKD and CVD via various mechanisms and also the complexities and barriers to the investigation and management of CVD in this context. In doing so we hope to provide practical guidance on the management of these patients going forward.

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14.2 Epidemiology

Stroke risk when assessed by kidney function, as measured by estimated glomerular filtration rate (eGFR), demonstrated an inverse relationship with a stepwise increase in risk compared to the general population [8]. Those patients with end stage kidney disease (ESKD) receiving dialysis were at highest risk of stroke (7.1-fold increased risk). CKD staging no longer accounts for eGFR alone but also acknowledges proteinuria as an important marker of kidney dysfunction and a risk of progression to ESKD [9]. Proteinuria has also been established as a risk factor for stroke with a dose-response relationship between level of proteinuria and increasing risk of stroke [10].

When we consider the traditional stroke risk factors; hypertension, diabetes mellitus, dyslipidaemia, and atrial fibrillation, and we consider our CKD population, it is clear that there may be a confounding relationship between certain of these comorbidities and increased stroke risk in CKD [11, 12]. In particular, hypertension occurs in the majority of patients with CKD (67–92%) and is considered a major confounder when assessing the relationship between stroke and CKD [4]. Atrial fibrillation (AF) is one of the most frequently diagnosed cardiac arrhythmias found in the general population and has been found to have a bidirectional relationship with CKD in a cause and effect loop and is therefore expectedly seen with increasing frequency in those with more advanced CKD and contributes to the increasing risk of stroke in CKD patients [13]. Patients with CKD who are diagnosed with atrial fibrillation carry a poor prognosis and have been found to be at higher risk for heart failure, myocardial infarction, and all-cause mortality [14], and in studies that adjusted for age, hypertension, and cardiac disease demonstrated a higher risk of stroke and death (HR 2.00, 95%CI 1.88 to 2.14 and HR 1.76, 95% CI 1.71 to 1.82, respectively) [4].

The period surrounding initiation of renal replacement therapy (30-day period before and after) has been found to be a particularly high-risk time period for the development of stroke and transient ischaemia attack (TIA) (threefold risk) [15]. When comparing renal replacement therapy modalities, haemodialysis is most strongly associated with stroke risk [7]. However, this is likely confounded by the reasons for choosing this treatment modality (for example, they may have failed peritoneal dialysis as CKD progressed with reduced urine output). Intermittent in-centre haemodialysis remains the most commonly prescribed form of dialysis, with patients normally attending three times a week with a period of prolonged interdialytic gap towards the close of the week- the time following this gap has been associated with an increased risk of stroke [16].

Stroke is an umbrella term encompassing a multitude of intracranial pathologies of varying aetiologies and pathophysiology. ESKD is associated with a sevenfold increased risk of ischaemic stroke and a ninefold increased risk of haemorrhagic stroke, with as high as one third of patients presenting with intracranial haemorrhage (ICH) having CKD [4, 17]. CKD has been shown to increase the risk of all stroke subtypes [12] but delineating the varied risk by subtype in the CKD population is an area that requires further study.

The increased risk of stroke in this already vulnerable population confers a higher risk of disability or poor functional outcomes post stroke (25% risk 95% CI 5–48% of modified rankin score ≥ 2 at discharge), increased morbidity and mortality (138% risk of in-hospital mortality, 95% CI 61% to 257%) compared to the general population post stroke and overall they suffer from more severe strokes at time of presentation (higher National Institutes of Health Stroke Scale NIHSS) [18].

14.3 Pathophysiology and Risk Factors

In order to discuss the pathophysiology of stroke in CKD patients, one must examine a multitude of risk factors which can be categorised as traditional, non-traditional, and dialysis related risk factors. In patients with CKD, the presence of these risk factors culminates in a pro-thrombotic

milieu in accordance with Virchow's triad of vessel wall damage, stasis of blood flow and hypercoagulability [19]. In contrast to this pro-thrombotic state that we associate with ischaemic stroke, it has also been suggested that the clot formed in patients with CKD is atypical and may confer an increased risk of bleeding secondary to platelet dysfunction in the setting of uraemia and anaemia of CKD, particularly in the context of albuminuria [20].

Renal and cerebral perfusion are governed by auto-regulatory mechanisms mediated by the surrounding rich capillary networks at both sites (glomeruli and blood brain barrier respectively) [21]. This shared pathophysiology may account for the susceptibility of both sites to damage via the traditional "vascular" risk factors.

Traditional risk factors include hypertension, atrial fibrillation, diabetes, carotid artery disease, obesity, and dyslipidaemia. As discussed above, these conditions often present as comorbid diagnoses in the presence of CKD and can significantly confound the risk of stroke in this population.

Hypertensive vascular damage or "strain vessel hypothesis" has been proposed as a mechanism linking CKD and stroke, with exposure of the juxtamedullary afferent arterioles and the deep perforating arteries to chronic hypertension resulting in these "strain" vessels developing hyaline arteriolosclerosis and impaired autoregulation resulting in glomerular hypertension and sclerosis and thus a decline in renal function and worsening systemic hypertension [22]. The deep perforating arteries of the brain develop a similar lipohyalinosis that also results in impaired autoregulation and the development of reduced cerebral blood flow and consequently increased ischaemic and haemorrhagic events in the areas supplies by these strain vessels [23]. Although hypertension is a major confounding factor in the relationship between CKD and stroke, the relationship is still seen in models when adjusted for hypertension [4]. Thus, this is unlikely the sole contributing mechanism for this relationship.

Non-traditional risk factors occur as a direct consequence of CKD [5]. Those with CKD are considered to be in a state of chronic inflammation contributing to endothelial damage, a hypercoagulable state and the generation of reactive oxygen species. Another hypothesis for the relationship between CKD and stroke also focuses on their shared anatomy and auto-regulatory function but identifies albuminuria as a marker for more generalised endothelial dysfunction leading to an increased risk of vascular events, the "Steno Hypothesis" [24]. Uraemia/uraemic toxins are associated with increased atherosclerosis and dyslipidaemia [25] but also platelet dysfunction increasing both the thrombotic and haemorrhagic risk in CKD [20]. CKD mineral-bone disease, and more specifically hyperphosphataemia, are associated with arterial medial calcification and potentiate vascular stiffness that can contribute to LVH and increase the risk of poor cardiovascular outcomes [26].

Haemodialysis confers its own independent risk factors for stroke mainly due to blood pressure variability, intermittent episodes of cerebral hypoperfusion which lead to chronic white matter changes, and vascular remodelling with increased arterial stiffness secondary to long-term dialysis [27]. It is likely that the period following the long interdialytic break is the time in which dialysis patients are most vulnerable to cerebral events due to haemodynamic variability. Following the prolonged interdialytic gap, dialysis patients are increasingly volume overloaded and hypertensive and more susceptible to intradialytic haemodynamic instability secondary to abnormal autonomic function [28].

14.4 Investigations

The main premise of stroke care and investigation remains based on the overarching principle that "time is brain" [29]. To reduce the risk of time delays in accessing necessary interventions, the assessment and investigation of stroke is generally a strictly protocolled practice in most centres. The protocol or pathway usually includes an initial rapid history assessment to establish risk factors, timelines, and contraindications to thrombolysis, a clinical exam using the international National Institutes of Health Stroke Scale

(NIHSS) assessment as a diagnostic and prognostic tool and CT brain imaging including both non-contrast, contrast angiography and perfusion imaging.

The challenge that presents in the CKD cohort is accessing timely investigation and diagnosis due to clinical concerns regarding contrast-induced nephropathy [30]. It is important to recognise that the theoretical risk of contrast-induced nephropathy has not been demonstrated in a recent meta-analysis which examined 14 studies with 5725 patients undergoing CT angiography and perfusion and 981 patients undergoing non-contrast CT. The risk of acute kidney injury was lower in patients who received a contrast load compared with those who did not [31]. Additionally, comparing those who had prior diagnoses of CKD with those who did not, there was no significant difference in risk of acute kidney injury.

MRI is another imaging modality of import in stroke. MRI can be under-utilised in CKD patients due to concerns regarding gadolinium exposure leading to nephrogenic systemic fibrosis [32]. Current MRI protocols in stroke investigation focus on diffusion weighted imaging or susceptibility weighted imaging/gradient echo and fluid-attenuated inversion recovery (FLAIR) sequences and are in fact gadolinium free.

Based on the current evidence, one should advocate for CKD patients to receive the standardised investigations including contrast angiography and stroke-protocol MRI [33].

14.5 Acute Management

Disparities exist between the provision of stroke management in the general population versus the CKD patient cohort [34, 35], in particular with regard to access to intravenous thrombolysis with reports of significant delays in administration and also under-utilisation of this treatment method in the CKD cohort [30]. This deviation from the provision of evidence-based medicine in the CKD cohort spans across the initial stroke intervention chosen, the use of antiplatelet agents, the care of patients in a formal stroke unit and preventative interventions such as smoking cessation and statin therapy [34, 35]. The failure to provide evidence-based care in CKD is likely owing to the current lack of evidence in this field and the concerns regarding CKD/dialysis patient frailty and the increased risk of bleeding reported in this population [36].

1. Thrombolysis:

   Current best practice guidelines recommend the use of intravenous thrombolysis (IVT) in acute ischaemic stroke management. Better functional outcomes have been reported in patients who received IVT within 4.5 h of stroke onset [37] but lately this timeline has been expanded up to 9 h in specially selected patients, normally based on the findings of CT perfusion imaging and evidence of salvageable ischaemic brain tissue (Penumbra) versus truly infarcted tissue (Core) [38]. To date, most randomised control trials using IVT have failed to include patients with advanced CKD or, if included, failed to report stratified CKD outcomes. Studies to date in this area including a meta-analysis of seven observational studies, a post hoc analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study and a U.S. based registry study all demonstrated increased mortality in those with CKD receiving IVT [39–41]. However, they failed to establish this increased mortality risk as being secondary to intracerebral haemorrhage (ICH) but instead found that these multi-morbid patients were at a higher risk of hospital acquired complications such as infections and deep venous thrombosis. Based on current evidence available, with a clearly established benefit to receiving IVT in the general population, it is proposed that IVT should be used in eligible patients with CKD and in those on dialysis once a normal activated partial thromboplastic time (APTT) has been resulted [33].
2. Endovascular and Surgical Intervention.

   There is a similar paucity of studies in the area of thrombectomy or endovascular clot retrieval in patients with CKD. In the absence of any clear evidence against the use of this

intervention in CKD patients, we advocate for its use in suitable cases regardless of CKD stage or dialysis status [33]. Dialysis patients likely present a therapeutic challenge in terms of endovascular access and the increased bleeding risk but to date an analysis of 915 dialysis patients post thrombectomy showed lower in hospital mortality and moderate-severe disability compared with no treatment in this cohort [42]. Intervention with thrombectomy in posterior circulation stroke appears to be associated with increased ICH risk in the presence of CKD [43], but the use of thrombectomy in posterior circulation stroke remains an early and evolving intervention with benefits and risks still being established [44]. Surgical intervention such as decompressive hemi-craniectomy lacks specific evidence in those with CKD but should be offered to those who would otherwise be eligible for intervention.

3. Stroke unit.

   In acute stroke, admission to a dedicated stroke unit has shown both a mortality and morbidity benefit with reduced rates of post stroke dependency in the general population, with a number needed to benefit of 6 [45]. Patients with CKD, and in particular those on dialysis, are often cohorted to a renal ward regardless of reason for presentation due to nursing familiarity with this complex patient cohort. However, the benefit of acute stroke care in a specialised unit is maintained from the general population into those with established CKD and should be encouraged [35].

4. Dialysis considerations.

   Management of intermittent dialysis in the post stroke period presents a number of clinical challenges managing intracranial pressure, cerebral perfusion and anticoagulation [33]. Studies have shown that during intermittent haemodialysis subclinical cerebral oedema can occur [46]. In patients who have acquired an acute brain injury post stroke, an increase in intracranial pressure and increasing oedema may prove deleterious. Intracranial pressure may also be affected by changing osmolality during dialysis [47] and another factor to consider is intradialytic blood pressure and volume changes that may result in cerebral hypoperfusion and with it extension of the penumbra [27, 48]. The use of systemic anticoagulation in the acute post stroke period increases the risk of haemorrhagic transformation in the case of ischaemic stroke but also ICH extension and potential progression to herniation.

Current practice recommendations come from expert opinion based reviews and aim to avoid further intracranial insults via the above mechanisms [49, 50]. Continuous renal replacement therapy strategies have been shown to reduce the risk of cerebral oedema and hypoperfusion and thus it is recommended for use in the post-stroke period particularly in the case of patients with large infarcts, with ICH or in those who have blood pressure dependent infarcts (secondary to large vessel stenosis) [51]. Something that requires consideration in the case of continuous renal replacement therapy is the need for anticoagulation within the circuit. In this instance, regional anticoagulation with citrate is most appropriate due to its selective block of the haemostatic cascade within the circuit without effecting the circulating patient's blood [52].

Given the risk of worsening oedema and herniation syndromes in ICH, it is recommended that dialysis should be delayed if appropriate until the patient has stabilised [53].

In those who are felt to be safe to proceed to intermittent haemodialysis (a decision made on a case-to-case basis by clinicians), there have been suggestions of using shorter dialysis times to limit changes in osmolality and of utilising additional osmoles such as mannitol or hypertonic saline. Additionally, it has been suggested that using a cooler dialysate during this acute stage would limit cerebral hypoperfusion by inducing vascocontriction and therefore avoiding intradialytic hypotension [54]. The recent MYTEMP trial has reported discordant results compared to previous studies that supported

this hypothesis and calls into question the efficacy of this therapeutic intervention [55]. However, alternate studies focusing on MRI brain findings demonstrated a reduction in white matter changes when dialysis was performed at 0.5° below core body temperature compared to a standard 37°, making this an intervention that should be considered at an individual level [54].

Peritoneal dialysis may be superior to intermittent haemodialysis during this period but we would still recommend avoiding large volume, high glucose exchanges if possible to reduce the risk of osmotic changes [56].

Importantly, when considering the post-stroke period, one wants to optimise the patients' ability to engage with the multidisciplinary rehabilitation team and the timing and form of dialysis should take this into consideration where possible.

14.6 Preventative Therapies

14.6.1 Lifestyle Modifications

Although specific data on stroke risk reduction in this group is lacking, lifestyle modifications such as salt restriction [57], weight management [58], regular exercise [59], and smoking cessation [60] have been shown to improve intermediate outcomes associated with vascular risk such as blood pressure, lipid profiles, insulin resistance, and proteinuria, and are therefore, strongly encouraged in CKD.

14.6.2 Antiplatelet Therapies

Unfortunately, patients with moderate-to-severe CKD were excluded from most clinical trials evaluating efficacy and safety of antiplatelet agents so there is little evidence to inform guidelines in this area, particularly for primary prevention [61]. In a meta-analysis of three trials (HOT, Heart and Renal Protection [HARP], Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes [JPAD] trial) that studied the effect of antiplatelet therapy for primary prevention in CKD, there was no statistically significant reduction in major cardiovascular events including stroke (RR = 0.92, 0.49–1.73, $p = 0.79$) or in mortality (RR = 0.74, 95% CI 0.55 to 1.00, $p = 0.05$) [62]. However, there was an increase in major bleeding events (RR = 1.98, 95% CI 1.11 to 3.52, $p = 0.02$). The Aspirin to Target Arterial events in Chronic Kidney Disease (ATTACK) trial (NCT03796156) is an open-label, multicentre primary prevention trial of aspirin in CKD currently underway that may help clarify the role (or lack thereof) of aspirin in this setting. There is somewhat better evidence to support the use of antiplatelet therapy in secondary vascular prevention in CKD. In a large Cochrane review of 50 RCTs (27,139 participants), antiplatelet agents reduced the risk of myocardial infarction (RR = 0.87, 95% CI 0.76–0.99), but not all-cause mortality (RR = 0.93, 0.8–1.06), cardiovascular mortality (RR = 0.89, 0.70–1.12) or specifically stroke (RR = 1.00, 0.58–1.72) [63]. However, it is unlikely that the large benefits of aspirin as demonstrated in the general population [64] would be completely nullified in patients with CKD and the guidelines consistently recommend its use for secondary prevention in this setting [61, 65, 66].

14.6.3 Anticoagulation

Similar to antiplatelet therapy, anticoagulation is highly effective in the general population [67] but tends to be underused in the renal population owing to bleeding or vascular calcification concerns, and uncertain benefit in the dialysis population [68]. However, there is clear, consistent evidence of the efficacy of warfarin for the prevention of stroke in patients with CKD albeit with a more variable effect on bleeding events [69, 70]. Novel oral anticoagulants (NOACs) appear to even more effective in CKD, as highlighted by a recent, large systematic review and meta-analysis of 11 trials (16, 787 participants) where they were associated with a lower risk of stroke or systemic embolism (RR = 0.79, 0.66 to 0.93), haemorrhagic stroke (RR = 0.48, 0.30 to 0.76), and all-cause death (RR = 0.88, 0.78 to

0.99) when compared with vitamin K antagonists [71]. There was no difference in the risk of bleeding though and this meta-analysis was limited only to patients with a creatinine clearance >25 mL/min. Reassuringly, reversal agents such as idarucizumab appear to be safe and effective in CKD [72].

Anticoagulation use in dialysis patients is more problematic. Multiple meta-analyses do not support a protective effect for warfarin in the prevention of ischaemic stroke and suggest that it is associated with increased risk of major bleeding [70, 73]. However, these have been based solely on observational cohort studies as there are no trials that have addressed this question. Furthermore, many of the included studies do not report time in the therapeutic range (TTR) which may confound some of the risk estimates. In a Danish registry study of 10,423 warfarin-treated AF patients, a TTR < 70% was associated with a higher risk of stroke/thromboembolism (HR = 1.39, 1.20–1.60) and bleeding (HR = 1.22, 1.05–1.42) among patients with eGFR of 30–59 mL/min/1.73 m^2, suggesting that the quality of warfarin monitoring and management may similarly influence the efficacy and safety of warfarin in dialysis patients [74].

Vitamin K antagonists such as warfarin have also implicated in the progression of vascular calcification in these patients due to inhibition of the enzyme matrix gamma-carboxyglutamate Gla protein that scavenges calcium phosphate in tissues [75]. A recent multi-centre RCT investigated the impact of vitamin K status on vascular calcification in 132 patients on haemodialysis with AF [76]. Patients were randomised to vitamin K antagonists, rivaroxaban, or rivaroxaban plus vitamin K2 supplementation. Changes in coronary artery, thoracic aorta, and cardiac valve calcium scores and pulse wave velocity, as used to measure vascular calcification progression, were not significantly different among the treatment arms. There was also no difference in all-cause death, stroke, and cardiovascular event rates between the groups. The ongoing trial (AVKDIAL [NCT02886962]) will compare vitamin K antagonists with no anticoagulation in dialysis-dependent patients with AF may help definitively answer the question of risk:benefit ratio of warfarin in ESKD.

There is some promising observational data on NOAC use in dialysis patients. A retrospective cohort study based on United States Renal Data System (USRDS) data compared warfarin versus apixaban in 25,523 dialysis patients with AF [77]. Although there was no overall difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR = 0.88, 0.69–1.12; $P = 0.29$), apixaban was associated with a lower risk of major bleeding (HR = 0.72, 0.59–0.87; $P < 0.001$). However, standard-dose apixaban was associated with lower risks of stroke/systemic embolism and death when compared with lower-dose apixaban and warfarin. The RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF) trial was unfortunately terminated early due to loss of funding, and thus, only recruited 154 patients that were followed-up for 1 year [78]. Aprixaban resulted in similar rates of bleeding and strokes as warfarin among patients with ESKD on haemodialysis. TTR with warfarin was only approximately 44%. The Edoxaban Low-Dose for ElderR CARE AF patients (ELDERCARE-AF) study is another multi-centre, ongoing RCT that will compare the safety and efficacy of once daily edoxaban versus placebo in Japanese AF patients ≥80 years of age who are considered ineligible for standard oral anticoagulant therapy [79]. This group will include those with advanced CKD or who are dialysis-dependent. There is clearly a need for further dedicated dialysis trials of DOAC versus placebo.

Left atrial appendage occlusion devices, used to lower the thromboembolic risk in those with absolute or relative contraindications to long-term oral anticoagulation, appear to be equally effective in those with CKD with similar procedural safety [80]. Those with an eGFR <30 mL/min/1.73m^2 had a lower overall survival rate but the rate of non-fatal major adverse events during follow-up (stroke, TIA, and major bleeding) was not higher among patients with ESKD. However, an important limitation of this analysis was that it was a comparison based on expected event rates as opposed to trial-based evidence. There is also

a temporary requirement for anticoagulation in the periprocedural period which may not be possible in a high-risk group.

14.6.4 Dual Blockade

A secondary analysis of the COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS) trial revealed promising results for patients with CKD [81]. The COMPASS trial was a double-blind, double-dummy, randomised trial using a 3-by-2 partial factorial design conducted at 602 centres in 33 countries. In one randomised comparison, rivaroxaban with or without aspirin was compared with aspirin alone in patients with a history of stable atherosclerotic vascular disease (chronic coronary or peripheral artery disease). The other randomised comparison compares pantoprazole use with placebo and is still ongoing. The study, unlike many cardiovascular trials, was deliberately enriched with CKD patients, who accounted for 6276 patients out of 27,387 in total. The primary composite outcome of cardiovascular death, myocardial infarction, or stroke was reduced with rivaroxaban 2.5 mg BD plus aspirin in those with CKD (HR: 0.75; 95% CI: 0.60 to 0.94). Stroke as an individual endpoint was particularly reduced with dual blockade therapy (HR = 0.42, 0.25–0.70; p = 0.0007), and there was no excess bleeding in those with CKD as compared to those without. However, those with an eGFR <15 mL/min/1.73 m^2 were excluded from the trial and there was only approximately 150 people with an eGFR 15–29 mL/min/1.73 m^2 which may limit some of the generalisability of these results to all patients with CKD. In addition, those patients with a history of stroke in the preceding year were excluded, and only 5.2% of the included CKD patients had any prior history of cerebrovascular disease. Nonetheless, based on this trial, we would recommend considering low-dose rivaroxaban and aspirin for the prevention of stroke in those with an eGFR 30–59 mL/min/1.73 m^2 and a prior history of coronary artery or peripheral artery disease. Dual blockade may also have a role in secondary stroke prevention though further evidence is required. The Treatment of Cardiovascular Disease with Low-Dose Rivaroxaban in Advanced Chronic Kidney Disease (TRACK) trial (NCT03969953) may help answer this question as it will randomise high-risk advanced CKD patients including those with a history of coronary artery disease, peripheral artery disease, non-haemorrhagic non-lacunar stroke, diabetes mellitus, or those ≥65 years, to low-dose rivaroxaban or placebo.

14.6.5 Lipid-Lowering Therapy

The efficacy of statin therapy for the primary prevention of stroke in CKD patients was clearly demonstrated in the landmark Study of Heart and Renal Protection (SHARP) trial, in which 9270 CKD patients with CKD without pre-existing vascular disease were randomly assigned to placebo or to the combination of simvastatin 20 mg daily plus ezetimibe 10 mg daily [82]. There was a 25% reduction in ischaemic stroke in the treatment arm. In meta-analyses of trials of statins in patients with established cardiovascular disease, there was about a 40% reduction in the risk of stroke in patients with CKD as per the general population [83, 84]. High-intensity therapy (e.g., atorvastatin 80 mg or rosuvastatin 20 mg once daily) has also been shown to be safe and effective in this group [85]. According to KDIGO guidelines [66], all CKD patients over 50 years of age should therefore be started on statin plus/minus ezetimibe therapy. The American College of Cardiology (ACC) has additionally recommended the addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (or ezetimibe) to maximally tolerated statin therapy in high-risk patients with atherosclerotic cardiovascular disease and CKD where less than 50% LDL-C reduction has been achieved with statins, including high-intensity statins [86].

There appears to be a "statin resistance" in the dialysis population, possibly related to a heightened role of non-traditional risk factors (e.g., mineral and bone abnormalities, uraemia) [87],

additional lipid abnormalities (e.g., lipoproteins rendered highly atherogenic by oxidation or carbamylation), or intracellular cholesterol synthesis activated by inflammatory stress [88], and its pro-calcifying effects [89]. Multiple randomised trials [90, 91] including SHARP [82] did not find any benefit for statins in this population, with the exception of those with very high serum LDL-cholesterol levels (such as >145 mg/dL [3.8 mmol/L]) in a posthoc analysis of the 4D study (Die Deutsche Diabetes Dialyse Studie) [90]. For this reason, KDIGO guidelines, do not recommend starting statins de novo in dialysis patients [66].

14.6.6 Antihypertensive Therapy

Unfortunately, there has never been a dedicated blood pressure RCT in the CKD population for the prevention of stroke and most of the existing evidence has been derived from posthoc or subgroup analysis. The KDIGO 2020 Clinical Practice Guideline on the Management of Blood Pressure in CKD recommend a blood pressure of less than 120/80 mmHg in CKD for both primary and secondary prevention in patients where this level can be feasibly tolerated. This recommendation has been heavily influenced by subgroup analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) in which targeting a systolic blood pressure (SBP) <120 mmHg compared with <140 mmHg reduced rates of major cardiovascular events and all-cause death in patients with CKD [92]. The risk of stroke was similar in both treatment groups (HR = 0.99, 0.57–1.70; P = 0.96) but the trial was stopped early (median follow-up 3.3 years) so follow-up may have been too short to see a cerebrovascular protective effect. The generalisability of the results may also be limited as people with diabetes, proteinuria >1000 mg/g or prior stroke were excluded. However, specific stroke benefits associated with more intensive BP control have been seen in other trials such as the China Stroke Primary Prevention Trial (CSPPT) [93]. In this posthoc analysis of 3230 hypertensive patients with eGFR 30–60 mL/min/1.73 m^2 and/or proteinuria, a time-averaged SBP of ≤135 mmHg was associated with lower risk of total first stroke compared to a time-averaged on-treatment SBP of 135 to ≤140 mmHg, (1.7% vs. 3.3%; HR = 0.51, 0.26–0.99).

As acknowledged by another recent KDIGO controversies conference [94], there is not much evidence to guide BP target thresholds in a secondary prevention setting, and the previous 2012 BP guidelines did not specifically address this group. A posthoc analysis of the Perindopril Protection against Recurrent Stroke Study (PROGRESS) showed that perindopril was associated with a 35% reduction in the risk of stroke CKD patients with a history of recently symptomatic cerebrovascular [95]. Perindopril prevented one stroke or other cardiovascular event among every 11 patients with CKD treated over 5 years, although it was unclear what the achieved blood pressure or level of urine albumin were in either arm of the trial. The Secondary Prevention of Small Subcortical Strokes (SPS3) study, in which patients with a history of lacunar stroke were randomised to a lower (<130 mmHg) versus higher (130–149 mmHg) target SBP included 474 patients with CKD [96]. Intensive BP control resulted in a statistically nonsignificant reduction in the cardiovascular composite outcome in CKD but with greater risk of kidney function decline.

The ideal BP target in dialysis patients for stroke prevention is evenly less clear with evidence of a U-shaped associations between change in SBP, all-cause mortality and cardiovascular mortality, whereby post-dialytic drops in SBP of up to 30 mmHg are associated with greater survival, but larger decreases of SBP are associated with greater mortality [97].

There is clearly a need for dedicated RCTs in CKD and dialysis patients to better establish BP targets for people with and without prior stroke.

14.6.7 Carotid Interventions

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was the only large randomised trial of carotid interventions

that reported results according to kidney function [98]. Surgery was highly effective for CKD patients with symptomatic high-grade stenosis resulting in a RR reduction of 82.3% (95% CI 54.5–93.1%) compared to 50.8% (95% CI 12.6–72.3%) for patients without CKD. The number needed to treat by surgery to prevent one ipsilateral stroke within 2 years was only four for patients with CKD. Rates of perioperative cardiac complications (myocardial infarction, congestive heart failure, and arrhythmias) were higher in the CKD group though perioperative death rates were similar between groups.

However, the majority of CKD patients included in the NASCET analysis had CKD stage 3a with a mean eGFR of 49 mL/min/1.73 m^2. In an analysis of the Vascular Study Group of New England database, 30-day mortality appears to increase with worsening kidney function, from 0.4% in mild CKD to 0.9% in severe CKD (defined as an eGFR <30 mL/min/1.73 m^2; $P = 0.01$) [99]. However, in a multi-variate regression model, CKD status did not predict 30-day stroke or death, and even in patients with severe CKD, there was an overall 5-year survival rate of 71%, contrasting with the bleaker outcomes for severe CKD with PVD whose 5-year survival rate is only 21% irrespective of intervention [100]. We would therefore agree with guidance from the Society for Vascular Surgery who recommend carotid endarterectomy for symptomatic CKD patients with moderate-severe stenosis [101]. However, careful perioperative assessment and management is essential given their higher rate of periprocedural complications.

Unfortunately, the perioperative and long-term outcomes after carotid endarterectomy in dialysis patients appear to be quite poor. In a retrospective analysis of 5142 dialysis patients in the US Renal Disease System-Medicare-matched database, there was a high rate of 30-day complications including stroke, MI, and mortality for both asymptomatic and symptomatic patients (2.7% vs. 5.2% [$P = 0.001$], 4.6% vs. 5.0% [$P = 00.69$], and 2.6% vs. 2.9% [$P = 0.61$], respectively) [102]. The overall 3-year survival was also only 46% and 42% in the asymptomatic and symptomatic cohorts respectively. We would therefore recommend carotid intervention in only a select group of high-risk, symptomatic dialysis patients. There is currently insufficient evidence to recommend stenting over carotid endarterectomy in either CKD or dialysis patients. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2; NCT02089217) is an ongoing set of trials, one of which will randomise patients in a 1:1 ratio to endarterectomy versus no endarterectomy and another will randomise patients in a 1:1 ratio to carotid stenting with embolic protection versus no stenting. This will include patients with an eGFR >30 mL/min/1.73 m^2 and may therefore provide further information to inform best clinical practice in this area. However, a dedicated trial of carotid interventions in symptomatic patients with high-grade stenosis who have advanced CKD or who are dialysis-dependent is clearly required.

14.6.8 SGLT-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors appear to have promising vascular benefits in CKD patients with type 2 diabetes mellitus as demonstrated by recent large placebo-controlled outcome trials [103–105]. However, their potential benefit for stroke prevention in the general population or this specific group is less clear. In an analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) trial which randomly assigned randomly assigned 10,142 participants with type 2 diabetes mellitus and high cardiovascular risk to canagliflozin or placebo, there was no significant difference in event rates between groups (HR = 0.87; 95% CI, 0.69–1.09), though there may have been too few events overall to detect a significant benefit [106]. However, a meta-analysis of 32 trials with 75,540 participants also did not find a class or individual effect for any of the 3 SGLT-2 inhibitors therapy for stroke prevention [107].

Before You Finish: Practice Pearls for the Clinician

- Stroke symptoms may be subtle in haemodialysis patients and therefore easily missed.
- Admission to the stroke unit is associated with reduced mortality for patients with CKD including for those who are dialysis dependent.
- In the absence of definitive trial evidence, the decision to anticoagulate and the choice of agent should be individualised in the haemodialysis population.

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15 Anemia and Disorders of Hemostasis in Chronic Kidney Disease

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Abbreviations

CHr	Reticulocyte hemoglobin content
CKD	Chronic kidney disease
CRP	C-reactive protein
EPO	Erythropoietin
GFR	Glomerular filtration rate
Hb	Hemoglobin
HIF	Hypoxia inducible factor
HIF-PHI	Hypoxia inducible factor- prolyl-hydroxylase inhibitors
HLA	Human leucocyte antigen (HLA)
HRC	Hypochromic red blood cells
JAK-2	Janus kinase-2
K/DOQI	Kidney Disease Outcomes Quality Initiative
KDIGO	Kidney Disease: Improving Global Outcomes
NICE	National Institute for Health and Care Excellence
NKF	National Kidney Foundation
PH	Prolyl hydroxylase
TSAT	Transferrin Saturation

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Before You Start: Facts You Need to Know

- Anemia is defined as a hemoglobin value below 13 g/dL in men and a hemoglobin value below 12 g/dL in women. Anemia is one of the most common complications of chronic kidney disease and its prevalence increases as glomerular filtration rate decreases.
- Anemia in chronic kidney disease is usually caused by iron deficiency, decreased erythropoietin production, and disturbances in hepcidin axis.
- In patients with chronic kidney disease, anemia is associated with increased mortality, higher cardiovascular risk, faster progression of chronic kidney disease, a higher risk of hospitalization and decrease in quality of life.
- Specific evidence-based guidelines have been published by several organizations for both screening and treatment of anemia in chronic kidney disease; these guidelines provide algorithms for the appropriate use of oral and intravenous iron preparations as well as use of erythropoietin treatment.
- Recently, hypoxia inducible factor-prolyl hydroxylase inhibitors have emerged as a promising treatment alternative with non-inferior efficacy compared to erythropoietin.
- Patients with chronic kidney disease also experience disturbances in hemostasis that increase risk of cardiovascular events along with thrombosis and bleeding episodes.

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15.1 Definition of Anemia

Anemia is defined by the World Health Organization as a hemoglobin (Hb) value below 13 g/dL in men and below 12 g/dL in women [1]. There is no widely accepted alternative definition of anemia specific to patients with chronic kidney disease (CKD) and the above values should lead to initiation of diagnostic workup in this patient population.

15.2 Prevalence of Anemia in Chronic Kidney Disease

Anemia is one of the most common complications of CKD. Although anemia may occur rarely in CKD stages 1 or 2, it is more likely to develop when the glomerular filtration rate (GFR) falls below 60 mL/min. As the CKD stage progresses, the risk of developing anemia increases. While the incidence of anemia is less than 5% in the early stages, approximately 80–90% of patients have anemia when the GFR falls below 15 mL/min [2–4]. Anemia develops earlier in diabetic patients with CKD [5].

15.3 Importance of Anemia in Chronic Kidney Disease

In addition to the well-known effects of anemia such as fatigue, depression, shortness of breath, decreased quality of life, and decreased working capacity; there are many problems that it causes in the long term. Studies have shown that anemia is associated with increased mortality [6], higher cardiovascular risk [7], faster progression of CKD [8], and higher risk of hospitalization [9] in patients with CKD.

15.4 Etiology and Pathophysiology of Anemia in Chronic Kidney Disease

The most important factor in the development of anemia in CKD is erythropoietin (EPO) deficiency. EPO is produced by fibroblast-like interstitial peritubular cells of the kidney. Secreted EPO binds to the EPO receptor on erythroid progenitor cells in the bone marrow, and this binding stimulates red cell production through activation of the janus kinase-2 (JAK-2) pathway. The number and function of EPO secreting cells decrease as CKD progresses.

Another important cause of anemia in CKD is iron deficiency which can be categorized as absolute and functional iron deficiencies. Absolute iron deficiency is the deficit in the total body iron stores in the liver, spleen, and bone marrow. Common causes of absolute iron deficiency are menstrual bleeding, gastrointestinal blood losses, blood clotting on dialyzers during hemodialysis sessions, frequent blood draws in hospitalized patients, and impaired gastrointestinal iron reabsorption due to proton pump inhibitors or phosphate binders. Functional iron deficiency is the insufficiency of iron utilization for erythropoiesis despite there is no depletion in the body iron stores. Hepatocytes, macrophages, and enterocytes transport iron through ferroportin channels located in the cell membrane. Hepcidin is a peptide hormone secreted by the liver that regulates iron absorption and homeostasis [10]. Iron overload increases hepcidin levels, while iron deficiency reduces its concentrations [11]. When stimulated by the presence of adequate levels of iron in the body, hepcidin binds to ferroportin channels, stimulating them to internalize and subsequently degrade, resulting in inhibition of release of iron from reticuloendothelial macrophages and hepatocytes into plasma and reduced gastrointestinal iron absorption. In the case of infection, hepcidin upregulation is a protective mechanism aimed at reducing the iron available to pathogens. Hepcidin levels are also elevated in inflammatory conditions such as CKD [12]; in this case, high hepcidin limits the availability of iron for red cell production and leads to a functional iron deficiency state. Besides inflammation; decreased renal clearance and reduced EPO synthesis contribute to elevation in hepcidin levels while iron or EPO therapy reduces hepcidin levels in addition to their primary goal of increasing Hb levels [13].

Table 15.1 Differential diagnosis of anemia in chronic kidney disease

Decreased erythropoietin synthesis	Hemoglobinopathies
Absolute/functional iron deficiency	Vitamin B12/folate deficiency
Bleeding	Multiple myeloma
Hemolysis	Anemia of another chronic diseases
Bone marrow disorders	Hypothyroidism
Hyperparathyroidism	Angiotensin converting enzyme inhibitor/angiotensin receptor blocker use

Anemia in patients with CKD often has more than one cause. Potential etiologies of anemia in patients with CKD are presented in Table 15.1.

15.5 Evaluation of Anemia in Chronic Kidney Disease

Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease that was published in 2012 and National Institute for Health and Care Excellence (NICE) Chronic Kidney Disease: Assessment and Management guideline that was published in 2021 are the two important guidelines that make clear recommendations about the evaluation of anemia in CKD [14, 15].

The KDIGO guideline suggests that for CKD patients without anemia, frequency of anemia testing should be at least once a year in stage 3, at least twice per year in stage 4 and pre-dialysis stage 5 and at least every 3 months for patients on dialysis. For CKD patients with anemia not being treated with an erythropoietin, it is recommended that patients with GFR <60 mL/min/1.73 m^2 have a Hb level checked at least every 3 months and patients on dialysis have a Hb checked monthly. Hb levels should also be checked when clinically indicated (e.g., any symptoms of anemia, bleeding or after surgery) [14].

Anemia investigation in patients with CKD should include complete blood count, absolute reticulocyte count, ferritin, transferrin saturation (TSAT), C-reactive protein (CRP), serum vitamin B12, and folate levels. Anemia in CKD is typically normocytic and normochromic. Coexistent iron deficiency or a hemoglobinopathy (e.g., thalassemia) can cause microcytosis, while deficiencies of folate or vitamin B12 and myelodysplasia can cause macrocytosis. Depending on the cause of the anemia in CKD patients, the reticulocyte count may be low (pure erythropoietin deficiency) or high (hemolysis, bleeding). Abnormalities in leukocyte and/or platelet levels are not typical for renal anemia and should prompt the search for alternative causes of anemia.

Additional testing may be required in selected patients based on clinical presentation. Testing the stool for occult blood may reveal the gastrointestinal cause of iron deficiency. Multiple myeloma should be excluded in patients presenting with anemia and bone pain, or in elderly patients with CKD of unknown etiology and anemia. Testing for myeloma includes a serum protein electrophoresis, a serum immunofixation electrophoresis, and a serum-kappa and lambda free light chain tests. Hb electrophoresis may be considered if a hemoglobinopathy is suspected clinically. Serum LDH and haptoglobin levels should be measured in every patient with suspected thrombotic microangiopathy, and the peripheral smear should be evaluated for schistocytes. The recommended tests for the evaluation of anemia in patients with CKD are presented in Table 15.2.

Table 15.2 Diagnostic workup of anemia in patients with chronic kidney disease

Recommended baseline laboratories	Extended laboratories
Complete blood count (Hemoglobin, white blood count and differential, platelet, red cell indices)	Tests for multiple myeloma (Serum protein electrophoresis, serum immunofixation electrophoresis, serum-free light chains)
Absolute reticulocyte count	Occult blood in stool
Serum ferritin	Thyroid stimulating hormone
Transferrin saturation	Hemoglobin electrophoresis
C-reactive protein	Tests for hemolysis (LDH, haptoglobin, peripheral smear, bilirubin, Coombs test)
Vitamin B12	Bone marrow biopsy
Folic acid	

The KDIGO guideline recommends routine use of serum ferritin levels and TSAT to assess body iron stores, rather than the gold standard bone marrow aspiration and staining. A serum ferritin level of <30 ng/mL and a TSAT of <20% is a strong indicator of absence of iron in the bone marrow. Normal or high serum ferritin levels do not guarantee that the iron stores are full, since serum ferritin is an acute phase reactant and subclinical inflammation is common in CKD. For this reason, iron stores may still be absent at ferritin levels above 200 ng/mL in hemodialysis patients. In general, absolute iron deficiency is defined as TSAT <20% and ferritin <100 mg/L in patients not receiving hemodialysis treatment or TSAT <20% and <200 mg/L in hemodialysis patients. Functional iron deficiency is defined as TSAT <20% and ferritin >100 mg/L in patients not receiving dialysis or TSAT <20% and >200 mg/L in hemodialysis patients. Measuring CRP levels may help to determine the presence of inflammation [16].

NICE guideline recommends measuring the percentage of hypochromic red blood cells (%HRC) and reticulocyte Hb content (CHr) as better methods for determining iron status. A %HRC greater than 6% and a CHr less than 29 pg indicate iron deficiency. The guideline recommends the use of ferritin and TSAT when the above tests are not available or where they are unreliable, such as in patients with thalassemia [15]. However, it should be noted that these tests are not widely used in daily clinical practice in most countries. Another limitation of %HRC is that samples must be fresh for analysis, as sample storage times longer than 6 h can lead to false elevations in %HRC.

Although inadequate erythropoietin secretion is the main cause of anemia in CKD, measurement of its serum level is not recommended by any guideline, as it is very difficult to interpret the serum erythropoietin response in a patient with anemia and kidney dysfunction. However, some authors suggest evaluating erythropoietin concentrations, measured as percentages adjusted for severity of anemia and level of kidney dysfunction, similar to child growth percentages, to identify whether there is erythropoietin deficiency indicative of renal anemia [17]. Measurement of serum hepcidin levels is not useful in distinguishing absolute iron deficiency from functional or predicting response to iron therapy [18] and is also not recommended by guidelines.

15.6 Treatment of Anemia in Chronic Kidney Disease

Treatment of anemia in patients with CKD alleviates symptoms of anemia, improves the exercise capacity and quality-of-life scores [19] and decreases the use of red blood cell transfusions which are associated with several side effects [20]. Although treatment of anemia in CKD may result in some regression of left ventricular hypertrophyI particularly in patients with severe anemia [21]; some other studies have failed to demonstrate that left ventricular hypertrophy improves with elevation of the Hb concentration [22, 23]. Furthermore, the effect of treatment on hard clinical end points such as cardiovascular and all-cause mortality and hospitalization is not clear. Another debate is about the effect of anemia treatment on the rate of progression of CKD. Although several small-scale studies suggested that treatment of anemia may have a potential to slow the progression of CKD [24, 25], this has not yet been proved in large randomized controlled trials or meta-analyses [26–29].

Relevant guidelines and their recommendations regarding the treatment of anemia in patients with CKD are presented in Boxes 15.1 and 15.2.

Box 15.1 Relevant Guidelines

1. *KDIGO Guidelines*

Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2021;99:1280–1295.

https://doi.org/10.1016/j.kint.2021.03.020.

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
http://kdigo.org/home/guidelines/anemia-in-ckd

2. *NICE Guidelines*

NICE guideline [NG203]. Chronic kidney disease: assessment and management 2021.
https://www.nice.org.uk/guidance/ng203

3. *National Kidney Foundation/ Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) Guidelines*

KDOQI US Commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. Am J Kidney Dis. 62(5):849–859.
https://www.kidney.org/sites/default/files/docs/kdoqi_commentary_on_kdigo_anemia.pdf

KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis. 2007;50(3):471–530.
http://www.kidney.org/PROFESSIONALS/kdoqi/guidelines_anemiaUP/index.htm

KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease: 2006. Am J Kidney Dis. 2006;47(5 Suppl 3):S11–145.
http://www.kidney.org/Professionals/kdoqi/guidelines_anemia/index.htm

4. *Renal Association Guidelines*

Renal association clinical practice guideline on anemia of chronic kidney disease. BMC Nephrol. 2017 Nov 30;18(1):345.
https://ukkidney.org/sites/renal.org/files/Updated-130220-Anaemia-of-Chronic-Kidney-Disease-1-1.pdf

Box 15.2 What the Guidelines Say You Should Do

Use of Iron to Treat Anemia in CKD

A trial of intravenous iron (or alternatively a 1–3 months trial of oral iron) should be given to patients with CKD when:

- An increase in Hb concentration without starting erythropoietin treatment is desired.
- An increase in Hb concentration or a decrease in erythropoietin dose is desired for those already on an erythropoietin treatment.
- TSAT is ≤30% and ferritin is ≤500 ng/mL (≤500 mg/L).

Use of Erythropoietin and Other Agents to Treat Anemia in CKD

- Weigh the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension) prior to starting erythropoietin therapy.
- For patients with CKD not on dialysis:

  Do not start erythropoietin for Hb concentration ≥10.0 g/dL (≥100 g/L) unless patients have symptomatic anemia despite sufficient iron stores or therapy.
- In general, erythropoietin should not be used to maintain Hb concentration above 11.5 g/dL (115 g/L).
- Erythropoietin dose should be chosen according to the patient's Hb concentration, body weight, and clinical circumstances.
- Choice of erythropoietin should be based on pharmacodynamics, safety information, clinical outcome data, costs, and availability.

Red Cell Transfusion to Treat Anemia in CKD

- When managing chronic anemia, avoid, when possible, red blood cell transfusions to minimize the general risks related to their use, especially in potential transplant recipients to minimize the risk of allosensitization.
- When managing chronic anemia, the benefits of red cell transfusions may outweigh the risks in patients in whom:

  Erythropoietin therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance).

  The risks of erythropoietin therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke).

Source: Data from KDIGO clinical practice guideline for anemia in chronic kidney disease [14].

15.7 Target Hemoglobin Levels

Although studies have demonstrated the positive effects of correcting anemia, there is some uncertainty about what the target Hb value should be. Findings in randomized studies that high target Hb levels are not beneficial or even harmful have led to changes in guideline recommendations to lower target Hb levels. Landmark clinical studies on target Hb levels for anemia in patients with CKD are presented in Table 15.3.

The Normal Hematocrit Study was conducted in 1233 prevalent hemodialysis patients with symptomatic heart failure or ischemic heart disease who were targeted at two different hematocrit levels (42% and 30%) using erythropoietin alfa. The primary endpoint was length of time to death or first nonfatal myocardial infarction. The hematocrit values obtained at the end of the study were 40% and 31%, respectively. There was statistically insignificant higher risk of primary outcome in the normal hematocrit group [RR 1.3 (95% CI 0.9–1.9)]. Risk of vascular access thrombosis was significantly higher in the normal hematocrit group compared to lower hematocrit group (39% vs. 29%, $P < 0.001$ respectively) [20].

In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial, 603 patients with anemia and GFR between 15 and 35 mL/min/1.73 m^2 (26% diabetic) were divided into two groups. Erythropoietin beta was used to achieve a normal Hb target (13–15 g/dL) or a subnormal Hb target (10.5–11.5 g/dL). Primary endpoint was a composite of time to sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, complications of peripheral vascular disease (amputation or necrosis), and angina pectoris or arrhythmia resulting in hospitalization for 24 h or more. The Hb values obtained at the end of the study were 13.5 and 11.6 g/dL, respectively. The percentage of patients reaching the primary endpoint was similar in both groups at the end of the three-year follow-up period, indicating that the higher Hb target did not confer benefit. In addition, all-cause mortality was higher in the high Hb target group. There was no difference in iron or transfusions administered in both groups. More patients in the high target group started renal replacement therapy. Patients with high Hb levels reported better quality of life [27].

In the Correction of Hemoglobin and in the Outcomes in Renal insufficiency (CHOIR) study, 1432 patients with Hb concentration <11 g/dL and GFR between 15 and 50 mL/min/1.73 m^2 (49% diabetic) were divided into two groups with different Hb targets. In one group the Hb target was 13.5 g/dL (12.8 g/dL achieved in the study), and the Hb target in the other group was 11.3 g/dL (this target was achieved). The drug used in this trial was erythropoietin alfa. Endpoints were death, myocardial infarction, stroke, and hospitalization for heart failure. The study was terminated early because of more events in the high Hb target group ($p = 0.03$). Also, patients in the high target Hb group had higher rates of progression to end-stage renal disease. There was a similar improvement in quality of life in both arms [28].

Table 15.3 Landmark clinical trials about target hemoglobin levels for anemia in patients with chronic kidney disease

Study (year)	US normal hematocrit study [20]	Trial to reduce cardiovascular events with Aranesp therapy (TREAT) [26]	Cardiovascular risk reduction by early anemia treatment with epoetin beta (CREATE) [27]	Correction of hemoglobin and outcomes in renal insufficiency (CHOIR) [28]
Patient type (*N*)	Dialysis with CAD or CHF (*N* = 1233)	CKD patients with DM eGFR 20–60 m/min/1.73 m^2 (*N* = 4038)	CKD patients, GFR 15–35 mL/min/1.7 m^2 (*N* = 603)	CKD patients, GFR 15–50 mL/min/1.73 m^2 (*N* = 1432)
Low target	HCT 30%	>9 g/dL	10.5–11.5 g/dL	11.3 g/dL
High target	HCT 42%	13.0 g/dL	13.0–15.0 g/dL	13.5 g/dL
1° endpoint	Death + MI	Composite endpoint: Cardiovascular event, death from cardiovascular cause, death from any cause	Composite endpoint: angina, heart failure, arrhythmias, stroke, sudden death, TIA, PVD	Composite endpoint: death, MI, stroke, CHF, hospitalization
Results	High target arm worse, relative risk for 10 endpoints was 1.3 (0.9, 1.9).	No statistically significant differences between the groups for time to first cardiac event, or mortality from cardiac or any other cause	No statistically significant difference	Target Hb 13.5 worse than Hb 11.3, HR for composite endpoint: 1.337, $p = 0.03$
	Total deaths:		Primary events:	Total deaths:
	High arm: 183		High arm: 58	High arm: 52
	Low arm: 150		Low arm: 47	Low arm: 36
Comment	Terminated early due to high arm losing	Randomized, blinded trial comparing erythropoietin to placebo Twofold increase in the rate of both fatal and nonfatal stroke in the treatment group	Excluded patients with rapid progression of CKD	Median follow-up was only 14 months as the trial was terminated early

CAD coronary artery disease, *CHF* congestive heart failure, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *Hb* hemoglobin, *HCT* hematocrit, *HR* hazard ratio, *MI* myocardial infarction, *PVD* peripheral vascular disease, *TIA* transient ischemic attack

In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study, 4038 patients with a diagnosis of type 2 diabetes with GFR between 20 and 60 mL/min/1.73 m^2, Hb concentration <11 g/dL, and TSAT >15% were separated into two groups. In patients in the treatment group, darbepoetin was used to achieve an Hb target of 13.0 g/dL (12.5 g/dL achieved in the study). Patients in the placebo group were given darbepoetin only when their Hb levels fell below 9 g/dL (mean Hb was 10.6 g/dL at the end of the study). The primary end points were the time to the composite outcome of death from any cause or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and the time to the composite outcome of death or end-stage renal disease. After a median follow-up of 29 months, there was no significant difference between groups in primary outcomes, but there was an approximately twofold increase in both fatal and nonfatal stroke rates in the high Hb target group (5% in high Hb target group vs. 2.6% in the low Hb target group). Mortality from malignancy was higher in the high target group, especially in patients with a history of malignancy. The requirement for transfusion was more common in the low Hb target group. While there was no difference in the rate of progression to end-stage renal disease between the groups, the quality of life was better in the high Hb target group [26].

Considering the results of all these studies, the followings may be suggested as the mechanisms underlying the increased cardiovascular risk of high Hb targets in the treatment of anemia in CKD [30]:

- Toxic effects of high-dose intravenous iron treatment.
- Increased viscosity and endothelial damage.
- Increased blood volume.
- Increased blood pressure.
- Toxic effects of non-biological erythropoietin.
- Increased thrombocyte functions.
- Pseudo-low measurement of Hb in hypervolemic hemodialysis patients leading to excessively high doses of erythropoietin.

The evidence from these randomized controlled trials had a great impact on the recommendations of guidelines regarding the target Hb values. Guidelines recommend a Hb target between 10 and 12 g/dL. Recommendations for each guideline is presented in Table 15.4.

One of the important points in the treatment of renal anemia that attracted attention in recent years is the importance of fluctuation of Hb levels under treatment. The causes of these fluctuations are changes in erythropoietin dose, insufficient iron stores, changes in fluid balance and acute diseases [33]. Hb variability has been shown to be associated with increased mortality in a study that included 34,963 hemodialysis patients [34]. To decrease the Hb variability Hb levels should be closely monitored during active treatment and doses of erythropoietin should be decreased rather than complete cessation when there is a higher-than-expected elevation in Hb levels.

Table 15.4 Recommendations of guidelines for target hemoglobin levels in anemia of chronic kidney disease

Guideline	Year of publication	Recommended target level of hemoglobin
KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target [31]	2007	11.0–12.0 g/dL >13 g/dL should be avoided
Kidney Disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease [14]	2012	10–11.5 g/dL >13 g/dL should be avoided
Renal association clinical practice guideline on Anemia of Chronic Kidney Disease [32]	2017	10–12 g/dL
NICE guideline [NG203]. Chronic kidney disease: Assessment and management [15]	2021	10–12 g/dL

15.8 Iron Treatment

Except for the patients with already very high TSAT and ferritin levels, the initial treatment of anemia associated with CKD is iron replacement, as uncorrected iron deficiency is a common cause of erythropoietin hyporesponsiveness and iron treatment may obviate the use of erythropoietin with potential adverse effects or may ensure the use of a lower dose of erythropoietin. In the study conducted by Besarab et al., it was found that patients with a TSAT between 30% and 50% had a lower erythropoietin requirement than patients with a TSAT between 20% and 30% [35]. 2012 KDIGO guideline recommend a trial of iron replacement if an increase in Hb or a decrease in erythropoietin dose is desired in patients with TSAT below 30% and ferritin <500 ng/mL [14].

Iron supplementation can be given either orally or intravenously. Oral route is cheap and convenient since there is no requirement for intravenous access. However, low rate of absorption due to elevated hepcidin, gastrointestinal adverse effects, low compliance to multiple tablets, and potential drug interactions are disadvantages of oral iron treatment. Intravenous route is more effective in raising Hb levels [36, 37] but can lead to hypersensitivity reactions, requires placement of a parenteral line that may damage blood vessels which may be needed for future dialysis access placement in pre-dialysis patients and may lead to iron accumulation if used in excessive amounts in long-term treatment especially in hemodialysis patients [38]. Intravenous iron treatment has a potential to increase fibroblast growth factor-23 levels which may have unwanted cardiac effects

Table 15.5 Oral iron preparation overview

Preparation	Usual daily dose for treatment of anemia in chronic kidney disease	Tablet size (mg)	Amount of elemental iron (mg)/ pill
Ferrous sulfate	2–3 × 1	325	65
Ferrous gluconate	3 × 2	325	35
Ferrous fumarate	2 × 1	325	108
Iron polysaccharide	2 × 1	150	150
Ferric citrate[a]	3 × 1–2	1000	210
Ferric maltol	2 × 1	30	30

[a]Mainly used as a phosphate-binder

and may cause hypophosphatemia [39]. Intravenous route is recommended for patients under dialysis treatment [14]. However, when deciding on the route of iron administration for pre-dialysis patients, several factors should be considered, including severity of anemia, history of response to orally administered iron and side effects, number of daily medications, expected patient compliance with oral iron, and cost. If intravenous route is used in pre-dialysis patients, high-dose low-frequency treatments can be considered which is possible with novel iron preparations. Oral and intravenous iron preparations are given in Tables 15.5 and 15.6, respectively.

Table 15.6 Intravenous iron preparation overview

Preparation	Test dose required	Typical dosing regimen	Total dose	Risk of anaphylaxis
Iron dextran	Yes—0.5 mL	Dose (mL) = 0.0442 (desired Hb – Observed Hb) × LBW + (0.26 × LBW)	One dose can complete course	US box warning: IV iron preparations carry risk of anaphylaxis, HMW Fe > LWM Fe
High molecular weight		Desired Hb: usually 14.8 g/dL	Concentration of iron dextran is 50 mg of elemental iron/mL	Anaphylaxis can occur even after a patient tolerates test dose
Low molecular weight		LBW in kg		
Iron sucrose	No	HD: 100 mg IV on 10 consecutive HD sessions	1000 mg of elemental iron	Low risk of anaphylaxis
		CKD: 200 mg × 5 doses within 14 days		
Iron gluconate	No	HD patients: 125 mg IV on 8 consecutive HD sessions	1000 mg of elemental iron	Low risk of anaphylaxis
Ferumoxytol	No	510 mg	1020 mg of elemental iron	Low risk of anaphylaxis
Ferric carboxymaltose	No	1000 mg (200 mg for dialysis patients)	1000–2000 mg of elemental iron	Low risk of anaphylaxis High risk of hypophosphatemia
Ferric derisomaltose	No	1000 mg	1000 mg of elemental iron	Low risk of anaphylaxis Not approved for hemodialysis patients in most countries
Ferric pyrophosphate citrate	No	27.2 mg (to dialysate) 6.75 mg (IV)	Administered in each hemodialysis session	Can be used either intravenous or by adding to the dialysate Only for maintenance, not for treatment of iron deficiency

Fe iron, *Hb* hemoglobin, *HMW* high molecular weight, *IV* intravenous, *LBW* lean body weight, *LMW* low molecular weight

When deciding on the subsequent iron therapy after initial therapy, hemoglobin response to recent iron therapy, ongoing blood losses, TSAT and ferritin trends, erythropoietin response, and the purpose of reducing the erythropoietin dose, if used, should be considered. Serum iron indices should be measured at intervals of 1 to 3 months but at least 1 week should elapse after the most recent intravenous iron dose. PIVOTAL and FIND-CKD trials compared higher ferritin targets with the previously accepted lower targets and provided some information about the rational use of iron. PIVOTAL study was conducted in 2141 hemodialysis patients who were under ESA treatment and had a serum ferritin of <400 ng/mL and TSAT <30%. The study compared administering high-dose intravenous iron sucrose in a proactive fashion (400 mg monthly; unless the ferritin concentration was >700 μg per liter or the transferrin saturation was ≥40%), with low dose iron sucrose, administered intravenously in a reactive fashion (0–400 mg monthly, with a ferritin concentration of <200 μg/L or a TSAT <20% being a trigger for iron administration). The use of a high-dose regimen of intravenous iron administered proactively resulted in a significantly lower risk of death or major nonfatal cardiovascular events as compared with that observed with a reactive, low dose regimen and also resulted in lower doses of erythropoiesis-stimulating agent being administered [40]. Similarly, FIND-CKD trial revealed that aiming higher ferritin target (400–600 ng/mL) resulted in better Hb control and less requirement for erythropoietin compared to lower ferritin target (100 to 200 ng/mL) [41]. KDIGO guideline which was published prior to PIVOTAL and FIND-CKD trials, did not recommended routine use of iron supplementation in patients with TSAT greater than 30% or serum ferritin >500 ng/mL [14]. However, more recent NICE guidelines and Renal Association guidelines suggest that additional iron treatment can be provided to increase Hb levels to target, until ferritin levels reach 800 ng/mL in pre-dialysis patients [15, 32]. These guidelines also suggest that proactive high-dose intravenous iron sucrose 400 mg every month (or equivalent) can be given to hemodialysis patients unless ferritin >700 μg/L or TSAT>40%. Since iron is lost in each hemodialysis session, regular iron replacement should be considered instead of waiting for iron stores to deplete for patients with Hb at target levels. The maintenance iron regimen can be adjusted not to exceed the upper ferritin limit, and patients generally require 50–60 mg of intravenous iron per week.

Although it was thought that parenteral iron infusions may cause a flare of arthritis in patients with certain rheumatic diseases, this is not a concern for new iron alternatives with less immunological properties [42]. There is a theoretical concern that intravenous iron can increase the infection risk as iron is essential for replication of microorganisms. This concern was not supported by the clinical trial data as risk of infection was similar in high and low dose groups in the PIVOTAL study [40, 43]. However intravenous iron is still discouraged by all of the guidelines during active infection.

Previously, iron dextran was the only intravenous iron available. It is no longer widely used because of its association with anaphylactic reactions. In recent years, safer alternatives containing iron surrounded by a carbohydrate moiety that minimizes the release of iron into the circulation have been added to treatment options. There are currently six FDA-approved parenteral iron preparations available:

15.8.1 Sodium Ferric Gluconate and Iron Sucrose

Unlike iron dextran, sodium ferric gluconate and iron sucrose carry a significantly lower—if any—risk of anaphylaxis; as a result, these agents do not require a test dose. Randomized controlled trials comparing these two agents do not show differences in rates of efficacy or occurrence of adverse events [44]. For patients with CKD, iron sucrose is generally given five times over 14 days at a dose of 200 mg for each infusion, or at a 100 mg dose for 10 doses in patients on hemodi-

alysis. Sodium ferric gluconate is generally only given to patients on hemodialysis at a dose of 125 mg for 8 sequential infusions but can be given to patients with CKD as well.

15.8.2 Ferumoxytol

Ferumoxytol is composed of small iron oxide particles coated by low molecular weight synthetic carbohydrates, and the safety profile is similar to that of both iron sucrose and iron gluconate. This agent also does not require a test dose, and in fact a full course of ferumoxytol consists of two 510 mg injections administered over 15 min, each 3–8 days apart.

15.8.3 Ferric Carboxymaltose

Ferric carboxymaltose consists of a ferric hydroxide core stabilized by a carbohydrate shell, allows for controlled delivery of iron to target tissues. For patients with CKD, the total dose required can be calculated by the table in the drug package insert using the weight and Hb level of the patient and changes between 1000 and 2000 mg. The daily dose should not exceed 1000 mg and the remaining dose should be administered at least 1 week later. However, in dialysis patients it is labeled for administration of maximum 200 mg per dialysis session. Headache is the most common side effect. Risk of hypophosphatemia seems to be higher with ferric carboxymaltose compared to other intravenous iron formulations [45].

15.8.4 Ferric Derisomaltose

Ferric derisomaltose is an iron carbohydrate complex composed of ferric hydroxide and the carbohydrate derisomaltose. It is an alternative parenteral intravenous iron for the treatment of anemia in CKD, however, it is not approved for dialysis population in most countries. It is generally used as a single dose of 1000 mg. It has a low risk of hypersensitivity reaction like the other new iron preparations.

15.8.5 Ferric Pyrophosphate Citrate

Ferric pyrophosphate citrate is a strong complex of ferric iron with pyrophosphate and citrate and lacks any carbohydrate moiety. It is indicated in patients under dialysis treatment and besides intravenous use it can also be administered via the dialysate [46]. It is used for the maintenance of iron that is regularly lost during each hemodialysis session rather than treating any deficiency so it is administered in each hemodialysis treatment. The dose is 27.2 mg in each hemodialysis session when added into the dialysate and 6.75 mg per hemodialysis session when injected intravenously.

15.9 Erythropoietin Treatment

Erythropoietin, which has been in use for nearly 35 years, has revolutionized the treatment of CKD-associated anemia and has resulted in a dramatic reduction in need for transfusions. Currently, majority of patients on hemodialysis are treated with erythropoietin. Iron deficiency should be adequately treated before erythropoietin therapy. Erythropoietin treatment is generally started after consideration of the potential benefits (improvement of symptoms, reduced transfusion rate) and risks (stroke, malignancy, vascular access thrombosis) when Hb levels are <10 g/dL and adequate iron stores are present (TSAT >20% and ferritin >100–200 ng/mL) [14]. However, treatment should be individualized and in selected patients with symptomatic anemia, erythropoietin treatment may be started at higher Hb levels after discussing the risks of the treatment with the patient. Since erythropoietin therapy causes functional iron deficiency, iron indices should be evaluated at least every 3 months during erythropoietin therapy and iron replacement should be considered. Erythropoietin can be administered intravenously or subcutaneously. Although it has been shown that the required dose of subcutaneous erythropoietin is less than the intravenous route [47], the intravenous route is still preferred in hemodialysis patients, while the subcutaneous route is preferred in pre-dialysis patients.

Erythropoietin alfa, erythropoietin beta, erythropoietin zeta, darbepoetin, and methoxy polyethylene glycol-epoetin beta are the erythropoietin alternatives that can be used. Erythropoietin alfa, beta, zeta have short half-lives and they must be used twice or thrice weekly during the correction phase of anemia. Darbepoetin has a longer half-life and can be administered once weekly. Methoxy polyethylene glycol-epoetin beta has a much longer half-life. In pre-dialysis patients, administration periods of erythropoietin may be lengthened for practical purposes. Dose requirement of darbepoetin in subcutaneous and intravenous routes are not different [48]. There is no robust evidence that different erythropoietin formulations have different efficacies. Strict cold chain is required for erythropoietin during transportation and storage. Initial doses of each formulation are different and maintenance doses should be determined based on the initial response of the Hb to erythropoietin (Table 15.7). Hb levels should be monitored every 2–4 weeks in the correction phase and every 1–3 months for stable patients in the maintenance phase. The minimum interval between erythropoietin dose adjustments should be 2 weeks. The aim is to increase Hb levels 1 to 2 g/dL per month. Because of the trials that indicated harm with higher Hb levels, FDA issued a boxed warning on erythropoietin stating that Hb targets >11 g/dL are not recommended [49].

There are some other points that should be considered during erythropoietin treatment. Erythropoietin use is generally contraindicated in the setting of active curable malignancy or a recent history of malignancy, as tumors may have erythropoietin receptors and stimulation with erythropoietin may result in tumor growth; this was supported by findings of the TREAT trial, which showed that patients who had a history of malignancy were significantly more likely to die of cancer if they received darbepoetin than if they received placebo [26]. While in general erythropoietins are avoided for patients with solid tumors, erythropoietin can be considered in patients with hematologic malignancies, as they are often used for supportive care in patients with leukemia or lymphoma on chemotherapy; however, use in multiple myeloma, a hematologic malignancy frequently associated with chronic kidney disease and anemia, remains controversial. Erythropoietin treatment can also increase the blood pressure via several mechanisms especially in patients with rapid increase in Hb levels [50] and they are relatively contraindicated in patients with uncontrolled hypertension. Especially high doses of erythropoietin may increase the risk of fistula thrombosis [51]. Other concerns are increased risk of stroke [26] and seizures [52].

Unfortunately, about 5 to 25% of patients present with erythropoietin resistance [53, 54]. Erythropoietin resistance is defined as inability to reach target Hb level despite a dose of 450 U/kg/week of intravenous erythropoietin, 300 μ/kg/week of subcutaneous erythropoietin or 1.5 μg/kg/week of darbepoetin [55]. The main cause of erythropoietin resistance is iron deficiency while hyperparathyroidism, inadequate dialysis, infection, inflammation and malnutrition are the other causes. In erythropoietin resistance, tests for other causes of anemia (vitamin B12, folate deficiency, bone marrow disorders, hemoglobinopathies) should be repeated. If there is no clear etiology for erythropoietin hyporesponsiveness, angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be discontinued. Patients with erythropoietin resistance have a poor prognosis. Although this poor prognosis is mainly due to the underlying cause of EPO resistance, studies also indicate that high doses of erythropoietin itself can be responsible for some of the untoward effects [56].

Pure red cell aplasia is a rare disorder characterized by the production of anti- erythropoietin antibodies induced by primarily with subcutaneous erythropoietin treatment. These antibodies have the capacity to bind both exogenous and endogenous erythropoietin, which in turn leads to severe transfusion-dependent anemia. Diagnosis depends on demonstrating absence of erythropoietic activity (very low peripheral reticulocyte count or bone marrow biopsy revealing few or no erythroblasts) and presence of anti-erythropoietin antibodies in an appropriate clinical scenario.

Table 15.7 Erythropoietin preparation overview

Class	Drugs	Dosing recommendations and comments[a]
1st generation	Epoetin alfa	Initial dose: 50–100 units/kg injected subcutaneously 3 times per week
		Increase dose by 25% if hemoglobin does not increase by >1 g/dL after 4 weeks
		If hemoglobin increases >1 g/dL in any 2-week period, reduce dose by ≥25%
		Avoid frequent dose adjustments, and increase no more than once every 4 weeks
		Maintenance dose should be individualized and is between 75–300 units/kg/week
	Epoetin beta	The initial dosage is 3 × 20 IU/kg body weight per week (sc) or 3 × 40 IU/kg per week (iv)
		For sc route the dosage may be increased every 4 weeks by 3 × 20 IU/kg per week if the increase of Hb is not adequate (< 0.25 g/dL per week) For iv route the dosage may be raised after 4 weeks to 80 IU/kg - three times per week - and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals
		For both routes of administration, the maximum dose should not exceed 720 IU/kg per week
		To maintain an hemoglobin of between 10 and 12 g/dL, the dosage is initially reduced to half of the previously administered amount. Subsequently, the dose is adjusted at intervals of 1 or 2 weeks individually for the patient (maintenance dose) In the case of subcutaneous administration, the weekly dose can be given as one injection per week or in divided doses three or seven times per week. Patients who are stable on a once weekly dosing regimen may be switched to once every 2 weeks administration. In this case, dose increases may be necessary
	Epoetin zeta	*Hemodialysis:* The starting dose is 50 IU/kg, 3 times per week. If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired hemoglobin concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L) is achieved (this should be done in steps of at least 4 weeks). The recommended total weekly maintenance dose is between 75 IU/kg and 300 IU/kg
		Pre-dialysis: Starting dose of 50 IU/kg, 3 times per week, followed if necessary by a dosage increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least 4 weeks). During the maintenance phase, it can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks. Appropriate adjustment of dose and dose intervals should be made in order to maintain hemoglobin values at the desired level: hemoglobin between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). Extending dose intervals may require an increase in dose. The maximum dosage should not exceed 150 IU/kg 3 times per week, 240 IU/kg (up to a maximum of 20,000 IU) once weekly, or 480 IU/kg (up to a maximum of 40,000 IU) once every 2 weeks
		Peritoneal dialysis: The starting dose is 50 IU/kg, 2 times per week The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections. Appropriate adjustment of the dose should be made in order to maintain hemoglobin values at the desired level between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L)

(continued)

Table 15.7 (continued)

Class	Drugs	Dosing recommendations and comments[a]
2nd generation	Darbepoetin alfa	*Recommended starting dose for patients on dialysis*: – 0.45 μg/kg intravenously or subcutaneously weekly, or – 0.75 μg/kg intravenously or subcutaneously every 2 weeks – Intravenous route is recommended for patients on hemodialysis
		Recommended starting dose for pre-dialysis patients: – 0.45 μg/kg intravenously or subcutaneously at 4 week intervals
		Increase dose by 25% if hemoglobin does not increase by >1 g/dL after 4 weeks. May also increase frequency
		If hemoglobin increases >1 g/dL in any 2-week period, reduce dose by ≥25%
		Do not increase dose more frequently than every 4 weeks (dose decreases may occur more frequently)
		When given subcutaneously in non-dialysis patients, half-life is 70 h (range 35–139 h)
3rd generation	Methoxy polyethylene glycol-epoetin beta	The recommended starting dose for the treatment of anemia in adult patients with chronic kidney disease who are not currently treated with an erythropoietin is 0.6 μg/kg body weight administered as a single intravenous or subcutaneous injection once every 2 weeks
		Once the hemoglobin has been stabilized, it may be administered once monthly using a dose that is twice that of the every-2-week dose and subsequently titrated as necessary
		May be administered once every 2 weeks or once monthly to patients whose hemoglobin has been stabilized by treatment with another erythropoietin treatment
		The dose of the drug given as a single intravenous or subcutaneous injection, should be based on the total weekly erythropoietin dose at the time of conversion (details in package insert)

[a]Source: Data from drug package inserts

Patients should be treated with immunosuppressive treatment and regular red blood cell transfusions are required.

15.10 HIF-PHI Inhibitors

Hypoxia inducible factor (HIF) pathway is a recently discovered pathway that is involved in the cellular responses to hypoxia [57]. The effects of hypoxia via this pathway are diverse but ones related to erythropoiesis are stimulation of endogenous erythropoietin synthesis, decreased hepatic hepcidin synthesis, and increase in transcription of genes that play a role in iron transport [58].

HIF is composed of alfa (HIF-1a, HIF2a, and HIF-3a) and beta subunits. Beta subunit is constitutively expressed while alfa subunits are regulated by degradation in the presence of oxygen and iron by prolyl-hydroxylase (PH) enzymes. During hypoxia PHI activity is reduced, resulting in an increased half-life of HIF alfa.

Hypoxia inducible factor-prolyl-hydroxylase inhibitors (HIF-PHI) are a relatively novel group of oral drugs developed for the treatment of CKD related anemia. HIF-PHI pharmacologically inhibit the degradation of HIF alfa subunit, mimicking the effect of hypoxia, and lead to increased erythropoiesis. Increase in endogenous erythropoietin levels are much smaller compared to intravenous erythropoietin, which may be clinically important as high erythropoietin doses are associated with higher cardiovascular risk. HIF-PHI have the capacity to induce erythropoietin synthesis in patients without residual renal function and even in patients with bilateral nephrectomies [59], due to their stimulation of hepatic erythropoietin production.

There are six HIF-PHIs (roxadustat, daprodustat, vadadustat, molidustat, enarodustat, decidustat) that differ somewhat in their structure and selectivity for the PH enzyme. Roxadustat is usually used three times a week, while other molecules are given once a day.

Many landmark studies have compared HIF-PHI with erythropoietin for the treatment of anemia in both dialysis patients and pre-dialysis patients. Studies in non-dialysis group mostly compared HIF-PHI with placebo, while in studies conducted in hemodialysis population, they were compared with erythropoietin alfa or darbepoetin.

Placebo-controlled studies in non-dialysis patients have demonstrated that HIF-PHIs effectively raise Hb in the treatment of anemia, with patients showing less erythropoietin, iron, and transfusion needs compared to placebo. Studies with active comparators in non-dialysis and dialysis patients have shown that HIF-PHIs are not inferior to erythropoietin. The most widely studied molecules are roxadustat, daprodustat, and vadadustat.

The OLYMPUS study was a placebo-controlled study of roxadustat in 2781 non-dialysis patients. The mean change in Hb from baseline was 1.75 g/dL versus 0.40 g/dL in the roxadustat and placebo groups, respectively ($P < 0.001$). In the roxadustat group, the need for transfusion was reduced by 63% and intravenous iron use was less [60]. The ROCKIES study compared roxadustat with erythropoietin alfa in 2133 dialysis patients (89.1% on hemodialysis). The mean Hb change from baseline averaged over weeks 28–52 was 0.77 g/dL with roxadustat and 0.68 g/dL with erythropoietin alfa, meeting the criteria for noninferiority. Transfusion requirements were similar in both groups, while intravenous iron dose was lower in the roxadustat group [61].

ASCEND-ND study compared daprodustat with darbepoetin in 3872 pre-dialysis patients. Mean Hb change from baseline averaged over weeks 28–52 was 0.74 g/dL with daprodustat and 0.66 g/dL with darpepoetin, meeting the criteria for noninferiority. Transfusion requirements and use of intravenous iron were similar between the groups [62]. ASCEND-D trial was conducted with daprodustat on 2964 hemodialysis and peritoneal dialysis patients. Active comparator drug was erythropoietin alfa in the hemodialysis patients and darbepoetin in peritoneal dialysis patients. The mean change in the hemoglobin level from baseline to weeks 28 through 52 was 0.28 ± 0.02 g/dL in the daprodustat group and 0.10 ± 0.02 g/dL in the erythropoietin group. There was no significant difference between the

groups. There was also no difference in terms of adverse cardiovascular events [63].

Vadadustat was compared to darbepoetin in pre-dialysis population in Pro2tect trial (n = 3471) and in dialysis population (n = 3554) in Inno2vate trials. Vadadustat was non-inferior to darbepoetin in both studies regarding efficacy [64, 65].

In general, studies have shown that HIF-PHI is not actually inferior to ESAs, although HIMALAYAS study in incident dialysis patients with roxadustat has shown that it may even be superior to ESAs in increasing Hb levels [66]. Although rescue treatments were used similarly to ESAs in most HIF-PHI studies, the SIERRAS study in dialysis patients required less transfusion with roxadustat than with epoetin-α (12.5% vs. 21.1%, p = 0.033) [67]. One of the main causes of ESA hyporesponsiveness is that inflammation blocks the mobilization of iron from the reticuloendothelial system via increased hepcidin levels. HIF inhibitors lower hepcidin levels, improve iron metabolism and stimulate erythropoiesis. Theoretically, HIF inhibitors may be superior to ESAs in patients with high CRP levels. Another positive effect of HIF-PHI is the reduction in LDL-cholesterol levels, which is especially evident with roxadustat.

Oral administration of HIF inhibitors provides several advantages, including the absence of pain and injection site reactions. The reduction in iron requirement limits exposure to the gastrointestinal side effects of oral iron and reduces the frequency of intravenous iron infusions in patients with CKD not undergoing dialysis, protecting the vessels for future arterio-venous fistula surgeries.

Although data are limited, these drugs have also been shown to be effective in the treatment of anemia in patients undergoing peritoneal dialysis [68]. On the other hand, there are no good quality randomized controlled studies on kidney transplant recipients. The HIF system has significant effects on the immune system, limiting the safety of recommending the use of HIF inhibitors without observing the results of high-quality studies in this patient group.

Contrary to the positive effects of HIF-PHIs on erythropoiesis, studies have raised some safety concerns about cardiovascular risk especially in the non-dialysis population. In the OLYMPUS study cardiovascular events were higher in the roxadustat group [60]. However, a pooled analysis of the three main studies of roxadustat in non-dialysis patients, including the OLYMPUS study, showed no increased major cardiovascular adverse events in patients using roxadustat compared to placebo [69]. Vadadustat also failed to meet the predetermined noninferiority criterion for cardiovascular safety against darbepoetin in the Pro2tect study in the non-dialysis population [64]. Consistent with these findings in the ASCEND-ND study, cardiovascular events were more common with daprodsutat than with darbepoetin [62]. In dialysis patients, cardiovascular side effects with roxadustat, daprodustat, and vadadustat do not appear to be different from erythropoietin [61, 63, 65].

In addition to their effects on erythropoiesis and the immune system, HIF inhibitors also regulate the functions of many hypoxia-responsive genes involved in various biological processes. One of the most notable of these functions is related to angiogenesis, cell growth, cell migration and apoptosis as they may be associated with an increased risk of malignancy [70]. To date, no increased risk of cancer has been found in patients using the drug in clinical trials. However, post-marketing and real-life data are required to definitively exclude the cancer risk associated with HIF inhibitors. Other potential side effects related to the mechanisms of action of these drugs are worsening diabetic retinopathy [71], increased cyst growth rate in polycystic kidney disease [72], increased risk of infection [73], development of pulmonary hypertension [74], increased vascular calcification, and increased cardiovascular risk [75]. Daprodustat is the only HIF-PHI approved recently by the FDA. However, of all the molecules, roxadustat is the most studied and has been approved for the treatment of anemia in many countries including the European Union. Vadadustat and daprodustat are also approved in some countries.

15.11 Other Drugs for Anemia

Peginesatide, androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline, which were previously recommended as alternative or complementary drugs, are not currently used in the treatment of anemia of CKD due to their lack of efficacy and/or side effect profiles.

15.12 Red Blood Cell Transfusion

Red blood cell transfusions, which have been used frequently in the past in the treatment of anemia due to chronic kidney disease and have significant negative effects, are now used much less frequently. Human leucocyte antigen (HLA) sensitization is one of the most important problems related to transfusions in patients with chronic kidney disease. HLA sensitization increases the waiting time of patients in the cadaveric list, makes transplantation impossible in some cases, and increases the risk of early graft loss after transplantation. Therefore, transfusions should be avoided as much as possible in patients eligible for kidney transplantation.

Although the risk of transmission of infection has decreased because of improvements in infection screening compared to the past, another potential problem with transfusions is the risk of hepatitis and HIV. The other potential complications are acute lung injury, hypothermia, coagulopathy, iron overload, hemolysis, hyperkalemia, volume overload, metabolic alkalosis, and hypocalcemia.

In patients with EPO resistance, previous or current malignancy, and a history of stroke the risks of ESA treatment may be considered higher than the risk of transfusions. In chronic anemia due to CKD, the signs and symptoms of anemia rather than a specific Hb threshold should guide the transfusion decision. Transfusion should be given if Hb is <7 g/dL in patients with active bleeding, unstable acute coronary syndrome, anemia requiring rapid preoperative correction, or patients with anemia severe enough to result in tissue hypoperfusion and hypoxia [14].

15.13 Normal Hemostasis

There are several steps of coagulation. The process starts with constriction of the injured vessel, followed by formation of a temporary platelet plug (primary hemostasis) and then coagulation system becomes activated, and fibrin plug or the final clot forms (secondary hemostasis). The final step is the resolution of the fibrin clot (fibrinolysis). The proper clotting process depends on healthy communication between endothelial cells and platelets, a balance between procoagulant and anticoagulant factors and a balance between thrombin-stimulated fibrin clot formation and plasmin-induced clot lysis [76]. Patients with CKD may have several derangements in all these aspects and CKD is associated with both a prothrombotic tendency and increased bleeding risk. The mechanisms underlying why some patients are more prone to thrombosis leading to extreme cardiovascular events, while others are prone to spontaneous or procedural bleeding are not well known. However, thrombosis is more common in the early stages while bleeding is more common in patients with advanced renal failure.

15.14 Increased Risk of Bleeding in Chronic Kidney Disease

Patients with CKD has a higher risk of bleeding compared to general population [77]. The most common bleedings are gastrointestinal bleedings, retinal hemorrhages, intracranial bleedings, ecchymoses, and bleedings from vascular accesses.

Primary hemostasis disorders are mainly responsible for the high bleeding risk encountered in CKD. Although thrombocytopenia is sometimes found in patients with CKD due to hemodialysis, drugs or an underlying disease (SLE, TTP, etc.), main reason for the increased risk of bleeding is the dysfunction of numerically normal platelets. Binding of platelets to damaged endothelium (platelet adhesion) and adhesion of platelets to each other (platelet aggregation) requires the interaction of many molecules and receptors on platelets and endothelium. Since the

dysfunction of platelets can be reversed by hemodialysis, several uremic toxins are thought to be responsible for the abnormalities in these mechanisms [78].

Anemia contributes to platelet dysfunction because low numbers of circulating red blood cells cause platelets to move in the middle of the vessel rather than the lower endothelium and the injury site, impairing platelet adhesion to the injured vessel wall [79]. Some uremic toxins increase the levels of nitric oxide (NO) that inhibits platelet function by modulation of vascular tonus [80].

Drugs are common causes of bleeding in patients with CKD. Antibiotics and non-steroidal anti-inflammatory drugs can cause prolonged bleeding, but the most important drugs to be aware of in this population is antiaggregant and anticoagulant drugs. Considering that the cardiovascular diseases are prevalent in CKD, it is not surprising that aspirin use is quite common in this population. Studies indicate that prolonged bleeding time secondary to aspirin use is enhanced in patients with CKD [81]. Half-life of some anticoagulants in these patients is prolonged because of impaired renal clearance. The doses of anticoagulants should be properly adjusted according to the renal function of the patients.

Although hemodialysis treatment helps to improve bleeding tendency in uremic patients by removing uremic toxins, the procedure itself may cause an increased risk of bleeding in some patients due to the effect of heparin used and the continuous activation of platelets due to exposure of blood to artificial surfaces [82].

Although clinical significance is debated, bleeding risk can be assessed through some diagnostic tests. Skin bleeding time is the most widely known test and is performed by measuring the bleeding stop time of two standard incisions made on the volar aspect of the forearm under a pressure of 40 mmHg provided by a sphygmomanometer. Platelet function analyzer, platelet aggregation test or activating clotting time are the other tests to assess bleeding risk [79].

There are several options for the treatment of uremic bleeding or for prevention of bleeding before surgical procedures. Administration of 0.3 μg/kg intravenous desmopressin can improve platelet function by releasing vWF and factor VIII into the plasma from the endothelium. 10 units of cryoprecipitate which is rich in vWF and factor VIII given over 30 min improves the bleeding tendency within 1 h. Oral conjugated estrogen (0.6 mg/kg for 5 days) is rarely used as an alternative treatment. Correction of anemia with erythropoietin or red blood cell transfusion may help bleeding as increased red cell mass helps the platelets to aggregate. The most effective treatment for bleeding in the uremic patient is hemodialysis without anticoagulation to remove uremic toxins that inhibit the clotting process.

15.15 Increased Risk of Thrombosis in Chronic Kidney Disease

The risk of thrombosis is also increased in CKD and its pathogenesis is multifactorial [83]. Imbalances between the levels of pro- and anticoagulation factors play a primary role, but also increased platelet activity contributes to high risk of thrombosis. The increased thrombosis risk in CKD is in both arterial and venous systems. Clinical presentation may include deep venous thrombosis, pulmonary thromboembolism, vascular access thrombosis, thrombosis of venous hemodialysis catheters, acute coronary syndrome, and ischemic stroke. The increased thrombosis risk is associated with increased morbidity and mortality.

Inflammation is common in CKD and is associated with thrombosis as proinflammatory markers increase levels of fibrinogen and some other coagulation factors [84]. Even in the absence of inflammation, patients with CKD have higher levels of procoagulant factors, while levels of anticoagulant molecules such as anti-thrombin are reduced [85, 86]. Activation of renin-angiotensin-aldosterone system contributes to increase thrombosis by increasing levels of fibrinogen, D-dimer, and plasminogen activator inhibitor [87].

Patients with CKD has a high burden of comorbidities (especially diabetes, hypertension,

and dyslipidemia) and resulting endothelial cell damage with or without major atherosclerosis of the vessels are among the other causes of thrombosis in CKD. Plasma levels of homocysteine may be considered as another risk factor for thrombosis. The presence of antiphospholipid antibodies and heparin induced thrombocytopenia are also associated with thrombotic events in CKD.

Even mildly increased albuminuria is associated with increased thrombosis risk [88] but the risk becomes exceedingly high in patients with nephrotic syndrome. The mechanism includes urinary loss of anticoagulant production and increased hepatic synthesis of some procoagulant factors. Markers of platelet activity are also increased in nephrotic syndrome [89–91].

Platelet dysfunction is known to be more prominent in CKD, however, platelet aggregation may also be exaggerated than expected in some patients. Atherosclerosis is one of the factors that enhance platelet aggregation. Uremia itself causes elevated levels some platelet markers increasing the platelet activation and aggregation [92]. Although artificial surfaces in hemodialysis thought to be associated with platelet activation, peritoneal dialysis patients have a higher risk of thrombosis which was thought to be secondary to peritoneal losses of some regulatory factors of hemostasis [93].

Microparticles are small membrane fragments of many cells, including endothelial cells, platelets, and macrophages. They are released from cell membranes by proteolytic cleavage and are increased in inflammatory conditions such as CKD. In these patients, they contribute to the thrombotic tendency by effecting the coagulation factors and platelets [94].

Antiaggregant therapy is indicated for secondary prophylaxis in patients with coronary heart disease and cerebrovascular disease. They significantly reduce the recurrent events but are associated with major and minor bleedings. On the contrary, they are not indicated for primary prevention [95].

Drugs for the treatment of arterial and venous thrombosis should be used cautiously in patients with CKD considering that diminished GFR may influence excretion of the drugs (Table 15.8).

Table 15.8 Dosage adjustment for anticoagulant drugs in chronic kidney disease

Drug	Route of elimination	Dose adjustment in chronic kidney disease[a]
Standard heparin	Liver and reticuloendothelial cells	No
Low molecular heparin	Primarily metabolized in the liver. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose	GFR < 30 mL/min → yes Anti-factor-Xa monitorization if possible
Warfarin	Almost entirely metabolized by cytochrome p450	No
Apixaban	Eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces	No
Dabigatran	Eliminated primarily in the urine	GFR 15–30 mL/min → yes Dosing recommendations cannot be provided when GFR < 15 mL/min
Rivaroxaban	Urine and feces	GFR 15–30 mL/min → data limited, Safer alternatives may be considered GFR < 15 mL/min → avoid use
Danaparoid	Mainly renal	Prefer to use argatroban
Argatroban	Metabolized in liver, excreted primarily in the feces, presumably through biliary secretion	No dosage adjustment is necessary in patients with renal dysfunction
Fondaparinux	Eliminated in urine mainly as unchanged drug	GFR 30–50 mL/min → use with caution GFR < 30 mL/min → contraindicated

[a]Source: Data from drug package inserts

Before You Finish: Practice Pearls for the Clinician

- Both primary care practitioners and nephrologists play a role in the diagnosis and management of the anemia associated with chronic kidney disease.
- Current guidelines recommend screening for anemia in any patient with glomerular filtration rate <60 mL/min.
- Prior to treatment with an erythropoietin, it is imperative to ensure that deficient iron stores have been treated appropriately.
- If iron deficiency is diagnosed, careful consideration should be given by the primary caretaker to exclude other causes prior to initiation of iron supplementation.
- Erythropoietin dose should be minimized as much as possible while providing maximum and safe quality-of-life benefit. Red blood cell transfusions should be used as sparingly as possible, especially in potential transplant recipients.
- Hypoxia inducible factor-prolyl hydroxylase inhibitors may be an alternative in the treatment of chronic kidney disease anemia, especially in erythropoietin-resistant patients.
- Antiaggregant and anticoagulant drugs should be used with caution in chronic kidney disease, and most of these drugs require dose adjustment according to the patient's glomerular filtration rate.

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Mineral and Bone Disorders in Chronic Kidney Disease

16

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Before You Start: Facts You Need to Know

- After 60 years of use, the term "renal osteodystrophy" was changed to "chronic kidney disease–mineral and bone disorders" (CKD–MBD).
- CKD–MBD group is a complex clinical syndrome including biochemical parameters and other surrogated markers.
- "Renal osteodystrophy" is reserved to describe the bone histological lesions.
- The key regulators of CKD–MBD are calcium, phosphorus, PTH, FGF23/Klotho, and the vitamin D hormonal system.
- The prevention and treatment of CKD–MBD needs to be done integrating all the components of the syndrome.

16.1 Mineral and Bone Disorders in CKD

16.1.1 General Aspects, Epidemiology, and Pathophysiology

In healthy individuals, kidneys regulate calcium and phosphorus homeostasis modifying their tubular resorption. Patients with CKD experience a progressive compromise of the homeostatic mechanisms, giving rise to different adaptive changes in calcium, phosphorus, parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF23)/Klotho levels. These elements and hormones exert their effects on several tis-

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sues, but they act mainly on their principal targets: the bone, kidney, and intestine.

For six decades, the mineral and bone abnormalities of CKD patients were known as "renal osteodystrophy." However, in 2006, the new term "chronic kidney disease–mineral and bone disorders" (CKD–MBD) was proposed by KDIGO guidelines (Box 16.1) to group and describe a more ample and complex clinical syndrome which includes not only biochemical and bone histological abnormalities but also other bone and cardiovascular complications such as fractures and cardiovascular abnormalities occurring in CKD patients. The term "renal osteodystrophy" was reserved to describe the bone abnormalities associated with CKD which require a bone biopsy for the diagnosis. For the latter, a new classification system was proposed based on parameters of bone turnover, mineralization, and volume (TMV) [1].

Box 16.1 Relevant Guidelines

1. KDIGO Guidelines.
   (a) KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2009;76(113):S1–130 [1].
   (b) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):S1–150 [17].
   (c) KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017;7(1):1–59 [20].
2. KDOQI Guidelines.
   (a) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1–266 [18].
3. Spanish Society of Nephrology Guidelines.
   (a) Spanish Society of Nephrology recommendations for controlling mineral and bone disorder in chronic kidney disease patients (S.E.N.-M.B.D.). Nefrologia. 2011;31 Suppl 1:3–32 [19].
4. Japanese Society for Dialysis Therapy Guidelines.
   (a) Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Ther Apher Dial. 2013;17(3): 247–88 [58].

The mineral and endocrine functions disrupted in CKD are critically important in the regulation of bone modeling during growth and bone remodeling during adulthood. These CKD–MBD are found almost universally in patients requiring dialysis but also in the majority of patients in CKD stages 3–5. In recent years, there has been an increased concern with the non-skeletal calcification which increases early in the course of CKD, due to the deranged mineral and bone metabolism, but it might also occur as a result of therapies used to correct the CKD–MBD themselves. Numerous cohort studies have shown associations between several CKD–MBD, such as bone fractures, vascular calcification, and cardiovascular disease with increased mortality.

As mentioned, the key regulators of bone and mineral metabolism are calcium, phosphorus, PTH, FGF23, Klotho, and the vitamin D hormonal system [2]. Even though there is still some debate concerning the chronology of changes, it is currently accepted that the increments in FGF23 and the reduction of serum Klotho are possibly the earliest events in the pathogenesis of CKD–MBD; both factors favor the reduction of 1-alpha-hydroxylase in the kidney, which in turn results in low levels of the active form of vitamin D (1,25-dihydroxyvitamin D_3-[$1,25(OH)_2D_3$] or calcitriol), impairing calcium absorption in the intestine favoring the

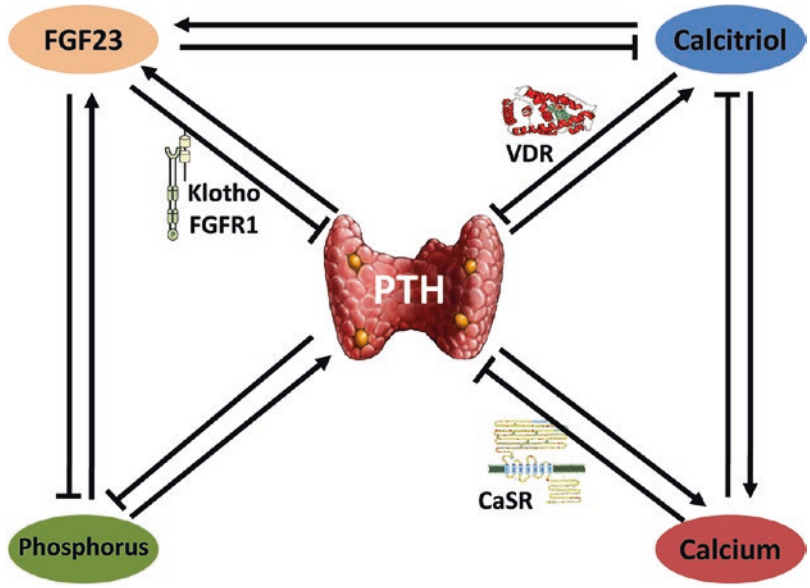

Fig. 16.1 Interrelationships between calcium and phosphorus and their hormones, PTH, FGF23/Klotho, and calcitriol. The calcium ability to increase FGF23 and the low and high phosphorus to increase and, respectively, decrease serum calcitriol are not shown in the figure

reduction in serum calcium. The decrease in serum calcium stimulates PTH synthesis and release, which in turn increases bone turnover, increases bone resorption, and stimulates 1-alpha-hydroxylase (see Fig. 16.1). All these mechanisms lead to compensatory increases in serum calcium [3].

In addition, in non-advanced phases of CKD, the increments of FGF23 and PTH increase urinary phosphorus excretion in order to avoid phosphorus accumulation [3]. Despite FGF23 and PTH featuring synergic effects to increase phosphorus excretion, both have opposite effects on calcitriol synthesis: FGF23 inhibits 1-alpha-hydroxylase, decreasing calcitriol synthesis, whereas PTH stimulates 1-alpha-hydroxylase production, thus increasing calcitriol synthesis (see Fig. 16.1). It has recently shown that phosphorus could also exert its action via calcium-sensing receptor (CaSR) [4]. FGF23 exerts its tubular effect binding to its Klotho co-receptor and activating FGFR-1 and FGFR-3 receptors, while PTH does so by binding to its specific receptor. Both increase phosphate excretion by reducing apical abundance of sodium-coupled cotransporters NaPi2a and NaPi2c via both PKA- and PKC-dependent pathways [5].

Both calcium and calcitriol act on the parathyroid cells through their specific receptors, the CaSR and the vitamin D receptor (VDR), respectively (see Fig. 16.1). While CaSR is a cell membrane receptor member of the G protein-coupled receptor family, VDR is a nuclear receptor that, when bound to vitamin D, acts as a transcription factor. The differences in the nature of the two ligands and their receptors lead to two different mechanisms of action with complementary functions on the parathyroid cells.

On the one hand, small decreases in extracellular calcium concentrations are rapidly sensed by the CaSR, triggering within seconds or minutes increments in PTH release. Small increases in calcium are also sensed by the CaSR, yielding opposite results. If the stimulus persists for longer periods (hours, days), calcium is able to regulate PTH synthesis post transcriptionally by modifying the mRNA stability through differences in binding of the parathyroid proteins to an element in its 3′-untranslated region. As a result, the decreases in serum calcium reduce mRNA degradation by increasing its stability and the half-life

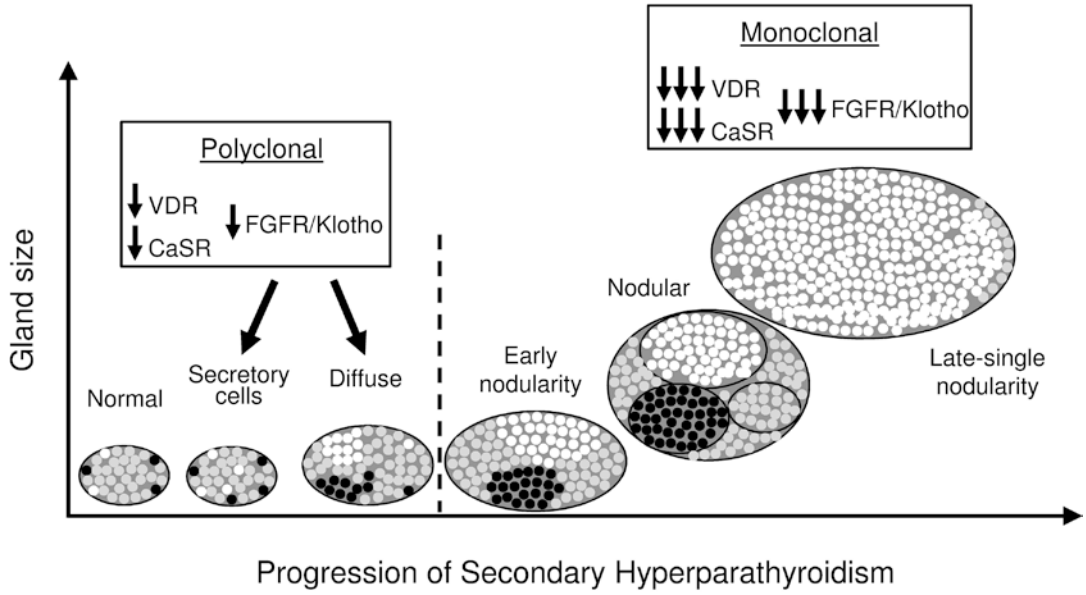

Fig. 16.2 Progression of secondary hyperparathyroidism: Initially, the parathyroid glands respond by increasing the number of secretory cells; this results in diffuse hyperplasia of the gland where cell growth is polyclonal and is accompanied by downregulation of CaSR, VDR, and FGFR/Klotho. As CKD progresses to end-stage renal disease (CKD stage 5), parathyroid hyperplasia evolves even further; monoclonal abnormalities lead to nodular hyperplasia of the glands associated with significant under-expression of CaSR, VDR, and FGFR/Klotho. (Modified from Tominaga et al. [6], with permission from John Wiley and Sons)

of mRNA PTH. On the contrary, the active form of vitamin D (calcitriol) acts at the transcriptional level and inhibits PTH gene transcription resulting in a reduction of PTH synthesis [3].

When kidney function decreases, all these complex and tightly interrelated mechanisms fail to adequately control the mineral metabolism. As a result, a progressive trend to reduce serum levels of calcitriol and increase phosphorus and calcium retention begins, ending at later stages of CKD, despite the permanent and progressive parathyroid hormone stimulation, in a manifest incapacity to control the mineral metabolism. As a result, in advanced stages of CKD–MBD, patients show severe forms of secondary hyperparathyroidism with diffuse and nodular hyperplasia and a significant reduction in CaSR, VDR, and FGFR/Klotho expression with a poor response of the parathyroid glands to the effect of calcium, VDR activators (VDRAs), and FGF23 (see Fig. 16.2) [2, 6].

Cross-sectional studies have shown the pattern of abnormalities in serum calcium, phosphorus, PTH, $25(OH)D_3$ (calcidiol), and calcitriol at different stages of CKD. As Fig. 16.3 shows, serum calcium and phosphorus values did not become abnormal until the glomerular filtration rate (GFR) fell around 30–40 mL/min. The abnormalities progressively increase starting from these values. By contrast, calcitriol started to decrease early in the course of CKD (GFR between 70 and 80 mL/min) and PTH increased a bit later (GFR between 60 and 70 mL/min) (see Fig. 16.3) [7].

Even though all the above discussed changes lead to the stimulation of the parathyroid gland and high bone turnover, the latter is not the most frequent histological finding of renal osteodystrophy in CKD patients. Due to the combination of several factors, such as aging, diabetes, and the medical management of CKD–MBD (calcium overload, high dose of VDRAs, aluminum salts), throughout the recent decades, the more frequent pattern of bone lesions has changed from high to low bone turnover forms of renal osteodystrophy (see Table 16.1, [8–14]). Recent studies also sug-

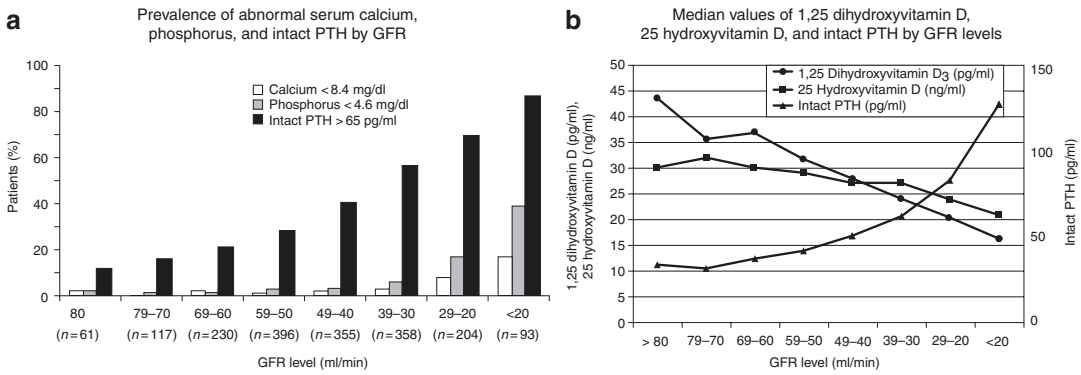

Fig. 16.3 Prevalence of abnormal mineral metabolism in CKD. (**a**) The prevalence of hyperparathyroidism, hypocalcemia, and hyperphosphoremia by GFR levels at 10 mL/min per 1.73 m^2 intervals. (**b**) Median values of $1,25(OH)_2D_3$, $25(OH)D_3$, and intact PTH by GFR levels. (Republished by permission from Macmillan Publishers Ltd.: Levin et al. [7])

Table 16.1 Change in the pattern of renal osteodystrophy throughout the recent decades from high to low bone turnover forms

	High bone turnover (%)	Low bone turnover (%)
Lorenzo et al. [8] (Spain)	71	25
Moriniere et al. [9] (France)	76	24
Sherrard et al. [10] (USA)	48	37
Hercz et al. [11] (USA)	50	50
Torres et al. [12] (Spain)	52	45
Ferreira et al. [13] (Portugal)	32	63
Asci et al. [14] (Turkey)	23	73

gest that an early inhibition of the Wnt/ßcatenin pathway may play a role in the pathogenesis of low bone turnover [15, 16]. Despite high and low bone turnover being quite different and also opposite extremes of the CKD bone abnormalities, they have been associated with similar clinical outcomes, such as a higher prevalence of vascular calcification and bone fragility fractures leading to a higher mortality risk.

16.2 Diagnosis of CKD–MBD

16.2.1 Biochemical Abnormalities

The changes in the biochemical parameters of CKD–MBD currently begin in CKD stage 3b, but the rate of change and the severity of abnormalities vary greatly among patients. Therefore, assessment should begin in stages 2-3a, and the frequency of assessments, the type and duration of the identified abnormalities, the degree and rate of change of GFR, and the concomitant therapy need to be taken into account to adapt the frequency of the assessments and the non-pharmacological and pharmacological interventions.

The diagnosis of CKD–MBD includes the use of laboratory testing of calcium, phosphorus, PTH, calcidiol, alkaline phosphatase (ALP) (total or bone specific), and the acid-base status together with other serum and urinary parameters used in the follow-up of patients with CKD. Although much progress has been made in the mechanisms involved in the role of FGF23/Klotho, its usefulness in routine clinical practice is still limited. The recommended frequency of assessment of these biochemical markers is detailed in Table 16.2 [1]. One important limitation of the biochemical markers used to diagnose, treat, and monitor CKD–MBD is the inter-assay variability and other variations as well (postprandial, diurnal, seasonal). The interpretation of values calls for the careful analysis of the type and precision of the assay used in order to avoid overemphasizing the role of minimal or inconsistent laboratory changes in the clinical decision-making process. The importance of one single abnormal value of any one bone and mineral serum biochemical markers should not be determinant. By

Table 16.2 What the guidelines say you should do? Serum calcium, phosphorus, and PTH measurement frequencies according to CKD stages

	Progressive CKD stage 3	CKD stage 4	CKD stages 5 and SD
Calcium and phosphorus	6–12 months	3–6 months	1–3 months
PTH and alkaline phosphatases	Baseline	6–12 months	3–6 months
Calcidiol	Baseline	Baseline	Baseline

Source: Republished by permission from Macmillan Publishers Ltd.: Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group [1], Copyright © 2009

Table 16.3 What the guidelines say you should do? Recommended values from KDIGO 2017 [20] for the main serum bone and mineral markers according to the degree of CKD

	CKD stages 3–5	CKD stage 5
Serum phosphorus	Lower elevated serum P levels towards the normal range	Lower elevated serum P levels towards the normal range
Serum calcium	Avoid hypercalcemia	Avoid hypercalcemia
Serum PTH	Maintain serum PTH within the normal or slightly elevated range in CKD stages 4–5	Maintain serum PTH within the range of 2 to 9 times more than normal range
Serum calcidiol	Maintain serum calcidiol within the safe and biologically optimal range (20–40 pg/mL)	Maintain serum calcidiol within the safe and biologically optimal range (20–40 pg/mL)

CKD chronic kidney disease, *P* phosphorus, *PTH* parathyroid hormone

contrast, the diagnosis and the management of CKD–MBD should be based mainly on the trend of changes; this aspect is even more relevant in the interpretation of serum PTH and ALP values.

In the last three decades, there has been a debate to better define the normal or acceptable upper and lower limits of these biochemical markers and thus guide managerial and therapeutical decisions. The KDOQI (Box 16.1), the European, and more recently the KDIGO and national guidelines have established different cutoff levels [1, 17–19]. Table 16.3, which considers mainly the 2017 KDIGO recommendations, summarizes what we should consider as adequate or acceptable values of the main serum bone and mineral markers according to the degree of CKD [20]. Most of the recommendations are backed by a reasonable scientific rationale, but, unfortunately, the degree of evidence based on randomized clinical trials is very low. At present, most of the best available evidence comes from population-based or cohort-based prevalence studies.

16.2.2 Bone Abnormalities

Bone tissue has excellent biomechanical properties: it possesses a great mechanical tension to tensile stress, which is lower than that of iron, but it is at least three times lighter and ten times more flexible than iron. This outstanding property of bone explains why during long periods of life, only a reduced number of bone fractures occur despite the remarkable number of falls suffered by most people. Bone has such clinically relevant biomechanical properties thanks to the activity of the bone remodeling units, which during the young adult life allow for the renewal of a mean of 5–10% of the skeleton per year. However, the capacity to renew bone tissue progressively decreases after age 50. Apart from the changes due to aging and gender differences, two bone disorders, osteoporosis and renal osteodystrophy, greatly influence bone turnover, since they exert an important impact on bone mass and bone quality.

The rate of bone turnover impacts both cancellous (trabecular) and compact (cortical) bone, and it depends on the activity of the bone remodeling units which are regulated by several factors; among them, PTH plays a key role. Cortical bone is the most abundant type (85% of the skeleton), but the most metabolically active one is trabecular bone. Trabecular bone decreases in CKD patients, but due to the quantity of cortical bone and also

the sustained major effect of PTH on the latter, in the current long-term evolution of the CKD–MBD, there is a predominant loss of cortical bone, which after several years of CKD leads to a generalized thin cortex with trabecular aspects due to insidious bone cortical erosions.

High serum PTH levels are associated with hyperdynamic bone. PTH stimulates bone cell proliferation and activity but also bone turnover. In secondary hyperparathyroidism, the cycles of the bone remodeling units are more rapid and active, but also more bone remodeling units are activated; as a result of these two mechanisms, an abnormal, immature, non-lamellar bone matrix is formed. At the end, a woven and less resistant bone is produced, which yields an increased fracture risk. Very high serum PTH levels (>450 pg/mL) have a good predictive value for high bone turnover, but moderately high serum PTH values (300–450 pg/mL) do not exhibit a good correlation with bone turnover; in fact, normal or low bone turnover can be found within these ranges of serum PTH values.

Low PTH levels are associated with adynamic bone, low bone cellular activity, and bone turnover [21]. Consequently, the inadequate renewal of bone increases its fragility. In practice, adynamic bone is currently suspected when serum PTH levels are below the normal values. PTH levels lower than 150 pg/mL have a good predictive value for low bone turnover and adynamic bone, but PTH between 150 and 450 pg/mL, currently considered normal or adequate serum PTH values, can be associated with adynamic bone [22]. Then, despite the measurement of serum PTH levels in CKD patients being the current noninvasive method to assess bone turnover, its specificity within the previous mentioned ranges is limited. Overall, the clinical consequences of low bone turnover observed in adynamic bone are similar to those observed in osteoporosis, with a higher prevalence of bone fractures and more frequent and severe vascular calcification compared with patients in whom bone turnover remains close to normal [21].

For the precise diagnosis of high or low bone turnover (mainly for the latter), it is necessary to perform a bone biopsy. An increased number of osteoclasts and osteoblasts, a non-laminar osteoid, woven bone, high bone formation rate with high activation frequency, normal or high mineralization rate (double tetracycline labeling), and increased marrow fibrosis are typically found in high bone turnover states. By contrast, the reduction or absence of osteoblasts and osteoclasts, a decreased or null osteoid formation, and low or no bone mineralization rate (low or absent tetracycline labeling) with low activation frequency are found in adynamic bone [21]. Another histological diagnosis associated with low bone turnover is osteomalacia, which was the most common form of low bone turnover in the 1970s and 1980s and it was associated with aluminum overload. The proper control of the sources of aluminum exposure (aluminum in dialysis fluids and the reduction of the massive use of aluminum-containing phosphate binders) has drastically reduced the incidence of osteomalacia in CKD patients.

A decrease in BMD and changes in the bone microarchitecture occur early in CKD and worsen as the disease progresses. As a result, CKD patients present flaws in the quantity and quality of bone, resulting in a higher risk of bone fracture, mainly of non-vertebral bone fractures [1, 21, 23–25]. The measurement of bone mass as bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) is the best noninvasive marker to predict bone fractures in the general population, as well as in CKD patients as it has recently described [20, 26–31].

Bone strength is determined by the density and quality of the bone, but the BMD measured using DXA is not able to capture bone quality (cortical and trabecular microarchitecture). Changes in quality are better studied using high-resolution peripheral quantitative computed tomography (HR-pQCT).

16.2.3 Diagnosis and Type of Vascular Calcification

The predisposition of patients with CKD toward developing vascular calcification was already mentioned in the nineteenth century; but now it has great interest in nephrology because it is closely related to cardiovascular disease and

Table 16.4 Traditional and nontraditional uremia-related risk factors for vascular calcification in CKD patients

Traditional risk factors	Nontraditional risk factors (uremia related)
Hypertension	Time in dialysis
Diabetes mellitus	Hyperphosphoremia
Tobacco	High calcium–phosphorus product
Genetic	Hyperparathyroidism and hypoparathyroidism
Age	High dosage of vitamin D metabolites
Dyslipidemia	Low fetuin-A
History of premature coronary heart disease	Poor nutrition (low albumin)
Vitamin K inhibitors (warfarin)	Chronic inflammation (high IL-1, IL-6, TNF-α)
	Hyperhomocysteinemia
	Advanced glycated end products
	Oxidative stress

IL-1 Interleukin 1, *IL-6* Interleukin 6, *TNF-α* tumor necrosis factor-alpha

mortality. The presence of vascular calcifications was included in KDIGO guidelines for the classification of mineral and bone disorders of chronic kidney diseases (CKD).

Vascular calcification was initially thought to be a passive, degenerative process; however, the evidence now suggests that it is an active process, a dysregulation of the equilibrium between promoters and inhibitors of calcification. Several uremic factors, including abnormalities in the mineral metabolism, age, diabetes, dyslipidemia, hypertension, smoking, inflammatory process, oxidative stress, genetic factors, are implicated [32]. Table 16.4 summarizes the traditional and nontraditional uremia-related risk factors for vascular calcification in CKD patients.

Despite the debate still exists somewhat, it has been suggested that a lateral abdominal X-ray and an echocardiogram, both simple and inexpensive procedures, can be effectively used to detect vascular and valvular calcification, respectively.

Most studies examining calcification have been performed using CT-based techniques (electron beam tomography and multi-slice computed tomography, EBCT and MSCT, respectively), which are quite sensitive methods for the detection of and quantification of calcium in the vessels. However, these more precise techniques are not widely available. The localization and extension of vascular calcification can be scored in a reproducible manner using X-ray. Several available methods such as the Kauppila, Adragao, and others are able to quantify and score vascular calcification, featuring a good correlation with the CT-based gold standard techniques and also with outcomes such as mortality.

An association of higher mineralized bone volume evaluated in bone biopsies, with a lower vascular calcification score assessed by plain X-ray was showed [33]. In addition, valvular calcification detected by echocardiography is a good predictor of coronary artery calcium. The information provided by these studies should help not only to evaluate risk and prognosis but also to guide the therapeutic management of CKD patients [34–36].

There are three types of arteries which differ according to their size and structure: elastic or large-caliber arteries, muscular or medium-caliber arteries, and small-caliber arteries.

The elastic or large-caliber arteries are responsible of conducting the blood to the distribution arteries; they show a relatively thin wall in proportion to their diameter and a rather thick tunica media containing more elastic fibers than smooth muscle with a fairly thin adventitia. The aorta, the subclavia, and the common carotid arteries belong to this group. The muscular or medium-caliber arteries are capable of withstanding further vasodilatation and vasoconstriction to adjust the volume of blood to the perfusion requirements; they have a tunica media which contains a high proportion of smooth muscle. The axillary, brachial, radial, coronary, femoral, and tibial arteries are included in this group. Finally, the small-caliber arteries are responsible for regulating the local blood flow and perfusion pressure through luminal size variations caused by vasoconstriction and vasodilatation; they are less than 2-mm thick, and their tunica media contains only smooth muscle. This group includes, among others, the palmar arch and the digital arteries [34].

Vascular calcification can occur in the intima and the media layers. Intimal calcification begins and progresses throughout lifetime mainly under the influence of genetic and lifestyle circumstances. Intimal calcification is associated with atherosclerosis including endothelial dysfunction, intimal edema, lipid cell formation, and blood cell migration that may cause a plaque rupture, leading to the formation of a thrombus. It is currently associated with chronic arterial inflammation exacerbated by well-characterized risk factors, such as hypertension, diabetes, hypercholesterolemia, obesity, smoking, and a family history of heart disease.

Calcification of the media occurs in the elastic lamina of large-caliber and medium/small-sized arteries. It seems to be independent of atherosclerosis but can coexist with it. This type of calcification was known initially as *"Monckeberg sclerosis,"* and it has been radiographically described as railroads. It affects the arteries that are less likely to develop atherosclerosis, such as visceral abdominal, thyroid, lung, limb, and femoral arteries, but it is also common in the aorta.

16.2.4 Epidemiology and Pathophysiology of Vascular Calcification

CKD patients exhibit a very high prevalence of vascular calcifications exceeding the percentage observed in the general population of the same age, sex, and region (see Fig. 16.4), leading to cardiovascular disease, decreased life expectancy, and mortality, even in the early phases of CKD. Moreover, calcification of the cardiac valves involves a high risk of cardiovascular dysfunction. A study in patients in CKD stage 5D has shown that vascular calcifications are frequently localized in high-caliber arteries, such as the aorta (around 80%); medium-caliber arteries, including coronary arteries (around 60–70%); and small-caliber arteries (20–30%), reflecting the heterogeneity of the three categories of arteries previously described [34]. Time on hemodialysis has been positively associated with vascular calcification, particularly in medium-caliber arteries. Each year on dialysis increased the risk of developing vascular calcifications by

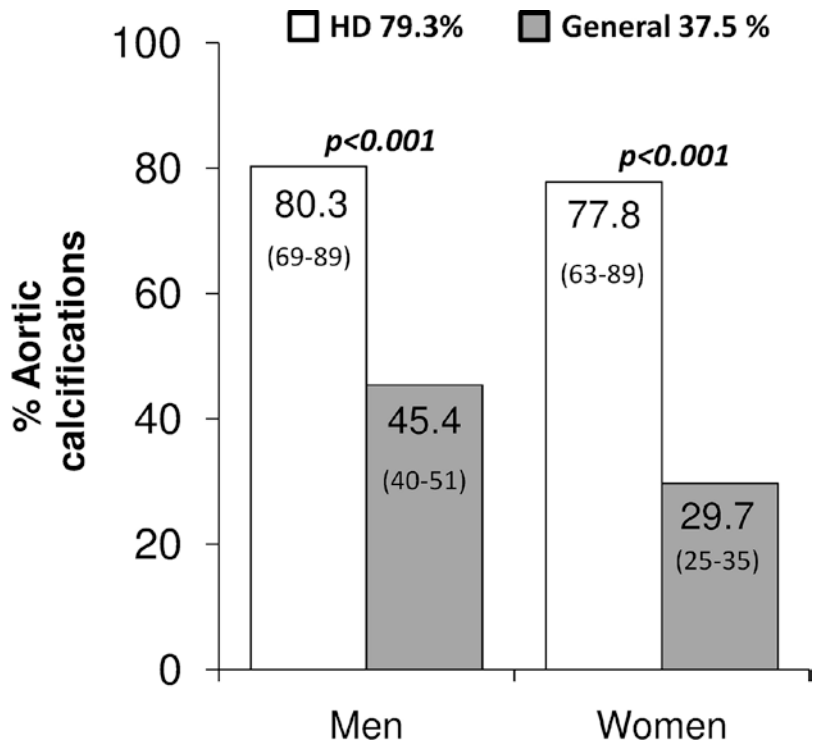

Fig. 16.4 Differences in the prevalence of aortic calcifications in hemodialysis (*HD*) patients and in a randomly selected general population of the same age and region (Asturias, Spain) (control). $p < 0.001$ HD patients ($N = 92$) compared to general population ($N = 245$). (Adapted with permission of the American Society of Nephrology, from Cannata-Andia et al. [59])

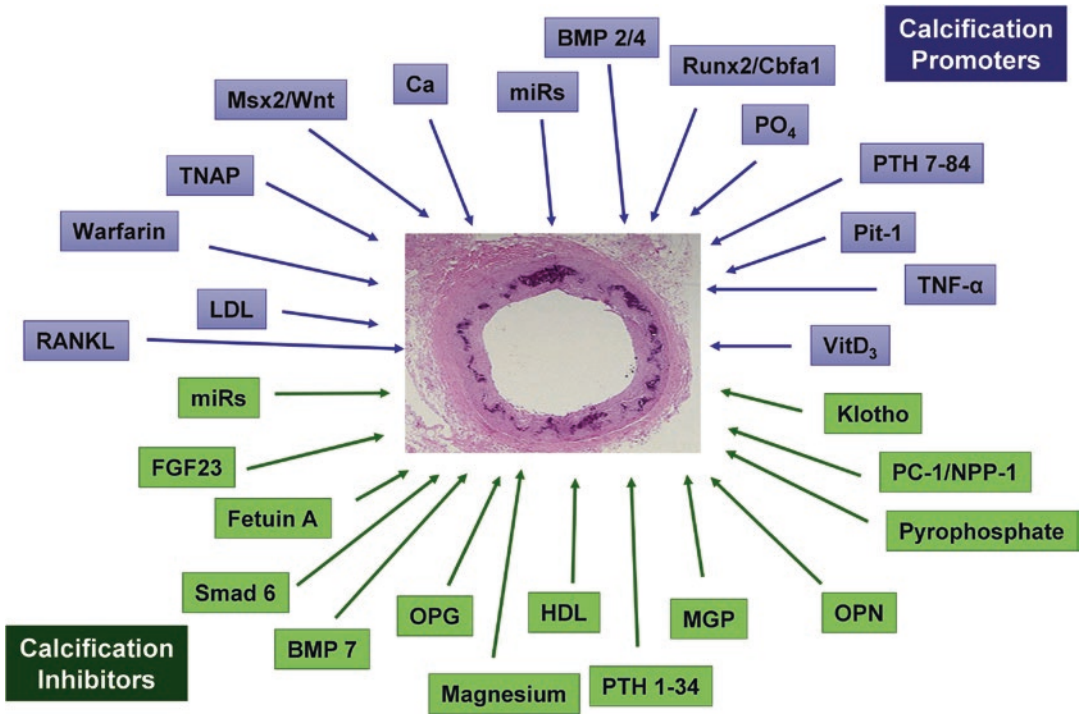

Fig. 16.5 Promoters and inhibitors of vascular calcification. RANKL, receptor activator of nuclear factor-kappa B Ligand; *LDL* low-density lipoprotein, *ALP* alkaline phosphatase, *Ca* calcium, *BMP* bone morphogenetic proteins, *P* phosphate, *TNF-α* tumor necrosis factor-alpha, *Vit D_3* calcitriol, *MGP* matrix GLA protein, *HDL* high-density lipoprotein, *OPG* osteoprotegerin, *OPN* osteopontin, *FGF23* fibroblast growth factor 23. (Modified with permission of Oxford University Press from Nephrol Dial Transplant. 2011; 26, 3429–3436) [60])

approximately 15% [37]. The mechanisms by which vascular and valvular calcification are produced are complex. It is not a mere precipitation of calcium and phosphate; it involves active and modifiable processes. This regulated process involves several changes, such as a decrease of vascular calcification inhibitors, an increase of vascular calcification promoters (see Fig. 16.5), and the formation of calcification vesicles; the result is the induction of a cellular phenotypic change of vascular smooth muscle cells which are turned into bone-like cells. The outcome is the formation of bone tissue inside the artery wall [38–40].

Among the promoters of vascular calcification, high serum phosphorus is considered the most important uremia-related, nontraditional risk factor associated to vascular calcification in CKD patients. Phosphorus is capable of acting as a secondary intracellular messenger, activating several molecular pathways related to bone formation. It reaches the intracellular space via a specific Na-dependent channel called Pit1 and exerts some important actions, such as the blockade of Pit1 which prevents vascular calcification. In vitro experiments have demonstrated that high intracellular phosphorus levels may directly increase Cbfa1, the bone-specific transcription factor, resulting in the activation of several osteogenic pathways and factors, including bone morphogenetic proteins (BMPs) which lead to the phenotypic changes of vascular smooth muscle cells into bone-like cells. Phosphorus also promotes the expression of osteocalcin and ALP in the vasculature.

Among the inhibitors of vascular calcification, pyrophosphates, fetuin-A, osteoprotegerin (OPG), and matrix Gla protein (MGP) are the most studied either in tissue or in serum. In the former, pyrophosphates are located in the vascu-

lar matrix to preserve the vascular smooth muscle cells phenotype inhibiting calcium phosphate crystal formation and the change of vascular smooth muscle cells into bone-like cells. In serum, the most abundant inhibitors of vascular calcification are fetuin-A, OPG, and MGP. Fetuin-A, a known inhibitor of osteogenesis, is capable of hampering vascular calcification. OPG holds back osteoclast differentiation, modulating bone resorption through its action as a decoy receptor of RANKL, but it may also act as inhibitor of vascular calcification [41].

Players such as FGF23 and its co-receptor Klotho have been also related with vascular calcification. FGF23 and Klotho knockout mice showed low bone mass and accelerated aging with widespread tissue calcification [42, 43]. The mechanisms by which FGF23/Klotho affects bone health and vascular calcifications may involve phosphorus excretion, vitamin D synthesis, and also PTH regulation. More recently also the microRNA have been implicated in the process of vascular calcification [38, 44] (see Fig. 16.5).

16.2.5 Vascular Calcification and Bone Health

Most of the previously discussed factors, either promoters or inhibitors of the vascular calcification process (see Fig. 16.5), have been related not only with vascular calcification but also with bone health, a fact which suggests there might be several links and common pathways between bone and vascular disorders. Vascular calcification, bone loss, and fragility fractures are very common disorders associated with aging, both in CKD patients and in the general population. Several studies have drawn attention to the fact that apart from aging, there might be other common factors linking vascular calcification and bone health. Even though these factors are not still fully understood, in CKD patients and in animal models, there is evidence that the progression of vascular calcification is directly associated with the reduction of bone mass and an increased risk of fragility fractures. The more severe the vascular calcification, the greater the loss of bone mass [35, 38].

16.2.6 Calciphylaxis

Calciphylaxis, also called calcific uremic arteriolopathy when it affects patients with CKD, is a clinical syndrome characterized by necrotic ulceration of the skin due to calcification of the media, with fibrosis of the arteriolar intima and subsequent cutaneous ischemia due to thrombosis. It usually occurs in patients receiving renal replacement therapy, either dialysis or kidney transplantation, and in patients with deficient glomerular filtration rate. Although abnormalities in mineral bone metabolism seem to be the main cause, other factors can contribute to its pathogenesis. Thus, calciphylaxis can also occur in patients with normal glomerular filtration rate, especially those who are elderly or with a vascular disorder [45].

Irrespectively on their renal function, calciphylaxis patients share certain histologic features (arteriolar calcification that leads to vessel narrowing, ischemia and microthrombosis), that suggest a common final pathway for the disease [46].

Calciphylaxis lesions exhibit two types of manifestations: - The disease may have an insidious onset, in which patients are asymptomatic, although they may experience pruritus and present with cutaneous lamellar erythema. - Alternatively, the disease may have a rapid evolution, with very painful ischemic purpura, in which the pain is disproportionate to the skin lesion and there is subsequent progression to ulceration and skin necrosis. Both types of lesions can occur simultaneously. The first type has a mortality rate of about 30%, and the second type has a mortality rate of approximately 80% [47].

The distribution of skin lesions is heterogeneous, and there are two typical patterns [48]. A distal pattern occurs in approximately 90% of cases. These patients present with lesions in the lower extremities, especially between the ankle and calf, although there are reports of lesions in the fingers, hands and even the genitals. A proxi-

mal pattern occurs in approximately 10% of cases. These patients present with lesions in areas with more adipose tissue such as the trunk, inner thighs, buttocks and occasionally the breasts. In addition, both patterns can coexist in the same patient. A small number of patients (<1%) have atypical lesions, in that they appear in unusual locations. In general, the proximal pattern is associated with a worse prognosis.

The pathogenesis of this form of severe vascular calcification is not yet fully understood, and apart from the uncontrolled mineral metabolism, dysregulation of some calcification inhibitors such as fetuin-A, MGP, and vitamin K have been implicated in its pathogenesis.

16.3 Management of CKD–MBD

16.3.1 Management of Biochemical Abnormalities

Even though for didactic reasons we shall describe individually the management of the main mineral and bone disorders, it is important to emphasize that in CKD–MBD, all the parameters need to be evaluated and put together in an integrated manner as they all are very tightly interrelated players [22, 49].

In CKD stages 3–5, there is a clear trend to have a positive phosphate balance; thus, therapeutic strategies aim to avoid the accumulation of phosphorus. The rationale behind the importance of controlling serum phosphorus is based on epidemiological and solid experimental studies which have shown that hyperphosphoremia is an important risk factor, not only for secondary hyperparathyroidism but also for cardiovascular disease and mortality [3]. In addition, despite the lack of evidence from randomized controlled trials that lowering serum phosphorus levels can improve clinical outcomes, most strategies aim to reduce serum phosphorus in CKD in patients with hyperphosphoremia. The approaches to achieve this goal include three levels of action: reduction of dietary phosphorus intake, use of phosphate-binding agents, and increasing phosphorus removal by adding more hours of dialysis.

The control of serum phosphorus through dietary phosphorus restriction merits specific and important comments. The factors affecting gastrointestinal phosphorus absorption include vitamin D levels and phosphorus food content and bioavailability. Currently, the sources of dietary phosphorus are protein-rich foods, which in a non-vegetarian Western diet may represent around 60% of the dietary phosphorus. Foods rich in phosphorus include dairy products, meat, fish, legumes, nuts, and chocolates. In addition, a great amount of phosphorus (e.g., inorganic phosphate) with a high bioavailability are found in food additives and preservatives. The phosphate content of plants is high in phosphorus, but its bioavailability and gastrointestinal absorption is low. The reduction of dietary phosphorus intake has a clear limitation: the need to ensure an adequate protein intake to avoid under nutrition. In fact, a restrictive prescription of dietary phosphorus has been associated with poorer indices of nutritional status, and a stepwise trend toward greater survival with more liberal phosphorus prescription has been postulated.

To obtain a higher removal of phosphorus, increasing the hours of dialysis, either by prescribing prolonged nocturnal dialysis or short daily dialysis, has become a useful approach to control hyperphosphoremia and to reduce serum PTH levels and the dose of phosphate binders prescription in CKD 5D patients. However, despite the progressive use of the two aforementioned useful strategies, still most patients in CKD stage 5D (between 80 and 90%) need the use of phosphate-binding agents to control hyperphosphatemia.

There is recent evidence that lowering serum phosphorus would lead to improved clinical outcomes [50]. As a safe strategy, the recent review of the KDIGO guidelines suggest that serum phosphorus should be maintained as close as possible to the normal range at all stages of CKD [1, 17]. The use of moderate phosphate-restricted diets in combination with phosphate-binding agents has become a reasonable approach to avoid phosphorus accumulation in patients in CKD stages 3–5D. This strategy allows a more liberal diet which leads to a better nutritional sta-

tus which can positively impact survival, as it has been shown in recent large-scale epidemiological studies.

Several observational studies and clinical trials have shown that all available phosphate-binding agents are effective in reducing serum phosphorus, but to date, the available data do not support a strong superiority of the novel non-calcium-containing phosphate-binding agents on outcomes such as cardiovascular and mortality endpoints. In addition, the great differences in dietary phosphorus intake and availability of phosphate binders around the world, the different economic and social scenarios, and the individual clinical circumstances of each CKD patient are enough reasons to avoid making general and conclusive recommendations for the generalized use of one specific phosphate-binding agent [51, 52].

However, based on the analyses of the individual circumstances of CKD patients, it is reasonable that the choice of the phosphate binder would take into account several aspects, such as the stage of CKD, the presence of other components of CKD–MBD, and any concomitant therapies. In CKD stages 3–5D patients with persistent or recurrent hypercalcemia, arterial calcification, adynamic bone disease, and persistent low serum PTH levels, the use and dose of calcium-based phosphate binders, calcitriol, or other less hypercalcemic and hyperphosphoremic VDRAs should be carefully and individually evaluated. It is recommended to avoid or restrict the long-term use of aluminum-containing phosphate binders to prevent aluminum overload.

Regarding calcium, apart from the limitations already discussed about the use of calcium-based phosphate agents and the need to individualize the therapy, the most appropriate approach for CKD stage 5D patients is to use a dialysate calcium concentration between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L). It is important to stress that the combined use of a high calcium concentration in the dialysate (>1.50 mmol/L) together with calcium-based phosphate binders should be avoided as they would increase the risk of calcium overload in CKD 5D patients.

In the case of CKD stages 3–5 patients not on dialysis, it is suggested that if PTH levels are above the upper normal limit of the assay, they should be first evaluated for hyperphosphoremia, hypocalcemia, and calcidiol deficiency and correct them if they are present. If serum PTH increases progressively and remains persistently above the upper limit despite having corrected the abovementioned factors, treatment with VDRAs could be initiated but the risk of hypercalcemia should be carefully evaluated. There are several VDRAs in the market (see Table 16.5); all of them are effective in PTH suppression even though they may have a differential effect in calcium and phosphorus absorption [53].

The approach is different for CKD stage 5D patients, for whom the KDIGO guidelines suggest to maintain serum PTH levels within the range of approximately two to nine times the upper normal limit for the assay [1]. Accordingly, changes in therapy should be based on the observed trends of changes, and therapy should be initiated or modified to avoid any progression to serum PTH levels outside this range in either direction always evaluating and correcting modifiable factors such as hyperphosphoremia and

Table 16.5 Comparisons between the different generations of VDRAs most used

	First generation	Second generation	Third generation
Generic name	Calcitriol (1α,25-dihydroxyvitamin D_3)	Alfacalcidol/doxercalciferol (1α-hydroxyvitamin D_3/D_2)	Paricalcitol (19-nor-1α,25-dihydroxyvitamin D_2)
Characteristic	Mimics endogenous VDR hormone	Molecular modifications at the side chain	Molecular modifications at the side chain and A-ring
Comments	Active upon administration	Requires activation in the liver	Active upon administration
Well-established clinical indications	SHPT in CKD Osteoporosis	SHPT in CKD Osteoporosis	SHPT in CKD

SHPT secondary hyperparathyroidism, *CKD* chronic kidney disease

hypocalcemia, phosphate intake and vitamin D status [20]. This recommendation makes it difficult to be implemented in clinical practice due to the wide range of PTH normality, then the KDOQI ranges (serum PTH levels between 150 and 300 pg/dL) and similar ranges from national guidelines are also currently used in practice [18, 19]. Despite the absence of definitive evidence, several large-scale observational studies released after the CKD–MBD KDIGO guidelines were published have confirmed that in CKD patients, the better outcomes are associated with serum PTH values around 150–300 pg/dL [54, 55].

To reduce PTH in CKD stage 5D patients, the suggested management is the use of calcimimetics and/or VDRAs. The selection of the initial drug for the treatment should be based on serum calcium and phosphorus levels and other aspects of CKD–MBD, such as the presence of vascular calcification. When using calcimimetics, if hypocalcemia is present, they should be reduced by adding VDRAs, if these changes are not enough calcimimetics should be stopped. Likewise, when using VDRAs, if either hyperphosphoremia or hypercalcemia is present, they should be reduced or stopped. The association of both drugs currently renders benefits. All changes in the therapy of secondary hyperparathyroidism should take into account other aspects, signs, symptoms, severity of the disorders, and concomitant medications.

If PTH levels fall and reach the range of low bone turnover, the use of VDRAs and/or calcimimetics should be reduced or stopped. In patients with severe hyperparathyroidism who did not respond with a clinically meaningful reduction of serum PTH levels after following the previous recommendations, parathyroidectomy should be considered. Even though there is no agreement regarding at which serum PTH level a parathyroidectomy should be indicated, the most current practice is to perform any type of parathyroidectomy when patients maintain PTH levels above 800 pg/mL despite an adequate medical treatment. Subtotal parathyroidectomy and total parathyroidectomy with parathyroid implants are the two techniques more currently used.

16.3.2 Osteoporosis

The CKD–MBD constellation also includes the study of bone fragility fractures, which may appear due to high and low bone turnover states but also due to the combination with osteoporosis, an age-dependent and highly prevalent bone disorder whose importance has greatly increased due to aging of the CKD population [20, 26–28].

In osteoporosis there is a reduction in bone mass with no specific defect in bone formation. This occurs because the balance between bone formation and bone resorption is lost, favoring the latter. As a result, less new bone is formed to replace bone loss. The DXA definition of osteoporosis and the bone mass criteria followed for its diagnosis were adopted for the first time by the World Health Organization (WHO) in 1993. It stands as "a disease characterized by low bone mineral density and micro architectural deterioration leading to low bone strength and increased risk of fractures." Strictly speaking, the definition applied only to Caucasian postmenopausal women, and it was conceived to be used for diagnostic purposes, but not for treatment. However, its use progressively expanded to include men and also to help in the treatment decision process. The WHO definition of osteoporosis never included the CKD condition.

The *T*-score of the DXA measurement is used for the assessment of BMD and for the definition of osteoporosis. Each *T*-score difference in BMD represents 1 standard deviation (SD) from the peak bone mass. Values up to −1 SD BMD below the mean peak bone mass are considered normal; values between −1 SD and − 2.5 SD BMD are indicative of osteopenia, and values below −2.5 SD BMD are indicative of osteoporosis (see Fig. 16.6) [21]. BMD measurement plays an important diagnostic, preventive, and managerial role in the general population and also in CKD patients [20, 26–28, 30].

In addition to the aforementioned limitations in the interpretation of BMD, restrictions exist in the treatment of osteoporosis in CKD patients. Apart from the possibility of using calcium supplements and VDRAs (drugs which are also used in the management of osteoporosis), due to the

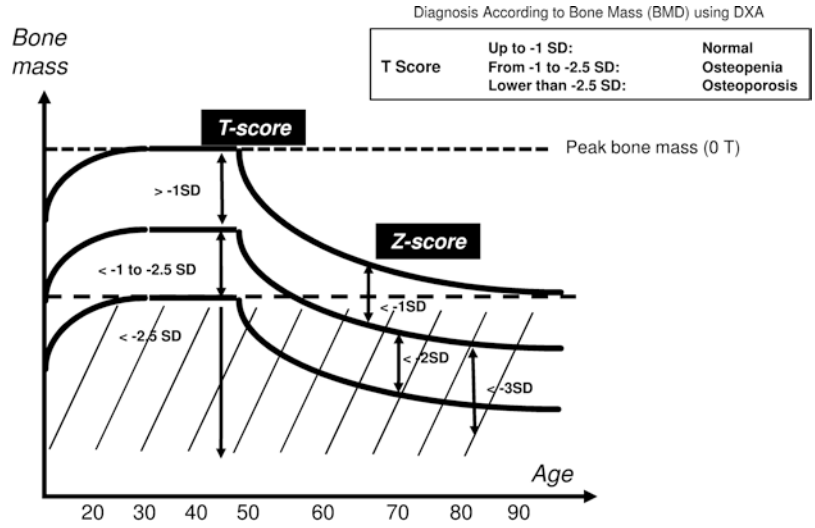

Fig. 16.6 The WHO osteoporosis diagnostic criteria: *T*-score values for normality, osteopenia, and osteoporosis using DXA. (Adapted with permission of Società Italiana di Nefrologia, from Cannata-Andia et al. [21])

complexity of CKD–MBD, the use of the currently available antiosteoporotic compounds also presents additional limitations. There are two main reasons for such limitations: the first is the fact that all large-scale, long-term clinical trials carried out to register active antiosteoporotic drugs have specifically excluded patients with low kidney function, particularly CKD stages 4–5; the second reason is the fact that kidneys play a key role in the clearance of some of these compounds (e.g., bisphosphonates and strontium ranelate). Thus, the available evidence comes from the post hoc analysis of the studies, selecting patients with reduced kidney function in whom the drug was administered. In some of these studies, there were enough CKD stage 3 patients, but that was not the case with CKD stages 4–5 patients.

Despite the mentioned limitations [1, 17, 20, 27–30], CKD stages 1–3 patients should be managed as the general population; CKD stage 3 patients should be individually evaluated taking into account other important biochemical parameters such as PTH values. In CKD stage 3B, since GFR is low (45–30 mL/min), it is necessary to carefully monitor the progression of kidney failure and the serum PTH levels. The prescription of bisphosphonates is still not recommended in patients with GFR <30 mL/min without a strong clinical indication. In general, patients with biochemical anomalies, such as PTH or other serum bone parameter abnormalities, should be managed differently, and the treatment choices should take into account the magnitude and reversibility of those biochemical abnormalities as well as the progression of CKD. Before using any osteoporotic drug, all the abnormalities of Ca, P and PTH should be connected as much as possible. A bone biopsy can be always considered for this type of patients, and a greater caution needs to be taken when considering the use of antiresorptive agents when PTH levels are normal/low or low. In the latter, bisphosphonates is not indicated because the risk of further reduction of bone turnover and bone fragility due its long-term deposition in bone. Denosumab has been the drug more used because it is not cleared by the kidney and its long-term action greatly decreases after 6 months.

16.3.3 Vascular Calcification

Another important aspect of CKD–MBD is to follow strategies to minimize or avoid the progression of vascular calcification. Any strategy designed to reduce the impact of vascular calcification needs to take into account primary prevention measures to control cardiovascular risk factors. It is crucial to promote a healthy lifestyle, a balanced diet, regular physical exercise, smoking cessation, and a low alcohol intake. Once vascular calcifications appear, secondary prevention must aim to reduce their complications,

intensifying the measures and treatments previously described. Most strategies to reduce vascular calcifications focus on several risk factors such as hyperphosphoremia, hypercalcemia, secondary hyperparathyroidism, smoking, dyslipidemia, hypertension, diabetes, inflammation, and to stop the use of warfarin [56].

16.3.4 Calciphylaxis

Despite calciphylaxis is an infrequent form of vascular calcification, its management remains a challenge. The treatment of calciphylaxis is based on three complementary levels [57]: proper medical-surgical management of ulcers (analgesia, surgical debridement, antibiotic therapy, hyperbaric oxygen therapy); modification of all possible factors that could precipitate ectopic calcification (adjust or normalize diet, stop use of calcium-based phosphate binders, stop use of vitamin D active metabolites, normalize PTH blood levels, and overall stop use of vitamin K antagonists); use of one or more alternative therapies to inhibit the cutaneous calcification process (sodium thiosulfate, bisphosphonates).

Before You Finish: Practice Pearls for the Clinician

- The changes in biochemical parameters of CKD–MBD currently begin in CKD stage 3, with important variations among patients. Assessment should start at this stage.
- The optimal or normal values for each of the serum biochemical markers of CKD–MBD have been obtained from population- or cohort-based studies. A single value can alert, but the diagnosis and management should be guided considering also the trend of changes.
- In CKD, both high and low bone turnover and osteoporosis are associated with vascular calcification, bone fractures, and increased mortality.
- Calcium overload should be avoided at all stages of CKD. Excess of calcium and phosphorus are two potent but avoidable promoters of vascular calcification with negative impact in outcomes.
- In CKD stages 3–5D, there is a clear trend to a positive phosphate balance that needs to be avoided using the available strategies but taking into account that aggressive dietary restriction of phosphorus may lead to undernutrition with possible negative effect on survival.

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17 Protein–Energy Wasting and Nutritional Interventions in Chronic Kidney Disease

Lale Ertuglu and T. Alp Ikizler

Before You Start: Facts You Need to Know

- Protein–energy wasting is highly prevalent in CKD patients and is a significant predictor of their survival.
- Screening and assessment of nutritional status in CKD and ESRD patients are complicated due to a number of coexisting factors.
- The etiology of PEW in CKD and ESRD patients is multifactorial requiring a comprehensive approach.
- A number of preventive measures can be taken to avoid development of PEW.
- In patients where preventive measures cannot maintain adequate nutritional status, nutritional supplementation is shown to be effective in replenishing protein and energy stores.

17.1 Protein and Energy Wasting in CKD: Definition, Epidemiology, and Clinical Relevance

Among a number of complications of CKD, development of a state of metabolic and nutritional derangements, more aptly called protein–energy wasting (PEW) of chronic kidney disease, constitutes a major role [1].In general terms, PEW is the state of decreased body stores of protein and energy fuels (i.e., body protein and fat masses) [2]. In CKD, protein or energy depletion can result from an inadequate diet (e.g., anorexia), nonspecific and specific inflammatory processes, factors related to renal replacement therapies, and metabolic and hormonal derangements. Regardless of the etiologic factors, the common physiological phenotype in PEW of CKD is the altered balance between protein synthesis and breakdown toward loss of lean body mass. The absolute or relative decreased lean body mass in turn predisposes the CKD patients to undesirable consequences such as increased risk for infections, development and progression of cardiovascular disease, and progressive sarcopenia and frailty, all of which are directly associated with increased risk of hospitalizations and death.

Virtually every study evaluating the nutritional status of patients with advanced CKD reports some degree of inadequate nutritional status in this population, particularly regarding protein and energy depletion. Due to the many different diagnostic tools utilized in separate studies, the prevalence of PEW in this patient population varies widely among different reports, ranging from 20 to 60%. Once CKD patients are initiated on maintenance dialysis, the extent of PEW becomes more evident. Although there is

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evidence of improvement in nutritional parameters within 3–6 months following initiation of hemodialysis, PEW is still present in up to 54% or more of the maintenance dialysis patients, and the prevalence seems to increase as the time on dialysis extends [3].

Most of the epidemiological reports on nutrition in CKD patients have been mainly based on serum albumin concentrations. In the baseline phase of the Hemodialysis (HEMO) Study, 29% of the patients had albumin levels below 3.5 g/dL. Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggest a lower prevalence of hypoalbuminemia in countries other than the USA such that the lowest mean serum albumin level was observed in the United Kingdom for Europe, whereas the United States value was significantly lower than in all European countries (3.60 vs. 3.72 g/dL [36 vs. 37 g/L]). In a separate analysis, Japan had significantly higher albumin compared with the USA when adjusted for patient age, sex, and day of laboratory draw. In DOPPS II, 20.5% of the US patients had a serum albumin level less than 3.5 g/dL (35 g/L). Results from the DOPPS also showed a prevalence ranging from 7.6% (the USA) to 18% (France) for moderately malnourished and 2.3% (Italy) to 11% (the USA) for severely malnourished maintenance hemodialysis (MHD) patients as diagnosed by subjective global assessment (SGA).

The clinical relevance of the aforementioned data is that practically every nutritional marker used in CKD patients has been associated with hospitalization and death risk. These observations are reproducible irrespective of patient demographics and geographical area. Recent epidemiological data also indicate a survival benefit with improvement in these markers over time. This alleged benefit has been observed for serum albumin and body mass index.

17.2 Screening and Assessment of Nutritional Status in CKD

A clinically meaningful assessment of nutritional status should be able to identify and risk-stratify patients with PEW, distinguishing the causes and consequences of both PEW and the underlying disease states, and determine whether there is potential benefit from nutritional interventions [*3*]. Therefore, no single nutritional marker is likely to adequately phenotype this comorbid state, and a comprehensive assessment of protein and energy nutritional status requires several different measurements. It is also important to apply the nutritional markers according to their appropriate use, i.e., for screening or assessment. Screening parameters are generally collected routinely in clinical practice, taking minimal to no training. They can be completed by any health professional and can provide a trigger to conduct more extensive assessment or to determine best course of treatment. Assessment, on the other hand, generally requires extensive training and provides comprehensive information to inform nutritional diagnosis, intervention, and monitoring plan. Table 17.1 provides a list of screening and assessment tools that can be used to both identify patients at risk and diagnose the ones with PEW.

According to the most recent KDOQI guidelines, patients with CKD 3-5D should be screened for nutritional abnormalities and potential PEW at least biannually. Patients should be referred to a registered dietitian nutritionist (RDN) for comprehensive assessment annually, either when nutritional screening is positive for possible malnutrition or PEW or when initiating on maintenance dialysis.

A diagnosis of PEW necessitates confirmation by several tools (Box 17.1) and can be as strict as requirement of multiple findings as sug-

Table 17.1 Suggested strategies to screen and assess nutritional status in advanced CKD

Screening	Threshold for detailed assessment
Body weight	Continuous decline or <85% IBW
Dietary nutrient intake	DEI <25 kcal/kg IBW/day
	DPI <0.8 g/kg IBW/day
Serum albumin	<4.0 g/dL
Serum creatinine	Relatively low value
MST	>2

Assessment	Threshold for intervention
Serum prealbumin	<28 mg/dL
hsCRP	>10 mg/dL
Anthropometrics	Deviation from norms
SGA	B or C (moderately or severely malnourished)
MIS	>5

Diagnosis (2 of the 4)[a]	Threshold for intervention
Serum chemistry	
Albumin	<3.8 g/dL
Prealbumin	<28 mg/dL[b]
Cholesterol	<100 mg/dL
Body mass	
BMI	<23 kg/m^2
Weight loss	>5% over 3 months or 10% over 6 months
Total body fat %	<10%
Muscle mass	
Muscle wasting	>5% over 3 months or 10% over 6 months
Reduced MAMC	>10% reduction compared to norms
Creatinine appearance	<1 g/kg/IBW
Dietary intake	
Low DPI	DPI <0.8 g/kg IBW/day
Low DEI	DEI <25 kcal/kg IBW/day

Source: Adapted from Ikizler [4], with permission of the American Society of Nephrology
IBW ideal body weight, *DEI* dietary energy intake, *DPI* dietary protein intake, *MST* malnutrition screening Tool, *hsCRP* high-sensitivity C-reactive protein, *SGA* subjective global assessment, *MIS* malnutrition inflammation score
[a]ISRNM criteria [2]
[b]Influenced by kidney function

gested by International Society of Renal Nutrition and Metabolism (ISRNM) criteria (Table 17.1) or could be less specific as suggested by others [5]. It is important that a number of considerations must be made on the unique situation of CKD patients for appropriate screening and assessment of their nutritional status (Box 17.2).

Box 17.1 What the Guidelines Say You Should Do: Nutritional Assessment in CKD

There is no strong evidence over the use of one tool over another to screen for and diagnose PEW.

Body composition: When available, Dual-Energy X-Ray Absorptiometry (DEXA) can be used in patients with CKD 1-5D. Although this method can be influenced by volume status in dialysis patients, it is still considered gold standard for assessment of body composition. For patients on MHD, the use of bioimpedance or preferably multi-frequency bioelectrical impedance (MF-BIA) is recommended as an alternative.

Biochemical markers: Serum albumin, serum prealbumin, and normalized protein catabolic rate should not be interpreted in isolation due to their dependance on non-nutritional factors.

Handgrip Strength: When baseline data are available, repetitive handgrip strength date can be used as an indicator of protein energy status and functional status overtime.

Assessment of Energy Requirements: In the absence of indirect calorimetry, which remains the gold standard for estimation of resting energy expenditure, disease-specific predictive energy equations can be used.

Composite Nutritional Indices: For patients with CKD 5D, the use of Subjective Global Assessment (SGA) is recommended.

Assessment of Dietary Intake: For patients with CKD 3-5D, the use of a 3-day food record is recommended.

Source: KDOQI 2020.

Box 17.2 Factors That Affect Interpretation of Nutritional Markers in CKD

- Fluid status: Altered body composition and biochemical markers.
- Systemic inflammation: Increased (hsCRP) or decreased (albumin, prealbumin, cholesterol) acute phase protein synthesis.
- Proteinuria: A major determinant of serum albumin levels.
- Residual renal function: Some biochemical markers such as prealbumin are cleared by the kidneys.

17.3 Etiology of Protein–Energy Wasting

The etiology of PEW in CKD is complex and multifactorial. As stated in a recent consensus statement by the ISRNM [*1*], although insufficient food intake (true undernutrition) due to poor appetite and dietary restrictions contributes, other highly prevalent factors are required for PEW to develop. These include alterations related to advanced CKD such as increased energy expenditure, persistent inflammation, metabolic acidosis, and multiple endocrine disorders that render a state of hypermetabolism leading to excess catabolism. In addition, comorbid conditions associated with CKD, poor physical activity, frailty, and the dialysis procedure per se further contribute to PEW. Figure 17.1 provides a conceptual model for etiology of PEW in CKD and its clinical consequences [6].

17.4 Prevention of PEW: A Cause-Specific Approach

Since a large number of factors affect nutritional and metabolic status in CKD patients leading to multiple adverse consequences [1], prevention and treatment of PEW of CKD should involve an integrated approach to reduce protein and energy depletion, in addition to therapies that will avoid further losses and replenish already wasted stores (Fig. 17.1).

17.4.1 Dietary Nutrient Intake in CKD Patients

A frequent and important cause of PEW in advanced CKD patients is inadequate dietary

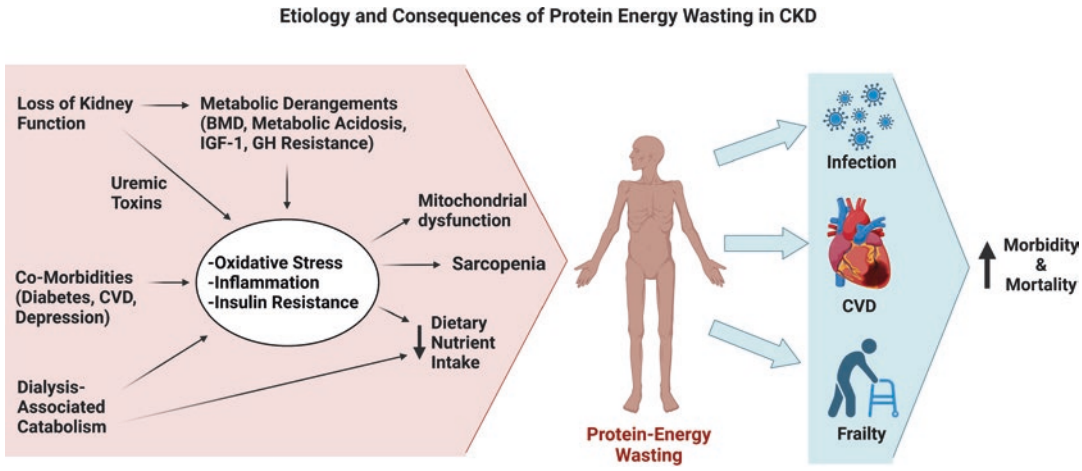

Fig. 17.1 Etiology and Consequences of Protein Energy Wasting in CKD. The conceptual model for etiology and consequences of protein–energy wasting (PEW) in chronic kidney disease. *BMD* bone mineral disorders, *IR* insulin resistance, *HPT* hyperparathyroidism, *GH* growth hormone, *CVD* cardiovascular disease

protein and energy intake relative to their needs, primarily due to uremic anorexia [1]. Anorexia has long been considered to be the hallmark of advanced CKD, and patients spontaneously restrict their dietary protein intake often to levels less than 0.6 g/kg/day when estimated glomerular filtration rate (eGFR) falls below 15 mL/min. Anorexia in CKD may develop as a result of retention of uremic toxins, intercurrent illness, and inflammation. Inadequate nutrient intake may also be secondary to comorbid illness that affects gastrointestinal function, depression, and poor socioeconomic situation. In clinically stable stage 3–5 CKD patients not on dialysis, dietary protein and energy intakes of 0.55–0.60 g/kg of body weight per day and 25–35 kcal/kg of body weight per day, respectively, are sufficient to preserve their protein stores throughout the progression of kidney disease. However, these levels should be increased when hypermetabolic conditions such as acute illness and hospitalizations occur. Another important implication of anorexia in advanced CKD is its use as a relative indication for initiation of maintenance dialysis, especially when associated with other symptoms or findings such as significant weight loss. Kidney replacement therapy often leads to an improvement in anorexia.

Since CKD is accompanied with a variety of comorbidities and metabolic derangements, and the nutritional needs of patients change through the course of the disease, a specialized nutritional health care in the form of Medical Nutrition Therapy (MNT) is recommended. MNT requires the collaborative work of a registered dietitian nutritionist, physicians, and other health care providers including nurse practitioners and physician assistants. The goal of MNT is tailoring of meal plans based on nutritional assessment, comorbidities, and individual needs. Dietitians experienced in CKD management can effectively address barriers to nutritional intake, offer nutritional education, and induce beneficial behavioral change while providing holistic dietary approach. Although the available RCTs investigating the effects of MNT on nutritional status do not provide consistent data to establish the value of MNT in the prevention and management of PEW [7], they are limited by differences in the implementation of MNT and the measures of outcome.

17.4.2 Dietary Protein Restriction in CKD and the Use of Ketoacids

Dietary protein restriction, with or without supplementation of keto-analogs of certain amino acids, has long considered to be an attractive intervention to slow progression of kidney disease [8]. As suggested by a number of meta-analyses, this effect is real, albeit relatively small in the context of progressive kidney disease [9]. Several smaller studies indicate that the favorable effects of dietary protein restriction extend beyond slowing the progression. These include amelioration of metabolic acidosis and insulin resistance, antioxidant effects, and decreasing dietary phosphorus load. Current guidelines recommend a daily protein intake of 0.55–0.6 g/kg in stages 3–5 CKD without diabetes to delay the initiation of dialysis and reduce the risk of death. For patients with diabetes, a higher level of protein intake is suggested to achieve glycemic control (0.6–0.8 g/kg per day). In patients on MHD or PD, a daily protein intake of 1.0–1.2 g/kg is recommended to maintain nutritional status. The recommended level of protein intake in very-low-protein diets [sVLPD] is 0.28–0.43 g/kg with additional keto acid/amino acid analogs to meet the daily protein requirement of 0.55–0.60 g/kg. These recommendations are for metabolically stable patients, and special attention should be given during periods of acute catabolism that may raise nutritional needs. Nevertheless, the optimal range of dietary protein restriction to exert the most beneficial metabolic outcomes is not established, and the applicability of dietary protein restriction is limited by compliance.

In addition to protein restriction alone, a number of studies have also examined the effects of keto or amino acid-supplemented low-protein diets [sLPD] or very-low-protein diets [sVLPD] benefit from keto/amino acid-supplemented protein-restricted diets (Box 17.3) [10].

Box 17.3 Considerations for Maximum Efficacy and Safety of Administration of Keto/Amino Acid-Supplemented Protein-Restricted Diets

- Patient selection: Motivation and ability to follow a protein-restricted diet.
- Gradual implementation of intervention (i.e., progressive 0.2 g/kg/day steps).
- Support and educational tools along with regular dietary counseling (every 2–3 months initially).
- Involvement of dieticians.

An important consideration regarding dietary protein restriction in CKD is the potential to adversely affect the nutritional status of patients. These concerns have been mostly defied by a number of studies showing that well-designed diets, planned by skilled dietitians and followed by motivated and compliant patients, are effective and do not have harmful effects on the nutritional condition. Long-term follow-up of several relatively large cohorts of CKD patients who received 0.47 g/kg/day protein with the keto acid supplementation showed no detrimental effect on the outcome of the patients after initiating any kind of renal replacement therapy. It was also demonstrated in a 5-year follow-up study that CKD patients treated with LPDs were found to rapidly increase their dietary protein intake with a gain in lean body mass index after beginning the renal replacement therapy with a low mortality and morbidity rate. Accordingly, one can conclude that prescribing low-protein diets with or without keto or amino acid supplementation with adequate caloric intake and close supervision does not seem to lead to protein–energy wasting. Protein intake should be increased during infection, immunosuppressive treatment or hospitalization with acute illness.

Several studies comparing the metabolic effects of different protein types (animal vs. plant) in CKD patients have suggested that plant-based diets may confer benefits on lipid profile and inflammatory status [11]. While the evidence is inadequate to advocate for the consumption of a particular protein type over another for prevention of PEW, current guidelines recommend prescription of Mediterranean diet to non-dialysis patients with CKD 1–5 for potential benefits on lipid profiles. Adherence to health dietary patterns, including the Mediterranean diet that consists of high intake of vegetables, fruits, legumes, whole grains and olive oil, may also slow down the decline in kidney function and improve survival [12].

17.4.3 Renal Replacement Therapy as a Catabolic Stimulus

A minimum dose of dialysis is required to avoid uremic anorexia and maintain optimal dietary nutrient intake. Based on the data from large randomized clinical trials, current guidelines for adequate dialysis are considered sufficient to preserve the nutritional status although HEMO study showed that MHD patients lose weight over time regardless of "adequate" dialysis dose. Increasing dialysis dose beyond current targets has not been shown to improve the nutritional status any further. There is suggestion that the use of high-flux dialysis membranes provides a nominally significant survival benefit in patients with baseline serum albumin levels <40 g/dL and with diabetes mellitus. The results of the Frequent Hemodialysis Network trial indicate no appreciable difference in nutritional markers between subjects randomized to 6×/week in-center HD versus standard 3×/week in-center HD.

In ESKD patients on maintenance dialysis, there are additional protein catabolic processes such as the unavoidable loss of amino acids (6–8 g per HD session and 1–2 g per day during PD) and albumin into the dialysate and the inflammatory stimulus associated with the dialysis procedure or other components of ESKD (i.e., hemodialysis catheters) (Table 17.2). This

Table 17.2 Considerations for Dietary Protein Requirements

Decreased requirements	Increased requirements
Over ideal body weight	Maintenance dialysis
Age > 60 years	Undernutrition
Limited activity	<60 years
Bed bound (no concurrent illness)	Routine or increased physical activity
	Acute illness, hypermetabolic state

Source: Data from NKF/KDOQI [15]

Table 17.3 What the guidelines say you should do: protein intake recommendations in CKD

	Non-dialysis CKD	Hemodialysis	Peritoneal dialysis
National Kidney Foundation K/DOQI [*8*]	0.55–0.60 g/kgBW[a]/day Or 0.28–0.43 g/kg with additional keto acid/amino acid analogs to meet 0.55–0.60 g/kgBW[a]/day For diabetic patients = 0.6–0.8 g/kgBW[a]/day	1.0–1.2 g/kgBW/day	1.0–1.2 g/kgBW/day
British Dietetic Association [*9*]	N/A	>1.1 g/kgBW/day	>1/2 g/kgBW/day
ESPEN (Nutritional support) [*10*]	0.6–0.8 g/kgBW/day	1.2–1/4 g/kgBW/day	1.2–1.5 g/kgBW/day
	Illness 1.0 g/kg	Illness >1/5 g/ideal body weight kg/day	

>50% of high biological value (i.e., complete protein sources, containing the full spectrum of essential amino acids)
[a]BW = ideal body weight in nonobese patients. Use adjusted body weight in obese patients = ideal body weight + 0.25 × (actual body weight − ideal body weight)

requires that dietary protein intake targets need to be adjusted once the patient is initiated on maintenance dialysis, which is provided in Table 17.3 [13]. Along with the protein intake, energy intake should be adjusted based on the physical activity levels as shown in Box 17.4. An important consideration regarding strategies to improve dietary protein intake in ESKD patients is the potential increase in the intake of several potentially harmful elements, especially phosphorus [14]. Dietary recommendations to improve protein intake should take into account the phosphorus content of the specific protein sources (i.e., vegetarian diet leading to lower serum phosphorus levels) and other phosphorus-containing nutrients especially the ones with additives/preservatives in processed food.

Box 17.4 What the Guidelines Say You Should Do: Energy Intake Recommendations in CKD

Sufficient energy (kcal) intake is critical to promote nitrogen balance.

Early and Predialysis CKD.

Stages 1-5D: 25–35 kcal/kg body weight per day based on age, sex, level of physical activity, body composition, weight status goals, CKD stage, and concurrent illness or presence of inflammation to maintain normal nutritional status.

17.4.4 Systemic Inflammation

Systemic inflammation is a major contributor to PEW of CKD [6]. The elevated systemic concentrations of pro-inflammatory cytokines are thought to play an integral role in the muscle catabolism of ESKD patients. Interleukin-6 (IL-6) causes increased muscle proteolysis, which can be ameliorated by the administration of IL-6 receptor antibody and interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNFα) can cause anorexia through their effects on the satiety center in the central nervous system. TNF-α and IL-6 can also induce muscle wasting through stimulation of mitophagy and mitochondrial dysfunction in the muscle, which can be reversed by TNF-α and IL-6 inhibitors [16]. Finally, inflammation aggravates insulin and growth hormone resistance, and therefore decreases the anabolic effects of both hormones on muscle.

There are a number of factors that can cause systemic inflammation in CKD and ESKD

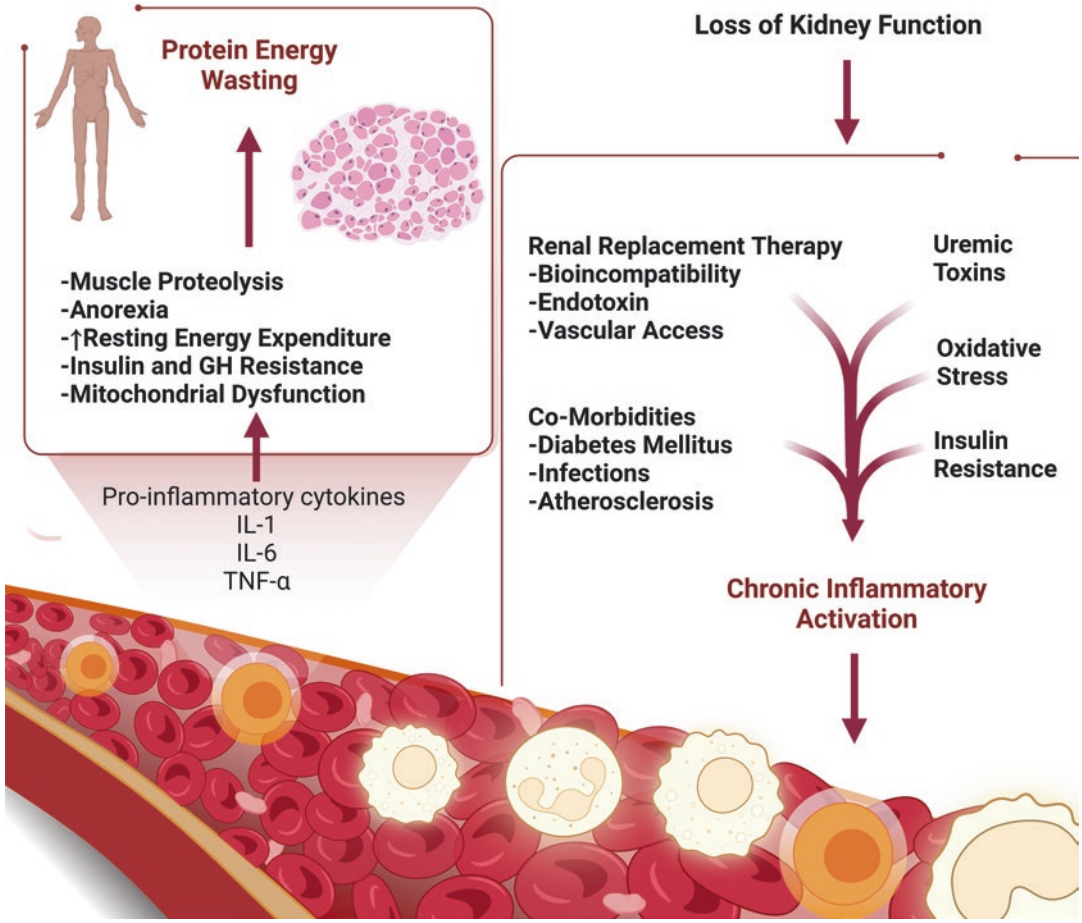

Fig. 17.2 The role of chronic inflammation in the development of protein–energy wasting

patients (Fig. 17.2). The most crucial step for treatment of systemic inflammation is elimination of etiologic factors such as the use of central hemodialysis catheters in MHD patients. As the dialysis procedure per se might stimulate the immune system, pro-inflammatory effects of dialysis membranes and fluids should also be taken into account in maintenance dialysis patients. Many uremic toxins are also known to be pro-inflammatory. Appropriate management of fluid status might improve systemic inflammation in ESKD patients since volume overload leads to immunoactivation and increased cytokine production via bacterial or endotoxin translocation. Lifestyle interventions including healthy dietary patterns and exercise might also alleviate the chronic inflammatory burden in CKD (reviewed in detail [11]).

A number of modifiable and non-modifiable factors lead to the chronic inflammatory state of chronic kidney disease, leading to protein–energy wasting.

17.4.5 Comorbidities in CKD

CKD patients often have other comorbid diseases that can adversely affect their nutritional status such as diabetes mellitus, cardiovascular disease, and depression. Diabetic CKD patients are likely to suffer protein depletion because of associated gastrointestinal disturbances (e.g., diabetic gastroparesis, nausea and vomiting, bacterial overgrowth in the gut and pancreatic insufficiency, impaired protein absorption in the gut) and increased protein breakdown secondary to insulin resistance. Polypharmacy worsens these gastrointestinal complications. Uncontrolled hyperparathyroidism and cardiac cachexia are associated with systemic inflammation and increased energy expenditure. Depressive symptoms, which are common in CKD and ESKD patients, are linked to fatigue, lack of appetite, and weight loss. Early recognition and treatment are important components in the prevention of PEW.

17.4.6 Metabolic Acidosis

Metabolic acidosis is associated with increased muscle protein catabolism and promotes PEW in patients with advanced CKD. Metabolic acidosis stimulates the oxidation of essential amino acids and further raises protein requirements for patients on maintenance dialysis. Oral or intradialytic (specifically in PD patients) bicarbonate supplementation was associated with increased dietary protein and energy intake, improved midarm muscle circumference (MAMC), and improved serum albumin level, and progression of CKD was slowed in stage 3–4 CKD patients. A steady-state serum bicarbonate level should be greater than 24 mmol/L in CKD patients not yet on maintenance dialysis and PD patients. Based on epidemiological data, a target of predialysis serum bicarbonate level of 22–24 mmol/L is recommended in MHD patients.

17.5 Treatment of Protein–Energy Wasting

17.5.1 Oral and Enteral Nutritional Supplementation

In certain CKD and ESKD patients, the aforementioned standard preventive measures are unable to diminish loss of protein and energy stores [17]. In these circumstances, nutritional supplementation is a suitable next step with appropriate indications (Fig. 17.3; Box 17.5).

The efficacy of oral supplementation has been studied in multiple settings (reviewed in detail by Ikizler et al. [6]). The beneficial nutritional effects of these supplements ranged from improvements in serum biomarkers such as albumin, prealbumin, and transferrin to gains in different body compartments such as weight and lean body mass and improvements in quality of life and physical functioning. The effects were evident as early as within a month and were sustained in most if not all studies. It is important to note that oral supplementation is the first choice for these patients. If it is not sufficient, enteral tube feeding should be instituted. For patients who are unable to tolerate nutritional supplementation by mouth, nasogastric tubes, percutaneous endoscopic gastroscopy, or jejunostomy tubes can be considered. Enteral tube feeding is most often used in conditions such as severe anorexia, swallowing troubles secondary to neurologic or head and neck diseases, perioperative periods, and stress. Hospitalized or institutionalized CKD patients also often ingest even lower amounts of their usual protein and energy intake (as low as 66 and 50%, respectively).

Oral supplementation should be given two to three times a day, preferably 1 h after main meals and/or during dialysis for MHD patients. Oral supplementation can provide an additional 7–10 kcal/kg per day of energy and 0.3–0.4 g/kg per day of protein. This requires a minimum spontaneous dietary intake of 20 kcal/kg per day

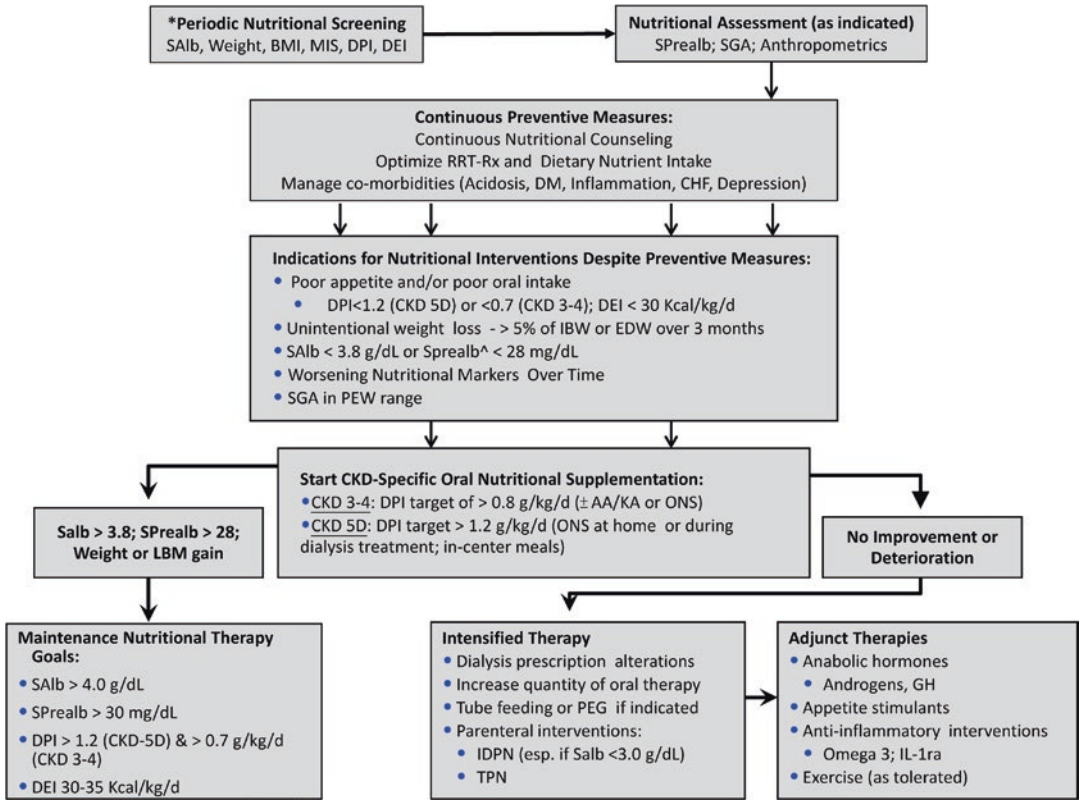

Fig. 17.3 Algorithm for nutritional management and support in patients with chronic kidney disease. *Minimum every 3 months, monthly screening recommended. ^ Only for ESKD patients without residual renal function. *SAlb* serum albumin (measured by bromocresol green), *BMI* body mass index, MIS malnutrition–inflammation score, *DPI* dietary protein intake, *DEI* dietary energy intake, *SPrealb* serum prealbumin, *SGA* subjective global assessment, *RRT- Rx* renal replacement therapy prescription, *DM* diabetes mellitus, *CHF* congestive heart failure, *CKD* chronic kidney disease, *PEW* protein–energy wasting, *LBM* lean body mass, *ONS* oral nutritional supplement, *PEG* percutaneous endoscopic gastrostomy, *IDPN* intradialytic parenteral nutrition, *TPN* total parenteral nutrition, *GH* growth hormone, *IL- 1ra* interleukin-1 receptor antagonist. (Reprinted from Ikizler et al. [6])

of energy and 0.4–0.8 g/kg per day of protein in order to meet the recommended dietary energy intake (DEI) and dietary protein intake (DPI) targets. Oral nutritional supplements are typically multi-nutrient containing a mix of macronutrients (protein, carbohydrate, fat) and micronutrients (vitamins, minerals, trace elements). Most are liquid, but there are also puddings and bars available. Different flavors and components can be used to improve compliance and tolerability. Different formulations, including disease and stage (kidney) specific, are also available [18] (Box 17.6).

Despite a large body of evidence indicating the nutritional efficacy of supplementation, there are a few studies that have carefully assessed their effects on hospitalization and mortality. Two large-scale observational studies reported significant survival benefit in favor of hypoalbuminemic MHD patients receiving nutritional supplementation versus similarly matched controls. In these studies, oral nutritional supple-

ment use was associated with higher serum albumin, lower hospitalization, and lower mortality. Another observational study including hemodialysis patients receiving oral nutritional supplementation during dialysis as part of a pilot program in more than 400 facilities found major reductions in missed dialysis treatments (33%) as well as in deaths among patients receiving supplementation compared to controls. Paradoxically, serum albumin levels were also lower in these patients. The limitations of these studies include their retrospective design, convenience sampling, and residual confounding from unmeasured variables. There are no prospective RCTs to examine the effects of oral nutritional supplementation on mortality and morbidity.

Box 17.5 What the Guidelines Say You Should Do: Nutritional Supplementation in CKD

- In patients with CKD 3–5 at risk of or with PEW, oral nutritional supplementation is recommended if target protein and energy intake cannot be met with dietary counseling alone.

  General indications for initiation of oral supplementation include but not limited to weight loss of 7.5% or more in 1 month, eating <75% of usual meals for 1 month and mild to moderate loss of subcutaneous fat stores or muscle mass.
- In patients with CKD 1-5D whose protein and energy requirements cannot be met with dietary counseling and oral nutritional supplements, enteral tube feeding should be initiated.
- If oral and enteral nutritional supplementation has been unsuccessful, total parenteral nutrition (or intradialytic parenteral nutrition for patients on MHD) should be added.

Source: KDOQI, Core Curriculum in Nephrology.

Box 17.6 Considerations for Oral Nutritional Supplementation

- Timing should be arranged to maximize tolerability (preferably 2–3 times daily after meals).
- Potential gastrointestinal symptoms and other barriers to compliance should be monitored.
- Patient preferences for taste and product type should be considered.
- Low electrolyte, kidney specific supplements may be prescribed as needed.

17.5.2 Intradialytic Parenteral Nutrition (IDPN)

Parenteral provision of nutrients, especially during the HD procedure (i.e., IDPN), has been shown to be a safe and convenient approach for individuals who cannot tolerate oral or enteral administration of nutrients (Box 17.7). Studies suggest that IDPN in conjunction with dietary counseling or oral nutritional supplements leads to improved BMI, skinfold measurements, and MAMC as well as serum biomarkers including albumin and prealbumin in patients who cannot achieve adequate protein and energy intake with oral supplements alone. Parenteral nutrition is also administered in hospitalized patients with underlying CKD or newly developed acute kidney injury. The indications for parenteral nutrition in these patients are similar to any patients admitted to hospital. Box 17.8 outlines the additional guidelines that should be considered in ESKD patients (Box 17.8).

Box 17.7 What the Guidelines Say You Should Do: Intradialytic Parenteral Nutrition (IDPN) in ESKD Patients

- In non-acutely ill malnourished HD patients, IDPN is infused through the venous line during dialysis with constant rate of infusion throughout the whole session.

- The rate should be progressively increased from 8 mL/kg during the first week to a maximum of 16 mL/kg.
- There should be controlled ultrafiltration to compensate fluid intake, and 75 mmol of Na should be added per liter of IDPN.

Box 17.8 Relevant Guidelines

1. Ikizler, TA. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. AM J Kidney Dis. 2020; 76, S1–S107.
2. Cano N, Fiaccadori E, Tesinsky P, Toigo G, Druml W; DGEM (German Society for Nutritional Medicine), et al. ESPEN guidelines on enteral nutrition: adult renal failure. Clin Nutr. 2006;25(2):295–310 [*10*].
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The efficacy of IDPN has been shown in several studies, albeit most of those are hampered by some design issues. In terms of comparison to oral supplementation, a large RCT showed that similar improvements in nutritional parameters are observed when adequate and comparable protein and energy are provided to the patients [*15*]. Other clinically relevant conclusions that can be driven from available RCTs using IDPN or ONS include the direct correlation between response to nutritional supplementation and the severity of PEW and the amount of nutrients received, diabetic patients showing a reduced response to nutritional support in terms of serum albumin and the observation that inflammatory status does not significantly affect the response to nutritional support. It should be noted that high cost of IDPN therapy and the regulatory concerns remain the greatest barriers for the use of IDPN, which should be reserved for patients where PO or enteral supplements are not feasible. Similar studies using amino acids in dialysate (AAD) as a nutritional intervention in PD patients with PEW have shown that AAD remains to be a viable option in PD patients with PEW who cannot tolerate or are not suitable for PO and other enteral supplements.

17.5.3 Adjunctive Therapies

17.5.3.1 Exercise

Abnormalities in muscle function such as reductions in oxidative capacity and type 1 fibers, exercise performance, and physical activity begin in the early stages of CKD and progress dramatically as ESKD develops [19]. A number of studies have shown the efficacy of cardiopulmonary fitness training in ESKD patients, whereas relatively few studies have examined the role of exercise training on stimulating the muscle growth. Collectively, the available data indicate that the presumed beneficial effects of exercise such as improvements in muscle quality and quantity, strength, and physical functioning are not consistently observed in ESKD patients. The possible explanations for the limited efficacy of exercise in CKD patients include the limitations of methods to assess body composition, inadequate intensity and/or duration of exercise, and the lack of understanding of the actual metabolic and morphologic abnormalities related to PEW in the setting of advanced CKD.

17.5.3.2 Anabolic Hormones

Recombinant human growth hormone (rhGH), an approved treatment of short stature in pediatric CKD patients, leads to improved growth, confirming that rhGH could overcome GH resistance associated with CKD. GH has anabolic activity in adults by increasing protein synthesis and reducing proteolysis in the muscle. In adults with CKD, resistance to native GH may be responsible for the premature decline in body composition. Short-term rhGH administration in hemodialysis patients has been shown to improve net muscle protein balance and increase in lean body mass. In a large multicenter RCT, significant decreases were observed in C-reactive protein (CRP) and homocysteine levels along with increases in serum high-density lipoprotein (HDL) cholesterol and transferrin levels in hypoalbuminemic MHD patients. Unfortunately, this large RCT was prematurely terminated due to slow recruitment, without the ability to assess the effects of rhGH on hospitalization or death.

Testosterone deficiency is also very common in male MHD patients and is associated with decreased muscle function and increased mortality risk. Several RCTs performed in MHD patients showed significant benefits of nandrolone decanoate (ND) treatment in both anthropometric and biochemical parameters including body weight, body mass index, skinfold, MAMC, and serum levels of total protein, prealbumin, and transferrin. No consistent effect of ND was demonstrated on physical functioning in several studies, and high-dose ND (100 mg/week) was intolerable in females because of its virilizing effects. In clinical practice, anabolic steroids could be used for preventing sarcopenia, albeit under close supervision, and its use should be limited to 6 months.

17.5.3.3 Other Therapies for Treatment of PEW in CKD

Appetite stimulants have been long used for increasing nutrient intake in patients with chronic diseases and malnutrition. Examples of pharmacological agents that may stimulate appetite include megestrol acetate, dronabinol, cyproheptadine, melatonin, thalidomide, and ghrelin. Most of these drugs have not been studied systematically in CKD patients. In several small studies, megestrol acetate stimulated appetite and induced small increases in serum albumin and weight in maintenance dialysis patients, but significant adverse effects including overhydration, excessive weight gain, gastrointestinal symptoms, and hyperglycemia were reported [20]. The safety of using megestrol acetate beyond short durations in patients receiving dialysis remains unknown. Large-scale prospective studies are needed to assess whether these drugs provide adjunctive nutritional therapy for CKD patients. Ghrelin is an orexigenic peptide released primarily from the stomach, which increases appetite and adjusts both short- and long-term energy balances making it a good candidate for treatment of anorexic ESKD patients. Several small studies in PD patients showed increased calorie intake with short-term ghrelin administration. When comorbidities and potential dialysis-related causes of inflammation have

been evaluated and appropriately treated, other anti-inflammatory treatment strategies such as anti-oxidative and/or bioecological strategies or targeted anti-cytokine therapies could be considered in CKD patients who are persistently inflamed. There are no large-scale studies examining the effects of any of the targeted anti-inflammatory agents on nutritional markers in CKD patients.

17.5.3.4 Obesity in CKD

Insulin resistance (IR), glucose intolerance, prediabetes, and diabetes mellitus represent a continuum of abnormalities in glucose and insulin homeostasis, which are highly prevalent in CKD and ESKD patients. Obesity plays a central role in initiation and/or acceleration of these derangements [21]. Insulin resistance is an established risk factor for the development of cardiovascular and all-cause mortality in CKD patients, including those on dialysis. In addition, protein metabolism is dramatically affected by IR, leading to increased catabolism, to result in a higher incidence and prevalence of PEW. Insulin resistance can be caused by underlying metabolic acidosis, oxidative stress, inflammation, accumulation of uremic toxins, vitamin D deficiency, physical inactivity, and the accumulation of fat mass, in particular truncal fat mass, which is common in these patients [22].Appropriate management of factors leading to or worsening IR is an important strategy to prevent or treat PEW in CKD patients.

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Obesity increases the risk for CKD and its progression to ESKD in addition to carrying markedly increased risk for other comorbid complications, such as type 2 diabetes, cancer, hypertension, dyslipidemia, cardiovascular disease, Alzheimer's disease, and sleep apnea [21] . Obesity also leads to sarcopenia in CKD and ESKD patients. Obesity induced decrease in adipokine secretion combined with increased inflammation, and insulin resistance leads to muscle wasting and sarcopenia. Decreased physical activity and physical functioning in return further worsens obesity leading to the "sarcopenic obesity" phenotype which is characterized by a vicious cycle. Management of obesity in stage 1–5 CKD patients, not on maintenance dialysis and kidney transplant patients, is similar to general population. Specifically, lifestyle changes such as walking or cycling instead of driving, routine exercise such as 30 min 3×/week walking or running, and calorie restriction are key management strategies. Calorie restriction includes reduction by 500 kcal/day in the absence of physical activity, which could lead to weight loss of 1 lb./week. Among the anti-obesity drugs approved by the US Food Drug Administration, glucagon-like peptide 1 agonist liraglutide is the only that can be safely used in all stages of CKD. Liraglutide can lead to a weight loss of 8 kg on average and is especially preferable in obese CKD patients with diabetes. In a large RCT, liraglutide was shown to reduce the risk of major cardiovascular events and mortality in patients with type 2 diabetes and CKD [23].

Management of obesity of maintenance dialysis patients is more controversial. In the general population, a high BMI is associated with increased cardiovascular disease and all-cause mortality. However, the effect of overweight (BMI: 25–30) or obesity (BMI: >30) in ESKD patients is paradoxically in the opposite direction; i.e., a high BMI is associated with improved survival. It is suggested that residual confounding by protein–energy wasting, inflammation, and competing mortality risk factors explain this phenomenon. Despite overwhelming epidemiological data on this association, a generalization of this sort, i.e., increased BMI is always good in ESKD, would actually be inappropriate, and further consideration of certain phenotypic features is necessary for proper management of these patients. For example, additional data indicate that also differences in body composition, i.e., total fat mass versus muscle mass and visceral versus non-visceral fat mass, could be the underlying mechanism leading to differing morbidity and mortality risk in ESKD patients. Accordingly, certain ESKD patients may benefit from weight loss. These include candidates for kidney transplantation, diabetic ESKD patients with poor

glycemic control, and patients with significant issues with physical activity due to morbid obesity. There are no pharmacological agents approved for weight loss. Bariatric surgery can be considered if above measures fail and if BMI >45 kg/m^2.

Before You Finish: Practice Pearls for the Clinician

- Screening and assessment of PEW require special consideration in CKD patients. Screening for patients at risk can be completed by any health professional and should provide a trigger to conduct more extensive assessment. Assessment should be performed by individuals with training and should guide intervention and monitoring plan.
- In CKD and ESKD patients, in whom a number of catabolic signals dominate, it is critical to maintain a dietary protein and energy intake relative to needs.
- Preemptive treatment of concurrent conditions that contribute to catabolism, such as metabolic acidosis, insulin resistance, and systemic inflammation, is of paramount importance for the prevention of PEW.
- Supplemental nutrition could be indicated in a significant number of CKD and ESKD patients, especially the ones with comorbid conditions and elderly.
- When prescribing oral nutritional support, physiological aspects of the patient and supplement, tolerability, nutritional efficacy, and availability should be taken to account. In general, oral or enteral nutrition are preferable to intradialytic or daily parenteral nutrition.
- Oral nutritional supplementation, especially when provided around the time of hemodialysis such as intradialytic administration, has been shown to exert both short- and long-term nutritional benefits in maintenance dialysis patients.
- Oral nutritional supplementation may improve clinical outcomes based on cohort studies. However, there are no large adequately powered randomized clinical trials that have tested the effectiveness of nutritional interventions on morbidity and mortality.

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Metabolic Acidosis and Chronic Kidney Disease

18

Jeffrey A. Kraut and Glenn T. Nagami

Before You Start: Facts You Need to Know

- A decrease in bicarbonate generation with chronic kidney disease (CKD) leads to acid retention in the body. Initially this acid is retained in interstitial tissues without causing a change in systemic acid-base parameters, a stage termed eubicarbonatemic metabolic acidosis. Eventually as CKD progresses, a fall in the systemic bicarbonate level is also observed (overt metabolic acidosis).
- Eubicarbonatemic metabolic acidosis can be observed as early as stage II CKD (GFR 60–90 mL/min). Overt metabolic acidosis usually occurs when the estimated glomerular filtration rate (eGFR) falls below 25–30 mL/min, but may occur at higher levels of eGFR, particularly in the presence of concurrent disorders which affect renal bicarbonate generation such as hyporeninemic hypoaldosteronism or damage to the kidney collecting duct or with excessive dietary acid loads.
- Major adverse effects of both untreated eubicarbonatemic and overt metabolic acidosis include muscle wasting, bone disease, progression of CKD, and increased mortality.
- Acid-base parameters including pH, PCO_2, and [HCO_3^-] should be checked upon first evaluation, and then serum [Total CO_2] should be checked at least annually in stage 3a CKD, every 4–6 months for stage 3b CKD and approximately every 1–3 months in stages 4 and 5 CKD.
- Treatment of metabolic acidosis with base and/ or reduction in net endogenous acid production to reduce interstitial acidity slows the progression of CKD, decreases muscle wasting, and improves bone disease.
- New recommendations are to initiate base treatment when serum bicarbonate is ≤24 mEq/L with the goal of raising it to between 24 and 26 mEq/L.
- Guidelines for the detection and treatment of eubicarbonatemic metabolic acidosis are under investigation.

18.1 Introduction

Acid is produced from metabolism of ingested foodstuffs each day. The kidneys are responsible for generating a sufficient quantity of base to

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neutralize this acid and thereby maintaining normal acid-base balance. With the development of chronic kidney disease (CKD), base generation rates can fall below acid production rates leading to hydrogen ion retention and positive acid balance [1]. The acid retained can cause the progression of CKD, development or exacerbation of bone disease, and wasting and dysfunction of muscles. Furthermore, in children it can impair growth [2].

In this chapter, we review the pathophysiology of the metabolic acidosis of CKD, the characteristics of the metabolic acidosis, the nature and mechanisms of cellular dysfunction, and the present recommendations for its treatment.

18.2 Pathophysiology

The serum bicarbonate (traditionally measured by the laboratory as [total CO_2]) is normally maintained between 23 and 29 mEq/L (mean, 24 mEq/L) and blood pH between 7.38 and 7.42 (mean, 7.40). The kidney is responsible for maintaining a normal serum bicarbonate concentration by reclaiming the large quantity of bicarbonate which is filtered by the glomeruli (approximately 4500 meq/d with normal GFR, and generating sufficient bicarbonate to match the daily net endogenous acid production rate (NEAP). The NEAP is derived from the metabolism of mostly animal proteins with their content of sulfur-containing and cationic amino acids. Dietary base is derived from the metabolism of fruits and vegetables. NEAP may vary in individuals with chronic kidney disease and largely depends on the nature of the diet.

Estimates of NEAP from diet recall of thousands of individuals participating in the Third National Health and Nutrition Examination Survey (NHANES) [3] revealed that the median acid load was 47 meq/d with 25% of individuals having less than 39 meq/d and 25% having greater than 59 meq/d of acid load. Thus, the necessary response of the kidney to maintain acid-base balance by generating sufficient quantities of base to neutralize NEAP will vary according to the diet. Generation of base by the kidneys occurs as a result of urinary excretion of hydrogen ions, in the form of titratable acid excretion ($H_2PO_4^-$) (approximately 1/3 of the acid load) and the generation of bicarbonate from the metabolic and transport processes resulting in ammonium excretion (approximately 2/3 of the acid load). However, with acid challenges from diet or disease, an increase in urinary ammonium excretion (NH_4) accounts for the majority of the increased acid excretion. Figure 18.1 illustrates the need for a balance between acid production from diet and acid excretion by the kidneys for maintaining a normal acid-base status.

Impairment in the kidney response to acid challenges in CKD could theoretically occur from a defect in bicarbonate reabsorption or in the generation bicarbonate. A defect in renal bicarbonate reabsorption occurs in a minority of patients with CKD. The major cause of acid retention in CKD is decreased ammonium excretion (from the usual quantity of 40 mEq/d to less than 20 mEq/d). This decrease in ammonium excretion is primarily a consequence of a reduction in the number of functioning nephrons, as ammonium excretion per residual nephron is actually increased above normal. As a result, rates of net acid excretion fall below rates of acid production leading to hydrogen ion retention. Studies in patients with a stable, albeit reduced GFR, have demonstrated that they are in continual positive hydrogen balance despite having a stable serum bicarbonate concentration [4]. The stability of serum bicarbonate at any given level of GFR has been attributed to buffering of retained hydrogen by tissue buffers, primarily those residing in bone, muscle, and kidney [5].

In some patients, superimposed defects in tubular hydrogen secretion and/or ammonia production can lead to more severe metabolic acidosis or its appearance earlier in the course of CKD especially in individuals who have a large NEAP. The most common cause for this exacerbation of metabolic acidosis is a reduction in aldosterone synthesis found with hyporeninemic hypoaldosteronism [6]. However, it can also be due to impaired proton excretion resulting from damage to the tubules residing in the renal medulla such as can found in patients with sickle

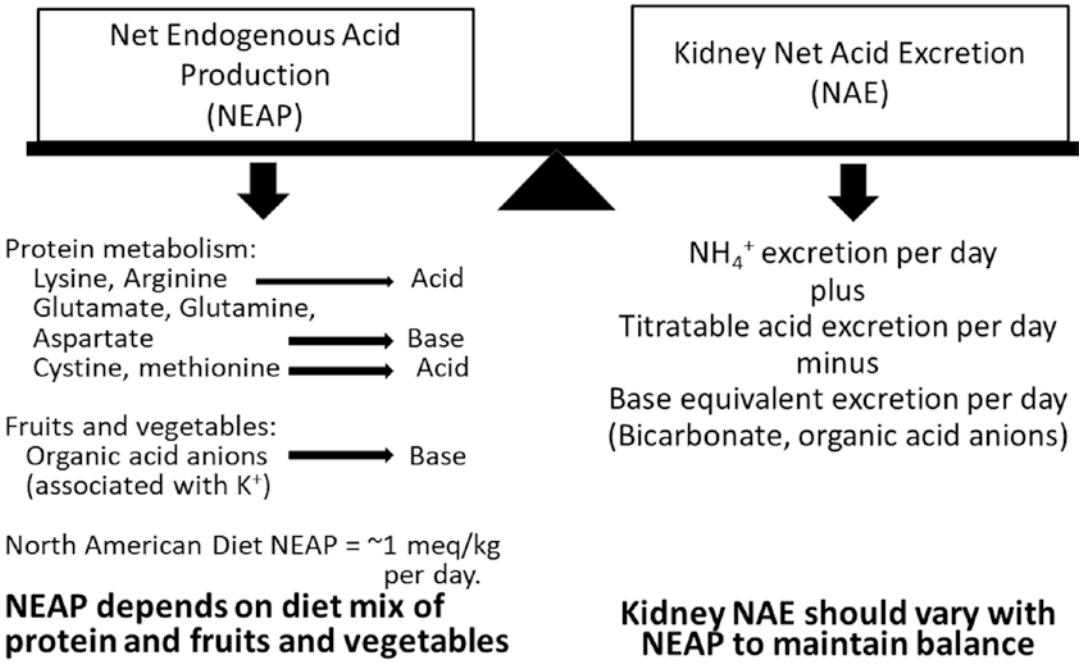

Fig. 18.1 Normal acid-base homeostasis is maintained by balancing Net Endogenous Acid Production (NEAP) from metabolism and Net Acid Excretion (NAE) by the kidney. In general, increased protein intake relative to fruits and vegetables will result in more acid production which will need to be compensated for by the kidney, but the degree of compensation may be limited in chronic kidney disease

cell disease. Hyperkalemia out of proportion to the decrease in GFR which often accompanies these disorders contributes to the suppression of ammonia production and thereby to the development of metabolic acidosis. [7] Studies indicate that acid retention and positive acid balance can be observed with only mild reductions in GFR from the normal value of around 100–125 mL/min to between 60 and 90 mL/min (stage 2 CKD) [8]. At this stage, serum bicarbonate and blood pH are normal, and the acid appears to be sequestered in muscle, bone, and kidney. This stage has been termed normobicarbonatemic or eubicarbonatemic metabolic acidosis. [8] As kidney function declines further, hydrogen retention may become more extensive and a fall in systemic blood pH and bicarbonate can be observed. When overt metabolic acidosis develops, the reduction in serum [HCO_3^-] is usually mild (4–6 mEq/L), with serum bicarbonate ranging between 17 mEq/L and 22 mEq/L.

18.3 Clinical and Laboratory Characteristics

As noted above, acid retention without hypobicarbonatemia can be observed with only mild reductions in GFR. The exact prevalence of eubicarbonatemic metabolic acidosis is unknown. However, a recent survey of veterans (primarily male) revealed that approximately 25% of the patients had a GFR at which eubicarbonatemic metabolic acidosis has been described (stage 2 or more CKD). As renal function declines further, hypobicarbonatemia becomes more frequent. Thus, in the CRIC study [9], a serum bicarbonate less than 22 mEq/L (the definition of metabolic acidosis espoused by the National Kidney Foundation until 2020) was found in approximately 7% in individuals with stage 2 CKD rising to 35% in individuals with eGFR of 15–30 mL/min (stage 4) . Looked at another way, the majority of patients will develop hypobicar-

Table 18.1 Disorders associated with metabolic acidosis in patients with CKD

Disorder	Serum electrolyte pattern	Urine NH_4	Urine pH	Urine anion and osmolal gap	Comments
Chronic kidney disease	Normal anion gap early; mixed high and normal and then high anion gap	<20 mEq/d	<5.5	Abnormal	Acid retention can lead to eubicarbonatemic acidosis with stage 2 CKD and overt metabolic acidosis with stages 3 to 5
Hyporeninemic Hypoaldosteronism	Normal anion gap	<20 mEq/d	<5.5	Abnormal	Most common in diabetic patients; hyperkalemia out of proportion to reduction in eGFR; low renin low aldosterone levels present; treatment with mineralocorticoid or diuretics indicated
Tubular injury with tubular resistance to aldosterone	Normal anion gap	<20 mEq/d	>5.5	Abnormal	Common in patients with significant interstitial renal disease including patients with sickle cell disease; renin and aldosterone values are normal

Urine anion gap is defined as $Na^+ + K^+ - Cl^-$. In patients with ability to excrete acid appropriately, it is approximately—30 mEq/L, whereas it is positive in patients with impaired ability to excrete acid such as those with CKD. The urine osmolal gap is defined as measured urine osmolality—$2 \times Na^+ + K^+$ + urea nitrogen/2.8 + glucose/18. The difference if divided by 2 gives an approximation of NH_4 excretion. In normal patients it increases from 30 to 40 mEq/day to more than 150 mEq/day. In patients with CKD, it is usually <20 mmol/day

bonatemia once eGFR falls below 25–30 mL/min [10]. A small percentage of patients will maintain a normal serum bicarbonate concentration even in the presence of severe kidney failure (eGFR < 15 mL/min). The explanation for this occurrence is unclear.

The laboratory characteristics of the metabolic acidosis of CKD are summarized in Table 18.1. The metabolic acidosis can be of the normal anion gap variety early in the course of CKD, and then as CKD progresses excretion of phosphate and sulfate and organic anions become impaired so that they accumulate in the serum leading to the transition from a non-anion gap metabolic acidosis to a mixed non-anion gap and high anion gap metabolic acidosis, and finally to a high anion gap variety alone. The sensitivity of detecting an anion gap can be improved by adding a correction for albumin such that patients with earlier stages of CKD may be discovered to have an elevated anion gap [11] and such patients with adjusted anion gap levels had higher rates of mortality [11]. The presence of an anion gap is associated with larger dietary acid loads and with a higher risk for developing end-stage kidney disease [12]. Nevertheless, the general evolution of the type of acidosis is not uniform and may vary at different stages of CKD.

Hyperkalemia can be a pathogenetic factor in the development of a non-anion gap metabolic acidosis by its inhibitory effect on renal ammoniagenesis. Hyperkalemia is common with severe reductions of eGFR (<25–30 mL/min). However, it can also be observed with less severe reduction in eGFR, particularly when hyporeninemic hypoaldosteronism or significant tubular damage is present, such as observed in some cases of diabetes mellitus and urinary obstruction, or in sickle cell disease. Correction of hyperkalemia in patients with hyporeninemic hypoaldosteronism can result in the correction of metabolic acidosis [7].

Urine pH is appropriately acidic (<5.5) in the majority of patients with CKD reflecting their ability to acidify the urine. While titratable acid excretion is preserved due to enhanced excretion of phosphate until severe CKD supervenes, the excretion of ammonium is impaired earlier in the CKD course and is the major factor contributing the positive acid balance and metabolic acidosis.

18.4 Assessment of Acid-Base Balance in CKD

Since hypobicarbonatemia is often mild in patients with CKD, it sometimes can be difficult to distinguish the metabolic acidosis of CKD from chronic hypocapnia. Indeed, in one study a significant number of patients with CKD and hypobicarbonatemia had respiratory alkalosis [13]. Therefore, we recommend blood gas analyses be obtained upon first evaluation of these patients, even if the serum bicarbonate concentration is minimally perturbed. Although arterial blood gases are traditionally utilized for this purpose, recent studies have demonstrated that venous blood gases may suffice [14]. Measurement of urine pH in patients with a reduced serum bicarbonate concentration (obtained immediately upon voiding to prevent dissipation of CO_2) can be helpful in distinguishing patients with CKD alone or in combination with hypoaldosteronism (urine pH will be <5.5) from those with medullary tubular damage (urinary pH will be >5.5). Therefore, it can be worthwhile obtaining a measurement of urine pH in patients with hypobicarbonatemia.

Urinary ammonium excretion will be low in all patients with metabolic acidosis arising from kidney dysfunction, and therefore, estimates of urinary ammonium excretion are helpful in distinguishing the acidosis related to the presence of kidney disease to that caused by nonrenal mechanisms. Either indirect estimates of urinary ammonium excretion, such as those obtained using the urine anion gap or osmolal gap [15] or direct determination of urinary ammonium excretion [16] have been utilized. However, given the complexity of indirect estimates of urinary ammonium excretion, several investigators have found direct measurement of urinary ammonium excretion to be the most cost-effective and accurate method of assessing the kidney's contribution to acid-base balance [15]. In patients in whom kidney dysfunction is the only mechanism underlying the metabolic acidosis, urine ammonium excretion will be considerably less than the normal value of 40 mEq/day. On the other hand, if there is an increased acid load, urinary ammonium excretion can be greater than this value but substantially less than the 200 mEq/day which can be observed in healthy individuals with chronic mild metabolic acidosis and normal kidney function [17, 18]. Once acid-base parameters have been assessed and the presence of metabolic acidosis has been confirmed, blood gases need not be obtained again, but rather serum [Total CO_2] alone can be monitored. The recommended appropriate time of assessment for this parameter is given in Table 18.2. If patients are being treated with base or there is a subsequent reduction in GFR, more frequent determinations of serum bicarbonate might be necessary.

Table 18.2 Recommended frequency of measurements of acid-base parameters in patients with CKD

CKD stage	eGFR mL/min/1.73 m^2	Frequency of measurements	Comments
2	60–90	At least once per year	Patients can manifest eubicarbonatemic metabolic acidosis at this stage and a small percentage, <10% can have hypobicarbonatemia
3a	45–59	At least every 6 months	Hypobicarbonatemia begins to be more prevalent at this stage: In approximately 15% of patients. In acidemic patients hypobicarbonatemia can lead to severe kidney failure and needs to be treated aggressively
3b	30–44	At least every 3–4 months	
4	15–29	At least every 2–3 months	Hypobicarbonatemia is frequent: Seen in at least 35% of patients. Normalization of acid-base parameters is important to prevent complications and improve clinical condition for initiation of dialysis
5	<15	Once per month in dialysis patients; once 4–8 weeks in patients not on dialysis	A large majority of patients will be on chronic dialysis either hemodialysis or peritoneal dialysis

Measurements of venous blood gases should be done initially or when hypobicarbonatemia is present. Once metabolic acidosis has been established serum [total CO_2] can be obtained

In patients with eubicarbonatemic metabolic acidosis, the presence of acid retention might not be easily identified given the normal acid-base parameters. Recent studies in a small cohort of patients with presumed eubicarbonatemic metabolic acidosis have shown that a spot urinary citrate/creatinine ratio determination might be an effective way of detecting these patients as patients with acid retention should also retain citrate and have low rates of urinary citrate excretion [8, 19]. One study was limited to patients with stage 1 and 2 CKD [19], and it is unclear whether this would apply to lower levels of eGFR. Studies involving a larger number of patients are necessary to determine the role of an urinary citrate measurement in the evaluation of patients with CKD.

18.5 Adverse Effects of the Chronic Metabolic Acidosis of CKD and Rationale for Treatment

The adverse effects of acid retention are summarized in Box 18.1. As noted above, acid retained with CKD is first sequestered in muscles, bones, and kidney. During this early phase, as noted, systemic acid-base parameters might be within the normal range. However, even in this early phase adverse effects can be observed including acceleration of the progression of CKD [8, 20]. Although not well studied, it seems that as the metabolic acidosis becomes more profound that the adverse effects become more extensive. The mechanisms underlying the progression of CKD with acid retention are summarized in Fig. 18.2.

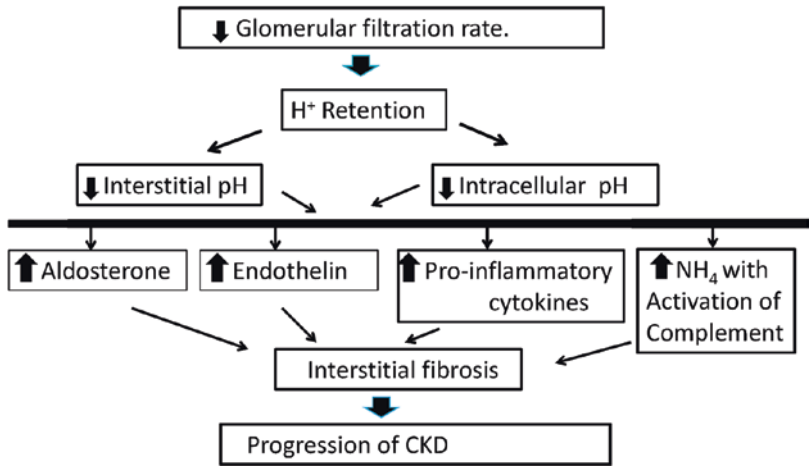

Fig. 18.2 Factors contributing to kidney interstitial fibrosis and progression of CKD with chronic metabolic acidosis. A reduction in interstitial pH causes excess production of endothelin, aldosterone, and proinflammatory cytokines. The accumulation of acid also causes the kidney to produce more ammonium which activates a complement-dependent inflammatory cascade. All of these factors lead to increase kidney fibrosis and a decline in kidney function

Box 18.1 Major Adverse Effects of Metabolic Acidosis

Effect	Stage of occurrence	Comments
Bone disease	Usually seen with later stages of CKD when significant hypobicarbonatemia is present	Both osteomalacia and osteitis fibrosa cystica described; lesions healed with base therapy
Stunted growth in children	Described in children with more severe hypobicarbonatemia; occurrence with less severe hypobicarbonatemia unclear	Growth improved with base therapy; impact of eubicarbonatemic metabolic acidosis not well studied
Acceleration in the progression of CKD	Can be seen with eubicarbonatemic metabolic acidosis, but more pronounced with hypobicarbonatemic metabolic acidosis	Base therapy slows progression
Muscle wasting with reduced muscle strength	Reported only in patients with hypobicarbonatemic metabolic acidosis	Base therapy reduces muscle wasting and improves muscle strength
Increased mortality	Reported in patients with significant acidemia	Impact of base therapy not studied

A reduction in interstitial pH and/or intracellular pH appears to be the primary signals inducing alteration in the factors causing cellular damage. The increased acidity in these compartments increases the tissue concentrations of angiotensin II, aldosterone, endothelin, and proinflammatory cytokines. Also, the augmented NH_4 production per remaining nephron causes activation of the complement pathway and cellular damage. All four of these factors cause increased renal fibrosis. Administration of base to lessen acid retention reduces the concentration of the hormones and the activation of complement slowing the progression of CKD.

Acid retention also exacerbates or produces damage to the bones. Both osteitis fibrosa and osteomalacia have been described with metabolic acidosis which is ameliorated by administration of base. Whether eubicarbonatemic metabolic acidosis is associated with bone damage is not known. However, since bone is an important buffering site for acid, this would be expected. Acid retention and metabolic acidosis is associated with muscle wasting and reduced muscle strength. Again, base administration reduces muscle wasting and improves muscle strength [21, 22].

Many factors affect mortality in patients with CKD. Several studies in patients with CKD, both before and after initiation of chronic maintenance dialysis, have shown a correlation between metabolic acidosis and increased mortality [23] . The mechanism(s) underlying this effect is unclear.

In summary, the development of metabolic acidosis is associated with a myriad of adverse effects which can have a dramatic effect on the quality of life and mortality of patients with CKD. The impact of acidosis on progression of CKD has been the effect most studied. The impact of acidosis on bone and muscle have been less broadly examined, and therefore further studies involving large cohorts of patients are desirable. The clinical studies performed so far indicate base therapy is beneficial in ameliorating many of these adverse effects providing a strong rationale for aggressive prevention and/ or treatment of the acidosis [2].

18.6 Treatment

Based on evidence that metabolic acidosis is associated with progression of chronic kidney disease, production or worsening of bone disease, and increased mortality, several kidney organizations including the National Kidney Foundation (NKF) have recommended administration of base to patients with hypobicarbonatemia. Initially the recommendation for base administration was the presence of a serum [HCO_3^-] concentration of less than or equal to 22 mEq/L. However, in 2019 the NKF changed

the criteria to recommend administration of base when serum bicarbonate was less than 24–25 mEq/L. Most experts and renal organizations now recommend that the serum bicarbonate should be raised to values between 24 mEq/L and 26 mEq/L. No randomized controlled studies have determined whether this criterion is appropriate, and this remains an important issue to assess. The potential adverse effects of over-correction of too high of a bicarbonate level have also to be raised. Therefore, the clinician should be vigilant to prevent over-correction of the acidosis.

An added layer of complexity has been added by the recognition that patients with eubicarbonatemic metabolic acidosis can have deleterious effects from the acidosis that are ameliorated by the administration of base [8]. Therefore, there could be a reason to initiate base therapy in patients with CKD even with minimal or no reductions in serum [HCO_3^-]. On the other hand, there remains potential risk of base therapy should it rise even slightly above normal. A recent randomized study indicated that although base therapy slowed progression of CKD, a serum bicarbonate above 24 mEq/L even when produced by measures other than base therapy was associated with a higher prevalence of congestive heart failure [9]. Moreover, others have suggested that an increased serum bicarbonate might provide an alkaline milieu that would predispose to deposition of calcium and phosphorus in tissues with resultant organ dysfunction. Be that as it may, we conclude that until randomized controlled studies which evaluate the risks and benefits of base therapy in patients with eubicarbonatemic metabolic acidosis and CKD are published, we are cautious about the use of base in the treatment of patients with eubicarbonatemic metabolic acidosis. Identifying individuals who may be at higher risk for developing acid retention may be helpful in choosing who needs special attention and validating newer ways to monitor treatment responses could add to the safety and effectiveness of more aggressive approaches to treatment. Individuals with a tendency to hyperkalemia from hyporeninemic hypoaldosteronism or those who consume a heavy animal protein intake may need dietary counseling about reducing dietary acid load. Clearly given the potential large numbers of individuals with this disorder, this remains a critical area of study.

In treatment of patients with base, the clinician should be very vigilant to assess patients for possible complications such as volume overload with exacerbation of hypertension and congestive heart failure. Also, strong emphasis should be given on control of serum calcium and phosphorus to lessen the risk of soft tissue and vascular calcifications. An increase in serum bicarbonate above normal should be prevented at all costs because of concern for exacerbation of heart failure or promotion of tissue calcifications.

Administration of sodium bicarbonate, sodium citrate (Shohl's solution), or an increase in the consumption of dietary fruits and vegetables are all effective in raising serum bicarbonate concentration. Sodium bicarbonate is inexpensive, but has the complication of producing excess carbon dioxide in the stomach which can be uncomfortable for the patient. The use of enteric-coated tablets might lessen this complication. The administration of sodium citrate (Shohl's solution) is effective and relatively inexpensive, but caution should be advised in patients who are taking aluminum-containing compounds such as sucralfate and AlOH-containing antacids. Citrate enhances the gastrointestinal absorption of aluminum which can accumulate and cause toxicity when kidney function is impaired.

Changes in dietary habits rather than administration of supplements might be the most cost-effective means of raising serum bicarbonate concentration. A reduction in animal protein intake in concert with increased intake of fruits and vegetables has been shown to be successful in raising serum bicarbonate with little complications [24]. Given the high potassium content of fruits and vegetables, however, one should be cautious about a possible increase in serum potassium with this regimen. Controlled studies up to now, however, have not found a significant increment in the appearance of this complication.

Recently a new drug, Veverimer has been developed that raising serum bicarbonate by

binding hydrogen ions in the stomach and causing their excretion in the stools. In contrast to sodium containing buffers, it does not deliver any sodium to the patient. In controlled studies, it raised serum bicarbonate by approximately 4 mEq/L in a matter of days and maintained it for several months [25]. The drug remains under study and is not yet approved by the FDA, but could be an attractive addition to the clinician armamentarium in the treatment of patients with CKD.

No matter what regimen is utilized, an estimate of base deficit should be obtained before embarking on therapy. This can easily be accomplished by subtracting the prevailing serum bicarbonate from the desired serum bicarbonate and multiplying this value by the approximate volume of distribution of administered bicarbonate, usually 50% body weight as shown below:

Bicarbonate deficit (mEq) = goal serum $[HCO_3^-]$ − prevailing serum $[HCO_3^-]$ × 50% bd wt (kg).

The calculation assumes no significant addition of acid or generation of base and so is only a very rough estimate. This calculation will allow the clinician to estimate not only how much base should be given, but also how long it will take before the target bicarbonate is reached. The serum $[HCO_3^-]$ can be raised slowly over a matter of days while observing the patient for evidence of various complications particularly exacerbation of hypertension or congestive heart failure. Once the target serum bicarbonate has been reached, base administration can be reduced to values that approximate the estimated rate of net endogenous acid production. This precaution will aid in ensuring the clinician does not overshoot the target serum bicarbonate concentration. The above approaches to treatment are summarized in Box 18.2.

Box 18.2 Recommendations for Treatment of Metabolic Acidosis with Chronic Kidney Disease

Reduce dietary protein intake to decrease acid generation. Consider substituting plant protein for animal protein. Be sure to maintain sufficient protein to preserve muscle mass and protein stores.

Provide base in various forms. Increase intake of fruits and vegetables while monitoring patients carefully for development of hyperkalemia. This might reduce the quantity of oral base required or eliminate it completely. See American Heart Association and National Kidney Foundation diets.

In patients with CKD not yet on dialysis, base can be provided in the form of sodium bicarbonate or sodium citrate. Calculate the bicarbonate deficit prior to administration of base to get an estimate of bicarbonate requirements. Use 50% body weight as the space of distribution of administered base. Once goal serum [total CO_2] of 24–26 mEq/L is reached reduce base administration to quantity required to neutralize NEAP.

Monitor patients' volume status and blood pressure carefully. Although sodium retention appears to be less than with sodium chloride there still can be volume overload or exacerbation of hypertension. Restrict dietary sodium intake to less than 1000 mg/day if possible.

If it receives FDA approval, veverimer given orally with sodium-restricted diet might be an effective method or raising serum [total CO_2] without giving sodium or potassium.

18.7 Conclusions and Future Directions

Acid retention with its adverse effects on cellular function is an important complication of CKD. Base administration is effective in preventing or treating the progression of CKD, muscle wasting, and bone disease that accompany the development of metabolic acidosis. The new agent Veverimer could provide an alternative to sodium bicarbonate and citrate that could raise serum [HCO_3^-] without adding a sodium load.

Further study of the most effective methods of treating metabolic acidosis in CKD are ongoing. Also, the exact prevalence and how to detect and treat patients with eubicarbonatemic metabolic acidosis remains an important focus of study.

Before You Finish: Practice Pearls for the Clinician

- Full acid-base parameters from venous blood including pH, pCO_2, and [HCO_3^-] should be obtained in patients with CKD, particularly if they have hypobicarbonatemia.
- Alkali therapy in the form of sodium bicarbonate or sodium citrate or increased intake of fruits and vegetables should be used to maintain a serum bicarbonate concentration between 24 and 26 mEq/L. The dose should be determined based on the estimated bicarbonate deficit.
- During alkali therapy, patients should be monitored carefully for the development of adverse effects and to ensure serum bicarbonate is maintained within the recommend level.

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19 Infectious Complications and Vaccination in Chronic Kidney Disease

Vivek Kumar and Vivekanand Jha

Before You Start: Things You Need to Know

- Infections are the second most common cause of morbidity and mortality in chronic kidney disease (CKD) patients.
- Infections increase the risk of adverse cardiovascular events in CKD.
- Uraemia-induced immune dysfunction, frequent visits to health-care facilities, frequent hospitalisation, need for vascular catheters and extracorporeal treatment increase infection risk.
- Preventing infections is of utmost importance both in pre-dialysis and dialysis-dependent CKD patients.

19.1 Infections and Chronic Kidney Disease

Chronic kidney disease (CKD) is recognised as an important global health-care concern. The Global Burden of Disease (GBD) 2017 study estimated global prevalence of CKD at 9.1% (95% CI: 8.5–9.8%) in 2017 with major burden in regions with lower socio-demographic indices [1]. Between 1990 and 2017, the global all age mortality due to CKD increased by 41.3%. In the United States (US), the National Chronic Kidney Fact Sheet 2017 released by Centers for Disease Control and Prevention (CDC) estimated that approximately 96% of those with mildly reduced kidney function or kidney damage were unaware of their CKD status [2]. Besides being common, CKD also has major impact on the outcome of other major non-communicable diseases like diabetes and hypertension, 35 and 20% of whom develop CKD.

Infection control remains a major public health goal worldwide. Over the last few decades, a complex interplay between infections and CKD has become evident. A number of infections can cause kidney disease, and CKD predisposes patients to various infections. Chronic infections with organisms like hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV) are still responsible for a substantial proportion of CKD in some parts of the world. In addition, infection-related acute

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kidney injury may not recover completely and lead to CKD. Since 2020, the human coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to significant addition in the overall burden of both acute and chronic kidney diseases and increased the morbidity and mortality in patients with pre-existing kidney disease.

The high incidence of infections in CKD patients, including those on dialysis and after kidney transplantation, has been known for decades. Infections are the second most common cause of morbidity and mortality in these patients after cardiovascular disease. A number of risk factors increase the risk for infections in patients with kidney disease (Box 19.1). These include alterations in specific functions of various components of innate and adaptive immune system (Box 19.2). These changes are also responsible for poor response to vaccinations and failure to maintain protective antibody titres in CKD.

Box 19.1 Risk Factors for Infections in Kidney Disease

1. Old age
2. Female sex
3. African American race
4. Presence of diabetes mellitus
5. Malnutrition
6. Hypoalbuminaemia
7. Impaired cutaneous defence
   (a) Severe oedema
   (b) Use of vascular access and peritoneal dialysis catheters
   (c) Needlestick injury for native arteriovenous fistulae or grafts
8. Therapy related
   (a) Use of immunosuppressive drugs for treatment of basic disease
   (b) RBC or blood products transfusion
   (c) Contaminated caregiver's hands or gloves, equipment, supplies and environmental surfaces
   (d) Use of iron preparations[1]
   (e) Bioincompatible dialysis (footnote 1)
9. Increased hospitalisation for non-infectious complications
10. Immunological dysfunction
11. Poor vaccine response

Box 19.2 Immune System Alterations in CKD

1. Polymorphonuclear leucocyte dysfunction
   (a) Increased reactive oxygen species production
   (b) Increased apoptosisSpontaneous activation and degranulation
   (c) Decreased phagocytosis
2. Depletion of antigen presenting cells
3. Monocyte dysfunction
   (a) Increased circulating monocytes (especially $CD14^{+}CD16^{+}$ monocytes)
   (b) Increased reactive oxygen species production
   (c) Increased basal integrin, toll-like receptor (TLR)-2 and TLR-4 expression
   (d) Increased cytokine production
   (e) Decreased phagocytosis
4. T-cell dysfunction
   (a) Decreased regulatory T (Treg) cells
   (b) Reduced CD4/CD8 T-cell ratio
   (c) Decreased memory T cells (both central and naïve)
5. B-cell dysfunction
   (a) Decreased B-cell number
   (b) Decreased antibody production

[1] Increase oxidative stress.

Though infections and cardiovascular disease may appear to be distinct clinical problems, modulation of underlying inflammatory state may be a common denominator linking the two in CKD. Data from United States Renal Data System (USRDS) Wave 2 study showed that the presence of bacteremia or septicaemia was associated with increased risk of death [hazard ratio (HR) 2.33, 95% confidence interval (CI) 1.38–2.28], myocardial infarction (HR 1.78, 95% CI 1.38–2.28), heart failure (HR 1.64, 95% CI 1.39–1.95), peripheral vascular disease (HR 1.64, 95% CI 1.34–2.0) and stroke (HR 2.04, 95% CI 1.27–3.28) [3]. Analysis of USRDS data revealed that the risk of cardiovascular events was increased by 25 and 18% at 1 and 3 months after an episode of infection-related hospitalisation compared to control periods [4]. Recent data on risk of cardiovascular disease in patients with CKD who were discharged after hospitalisation for sepsis also showed subsequent high risk of major adverse cardiovascular events (HR 1.42, 95% CI 1.37–1.47), myocardial infarction (HR 1.39, 95% CI 1.32–1.47), ischemic stroke (HR 1.46, 95% CI 1.40–1.52), hospitalisation for heart failure (HR 1.55, 95% CI 1.51–1.59) and all-cause mortality (HR 1.56, 95% CI 1.54–1.58) [5]. Data from the Canadian Study of Prediction of Risk and Evolution to Dialysis, Death and Interim Cardiovascular Events Over Time (CanPREDDICT), a prospective cohort study of patients with pre-dialysis CKD, showed independent association of infection with increased risk of cardiovascular ischemia (HR 1.80, 95% CI 1.24–2.60), congestive heart failure (HR 3.2, 95% CI 2.25–4.61), end-stage kidney disease (HR 1.58, 95% CI 1.22–2.05) or mortality (HR 3.39, 95% CI 2.65–4.33) in future [6]. These observational studies lend support to the intriguing hypothesis that the superimposition of macro-inflammatory events like bacterial infections over the persistent micro-inflammatory state of CKD might increase cardiovascular disease risk, despite apparent recovery from the infectious episode.

19.2 Epidemiology of Infections in CKD

For the purposes of discussion of infections, it is useful to divide the CKD population into two groups: pre-dialysis CKD and dialysis-dependent CKD. Besides becoming a defining moment for patient and treating physician as this change affects patient's daily lifestyle and management, initiation of dialysis also alters the risk and consequences of infection by repeatedly breaching the physical defences and altering immune functions.

Pre-dialysis CKD patients have three times more risk of developing infectious complications as compared to general population [7]. Medicare data showed that urinary tract infection (UTI), pneumonia and bacteraemia or sepsis were four times, three times and four times, respectively, more common in pre-dialysis CKD population in the USA compared to the general population [7]. Sepsis and pneumonia were encountered in end-stage renal disease (ESRD) patients ten times and five times more commonly than general population [7]. Data from Cardiovascular Health Study (CHS) showed that after a median follow-up of 11.5 years, risk of all-cause hospitalisation secondary to infectious events increased 16, 37 and 64% in participants over the age of 65 with estimated glomerular filtration rate (eGFR) of (calculated using serum cystatin C level) 60–89, 45–59 and 15–44 mL/min/1.73 m^2, respectively, as compared to those with eGFR ≥90 mL/min/1.73 m^2 [8]. The risks of UTI and pneumonia were 160 and 80% more in patients with eGFR 15–44 mL/min/1.73 m^2 when compared to those with eGFR ≥90 mL/min/1.73 m^2 [8]. Recent data from the CanPREDDICT cohort has shown infection rate of 14.3 infections/100 patient-years in patients with pre-dialysis CKD. Respiratory tract and urinary tract infections were the commonest, being recorded in 11.6% and 10.6% of the study cohort, respectively [6].

As per the latest 2021 USRDS Annual Data Report, adjusted hospitalisation rate for infection in 2019 in older patients (≥66 years, Medicare FFS beneficiaries) with CKD was 133

events per 1000 person-years [9]. This had declined by 10.7% between 2009 and 2019. The hospitalisation rate remained stable in patients with stage 3 CKD between 2009 and 2019. However, it decreased by 9% between 2009 and 2013 for patients with CKD stages 4–5 followed by 14% increase between 2014 and 2019. In 2019, hospitalisation rates for infection in patients with CKD stages 3 and 4–5 were 129 and 199 events per 1000 person-years, respectively. The overall hospitalisation rate for infection in patients with CKD was approximately 2.9 times higher as compared to those without CKD.

For adult patients with ESRD, USRDS reports that the adjusted rates of infection-related hospitalisation in 2019 in patients on haemodialysis, peritoneal dialysis and those with kidney transplant were 0.34, 0.44 and 0.24 admission events per person-year [9]. The adjusted rates for vascular access-related infections (in patients on haemodialysis) and peritonitis (in patients on peritoneal dialysis) were 0.14 and 0.03 admission events per person-year. These rates have largely remained stable over last 5 years since 2016. Sepsis was recorded as cause of death in 6.5%, 9.4% and 12.5% of patients who were receiving haemodialysis, peritoneal dialysis or were kidney transplant recipients, respectively, and had died during 2019. Previous USRDS reports have shown that rehospitalisation rate during transition to dialysis was highest if the index hospitalisation was infection related. During the quarter before initiation of dialysis, 44% of patients were readmitted within 30 days of discharge after an infection-associated hospitalisation. In the quarter after dialysis initiation, 44% of patients died or needed rehospitalisation within 30 days of discharge after infection-associated hospitalisation. Therefore, it appears that infections not only lead to acute problems but may also identify patients at higher risk of repeated hospitalisations. Whether this risk is related to infections or is a marker of otherwise poor underlying state is not clear.

19.2.1 Urinary Tract Infections

Urinary tract infections (UTI) are more common in certain subpopulations with CKD. These include patients with vesicoureteric reflux; interference with the normal flow of urine, either due to structural lesions, stricture, renal stone disease or secondary to functional problems like neurogenic bladder and diabetic cystopathy; or specific abnormalities like polycystic kidney disease. In addition to the frequency, some conditions can lead to more severe and/or special forms of UTI such as acute pyelonephritis, renal abscesses, renal papillary necrosis, emphysematous and xanthogranulomatous pyelonephritis or renal mucormycosis. In patients with CKD and UTI, presence of diabetes mellitus, indwelling catheter, length of hospital stay and infection with *Klebsiella* spp. have been independently associated with development of septicemia/urosepsis [10].

Another important consideration is distinguishing colonisation from true UTI especially in patients with underlying risk factors. A diagnosis of UTI should be made only when a patient is symptomatic, urinalysis shows significant pyuria (≥5 pus cells/hpf in centrifuged urine sample) and urine culture shows a significant growth. Asymptomatic bacteriuria is treated only in pregnant females and patients who have to undergo either surgery or instrumentation of the urinary tract which may involve mucosal breach. The 2019 Infectious Diseases Society of America (IDSA) update recommends starting broad spectrum antimicrobial treatment directed against urinary source in older patients with functional or cognitive impairment and bacteriuria, fever and other systemic signs consistent with sepsis but without any other localising features [11].

Established UTI in patients with CKD is treated as in general population. However, certain important considerations apply in this situation. First, if the basic disease leading to CKD is associated with any structural or functional alteration in the urinary tract, the initial treatment course is given for extended period (2–4 weeks depending on whether it is lower or upper UTI), and prophylaxis is given for 6–12 months if there are recurrent episodes of UTI. Second, the choice of antibiotics and their dosage may have to be changed in accordance with the degree of renal dysfunction. Nitrofurantoin which is commonly used for treatment and prophylaxis of UTI in general population is contraindicated in

patients with eGFR <50 mL/min/1.73 m^2. Third, risk of other complications like hyperkalaemia in CKD patients especially those on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may forbid long-term use of drugs like trimethoprim-sulfamethoxazole which are commonly used in general population for prophylaxis. Fourth, cyst infection is a unique form of kidney infection seen in polycystic kidney disease patients which requires prolonged course of antibiotics (up to 6 weeks) and at times may be refractory and thus require surgical intervention. Whereas trimethoprim-sulfamethoxazole remains the first choice in acute, uncomplicated, lower UTI in patients with CKD stage 3a, either ciprofloxacin or extended spectrum penicillin like pivmecillinam (especially in European countries where it is available) are recommended in CKD stages 3b–5. Local patterns of urinary tract pathogens and their drug sensitivities may be considered to modify recommendations in local context. It is important to note that the duration of treatment of acute, uncomplicated, lower UTI in females and males without any predisposing factors is different at 3 and 7 days, respectively. It is very important that attempts at modifying risk factors for recurrent UTI (e.g. surgical relief of obstruction, clean intermittent self-catheterisation in large volume neurogenic bladder) are made early as treatment becomes increasingly difficult because of urinary tract colonisation with drug-resistant organisms.

19.2.2 Pneumonia

Community-acquired pneumonia is a common cause of hospitalisation in general population. The risk of pneumonia increases progressively with fall in GFR. Compared to those without kidney disease, the incidence of pneumonia in patients with CKD is 2.3 times higher [12]. This risk further translates into increased severity of disease at admission and higher mortality rates during admission and at 1 month after discharge. *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia in CKD patients. Vaccination against pneumococcus has been shown to be beneficial in improving outcomes. It has also been shown to be cost effective in adults aged 50 years or older [13]. CKD patients are also at increased risk of developing severe forms of influenza.

19.2.3 COVID-19

Since early in 2020, the SARS-CoV2 virus infection became an important cause of morbidity and mortality in patients with kidney disease. COVID-19, which started in late 2019, has had direct and indirect effects which have greatly impacted the care of patients with kidney disease. Patients with CKD, ESRD on dialysis or kidney transplants are variably immunosuppressed, and hence, at high risk of acquiring this infection as well as development of complications. Though pneumonia leading to respiratory failure is the most important complication, COVID-19 is now recognised as a multi-system disease with both short- and long-term implications. Renal manifestations include proteinuria, microscopic haematuria, pyuria, tubular dysfunction, hyponatremia, occasional glomerular syndromes like podocytopathy, collapsing glomerulopathy, etc. and AKI. Though the reported incidences vary with the type of setting and study population, AKI has been reported to be a common complication in patients hospitalised with COVID-19. A recent meta-analysis reported overall incidence of AKI as 12.3% (95% CI 7.3–20.0%) [14]. Majority (77%) with AKI were critically ill and almost one-fourth needed dialysis. Not surprisingly, mortality was 13 times higher in patients with AKI as compared to those without AKI. Recent data on long-term renal outcomes after COVID-19 suggest that these patients, particularly those with AKI or long COVID, are at risk of major adverse kidney events (MAKE) in future. Data from a large cohort of US Veterans showed that for patients who survived beyond 30 days after COVID-19, the adjusted risk for AKI (HR, 1.94; 95% CI, 1.86–2.04), eGFR decline ≥30% (HR, 1.25; 95% CI, 1.14–1.37), eGFR decline ≥40% (HR, 1.44; 95% CI, 1.37–1.51), eGFR decline ≥50% (HR, 1.62; 95% CI, 1.51–1.74), ESRD (HR, 2.96; 95% CI, 2.49–3.51) and MAKE (HR, 1.66; 95% CI, 1.58–1.74) were

higher as compared to non-infected controls [15]. The treatment guidelines for COVID-19 are no different in patients with kidney disease except for the fact that caution may be needed with respect to drug interactions and dosing. For newer drugs, use in experimental settings is advocated till definite data becomes available.

Patients on maintenance haemodialysis constituted a special group that was hugely impacted by the COVID-19 pandemic. Disruption of medical facilities and diversion of resources towards containment of pandemic impaired access to dialysis. Overall, mortality in dialysis patients due to COVID-19 ranged between 20 and 30% which was almost four times higher than what was recorded in patients with pre-dialysis CKD [16]. In a meta-analysis that included kidney transplant recipients with COVID-19, AKI and mortality were reported in 50% and 23% of patients, respectively [17].

19.2.4 HIV Infection

The prevalence of CKD is increased in incident patients of HIV infection starting antiretroviral therapy. About one-third of patients with HIV infection have CKD. The spectrum of kidney involvement in HIV infection ranges from asymptomatic proteinuria to nephrotic syndrome, acute kidney injury or progressive decrease in GFR. A pathologic classification based on dominant involvement of glomerular or tubulointerstitial or vascular compartments or kidney disease due to other aetiologies in HIV has been proposed [18]. The majority of patients have HIV-associated nephropathy (HIVAN) which most frequently presents as nephrotic syndrome and is characterised histologically by collapsing glomerulopathy and variable tubulo-interstitial involvement. African American race, APOL1 high-risk variants, decreased CD4 counts and family history of kidney disease are risk factors for development of HIVAN. All patients with HIVAN should be given antiretroviral therapy irrespective of their eGFR. In CKD patients, the presence of HIV infection is considered a risk factor for accelerated decline in GFR. Conversely, presence of CKD is also a risk factor for progression of HIV infection. Drug interactions and drug-induced kidney injury are very important treatment considerations in patients with HIV and CKD. In patients with reduced eGFR, proteinuria, age >60 years or comorbidities like HCV co-infection, diabetes mellitus, uncontrolled hypertension or history of cardiovascular disease, the following nephrotoxic drugs may be avoided: atazanavir, lopinavir, indinavir and tenofovir disoproxil fumarate. The risk of lactic acidosis does not forbid the use of nucleoside analogues in patients with CKD, but careful monitoring is advisable. Though annual screening for kidney involvement by urine protein and eGFR estimation is recommended, this frequency should be increased to biannually in patients at risk of drug-induced kidney injury or those with presence of other comorbidities that predispose to kidney disease. Finally, as the life expectancy of HIV-infected population on therapy has progressively increased, unrelated risk factors for CKD, e.g. diabetes, hypertension, etc., have also become important now. Effectively treated ESRD patients for ≥6 months and without any opportunistic infections or malignancy may be candidates for kidney transplantation.

19.2.5 Vascular Access-Related Infections

Patients with CKD are at risk of potentially lethal vascular access-related infections later in the course of disease because attention is not paid to timely creation of appropriate access. As a result, large proportions of CKD patients start dialysis with central venous catheters. The risk is highest for non-tunnelled central venous catheters followed by tunnelled ones, arteriovenous grafts and native arteriovenous (AV) fistulae [19]. Amongst 1846 participants in the HEMO study, of whom only 7.6% were using catheters, first infection-related hospitalisation was due to non-access-related infection in 79% patients [20]. However, in HD population using catheters for vascular access at a large centre in the USA, non-access-related infections accounted for just 12% of all proven infectious episodes [21]. *Staphylococcus aureus*, coagulase-negative staphylococci and

enterococci are the most common organisms responsible for access-related bloodstream infections and may become complicated by infective endocarditis or osteomyelitis. Recent data highlight that increasing proportion of such infections are now being caused by gram negative organisms [19]. Of particular concern are infections with multidrug-resistant bacteria and nosocomial transmission to other patients. As a result of these problems, timely creation of AV fistulae, dubbed the 'Fistula First' initiative, is targeted at reducing catheter usage.

19.2.6 Blood-Borne Infections

Patients with CKD are at risk of acquiring blood-borne infections like hepatitis B and C due to repeated skin punctures, need of blood or blood products and sharing of contaminated machines, surfaces or supplies in hospitals. Better staff training, improved infection control practices, regular screening and universal vaccination of patients and staff have reduced the HBV prevalence and seroconversion rates [22]. HCV infection, an important problem with prevalence ranging from 0.7 to 18.1% in Asia-Pacific countries and 2.7 to 20% in Europe till few years back, is now being treated effectively with the advent of directly acting antiviral agents (DAA). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were updated in 2018 in view of new evidence that showed high effectiveness of DAA based therapies in patients with varying degrees of kidney dysfunction [23] (see Chap. 20). As is true for antiretroviral therapy, drug interactions need to be kept in mind while prescribing DAAs. KDIGO recommends strict infection control measures as the most important tool for preventing its spread.

19.2.7 Tuberculosis

Tuberculosis is an important infection in patients with CKD, with up to five times higher risk as compared to general population [24–26]. The risk is even higher in kidney transplant recipients at almost 11 times as compared to general population [24]. The diagnosis is not straightforward as the disease is more commonly extra-pulmonary with variable nonspecific manifestations like fever, weight loss, malaise, etc., which frequently delay diagnosis. Therefore, a high index of suspicion is required. As definitive diagnosis by culture takes a long time and absence of acid-fast bacilli on staining does not rule out tuberculosis, treatment is often started empirically in a significant proportion of patients on the basis of strong clinical suspicion and suggestive investigations, e.g. granulomatous inflammation on histopathology. There is controversy about the need and optimal method of screening for latent tuberculosis. However, the utility of screening in endemic regions with high prevalence of this disease is not clear. Interferon gamma assays like QuantiFERON-TB Gold test have been shown to be better than tuberculin skin test for detecting latent tuberculosis. Tuberculosis is treated as in non-CKD population, but drug dose modification for level of eGFR is recommended.

19.2.8 Other Infections

The incidences of dyspepsia and gastroduodenal disease are more in CKD patients as compared to general population. Though *Helicobacter pylori* infection has been found to be less prevalent in patients with chronic kidney disease, whenever present, it is treated as in patients with normal renal function [27]. Similarly, infective endocarditis is also treated as in general population. Patients with CKD and risk factors for development of infective endocarditis (prosthetic heart valves, valvular heart disease, valvular calcification, etc.) should receive antibiotic prophylaxis (amoxicillin 2 g or clindamycin 600 mg) prior to invasive dental and periodontal procedures.

It has been shown that mortality after septic shock due to various reasons is significantly more in patients with reduced GFR. In fact, eGFR <60 mL/min/1.73 m^2 remains an independent predictor of early and late mortality in patients with septic shock even after correction for comorbidities like diabetes, hypertension and cardiovascular disease.

The treatment of essentially all infectious diseases is same as in general population. However, drug dose modification or choosing alternative drug may be required as per patient's eGFR.

19.3 Infection Control in CKD

Globally, infection control and prevention is one of the biggest goals of public health. According to the World Health Organization (WHO), the objective of infection prevention and control is to ensure protection of those who might be vulnerable to an infection either in general community or while utilising health-care facilities. WHO identifies hygiene as the basic principle of infection prevention and control. Patients with CKD are treated in the same manner as are general non-CKD population for established infections. Important considerations in this population include the assessment of comorbidities and risk factors, antimicrobial dose adjustment for level of kidney function, consideration of drug interaction and preventing superimposed acute kidney injury due to infections or use of radiocontrast agents or drugs used to treat the infection.

19.3.1 Vaccination in Patients with CKD

In addition to general measures, timely vaccination is important in infection control (Box 19.3). The impact of vaccination in preventing, eliminating and eventually eradicating the disease has been convincingly demonstrated throughout the world through the universal immunisation programmes. The Advisory Committee on Immunization Practices (ACIP) in the US annually updates and recommends immunisation schedules for children and adults. Kidney disease patients are classified at having high infection risk. Although vaccination is effective in CKD, these patients mount an inferior response to vaccination and suffer relatively rapid decline in protective antibody titres as compared to general population.

Box 19.3 Measures Aimed at Reducing Infections in CKD Patients

1. Vaccination against vaccine-preventable diseases
2. Timely creation of dialysis access
3. Maximising use of native arteriovenous fistulae in prevalent and incident haemodialysis patients
4. Universal precautions to be followed at health-care facilities
5. Rationalising antibiotic use according to local antimicrobial resistance data
6. Practising hand hygiene by patient and caregiver

It is important to assess and record immunisation history of every CKD patient at initial presentation. Physicians should be aware of differences between contraindications and precautions with respect to vaccination. While a contraindication precludes vaccination because of significant risk of adverse events, a precaution either means slightly increased risk of adverse events or decreased immune response to vaccine.

Severe allergic reaction or anaphylactic response to a vaccine or its constituents (e.g. egg, gelatin, latex, adjuvants) is a contraindication. Usually, vaccines are not administered even in situations where precaution is advised. It is important to note that not all contraindications or precautions are permanent. Mild acute febrile illnesses, previous mild local reactions and breastfeeding are not contraindications to vaccination. Vaccination should be deferred for 4 weeks after recovery from acute febrile illnesses. Live virus vaccines (varicella, zoster and MMR) are contraindicated in pregnancy and states of severe immunosuppression, e.g. primary or acquired immunodeficiency, steroid dose equivalent of prednisolone dose $\geq$20 mg/day for $\geq$2 weeks, malignancies involving the bone marrow or lymphatic system, etc. Particular attention should be paid to storage conditions, vaccine diluents, dose, site and mode of administration. Adult vaccines are usually administered by intramuscular route

except varicella, zoster, MMR and inactivated meningococcal polysaccharide vaccine which are given by subcutaneous route. Multiple vaccines can be administered simultaneously, but sites should be separated by at least 1–2 in. However, if immune globulin is also administered, a different anatomic site should be used.

All HbsAg-negative and anti-HBs negative patients must be vaccinated against HBV at the time of initial diagnosis irrespective of the stage of CKD. Higher dose of 40 μg in a four-dose schedule (0, 1, 2 and 6 months) has been shown to achieve higher seroconversion rates [28]. Though seroconversion rates in pre-dialysis stages of CKD are better, they are still suboptimal as compared to general population. An anti-HBs titre of >10 IU/L is considered protective and titre below this level warrants booster dose. A number of strategies have been used to increase the immunogenicity: these include increasing dose and frequency of vaccination, intradermal route of administration, using pre-S2/S antigens, use of adjuvants like 3-0-desacyl-4′-monophosphoryl lipid A adsorbed on aluminium phosphate and immunostimulants like levamisole and granulocyte macrophage colony stimulating factor. The data, however, is inconclusive because of small sample sizes, variable doses and schedules and conflicting results. The antibody titres should be monitored annually in all previously vaccinated patients to ensure maintenance of protective levels.

Annual vaccination against influenza decreases the risk of hospitalisation and death in CKD patients. Only inactivated influenza vaccine is recommended. Pneumococcal vaccination is also recommended for all patients with renal failure. A large retrospective analysis of about 37,000 patients on dialysis in the US has shown that vaccination against influenza and pneumococcus was independently associated with survival [29]. As compared to no vaccination, adjusted odds ratio of all-cause mortality amongst patients vaccinated for influenza alone and both influenza and pneumococcal vaccination were 0.79 (95% CI, 0.72–0.86) and 0.70 (95% CI, 0.62–0.78), respectively. The KDIGO clinical practice guidelines for management of CKD also recommend vaccination against influenza, pneumococcus and HBV. ACIP recommends that except for meningococcal, *Haemophilus influenzae* type b and hepatitis A vaccines, all other recommended vaccines should be considered in adult patients with CKD if they have not received them (Table 19.1). Vaccination against *Staphylococcus aureus* has not been found to be effective in preventing septicaemia in dialysis patients and is not recommended. Routine paediatric immunisation schedule should be followed in children with CKD. Only inactivated polio vaccine should be used in patients with renal failure. As previously stated, live influenza vaccine is contraindicated, and caution is required before use of other live vaccines in children with CKD.

All patients with advanced CKD should preferably be vaccinated before kidney transplantation. The seroconversion rates come down drastically if vaccines are administered after transplantation. Live vaccines are contraindicated in kidney transplant recipients, and it is preferable to postpone other vaccinations till 6 months after transplant.

Vaccination is strongly advocated against COVID-19 in patients with CKD, ESRD or kidney transplant recipients, as these groups are at higher risk of developing severe COVID-19. As is expected, the response to vaccination is inferior as compared to that in normal individuals. Nevertheless, the neutralising antibody response improves with booster doses given after usual two-dose schedule for most of the vaccines. The emergence of newer variants of concern, higher likelihood of their antibody escape and possible waning of pre-existing antibody titres also speak for periodic booster doses, especially as vaccines are updated to provide protection against the new variants. Vaccine hesitancy was identified as an important barrier to vaccination, especially in poorly informed and under-privileged groups. Currently, four main types of vaccines are available: mRNA, killed whole virus, purified virus component and replication defective viral vector carrying pathogen gene vaccine. Access is variable depending on availability and local regulatory approvals. Preliminary data suggest that mRNA vaccines may be more

Table 19.1 Vaccine recommendations for adult patients (age ≥ 19 years) with chronic kidney disease

Vaccine	Dose	Frequency	Considerations
Hepatitis B[a]	3–4	Once Revaccinate with booster dose. Check anti-HBs titres if anti-HBs titres fall <10 mIU/L	
Inactivated influenza	Single	Annual	Precaution to be exercised for intranasally administered live, attenuated influenza vaccine in patients with renal disorders
Tetanus, diphtheria, pertussis (Td/Tdap)[b]	Single	Every 10 years	None
Varicella	Two (4–8 weeks apart)	Once	None
Human papillomavirus	2–3 doses	Once	Through age 26 years depending on age at initial vaccination or condition
Zoster	Two (2–6 months apart)	Once	Recommended for all adults aged ≥50 years irrespective of past history of herpes zoster
Measles, mumps, rubella (MMR)	1–2[c]	Once	None
Pneumococcal	1–2	One dose of PCV15 followed by PPSV23 at ≥8 weeks OR One dose of PCV20	None
Hemophilus influenzae type b	Single	Once	Recommended only in cases of anatomical or functional asplenia (preferably at least 14 days prior to splenectomy) 3 dose series 4 weeks apart 6–12 months after successful haematopoietic stem cell transplant (regardless of previous Hib vaccination)
Meningococcal	1–2 (MenACWY)	Revaccinate every 5 years till risk factors present	Recommended only in adults with anatomic or functional asplenia or persistent complement component deficiencies, complement inhibitor use, HIV infection or high risk, e.g. occupational exposure, dormitory residence, travel to hyperendemic or epidemic areas
	2–3 (MenB)		Wherever indicated, both MenACWY and MenB need to be administered

Hepatitis A[d]	2–3	Once	Recommended only in adults with risk factors, e.g. occupational exposure, HIV infection, drug abuse, gay men, chronic liver disease, travel to endemic areas
COVID-19	2 doses (4–12 weeks apart depending on type of vaccine)	Booster doses required depending on variant patterns, response to primary vaccination, etc.	Recommended for all (in patients on significant immunosuppression, decisions to be taken based on risk/benefit assessment)

Source: Data from Advisory Committee on Immunization Practices (ACIP) [30]

All are recommended in CKD patients without documented previous vaccination or disease except meningococcal and hepatitis A vaccines which are recommended only in certain high-risk groups. Note that zoster vaccination is recommended irrespective of previous zoster infection. The availability and types of vaccine may vary with regions. Kindly go through individual vaccine's manufacturer's recommendations

MenACWY Meningococcal serogroups A, C, W, Y vaccine, *MenB* Meningococcal serogroup B vaccine, *PCV15* Pneumococcal 15-valent conjugate vaccine, *PCV20* Pneumococcal 15-valent conjugate vaccine, *PPSV23* Pneumococcal 23-valent polysaccharide vaccine

[a] 40 μg/mL (Recombivax HB®) administered on a three-dose schedule at 0, 1 and 6 months or two doses of 20 μg/mL (Engerix-B®) administered simultaneously on a four-dose schedule at 0, 1, 2 and 6 months

[b] 1 dose Tdap, then Td or Tdap every 10 years in those who did not receive Tdap at or after age 11 years; give primary vaccination if patient did not receive primary vaccination for tetanus, diphtheria or pertussis

[c] Two doses recommended for adults who are students in postsecondary educational institutions, work in a health-care facility, plan to travel internationally or close personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps or rubella

[d] Administer in a two-dose schedule at either 0 and 6–12 months (Havrix) or 0 and 6–18 months (Vaqta) or 3 dose series of HepA-HepB (Twinrix) at 0, 1, 6 months

immunogenic as compared to adenoviral vector vaccines in dialysis patients [31]. However, patients should be encouraged to take vaccines as per availability and prevailing dosing recommendations. Decisions need to be individualised in cases with active autoimmune kidney diseases or on significant immunosuppressive therapy. Despite inferior immunogenic responses, vaccination does protect these patients against severe disease.

Despite recommendations, the overall vaccination rates remain low, varying from 26 to 65% and 15 to 46% in dialysis and pre-dialysis CKD patients, respectively. Targeted interventions at educating health-care staff coupled with regular monitoring and review have been shown to improve vaccination rates.

19.4 Conclusion

Infections are common cause of morbidity and mortality in CKD patients. Increasing patient age, presence of multiple comorbidities, the underlying immunosuppressive uraemic milieu and the use of dialysis catheters contribute to the infection risk, complicate clinical presentation and make management complex. Prevention of infections requires institution and implementation of appropriate guidelines including vaccination (Boxes 19.4 and 19.5). Tuberculosis is an important infection in certain geographic areas and requires high degree of clinical suspicion for timely diagnosis.

Box 19.4 What the Guidelines Say You Should Do?

1. All general principles of infection control and management apply in CKD population.
2. Always consider drug dose modifications and try to prevent drug-induced nephrotoxicity in patients with CKD.
3. Trimethoprim-sulfamethoxazole is the drug of choice for acute, uncomplicated, lower UTI in patients with CKD stage 3a.
4. Ciprofloxacin or extended spectrum penicillin like pivmecillinam is the drug of choice for acute, uncomplicated, lower UTI in patients with CKD stage 3b to 5.
5. Tuberculosis in CKD
   (a) Tuberculin skin testing may be negative in CKD patients despite infection.
   (b) Patients with active tuberculosis should receive standard chemotherapeutic agents for standard duration with drug dose modifications for level of eGFR.
6. HIV in CKD
   (a) All patients with HIVAN should be given antiretroviral therapy irrespective of their eGFR.
   (b) Annual screening for renal involvement by urine protein and eGFR estimation is recommended. However, this frequency should be increased to biannually in patients who are at risk of drug-induced kidney injury or have other risk factors for kidney disease.
   (c) Drug dose modification and interactions should be considered before prescribing drugs in CKD patients with HIV infection.
7. Vaccination in CKD
   (a) Consider individual's immune status and specific vaccine recommendations before using live vaccines in CKD patients.
   (b) All CKD patients should be vaccinated against hepatitis B virus, pneumococcus and influenza virus at diagnosis, if they are vaccination naive.
   (c) Revaccinate annually against influenza virus and every 5 years against pneumococcus.
   (d) Monitor anti-HBs titres annually and revaccinate with booster dose if titres are below <10 IU/L.
   (e) All patients should be encouraged to get COVID-19 vaccines as per prevailing recommendations.

Box 19.5 Relevant Guidelines

1. KDIGO Clinical Practice Guideline for Hepatitis C in Chronic Kidney Disease
   Executive summary of the 2018 KDIGO Hepatitis C in CKD Guideline: welcoming advances in evaluation and management. Kidney Int. 2018;94(4):663–73. (https://www.sciencedirect.com/science/article/pii/S0085253818304484?via%3Dihub)
2. Scottish Intercollegiate Guidelines Network
   Management of suspected bacterial urinary tract infection in adults. Scottish Intercollegiate Guideline Network Guideline No.88 July 2012 (http://www.sign.ac.uk/pdf/sign88.pdf).
3. Advisory Committee on Immunization Practices (ACIP) Guideline
   Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(7):229–33.
   (https://www.cdc.gov/mmwr/volumes/71/wr/mm7107a1.htm?s_cid=mm7107a1_w)
4. Infectious Diseases Society of America Guideline
   Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10):e83–e110. (https://academic.oup.com/cid/article/68/10/e83/5407612?login=true)
5. British Thoracic Society Guideline
   Milburn H, Ashman N, Davies P, Doffman S, Drobniewski F, Khoo S, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. Thorax. 2010;65(6):557–70. (http://thorax.bmj.com/content/65/6/559.long)
   NICE Guideline for tuberculosis (2016) (https://www.nice.org.uk/guidance/ng33/resources/tuberculosis-pdf-1837390683589)

Before You Finish: Practice Pearls for the Clinician

- Despite decrease in the rate of access-related and blood-borne infections, the overall rate of infections in dialysis patients remains high.
- Improving native arteriovenous fistula utilisation, reducing catheter use, timely vaccination and implementation of infection control guidelines are important for preventing access-related infections.
- CKD patients need to be vaccinated against hepatitis B virus, pneumococcus, COVID-19 and influenza as early as possible.
- Vaccination response may be suboptimal and needs monitoring in subjects with CKD.
- Management considerations include measures to prevent acute kidney injury and drug toxicity.
- Tuberculosis is important in certain geographic areas and requires high degree of clinical suspicion for timely diagnosis.

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Endocrine Disorders in Chronic Kidney Disease

20

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Before You Start: Facts You Need to Know

- The kidney is the site of synthesis and degradation of several hormones.
- CKD patients are characterized by the deficiency of hormones like erythropoietin, calcitriol, insulin-like growth factor, and testosterone.
- In contrast, the accumulation of insulin, prolactin, aldosterone, and growth hormone occurs in these patients.

20.1 Introduction

Endocrine abnormalities in patients with chronic kidney disease (CKD) may arise from a number of different causes, which are summarized in Table 20.1. Kidney plays a crucial role in the synthesis and degradation of several hormones. Moreover, different concomitant conditions like inflammation, malnutrition, and metabolic acidosis participate in the pathogenesis of endocrine alterations in these patients.

In CKD patients estimation of many hormones' serum concentration *per se* often fails to provide a correct assessment of the adequacy of patient's hormonal status (e.g. hormone concen-

Table 20.1 Selected pathomechanisms leading to endocrine abnormalities in chronic kidney disease

Type of defect	Example
Abnormalities of hormone production	
Reduced hormone production by the kidney	Erythropoietin, $1,25(OH)_2D_3$
Reduced hormone production in endocrine organs	Testosterone, estrogen
Abnormal secretion pattern (pulsatility; circadian rhythm)	PTH, GH, LH
Reactive hypersecretion of hormone to reestablish homeostasis	Erythropoietin, PTH, FGF 23
Inappropriate hypersecretion due to disturbed feedback	LH, prolactin, corticotropin
Abnormalities of hormone catabolism	
Decreased metabolic clearance	PTH, insulin, gastrin, leptin, adiponectin, vasopressin
Abnormalities of hormone action	
Disturbed activation of prohormones	Proinsulin, thyroxin (T_4)
Increased isoforms with potentially less bioactivity (due to posttranscriptional modifications)	LH
Increased hormone-binding proteins in serum reducing availability of free hormone	IGF
Decreased hormone-binding proteins increasing availability of free hormone	Leptin
Changed receptor number, structure, modification	Vitamin D receptor
Disturbed postreceptor cellular signaling	Insulin, GH

$1,25(OH)_2D_3$ 1,25-dihydroxyvitamin D_3, *PTH* parathyroid hormone, *GH* growth hormone, *LH* luteinizing hormone, *FGF 23* fibroblast growth factor 23, *IGF* insulin-like growth factor

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trations may be inappropriately high or low in the context of the magnitude of stimulating, or suppressing signals, the test may detect inactive hormone isoforms, or the response of the target organ may be altered—either aggravated or blunted—the so-called hormonal resistance frequently seen in uremia). It is therefore necessary to interpret serum hormone concentrations with the consideration of underlying clinical context (e.g. insulin concentration in relation to glucose concentration, parathyroid hormone—PTH concentration in relation to serum ionized calcium concentration).

20.2 Abnormalities in the Erythropoietin Secretion

In the adults, kidneys produce ca. 85–90% of circulating erythropoietin (EPO). The liver is the source of the rest 10–15% of circulating EPO. Within the kidneys, EPO is synthesized by peritubular, interstitial cells found mainly in the renal cortex and outer medulla. The main stimulus for EPO synthesis is renal hypoxia, which is caused by anemia or hypoxemia. Hypoxia stimulates the stabilization of hypoxia inducible factor (HIF), which is quickly degraded in normoxemic conditions. Among a wide set of genes activated by HIF the *Epo* gene is regulated with particular receptiveness—resulting in an extensive EPO-mRNA transcription. Besides hypoxia, also angiotensin II stimulates EPO production.

Conversely, inflammatory proteins (interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α)) inhibit EPO secretion. The serum EPO concentrations in anemic CKD patients are usually comparable to those obtained in non-anemic subjects with intact kidney function, but they are inappropriately low taking into account actual blood hemoglobin concentrations. Moreover in CKD patients the erythropoietin resistance also occurs [1, 2]. Anemia is the direct clinical consequence of EPO deficiency in CKD patients. The measurement of serum EPO concentration in CKD patients is not useful in clinical practice. Decisions concerning treatment with erythropoiesis-stimulating agents (ESAs) in CKD patients should be based on blood hemoglobin concentration and whole clinical status, and not on serum EPO concentration (see Chap. 15).

20.3 Abnormalities in the Vitamin D Metabolites

In the general population, vitamin D deficiency has been linked to increased prevalence of albuminuria, hypertension, cardiovascular diseases, metabolic syndrome, insulin resistance, and obesity. The prevalence of 25-vitamin D_3 deficiency increases with the progression of CKD and reaches 80% in CKD stage 5 patients. Moreover, in patients with nephrotic syndrome, the 25(OH)D_3 is lost with the urine and in CKD patients treated with peritoneal dialysis is lost with the peritoneal fluid (dialysate). Vitamin D supplementation in CKD patients is considered safe. In patients with clinical signs of vitamin D deficiency, i.e. hypocalcemia and hyperparathyroidism, such therapy may be recommended.

25(OH)D_3 is transported to the kidneys for further hydroxylation, resulting in the production of the active metabolite 1,25$(OH)_2D_3$. With worsening of kidney function, decline in the activity of 1α-hydroxylase, the enzyme converting 25(OH)D_3 to 1,25-dihydroxyvitamin D_3 (calcitriol) is observed. Moreover, less of 25(OH)D_3 is delivered to the kidney. Additionally, increased serum concentration of fibroblast growth factor 23 (FGF 23) may directly inhibit renal 1-α-hydroxylase, thus reducing the conversion of 25(OH)D_3 to 1,25$(OH)_2D_3$, and stimulating 24-hydroxylase which in turn increases the conversion of 25(OH)D_3 to biologically inactive 24,25 $(OH)_2D_3$. Therefore, in CKD stage 5 patients, serum 1,25$(OH)_2D_3$ concentration is reduced. Moreover, CKD patients develop organ resistance to the action of 1,25$(OH)_2D_3$, because of the decrease in the density of 1,25$(OH)_2D_3$ receptor (VDR). Recently, there is evidence growing that hypomagnesaemia is a potent factor in the development of vitamin D deficiency, as 1-α-hyroxylase, 24-hydroxylase and 25-hydrox-

ylase, as well as vitamin D binding protein activity are all dependent on the presence of Mg^{2+}.

The $1,25(OH)_2D_3$ deficiency in CKD patients plays an important role in the pathogenesis of secondary hyperparathyroidism, defective intestinal absorption of calcium, skeletal resistance to the calcemic action of PTH, defective mineralization of bone, growth retardation in children, and proximal myopathy. Clinical studies suggest that $1,25(OH)_2D_3$ deficiency increases cardiovascular and general mortality in CKD patients. The results of the small interventional studies suggested that treatment with calcitriol or other VDR agonists may reduce the mortality among these patients. Some published studies show that $1,25(OH)_2D_3$ deficiency increases proteinuria and paricalcitol treatment reduces proteinuria in CKD patients. However, these studies enrolled only modest number of patients, and therefore more, larger studies are needed in the abovementioned areas [3–5]. It is noteworthy though, that the recently published results of large placebo-controlled studies (VIDA and VITAL) showed no benefit of vitamin D intervention in patients from the general population.

The other abnormalities in the endocrine regulation of calcium and phosphate metabolism (among others, PTH and fibroblast growth factor 23) in CKD are discussed in detail in Chap. 16.

20.4 Abnormalities in the Hormones of the Hypothalamic–Pituitary–Gonadal Axis in Men with CKD

Men with CKD are characterized by a variety of derangements of the hypothalamic–pituitary–gonadal axis (Table 20.2). The most important abnormalities are related directly to the gonadal function.

20.4.1 Luteinizing Hormone

In CKD patients, the lack of appropriate cyclic release and decreased amplitudes of the secretory bursts of gonadotropin-releasing hormone (GnRH) by the hypothalamus lead to a loss of normal pulsatile luteinizing hormone (LH) release by the pituitary. The causes of impaired cyclic release of GnRH are hyperprolactinemia and high serum GnRH and LH concentrations caused mainly by their reduced renal clearances [5, 6].

Table 20.2 Abnormalities in the hormones of hypothalamic–pituitary–gonadal axis in chronic kidney disease

	Male	Female
LH	↑	↑
FSH	↑	N
Prolactin	↑	↑
Testosterone	↓	–
Estradiol	–	↓
Progesterone	–	↓

FSH follicle-stimulating hormone, *LH* luteinizing hormone, *N* normal

In the majority of CKD patients, basal serum LH concentrations are elevated. High serum LH concentrations in CKD patients result from a decreased rate of catabolism and lack of testosterone inhibition (due to low serum testosterone concentration in CKD) of GnRH secretion and secondarily also LH secretion.

20.4.2 Follicle-Stimulating Hormone

In CKD patients, serum concentrations of follicle-stimulating hormone (FSH) are in the upper normal range, or elevated. FSH is an important factor in spermatogenesis. It stimulates testicular growth and increases the production of testosterone-binding protein by Sertoli cells. In CKD patients, spermatogenesis is impaired despite elevated blood levels of FSH. This is probably due to the resistance of the testis to the action of FSH, due to primary testicular dysfunction, and also by the reduced serum inhibin concentration [5, 6].

20.4.3 Prolactin

Serum prolactin concentrations are elevated in the majority of male hemodialysis patients. Apart from elevated basal prolactin concentrations, the

circadian rhythm of prolactin secretion is also disturbed. Moreover, the sleep-induced secretory bursts are not observed, although episodic secretion occurs during the daytime. It seems that both diminished prolactin clearance and increased production rate (probably due to inadequate dopaminergic inhibition of prolactin release from pituitary) contribute to hyperprolactinemia in CKD patients [7, 8]. Prolactin accumulation leads to inhibition of GnRH pulsatile secretion and testosterone synthesis which resulted among others with sexual dysfunction and infertility. Interestingly, in some CKD patients, correction of the hyperprolactinemia by bromocriptine caused improvement of sexual function. There is evidence, suggesting that hyperprolactinemia may participate in the endothelial dysfunction frequently observed in CKD patients. The association between hyperprolactinemia and negative cardiovascular outcome was found in CKD patients. In a small clinical study in patients with CKD, it was found that reduction of serum prolactin concentration with bromocriptine reduced blood pressure and left ventricular hypertrophy [6–8].

20.4.4 Testicular Hormones

In most male hemodialysis patients, serum testosterone concentrations are low. The normal circadian rhythm of serum testosterone concentrations, with a peak at 4–8 a.m. and nadir at 8–12 p.m., is maintained in CKD patients. The response to 4 days administration of human gonadotropin is sluggish and delayed; no increase in testosterone concentration was seen after 8 h, but a two to threefold increase was seen after 4 days.

With respect to the other androgens, decreased serum concentration of androstenedione and dehydroepiandrosterone sulfate has been reported in men with CKD. The Sertoli cells in the testis are responsible for production of other hormones, such as inhibin and anti-Müllerian hormone. Concentration of both of these factors is reduced in CKD—which as it was already mentioned leads to the increase of serum FSH concentration *via* impaired negative feedback loop. This suggests that probably uremic damage of the testis is the primary cause of androgen deficit in men with CKD. Also, malnutrition participates in the reduction of serum testosterone concentration in men with CKD, and low-protein diet, essential amino acid, and keto amino acid analog supplementation tends to raise serum testosterone concentration [6, 7, 9].

Androgen deficiency in CKD males may cause changes in body composition: body fat increases, while lean body mass (mainly muscles mass) is reduced. Androgen deficiency leads also to CKD-related bone disease and higher incidence of bone fractures, anemia, and ESAs hyporesponsiveness (due to reduced growth of differentiated stem cells and decreased sensitivity of erythroid progenitors to EPO), depression, decreased libido, and impairment of sexual function. Finally, it was recently shown that low serum testosterone concentrations were associated with worse outcomes in male hemodialysis patients [6, 9].

Therapy with exogenous testosterone is not exempted from risks, but results of recent studies seem to suggest that transdermal testosterone replacement therapy might be safe and effective in reversing the symptoms of testosterone deficiency and improve life quality of life in men with CKD [8, 9].

20.5 Abnormalities in the Hormones of the Hypothalamic–Pituitary–Gonadal Axis in Women with CKD

Women with CKD present a variety of derangements of the hypothalamic–pituitary–gonadal axis (Table 20.2). The consequences of these abnormalities are anovulatory menstrual cycles and infertility.

20.5.1 Luteinizing Hormone

Serum LH concentration is elevated in most premenopausal CKD patients. In healthy premenopausal women, the secretion of LH is pulsatile. In

women with CKD, the lack of appropriate cyclic release of GnRH by the hypothalamus leads to a loss of normal pulsatile LH release by the pituitary. In healthy women, estradiol lowers the amplitude of LH pulses. In women with CKD, estradiol fails to influence the LH surge, suggesting impaired feedback loop which results in impaired ovulation. The clinical consequence of the loss of normal pulsatile LH release by the pituitary in CKD women is infertility [6, 10].

20.5.2 Follicle-Stimulating Hormone

In contrast to the abnormal serum LH concentration, the serum FSH concentration is normal in most premenopausal CKD female patients. Therefore the FSH/LH ratio is decreased. The decreased FSH/LH ratio suggests the occurrence of severe hypothalamic–hypophyseal axis dysregulation [10].

20.5.3 Prolactin

Serum prolactin (PRL) concentrations are often elevated in women with CKD and the increase of serum prolactin after the administration of thyrotropin-releasing hormone (TRH) is blunted. Also, improper diurnal rhythm of prolactin secretion is usually seen and the sleep-induced bursts of PRL secretion are usually absent, although episodic secretion of prolactin in the daytime was noted [6, 8, 10]. Hyperprolactinemia in women with CKD is mostly caused by the reduced renal clearance of PRL and to some extent, by the increase of PRL secretion in the pituitary gland, which is caused by inadequate dopaminergic inhibition. Thus, in CKD woman with hyperprolactinemia, amenorrhea occurs frequently.

20.5.4 Estrogens

In women with CKD, serum estradiol concentrations may be normal, but more often are decreased and are consistently lower in woman with CKD and concomitant hyperprolactinemia. In the second half of the menstrual cycle, serum progesterone concentrations are low because of the defective luteinization of the follicles. The hormonal derangements in CKD women are clearly the consequence of deregulation of the hypothalamic–pituitary–ovarian axis [10].

A major consequence of low serum estrogen concentration concerns bone disease [11]. Amenorrheic patients had not only lower serum estrogen concentrations but also lower bone mineral density, compared to normally menstruating women requiring dialysis. Small clinical interventional studies suggest that treatment with transdermal estradiol and cyclic addition of norethisterone acetate or treatment with raloxifene, a selective estrogen receptor modulator (SERM), may increase bone mineral density of the lumbar spine in hemodialysis postmenopausal women. Nonetheless taking into consideration the potential adverse cardiovascular effects of hormone replacement therapy, it must be emphasized that currently long-term studies of safety of hormone replacement or SERM therapy in women with CKD are not available.

20.5.5 Anti-Müllerian Hormone

Anti-Müllerian hormone (AMH) is a 140 kDa glycoprotein, which is mostly synthesized by the granulosa cells that are surrounding the oocyte in the maturing follicles. The most important physiological function of AMH is the inhibition of excessive recruitment and growth of other follicles. This leads to the selection of a dominant follicle and takes place in the follicular phase of the menstrual cycle. Serum AMH concentration tends to be constant during the entire menstrual cycle. It reflects the number of growing follicles and is proportional to the pool of primordial follicles. This is why serum AMH concentration is considered to be one of the best markers of ovarian reserve. The highest serum AMH concentration is found in women around 25 years of age, then it decreases with age, until circulating AMH is usually undetectable in postmenopausal woman. The diminishing serum AMH concentration may be an indicator of either physiological

or premature aging of the gonads. CKD women are characterized by significantly lower serum AMH concentration, which seems to suggest that a decrease in AMH secretion by the damaged granulosa cells and a reduction of ovarian reserve are the most pronounced causes of diminished fertility in women with CKD [6].

20.6 Abnormalities in the Growth Hormone/Insulin-Like Growth Factor (Somatotropic) Axis

The somatotropic axis comprises growth hormone (GH), insulin-like growth factor 1 and 2 (IGF-1 and -2), six IGF-binding proteins (IGFBP-1 to -6), and the IGFBP proteases (BP-Pr). All are involved in the modulation of somatic growth, cellular proliferation, and metabolism. Several abnormalities (Box 20.1) in the somatotropic axis have been reported in children and adults with CKD [12, 13]. The clinical consequence of these abnormalities is growth retardation and reduced final height in CKD children. It was also shown that growth failure in CKD patients is associated with increased morbidity and mortality [12, 14].

Box 20.1 Abnormalities in the Growth Hormone/Insulin-Like Growth Factor Axis in Chronic Kidney Disease

Growth hormone
Increased serum GH concentration
Peripheral resistance to GH due to defect in GH intracellular signal transduction
Insulin-like growth factor
Decreased IGF-1 serum concentration
Reduced free IGF-1 serum concentration
Increased IGFBPs (IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6) serum concentration
Presence of low molecular weight (1000 Da) inhibitor of IGF-1 in serum
Peripheral resistance to IGF-1 due to postreceptor defect in IGF-1 action

GH growth hormone, *IGF- 1* and *IGF- 2* insulin-like growth factor-1 and -2, *IGFBP* IGF-binding protein

20.6.1 Growth Hormone

In children and adult CKD patients, serum concentration of GH may be normal, or elevated, depending on the extent of glomerular filtration decrease. The increased serum GH concentration in CKD is caused by both a reduction of renal clearance and an increase of GH secretion. Also the half-life of GH in CKD patients is prolonged. Hyperglycemia induced by glucose infusion suppresses GH secretion in healthy individuals, not in CKD patients. Moreover, in CKD, the response of GH secretion to the administration of GHRH is exaggerated.

In CKD patients, high serum GH concentrations are counteracted by peripheral resistance to GH. The GH resistance appears to be both at the receptor and at the postreceptor level. Determination of the concentration of serum growth hormone-binding protein (GHBP), which is a cleaved product of the GH receptor, may be used to assess GH receptor density in tissues. GHBP serum concentration is low in children and adults with CKD. Resistance to GH is also due to defective intracellular signal transduction. The impaired phosphorylation and nuclear translocation of GH-activated STAT protein were also found. Hyperparathyroidism, metabolic acidosis, and inflammation may participate in the pathogenesis of GH resistance in CKD [12–14]. Noteworthy, recent data suggest a direct involvement of excess GH concentrations in the development of albuminuria, glomerular sclerosis, hypertrophy, and hyperfiltration, which is mostly caused by podocyte damage [14].

20.6.2 Insulin-Like Growth Factors

GH promotes linear growth partially by stimulating systemic and local concentrations of IGFs. IGF-1 and IGF-2 are produced locally by most tissues, including the growth plate, but the liver is the main source of circulating hormones. IGF-1 mediates most of the growth-promoting effects of GH. Serum IGF-1 forms complexes with six IGF-binding proteins (IGFBP-1 to IGFBP-6).

In advanced CKD, the serum concentration of IGF-1 is decreased and of IGF-2 is increased. In patients with advanced CKD, the resistance to the metabolic effects of recombinant human IGF-1 was found. Moreover the so-called somatomedin bioactivity in blood, an index of IGF activity measured by sulfate incorporation into porcine costal cartilage, is reduced in uremia. The discrepancy between normal or elevated total IGF serum concentration and its low bioactivity in CKD may be explained by increased serum concentration of IGFBPs, circulating IGF inhibitor and receptor or postreceptor defect.

Serum concentrations of four of the six IGF-binding proteins (IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6) are markedly higher in CKD patients. The increased binding capacity of IGF-1 decreases the concentration of free IGF-1. This imbalance between serum IGF-1 and serum IGFBP concentrations is relevant in the pathogenesis of growth failure in CKD.

A low molecular weight (1000 Da) inhibitor of IGF-1 has been identified in the serum of CKD patients, but molecular details have not yet been characterized.

Resistance to IGF-1 in CKD is also due to defective intracellular signal transduction (both autophosphorylation of the IGF-1 receptor tyrosine kinase and activity of the IGF-1R tyrosine kinase to the exogenous insulin receptor substrate 1) [12–14].

20.6.3 Growth Hormone Therapy

Demonstration of the resistance to the action of GH and IGF-1 in CKD provides the rationale for the use of GH in the treatment of CKD children with retarded growth despite normal or elevated hormone concentrations. Administration of recombinant human GH in prepubertal children with CKD caused an increase in growth rate and in standardized height without undue advancement of bone age or significant side effects. In adults, recombinant human GH administration stimulates muscle mass gain and may be used in the treatment of protein energy wasting [12–14].

20.7 Abnormalities in the Adrenocorticotropin–Cortisol Axis

The adrenocorticotropin–cortisol axis is only mildly affected in CKD. In CKD patients, serum adrenocorticotropin (ACTH) and cortisol concentrations are normal, or modestly elevated. The cortisol half-life is prolonged in CKD patients, and decreased catabolism may contribute to the mildly elevated serum cortisol concentrations in CKD [15].

Clinical consequences of the abovementioned modest hormonal alterations are unclear, but hypercortisolemia may cause osteopenia, disturbed distribution of adipose tissue, and increased protein catabolism.

In CKD patients, ACTH secretion cannot be suppressed by standard oral doses of dexamethasone, but higher doses of dexamethasone suppress ACTH secretion. Therefore, when Cushing syndrome is suspected in CKD patients, a 2-day dexamethasone test is recommended.

20.8 Abnormalities in Arginine Vasopressin

In CKD patients, the plasma arginine vasopressin (AVP) concentration is elevated. The major cause is decreased metabolic clearance rate. The main physiologic stimuli for AVP secretion are increased serum osmolality and decreased cardiac output or arterial vasodilation. The osmotic and nonosmotic regulation of AVP secretion in CKD is intact. In hemodialysis patients, the plasma AVP concentration increases during ultrafiltration and plasma volume contraction and decreases during hypervolemia. The clinical significance of the elevated plasma AVP concentration in CKD is still uncertain. Experimental and observational human studies suggest that high plasma AVP concentration may participate in the CKD progression [16, 17].

Copeptin (CT-proAVP) is the C-terminal part of the vasopressin prohormone. CT-proAVP is secreted with AVP, and it is easier to estimate than AVP itself. In patients with diabetic nephrop-

athy, high plasma CT-proAVP copeptin concentration predicts cardiovascular mortality [16, 17].

20.9 Abnormalities in the Thyroid Gland and Hypothalamic–Pituitary–Thyroid Axis

Abnormalities in the function of the thyroid gland and in the serum concentrations of thyroid hormones are common in patients with CKD. A detailed profile of the indices of thyroid status in CKD as compared to primary hypothyroidism and chronic nonthyroid, nonkidney illness is presented in Table 20.3 [18, 19].

20.9.1 Thyroid Hormones

The serum concentration of thyroxin (T_4) is usually normal. In contrast, triiodothyronine (T_3) concentration is frequently reduced in CKD patients. Low T_3 syndrome is the most common laboratory finding in patients with CKD and subclinical hypothyroidism is the most common thyroid disorder found in this group of patients. The reduction of serum T_3 concentration in CKD patients occurs due to the impaired conversion of T_4 to T_3 caused by the suppression of iodothyronine deiodinase activity. This results from, e.g. malnutrition, chronic metabolic acidosis, or inflammation. Furthermore, reduced clearance of inflammatory cytokines such as TNF-α and IL-6, which inhibit the extrathyroid expression of 1, 5′-deiodinase may also contribute to the decreased serum T_3 in CKD patients.

Noteworthy, patients with CKD and concomitant low serum T_3 concentrations appear usually clinically euthyroid. In this group, the decreased concentrations of thyroid hormones may not necessarily be the indicator of thyroid dysfunction, but are probably a reflection of the chronic illness and/or malnutrition.

Traditionally low serum concentrations of T_3 were regarded as an adaptive response to severe acute or chronic disruptions (e.g. starvation, sepsis, trauma, surgical procedures such as coronary artery bypass grafting, and apparently CKD) that allowed to diminish the basal metabolic rate to save energy. This state is classically called the "euthyroid sick syndrome," or in concordance to the latest suggestions the nonthyroidal illness syndrome (NTIS).

Table 20.3 Abnormalities of hypothalamic–pituitary–thyroid axis in chronic kidney disease, chronic nonthyroidal, nonkidney illness, and primary hypothyroidism

	T_4	T_3	rT_3	TSH
Chronic kidney disease	N, ↓	↓	N	N
Chronic nonthyroidal, nonkidney illness	N, ↓	↓	↑	N
Primary hypothyroidism	↓	↓	N	↑

N normal, *TSH* thyroid-stimulating hormone, *T4* thyroxin, *T3* triiodothyronine, *rT3* reverse triiodothyronine

There is evidence, however, suggesting that low serum T_3 concentration in CKD patients is related to the endothelial dysfunction, atherosclerosis, and cardiac abnormalities. In clinical studies low serum free-T_3 has been linked with the increased cardiovascular mortality in hemodialyzed patients. In contrast to the other chronic nonthyroid diseases, rT_3 serum concentration is normal in CKD patients. Clinical, as well as experimental studies conducted so far concerning levothyroxine supplementation in patients with NTIS yielded conflicting results. Therefore, there is still need for large studies to be conducted and evidence of benefits of a therapy in CKD subjects must be provided before it can be unequivocally recommended in these patients [19, 20].

20.9.2 The Thyroid-Stimulating Hormone

Despite a tendency to low serum concentrations of T_4 and T_3, the serum concentration of thyroid-stimulating hormone (TSH) is usually normal in CKD patients. The normal serum TSH concentration despite low serum concentrations of the thyroid hormones suggests an abnormal regulation of the hypothalamic–pituitary–thyroid axis. The TSH response to TRH is usually blunted. In CKD patients, the normal diurnal rhythm of TSH with a peak in the late evening or early morning is blunted, and the nocturnal TSH

surge is reduced. The pattern of pulsatile TSH secretion is also altered [8, 19].

20.9.3 Primary Hypothyroidism and Hyperthyroidism

Primary hypothyroidism is two to three times more frequent in CKD patients than in the general population. The diagnosis of hypothyroidism in patients with CKD is challenging since the typical signs and symptoms of hypothyroidism, such as pallor, hypothermia, and asthenia, are also common in the clinical picture of advanced CKD. The only reliable procedure to diagnose hypothyroidism in CKD is the finding of an elevated serum TSH concentration and clearly low serum T_4 concentrations. Heparin competes with T_4 at the binding site of the hormone-binding protein, causing an increase of serum T_4 concentrations for at least 24 h. Therefore, blood for the determination of thyroid hormones should be sampled before heparin administration at the beginning of a dialysis session. Clinical consequences of hypothyroidism in CKD are exacerbation of muscle wasting, anemia, and depression [19, 20]. Interestingly, despite the fact that no direct link between thyroid and kidney was elucidated, it seems that there is a reciprocal influence of these two organs. There is growing evidence that thyroid hormones have a direct impact on kidney structure and function, and if hypothyroidism is left untreated may exacerbate the course of CKD.

The prevalence of hyperthyroidism in CKD is similar to that found in the general population.

20.10 Aldosterone

Serum aldosterone concentrations are elevated in CKD patients when GFR is lower than 70 mL/min, and a correlation between serum aldosterone concentration and the rate of CKD progression is found [21].

The results of the small interventional studies suggest that treatment with spironolactone reduces proteinuria in CKD patients. Some new study results showed benefits of such treatment in patients with CKD and heart failure. However, these studies enrolled modest number of patients so no definitive conclusions can be drawn. Also, the recent systematic reviews of Cochrane database did not result in unequivocal conclusions in that matter. Conversely, the results of FIDELIO-DKD Study showed that treatment with finerenone can reduce the risk of CKD progression and cardiovascular events in type 2 diabetes patients. This only emphasizes the need of such large studies to definitely assess the safety and efficacy of aldosterone antagonist treatment [22, 23].

20.11 Abnormalities in Insulin and Glucagon

In patients with chronic kidney disease (CKD), abnormalities in carbohydrate metabolism are encountered at different levels of the insulin–glucose cascade (Box 20.2) [24, 25].

Box 20.2 Insulin Metabolism in Chronic Kidney Disease

Fasting hyperinsulinemia with prolonged insulin half-life and elevated blood levels of proinsulin and C peptide
Usually decreased early, but exaggerated late-insulin response to hyperglycemia induced by oral or intravenous glucose administration
Decreased peripheral sensitivity to insulin action, but normal suppression of hepatic glucose production by insulin

20.11.1 Insulin Secretion and Clearance

Insulin secretion is impaired in CKD. Causes of this impairment are among others high PTH and low serum $1,25[OH]_2D_3$ concentration.

The kidney plays an important role in insulin clearance. Insulin is filtered by the glomeruli and reabsorbed in the proximal tubule. In healthy subjects the renal clearance of insulin is about 200 mL/min. This value exceeds the glomerular

filtration rate (GFR), indicating that, in addition, peritubular uptake of insulin takes place. It is estimated that 6–8 U of endogenous insulin are daily removed by the kidney, accounting for 25–40% of the total removal of endogenous insulin. A decrease in the metabolic clearance rate of insulin is documented in patients with GFR <40 mL/min. In CKD patients, diminished insulin clearance accounts for fasting hyperinsulinemia. It also accounts for decreased insulin requirements in diabetic patients with impaired kidney function [25, 26].

20.11.2 Insulin Resistance

Peripheral resistance to insulin occurs frequently even in early stages of chronic kidney disease and is found in the majority of patients with advanced CKD. The main sites of decreased insulin sensitivity are skeletal muscles. It was demonstrated that the defect is located not only at the level of the insulin receptor but presumably at the postreceptor level. Impairment of phosphatidyl-inositol 3-kinase activity (PI3-K) was documented in CKD patients. Higher serum insulin concentrations are required to increase glucose uptake by skeletal muscle. The main factors responsible for insulin resistance in CKD are metabolic acidosis, inflammation, and oxidative stress. Those abnormalities act mainly through the promotion of expression of signal regulatory protein alpha (SRIPα) which impairs insulin signaling in skeletal muscles by dephosphorylation of tyrosines in the insulin receptor and insulin receptor substrate 1 (IRS1). Additionally, serum concentrations of insulin antagonists like glucagon and growth hormone are frequently elevated in CKD patients and may participate in the development of insulin resistance in those patients.

The resistance to the peripheral action of insulin is markedly improved after several weeks of hemodialysis or peritoneal dialysis. Presumably, besides the correction of metabolic acidosis, also yet unidentified dialyzable uremic "toxins" are involved in the pathogenesis of deranged insulin action. Such compounds with a molecular weight of 1–2 kDa are specific for CKD, because they are not found in nonuremic patients with insulin resistance.

A number of other factors have been identified which are involved in the pathogenesis of insulin resistance in CKD patients and which are potential targets for intervention. In hemodialysis patients, insulin resistance is ameliorated by treatment with erythropoietin or $1,25(OH)_2D_3$. Lifestyle changes like more vegetable oriented diet, protein restriction, and also antidiabetic medications like metformin, SGLT2 inhibitors, or GLP1 agonists may help in overbearing the insulin resistance in CKD patients [25, 26].

20.11.3 Clinical Consequences of Hyperglycemia and Insulin Resistance

Hyperglycemia and insulin resistance in CKD patients contribute to increased cardiovascular risk and CKD progression. Insulin resistance may also participate in the pathogenesis of the malnutrition often found in these patients. Insulin deficiency (or resistance) stimulates breakdown of muscle and activates a common proteolytic pathway via the ubiquitin–proteasome system. Insulin resistance also increases salt sensitivity through increased tubular sodium reabsorption and therefore contributes to hypertension [25, 26].

20.12 Abnormalities in the Cardiac Natriuretic Peptides

Serum concentrations of atrial natriuretic peptide (ANP) and brain or B-type natriuretic peptide (BNP) usually are elevated in CKD patients. Moreover, in these patients, the pulsatile secretion of ANP and BNP is characterized by abnormally high amplitude. The causes of high serum concentrations of ANP and BNP in CKD are an increase in intravascular filling and atrial distension, concomitant heart failure, and diminished renal clearance. The removal of fluid by ultrafiltration during dialysis therapy is associated with a decrease in the serum ANP and BNP concentrations.

The measurement of ANP and BNP serum concentration was used as a biochemical marker of volume overload in CKD patients. The weight of evidence indicates that measurements of serum

ANP and BNP concentration add little to the clinical examination of these patients. However, high serum concentrations of cardiac natriuretic peptides, particularly BNP, were strong predictors of cardiovascular mortality in CKD patients.

The estimation of serum concentrations of cardiac natriuretic hormones (BNP and N-terminal proBNP) could be useful for a differential diagnosis of heart failure in general population. In CKD patients, most studies indicate that the upward adjustment of diagnostic cut points preserves the usefulness of BNP and N-terminal proBNP for the differential diagnosis of heart failure [27].

20.13 Abnormalities in Cardiotonic Steroids

Cardiotonic steroids (ouabain and marinobufagenin) act as physiological regulators of sodium pump activity and are implicated in regulation of natriuresis and vascular tone. In CKD patients, the serum marinobufagenin but not ouabain concentration is elevated. Such an elevation seems to be of pathophysiological relevance because it was shown that in CKD patients erythrocyte Na/K-ATPase was inhibited, and serum marinobufagenin concentration exhibited a negative correlation with this enzyme activity [28]. The clinical significance of the elevated serum marinobufagenin concentration in CKD is uncertain. Results of experimental studies suggest that high serum concentration may participate in the pathogenesis of hypertension, diastolic dysfunction, and both cardiac and renal fibrosis in CKD.

20.14 Abnormalities in Gastrointestinal Hormones

An elevated serum gastrin concentration is found in CKD patients. The kidney is the main site of gastrin biodegradation; therefore, hypergastrinemia in uremic patients is mainly due to reduced renal degradation of this hormone. Hypergastrinemia in CKD patients is due predominantly to "big" gastrin (G34), but not "little" gastrin (G17) accumulation. G34 is biologically less active than G17. Postprandial gastrin secretion in CKD patients is similar to that in normal subjects, but the peak values were attained later and the response was more prolonged [29].

Elevated serum ghrelin levels were observed in CKD. Increased ghrelin serum concentration in CKD is due to the decreased degradation of ghrelin by the kidney. There are two forms of circulating ghrelin: acylated and des-acyl ghrelin. Acylated ghrelin promotes food intake, whereas des-acyl ghrelin induces negative energy balance. However, only serum des-acyl ghrelin concentration was elevated in CKD. It is suggested that elevated des-acyl ghrelin serum concentration may be involved in the pathogenesis of anorexia in CKD patients. The results of small interventional clinical studies suggest that ghrelin treatment in CKD patients enhanced food intake and may improve nutritional status [30].

The serum concentrations of other gastrointestinal hormones, such as cholecystokinin, gastric inhibitory peptide, pancreatic polypeptide, secretin, gastrin releasing peptide, vasoactive intestinal polypeptide, and motilin, are elevated in CKD patients. The pathophysiological importance of these findings remains to be elucidated.

20.15 Abnormalities in the Hormones of Adipose Tissue

The adipose tissue is an important endocrine organ producing biologically active substances (adipokines). An elevated serum concentration of different adipokines is found in CKD patients (Box 20.3). It was proved that some of them (such as leptin, adiponectin, resistin, and visfatin) are characterized by systemic actions [31].

Box 20.3 Abnormalities in the Hormones of Adipose Tissue in Chronic Kidney Disease

Leptin	↑
Adiponectin	↑
Resistin	↑
Visfatin	↑

Patients with CKD are characterized by increased serum leptin concentration. The decreased leptin clearance by failed kidneys leads to its accumulation in the circulation. Leptin stimulates the proliferation and the differentiation of hematopoietic stem cells. It is likely that the effects of leptin and erythropoietin are synergistic. Apart from this, hyperleptinemia stimulates the activity of the sympathetic nervous system and therefore likely plays a pathophysiological role in the CKD progression, pathogenesis of hypertension, and cardiovascular diseases [31].

Patients with CKD are characterized by increased serum adiponectin concentration. The increased serum adiponectin concentration in CKD patients is owing to the disturbances of its biodegradation and elimination by the failed kidneys. Clinical consequences of increased serum adiponectin concentration in CKD are not clear [31]. It seems however that in CKD patients due to the receptor resistance, the unique antiatherosclerotic actions of adiponectin are reduced.

Serum concentration of resistin is increased in CKD patients. The main cause of high serum resistin concentrations in CKD is its reduced renal clearance. Resistin, at concentrations seen in CKD patients inhibits neutrophil activity. Therefore, it may participate in the pathogenesis of the increased risk of infections in CKD patients. Resistin also appears to have a potential role in the pathogenesis of cardiovascular disease in CKD patients. Hemodialysis patients with the low serum resistin concentration had poor hospitalization-free survival [31].

The serum concentration of visfatin gradually increases with the loss of kidney function and is related positively to endothelial dysfunction. This adipokine stimulates adhesion of monocytes to endothelial cells. Visfatin may also play a role in the pathogenesis of malnutrition in CKD. A high serum visfatin concentration predicted mortality in CKD patients [31].

Box 20.4 What the Guidelines Say You Should Do [32]

- In patients with CKD stages 3–5D, 25(OH)D (calcidiol), levels might be measured; vitamin D deficiency and insufficiency may be corrected using treatment strategies recommended for the general population.
- In children and adolescents with CKD stages 2–5D and related height deficits, treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD–MBD, is recommended.

Box 20.5 Relevant Guidelines

***1. KDIGO Guideline*:** KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7:1–59.

Erratum in: Kidney Int Suppl (2011). 2017;7:e1.

Available at: https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf

Before You Finish: Practice Pearls for the Clinician

- The main clinical consequences of endocrine abnormalities in CKD patients are anemia, bone disease, and infertility.
- Decisions concerning treatment with erythropoiesis-stimulating agents (ESAs) in these patients should be based on blood hemoglobin concentration and whole clinical status, and not on serum EPO concentration.

- Vitamin D supplementation in CKD patients with clinical signs of overt vitamin D deficiency, i.e. hypocalcemia and hyperparathyroidism is recommended.
- Therapy with exogenous testosterone is not exempted from risks, but results of recent studies seem to suggest that transdermal testosterone replacement therapy might be safe and effective in reversing the symptoms of testosterone deficiency and improve life quality of life in men with CKD.
- There is no data from the large, clinical studies concerning the safety and efficiency of the estrogen therapy in women with CKD. The decision of hormone replacement therapy in female CKD patients should be individualized and made after discussion with gynecologist.
- The administration of recombinant human GH in prepubertal children with CKD causes an increase in growth rate without undue advancement of bone age or significant side effects.
- Blood samples for the assessment of thyroid hormones concentration should be taken before heparin administration at the beginning of a dialysis session.
- In CKD, decreased thyroid hormone concentrations may not necessarily indicate a state of overt hypothyroidism, but rather the nonthyroidal illness syndrome (NTIS) which is a reflection of the state of chronic illness and/or malnutrition.

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21 Liver and Gastrointestinal Tract Problems in Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- Gastrointestinal (GI) disease can be both the cause and the consequence of kidney disease.
- Individuals with liver disease, specifically cirrhosis, are at higher risk of developing acute and chronic kidney injury.
- Several diseases may concurrently affect both the GI tract and the kidney. This coexistence may thus be an important clue to the etiology of CKD.
- Nonspecific symptoms or signs, such as diarrhea or biochemical liver dysfunction, may in some patients be an important clue to the etiology of CKD.
- Infection by the hepatitis B and C viruses is more common in CKD patients than in the general population.

21.1 Liver and Gastrointestinal Tract Disease as Potential Clues to CKD Etiology

21.1.1 Liver and Kidney Disease from a Systemic Disease

21.1.1.1 Autosomal-Dominant Polycystic Kidney Disease

Several diseases may cause simultaneous liver and kidney damage. The detection of biochemical or imaging evidence of involvement in both organs may thus point to specific etiologies of chronic kidney disease (CKD). One major culprit is autosomal-dominant polycystic kidney disease (ADPKD), the most prevalent inherited kidney disease worldwide and the fourth most common cause of end-stage kidney disease (ESKD) following other common systemic conditions such as diabetes mellitus (DM), hypertension, and glomerulonephritis (GN).

ADPKD, despite its name, is a systemic disorder. Although frequently asymptomatic, it is associated with numerous extrarenal manifestations. The most common gastrointestinal manifestation is polycystic liver disease (PLD), followed by diverticular disease, ventral and inguinal hernias, pancreatic cysts, and different forms of biliary tree abnormalities, all of which play a role in the disease burden of patients affected by ADPKD. Most patients with PLD are asymptomatic and can be managed conserva-

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tively as it does not lead to hepatic dysfunction. However, massive liver enlargement can lead to compressive symptoms and surgical intervention is reserved for such patients to decrease cyst burden, with liver transplantation as a last option for selected patients in countries that do not rely on Model for End-stage Liver Disease-Sodium (MELD-Na) score for organ allocation.

Molecular diagnosis by identifying mutations in the PKD1 and PKD2 genes, although accurate, is variably used. It should be considered in cases of equivocal or atypical imaging findings and to diagnose family members of patients with ADPKD. A "unified criteria" has been proposed for diagnosis and exclusion by ultrasonography [1]. Currently, treatment is aimed towards delaying progression to ESKD as measured by loss of eGFR or by progression of total kidney volume (TKV) by MRI or CT. Conventional renoprotective strategies are recommended despite the lack of evidence supporting improvement of the above-mentioned outcomes. Novel ADPKD specific treatments have gained traction and many studies are currently underway. Only the TEMPO 3:4 trial has demonstrated the benefits of using Tolvaptan in ADPKD patients [2] and gained approval for its use by the FDA in 2018. Unfortunately, this treatment does not have evidence of benefit in PLD. Other drugs await new evidence, including somatostatin analogues.

21.1.1.2 Paraproteins in Liver and Kidney Disease

Another common systemic condition with manifestations in both kidneys and liver is amyloidosis (especially of the AL type). When amyloidosis is suspected, it should be investigated by the search of a paraprotein—a sign of clonal B cell lineage proliferation—followed by biopsy of an affected organ which should be carefully selected after an assessment of risks and benefit. Kidney manifestations usually include proteinuria and a decline in GFR.

Hepatic manifestations include hepatomegaly, portal hypertension, intrahepatic cholestatic jaundice, and liver failure. The prognosis is guarded if treatment is not urgently started. The aim of treatment in selected individuals is to suppress proliferation of abnormal cells secreting the culprit paraprotein and to attempt to stop the accumulation or even promote the removal of tissue deposits. Depending on the specific form of amyloidosis, dual liver-kidney transplantation could be curative, but recurrence is possible. Autologous-blood stem-cell transplantation could induce complete remission and depending on the severity of the renal and liver manifestations and the specific type of paraprotein deposit, could be the treatment of choice. Once a diagnosis is made, patients are usually referred to hematology-oncology specialists for further management.

21.1.2 Liver Disease as Cause of Kidney Disease

21.1.2.1 Hepatorenal Syndrome: Acute Kidney Injury

Individuals with liver disease, specifically cirrhosis, in addition to other well-known complications, are at higher risk of developing acute and chronic kidney injury. Several mechanisms interact and contribute to the development of kidney injury: decreased intravascular blood volume in the setting of hypoalbuminemia and loss of oncotic pressure, medications that promote increased gastrointestinal and urinary output, hemodynamic instability provoked by large volume paracentesis, GI bleeding and concomitant decreased oxygen-carrying capacity; nephrotoxic agents such as antibiotics for treatment and prevention of spontaneous bacterial peritonitis (SBP); inflammatory acute tubular injury (ATI) as a response to insults such as infection, endotoxins, etc.; antibiotic induced acute interstitial nephritis (AIN); glomerulonephritis such as membranoproliferative glomerulonephritis (MPGN) induced by hepatitis C virus (HCV), membranous nephropathy induced by hepatitis B virus (HBV), or secondary IgA nephropathy due to liver cirrhosis; abdominal compartment syndrome due to refractory ascites; increased serum bilirubin and bile acid precipitation in the renal tubules and parenchyma characterized by biliary casts; among others. Overtime, these recurring insults will lead to CKD and kidney failure.

Acute kidney injury due to hepatorenal syndrome (AKI-HRS) is an entity characterized by the overarching theme of reduction in renal blood flow secondary to maladaptive splanchnic vasodilation with concomitant activation of sympathetic nervous system and the renin-angiotensin-aldosterone system resulting in renal vasoconstriction, resulting in persistent ischemia with acute and chronic loss of kidney function that may lead to kidney failure. AKI-HRS is a diagnosis of exclusion. As such, multiple diagnostic criteria and approaches have been proposed, with the most popular one being the criteria proposed by the International Club of Ascites (ICA) in 1996 and revised in 2015 [3].

Diagnostic approach and treatment have been summarized in Fig. 21.1. The 2015 ICA criteria to diagnose HRS-AKI remain imperfect, and these pitfalls underscore the importance of individualizing diagnosis and treatment. Many urinary markers are being studied and are in the pipeline to improve our diagnostic accuracy, but data is still inconclusive. When all HRS-AKI criteria are met, and other non-ICA criteria are present (including FeNA <0.1%, bland urinary sediment, hyponatremia, decreased MAP below baseline, oliguria), a definitive diagnosis can be achieved.

Historically, the cornerstone of vasoactive therapy has been midodrine and noradrenaline in the background of appropriate doses of albumin and octreotide. Terlipressin has been the standard of care for the treatment of HRS in Europe and Asia, while in the USA, the FDA recently approved terlipressin for treatment of HRS-AKI after the CONFIRM trial [4] demonstrated that terlipressin was an effective treatment for reversal of HRS with an acceptable adverse event profile.

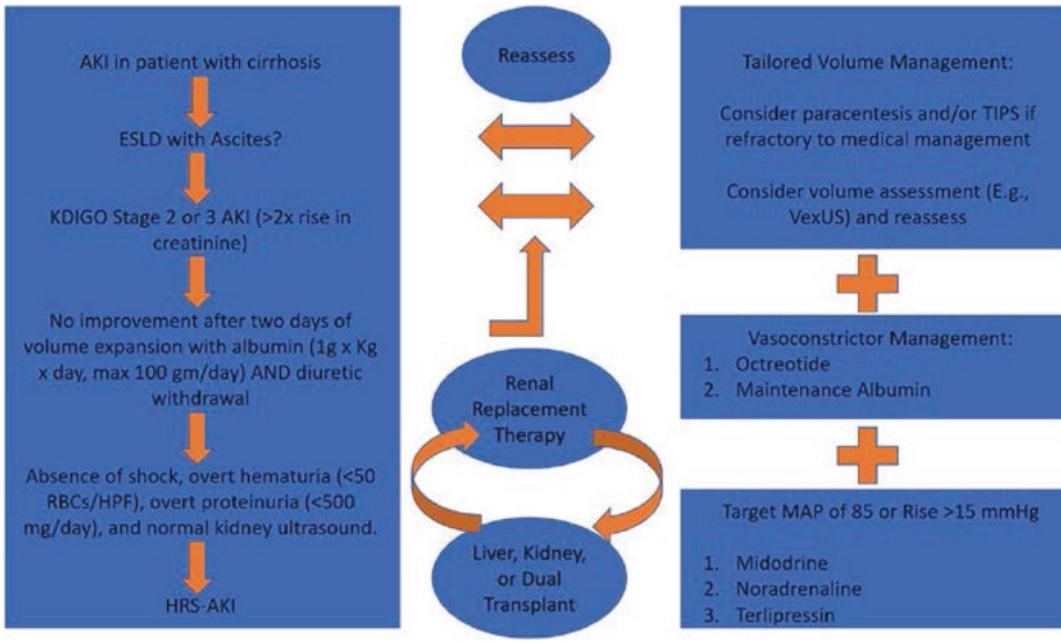

Fig. 21.1 Proposed diagnostic and therapeutic approach to hepatorenal syndrome -acute kidney injury (HRS-AKI). This algorithm uses the International Club of Ascites 2015 criteria to accurately diagnose patients with HRS-AKI, but it also suggests evaluation in aspects not covered currently. Initial assessment requires evaluation of ascites and volume status, which is a dynamic process that must be evaluated continuously. In parallel, vasoconstrictor management should be implemented in all patients who do not meet a goal mean arterial pressure (MAP) of 85 or >15 mmHg above their baseline with evidence of appropriate fluid resuscitation. Vasoconstrictor therapy should be initiated in the background of maintenance octreotide, albumin (with or without resuscitation protocol, depending on the volume assessment) in conjunction with vasopressors. The choice of pressor is dependent on several factors, including availability, severity on presentation, among others. If indicated, renal replacement therapy could be considered

Despite clear advances in the field, HRS-AKI remains a challenging entity and newer diagnostic modalities and therapeutic options are urgently needed. In the meantime, critical thinking and individualization of diagnosis and treatment are essential for better outcomes.

21.1.2.2 Infectious Liver Diseases as a Cause of Kidney Disease

As previously mentioned, Hepatitis B virus (HBV) infection is an important cause of membranous nephropathy, especially in children and in emerging countries. A case series of biopsy-proven membranous nephropathy from China ascribed the disease to HBV in 12% of cases [5]. The substantial reduction of the prevalence of HBV-associated membranous GN in several emerging countries since the advent of anti-HBV vaccination strongly supports the causal role of HBV. Thus, testing for HBV serological markers should be part of the etiologic investigation of any GN. Successful antiviral treatment is associated with improvement of the associated GN [6].

Similarly, HCV is one of the causal agents of what is now known as immune-complex mediated-MPGN, with or without circulating cryoglobulins. Testing for HCV should thus be part of any GN work-up and successful antiviral treatment may improve the associated GN. Kidney biopsy is not a pre-requisite to begin direct-acting antiviral (DAA) therapy in patients with chronic HCV infection and overt kidney manifestations. In selected patients, immunosuppressive agents (corticosteroids, cyclophosphamide, rituximab) may be required to treat hyperactive lesions (such as crescents/capillary necrosis) [7, 8].

21.1.3 Gastrointestinal Tract Disease

21.1.3.1 Kidney and GI Tract Disease from a Systemic Disease

Several diseases may concurrently affect both the GI tract and the kidney. This coexistence may thus be an important clue to the etiology of CKD. Two well know examples include IgA vasculitis (IgAV, formerly known as Henoch-Schonlein purpura) and atheroembolism. The former also has a renal-limited form known as IgA nephropathy (IgAN).

IgA Vasculitis

IgAV is the most common form of systemic vasculitis in childhood. It is much less common in adults. Median age at onset is 50 years and has a higher incidence in Caucasian and Asian populations with a male to female ratio of 10:2. The exact pathogenesis is currently unknown, but it probably involves a combination of environmental and genetic factors that can trigger a dysregulated activation of mucosal innate immunity, with subsequent secretion and activation of abnormal IgA antibodies that leads to inflammation and accumulation of immune complexes and end-organ damage, causing skin lesions (present in 80% of cases), arthralgias (84% of cases), and GI symptoms (roughly over 50% of cases). GI symptoms can range from mild (self-limited episodes of abdominal pain, nausea, and vomiting) to severe disease with gastrointestinal hemorrhage, bowel ischemia, necrosis, and perforation. Intussusception is a well-known serious complication which can lead to bowel obstruction that is more commonly seen in children.

Kidney disease is more common in adults, and it may present with new-onset hypertension or lower extremity edema. Kidney failure can occur in up to 30% of cases and on urinalysis, proteinuria, and hematuria are common findings. Thus, the coexistence of signs of GN (hematuria and proteinuria) together with bouts of abdominal pain, with or without GI tract hemorrhage, arthralgia, and/or skin purpura, should prompt consideration of IgA vasculitis as a potential etiology of AKI/CKD. The diagnosis may ultimately be confirmed by a biopsy of the affected organ.

Management of IgAV is summarized in Fig. 21.2. Several aspects need to be considered, including the heterogeneity of the disease, as multiple variants exist with varying degrees of evidence for different treatments. When kidney involvement is demonstrated, the cornerstone of management is supportive therapy for self-limiting to mild disease. Steroids should be reserved for severe forms of renal, mucocutane-

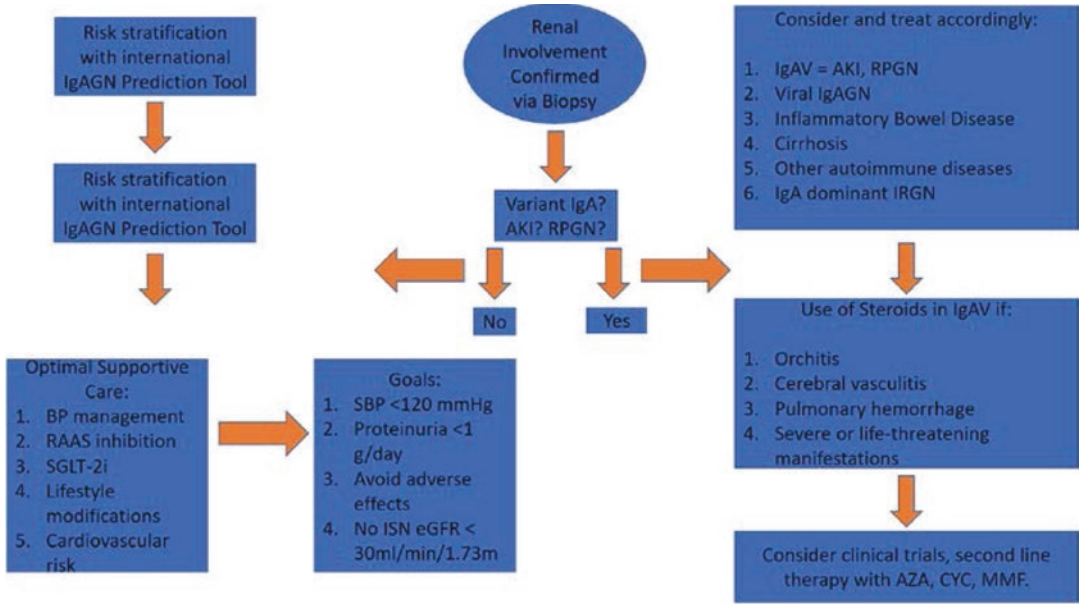

Fig. 21.2 Proposed therapeutic approach to IgAV with emphasis on kidney involvement. Note IgAV and IgAN are treated as different entities with similar approaches and considerations. The cornerstone of therapy includes optimal supportive care that may include NSAIDs for self-limited or mild symptoms involving skin, joints, and abdominal pain (not depicted). When kidney involvement is confirmed, optimal supportive care needs to be initiated including blood pressure with a target SBP of <120, maximally tolerated ACE-I or ARB, and immunosuppression with steroids should be considered if supportive management fails to control the disease or if proteinuria if >1 g/day, worsening eGFR, active hematuria in patients with preserved renal function (eGFR >30 ml/min/1.73 m^2). Second line therapy with other immunosuppressive agents should be considered when steroids fail to control the disease

ous, articular, or digestive tract disease. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) could be considered but evidence is still emerging and the data from IgAN could be extrapolated to IgAV with caution [9].

Atheroembolic Disease

Atheroembolism is a frequent cause or contributor to CKD in elderly patients with coexistent cardiovascular disease. Atheroembolism may affect various abdominal organs, including the bowel, in addition to the kidney. The coexistence of acute episodes of abdominal pain sometimes with peritoneal irritation, in a patient with a recent potential trigger of atheroembolism (e.g., coronary or peripheral angiography, initiation of anticoagulation, thrombolysis, etc.) should prompt investigation for atheroembolism, especially if peripheral eosinophilia is present. The management is supportive in most cases.

21.1.4 Diseases of the GI Tract or Pancreas as a Cause of CKD

21.1.4.1 Oxalate Nephropathy

Diseases of the GI tract may cause acute, subacute, or sometimes chronic kidney disease. Bowel diseases such as Crohn's disease, postsurgical short bowel syndrome, chronic pancreatitis, as well as orlistat therapy (prescribed for weight loss) all can cause steatorrhea. This can cause calcium binding to free fatty acids in the bowel lumen with a concomitant increase in free oxalate. Given this, more oxalate can be absorbed in the bowel, leading to hyperoxaluria and oxalate nephropathy. This is an under-recognized cause of kidney disease. Kidney dysfunction may be partly reversible after removal of the offending agent or resolution of etiology if possible. Treatment can also include oral calcium supplementation [10].

21.1.4.2 Phosphate Nephropathy

Preparations rich in sodium phosphate ("fleet enema") are convenient to clean the large bowel prior to colonoscopy but have recently been recognized as a cause of AKI, sometimes progressing to CKD [11]. The high phosphate content favors substantial phosphate absorption by the bowel, with the risk of renal deposition of calcium phosphate salts, especially in predisposed patients, such as CKD patients, the elderly, those using diuretics, or with diabetes, hypertension, congestive heart failure, active colitis, etc. The KDIGO CKD Guideline specifically recommends not to use oral phosphate-containing bowel cleaning preparations in patients with an eGFR <60 [12] (Box 21.1).

Box 21.1 What the Guidelines Say You Should Do

Oral phosphate-containing bowel preparations should not be used in people with a GFR <60 ml/min./1.73 m^2 or in those known to be at risk of phosphate nephropathy.

Source: Kidney Disease: Improving Global Outcomes (KDIGO) [12].

21.1.5 Concomitant Liver and GI Tract Disease and CKD

21.1.5.1 HCV as a Cause of Liver Disease in CKD

Several small sized studies have suggested that the prevalence of anti-HCV antibodies is high among patients with CKD 4–5, ranging from 3.0 to 14% [13–17]. This has recently been confirmed by the DOPPS in a much larger sample size [18]. These prevalence figures should be interpreted in the light of the known prevalence of HCV in the general population worldwide, known to be highest in Egypt; intermediate in Asia, the USA, and Southern/Eastern Europe; and lower in Northern Europe [19].

The importance of HCV as cause of liver damage in patients with CKD stage 4–5 has increased with the advent of preemptive kidney transplantation: understanding the characteristics of liver disease is important for the evaluation and management of potential renal transplant candidates. Lemos et al. [17] assessed the epidemiology and clinical significance of hepatitis C in a large cohort of CKD patients in Brazil. A total of 1041 patients with a creatinine clearance of 36 ± 18 ml/min/1.73 m^2 were enrolled (49% had CKD stage IV–V). Forty-one (3.9%) patients were anti-HCV positive (with viremia in 95% of them). A population study conducted in the same region reported anti-HCV prevalence of 1.4% ($P < 0.001$). Moreover, chronically HCV-infected patients presented significantly higher serum alanine aminotransferase (ALT) levels (1.3 vs. 0.4x ULN, $P < 0.001$). By logistic regression analysis, a history of blood transfusion before 1992, intravenous drug abuse, and ALT level all had an independent and significant association with chronic HCV.

In a prospective, observational study in 860 US patients, the anti-HCV positivity rate was seven to eight times greater at dialysis start (14.4%) than in the general population (1.8%). In these US inner city units, much of the HCV burden (prevalence 16.8%) was acquired prior to dialysis initiation, particularly among those who are younger and black or have history of drug use [15]. The authors concluded that risk factors for HCV infection in patients receiving dialysis now may differ substantially from those identified 20 years ago. Transmission of HCV in the setting of hemodialysis has clearly decreased because of a much safer blood supply, at least in the developed countries, the availability of erythropoiesis-stimulating agents, and better hygienic precautions. A substantial proportion of anti-HCV positive dialysis patients may nowadays have become infected before the initiation of dialysis.

HCV infection results in an increase in serum aspartate (AST) and alanine (ALT) aminotransferase levels. Unfortunately, the diagnostic value of AST/ALT measurement to assess acute or chronic HCV is rather weak in CKD patients. Lower serum aminotransferase values in dialysis patients than in healthy controls have long been

reported [20]. This phenomenon may extend to CKD patients. In a large ($n = 407$) cross-sectional survey of consecutive individuals with a serum creatinine <2 mg/dl, Fabrizi et al. [21] reported lower serum aminotransferase activity in comparison with healthy persons. The difference persisted in age-matched comparisons and after correction for viral markers (HBsAg and anti-HCV), AST 17.9 ± 8 vs. 20.4 ± 6 IU/I ($p = 0.0001$) and ALT 17.5 ± 10 vs. 21.7 ± 11.3 IU/I ($P = 0.0001$). Although this is a single cross-sectional study, it seems reasonable to state that in patients both with and without viral hepatitis, aminotransferase levels are higher in those with normal kidney function, probably intermediate in pre-dialysis, and lowest in patients on dialysis. Although the cause of this lower ALT/AST level in CKD are still disputed, the diagnostic implications are significant.

Since its previous iteration, the 2022 KDIGO guideline [22] has changed significantly due to new advances in HCV management, particularly in the field of antiviral therapy with curative intent, treatment of HCV-associated GN, and increased usage of HCV positive kidney grafts in transplantation (Box 21.2).

Box 21.2 What the Guidelines Say You Should Do

Detection and evaluation of hepatitis c virus in chronic kidney disease

- We recommend screening all patients for HCV infection at the time of initial evaluation of CKD (*1C*).
  - We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (*1A*).
- We recommend assessing HCV-infected patients with CKD for liver fibrosis (*1A*).
- We recommend an initial noninvasive evaluation of liver fibrosis (*1B*).
- When the cause of liver disease is uncertain or noninvasive testing results are discordant, consider liver biopsy (*Not Graded*).
- We recommend assessment for portal hypertension in CKD patients with suspected advanced fibrosis (F3L4) (*1A*).
- We recommend assessing all patients for kidney disease at the time of HCV infection diagnosis (*1A*).
  - Screen for kidney disease with urinalysis and estimated glomerular filtration rate (eGFR) (*Not Graded*).
- If there is no evidence of kidney disease at initial evaluation, patients who remain NAT-positive should undergo repeat screening for kidney disease (*Not Graded*).
- We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be followed up regularly to assess progression of kidney disease (*1A*).
- We recommend that all CKD patients with a history of HCV infection, whether NAT-positive or not, be screened, and, if appropriate, vaccinated against hepatitis A virus (HAV) and hepatitis B virus (HBV), and screened for human immunodeficiency virus (HIV) (*1A*).

Treatment of HCV infection in patients with CKD

- We recommend that all patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV be evaluated for direct-acting antiviral (DAA)-based therapy (*1A*).
- We recommend that the choice of specific regimen be based on prior treatment history, drug–drug interactions, glomerular filtration rate (GFR), stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities (*1A*). If pangenotypic regimens are not available, HCV genotype (and subtype) should guide the choice of treatment.
- All patients with CKD (G1-G5), on dialysis (G5D), and kidney transplant recipients (G1T-G5T) with HCV should undergo testing for hepatitis B virus (HBV) infection prior to DAA therapy (*Not Graded*).

Diagnosis and management of kidney diseases associated with HCV infection

- HCV-infected patients with a typical presentation of immune-complex proliferative glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy may be indicated in certain clinical circumstances (*Not Graded*).
- We recommend that patients with HCV-associated glomerulonephritis receive antiviral therapy (*1A*).
  - We recommend that patients with HCV-associated glomerulonephritis, stable kidney function, and without nephrotic syndrome be treated with DAAs prior to other treatments (*1C*).
  - We recommend that patients with cryoglobulinemic flare or rapidly progressive glomerulonephritis be treated with both DAAs and immunosuppressive agents with or without plasma exchange (*1C*).
    The decision whether to use immunosuppressive agents in patients with nephrotic syndrome should be individualized (Not Graded).
- We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerulonephritis who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (*1B*).
  - We recommend rituximab as the first-line immunosuppressive treatment (1C).

Source: KDIGO 2018 & KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease [22].

Characteristics of current antiviral regimens are summarized in Table 21.1. Pangenotypic oral direct-acting antiviral (DAA) therapy is highly effective and well-tolerated across all stages of CKD and ESKD, with or without transplantation, with demonstrated response rates ranging from 92 to 100% across the variety of DAA regimens. As such, interferon-based therapy is no longer used. In countries where pangenotypic treatment is readily available, the choice of regimen does not require ascertainment of HCV genotype prior to treatment initiation. Sofosbuvir, one of the main therapeutic agents that are available worldwide, is safe for all stages of CKD and ESKD. Protease inhibitors, on the other hand, are contraindicated in Child-Pugh B and C cirrhosis. Duration of treatment is dictated by factors unrelated to CKD status but usually ranges from 8 to 12 weeks. In kidney transplant patients, regimens should be selected carefully to avoid drug–drug interactions with common medications used in this patient population such as calcineurin inhibitors. The evidence is robust in hemodialysis patients whereas very few patients in these studies were on peritoneal dialysis. Reactivation of HBV infection is possible while on treatment, and given this, testing for HBV markers is indicated prior to treatment initiation. Patients with positive work-up should be carefully followed as they may potentially require treatment in case of HBV reactivation (more below).

The field of transplantation has benefited immensely from DAA as it has increased the pool of recipients and donors. KDIGO recommends that kidneys from HCV-infected donors be considered regardless of HCV status of recipients. HCV-infected recipients could be evaluated to undergo simultaneous liver-kidney transplant. Timing of treatment may depend on other factors, including donor type, severity of cirrhosis, and willingness of the patient to receive an organ from an HCV-infected donor. In living donation, donor should undergo standard cirrhosis work-up and DAA treatment when HCV infection is con-

Table 21.1 Characteristics of available oral direct-acting antivirals in hepatitis C virus infection

DAA regimens in HCV infection							
Brand	Generic	Abbreviation	NS3/4A	NS5B	NS5A	Tablets/Day	HCV genotypes
Harvoni	Ledipasvir/Sofosbuvir	LDV/SOF		x	x	1	All
Zepatier	Elbasvir/Grazoprevir	EBR/GZR	x		x	1	1a, 1b, 4
Epclusa	Sofosbuvir/Velpatasvir	SOF/VEL		x	x	1	All
Vosevi	Sofosbuvir/Velpatasvir/ Voxilaprevir	SOF/VEL/VOX	x	x	x	1	All
Mavyret	Glecaprevir/Pibrentasvir	GLE/PIB	x		x	3	All

Different direct-acting antivirals (DAA) regimens. The suggested duration of treatment for each regimen was not driven by CKD, but rather by other factors (presence of cirrhosis, prior DAA failure, specific genotypes)

firmed. Proceeding with living donation might be possible in the absence of extensive cirrhosis.

Previously, a liver biopsy was required before antiviral treatment. Since the 2018 KDIGO Guidelines, both the APRI index (the ratio of AST level to platelets) and transient elastography (or "Fibroscan") have been shown to be good noninvasive markers of the extent of liver fibrosis [23, 24]. Transient elastography has been validated both in the general population and in dialyzed patients so that despite the absence of large CKD series, it probably works in CKD as well. It measures the velocity of a low-frequency elastic shear wave propagating through the liver. This velocity is directly related to tissue stiffness. The result of transient elastography and/or serum markers have rendered liver biopsy optional in a majority of patients.

21.1.5.2 HBV as a Cause of Liver Disease in CKD

Similar to HCV, the prevalence rates of HBV in CKD patients are related to the local general population prevalence, with a north-to-south and west-to-east gradient. Reports from India and Turkey showed high HBsAg-positive rates of 7% and 10.5%, respectively [16, 24], whereas the rate of chronic HBsAg seropositive individuals with CKD from Spain and Italy was between 0 and 3.7%.

In a large cohort (n = 405) of CKD patients, the prevalence of HBsAg positivity was 3.7% [15], lower than in dialysis (8.7%) but greater than in healthy individuals of the same region (0.5%). Multivariate analysis showed an independent and significant association between AST level and HBsAg positivity.

Numerous risk factors may predispose CKD patients to HBV and/or HCV infections: these include high-risk behaviors (recreational drug use or unsafe sex) prolonged hospitalizations or frequent health-care utilization potentially increasing nosocomial exposure to blood–borne agents, impaired immune response from chronic uremia, and decreased vaccine responsiveness.

The management of HBV infection in patients with CKD has previously been reviewed extensively [6]. It should be pointed out here again that the dosage of many of the anti-HBV drugs, eliminated by the kidney, should be adapted to eGFR/CKD stage, as detailed in Table 21.2.

21.1.5.3 Other Causes of Liver Disease in Chronic Kidney Disease

Any therapeutic drug has the potential of causing hepatic damage, although some drugs are far more likely than others to do so. Susceptibility to developing such injury differs between patients. No firm evidence shows that patients with CKD stage 4–5 are more likely to develop drug-induced liver toxicity than other individuals. However, drug interactions have an important role in the pathogenesis of drug-induced liver disease in uremic patients, as these patients frequently receive multiple medications.

Drug-induced hepatic injury can be either hepatocellular or cholestatic; a complete list of medications capable of producing hepatic damage is beyond the scope of this chapter. NSAIDs are widely used, although less so in CKD patients, and may, albeit infrequently, cause hepatic damage [25]. Allopurinol and anabolic steroids may be hepatotoxic in CKD patients; numerous anti-

Table 21.2 Dose adjustments of nucleos(t)ide analogs and interferon according to creatinine clearance (CrCl)

CrCl (ml/min)	Lamivudine	Telbivudine	Adefovir	Entecavir	Tenofovir	Pegylated interferon
>50	100 mg/day	600 mg/day	10 mg/day	0.5 mg/day	245 mg/day	180 mcg SQ/week
30–49	100 mg first day, then 50 mg/day	600 mg/day two	10 mg/day two	0.25 mg/day	245 mg/day two	135 mcg SQ/week
15–29	35 mg first day, then 25 mg/day	600 mg/day three	10 mg/day three	0.15 mg/day	245 mg/day two–three	
5–14	35 mg first day, then 15 mg/day	600 mg/day three	10 mg/day three	0.05 mg/day	245 mg/week	

Source: Adapted by permission from Macmillan publishers Ltd.: Pipil et al. [6], copyright 2013
Please note that pegylated interferon is only recommended in nucleos(t)ide analog-naive patients
Adefovir and Entecavir are only recommended with a CrCl >10 ml/min
SQ subcutaneous, *mg* milligrams, *mcg* micrograms

biotics can also cause hepatic dysfunction, including tetracyclines, macrolides, trimethoprim-sulfamethoxazole, rifampicin, and isoniazid. Some cardiovascular medications are also hepatotoxic; for example, amiodarone and methyldopa cause cholestatic and hepatocellular injury, respectively. Monitoring of serum ALT and AST activity is recommended during treatment with HMG-CoA reductase inhibitors. Another potential cause of hepatic dysfunction is hepatic congestion due to heart failure. The diagnosis of drug-induced hepatotoxicity is made via a process of exclusion. Patients with elevated levels of serum ALT, AST, and/or gamma-glutamyl transpeptidase should be rechecked after the patient has abstained from potentially toxic substances. In the differential diagnosis of acute liver dysfunction in uremic patients, viral infections such as HBV and HCV, herpes simplex virus, Epstein–Barr virus, cytomegalovirus should be considered.

Ethanol-induced liver disease is an infrequent condition in uremic patients. Another form of liver disease receiving growing attention is nonalcoholic fatty liver disease. Risk factors include obesity, hyperlipidemia, and diabetes mellitus. All these factors have a growing prevalence and are associated with the prevalence of CKD too. The diagnosis is a histological but is seldom needed. Disease management involves correcting predisposing factors.

Another concern that is becoming prevalent is the frequent use of alternative medications such as herbal and health food store products by patients on complex medical regimens. The potential toxic effects of herbal products have been understudied, although at least some of these products may cause an elevation of serum levels of ALT, AST, or gamma-glutamyl transpeptidase. The most recent KDIGO Guideline for CKD specifically recommends not to use herbal remedies in CKD [12] (Box 21.3).

Box 21.3 What the Guidelines Say You Should Do

- Herbal remedies should not be used in people with CKD.

Source: Kidney Disease: Improving Global Outcomes (KDIGO) [12].

21.2 Gastrointestinal Tract

21.2.1 Upper Gastrointestinal Tract

21.2.1.1 Upper GI Tract Symptoms

Nausea and vomiting are frequent symptoms in patients with CKD. These may derive from various categories of causes.

1. Stage 5 (“terminal”) CKD: Although some degree of anorexia and nausea is common in CKD stage 4, such symptoms should not be prematurely ascribed to CKD. Even in the later stages alternative etiologies should

be worked-up. If symptoms are ascribed to terminal CKD, symptomatic treatment will usually be relatively unhelpful and initiation of renal replacement therapy will be required and relieve the symptoms within days.

2. Role of drugs: Many drugs commonly prescribed to CKD patients may cause nausea. In case of doubt, transiently withdrawing the agent may help clarify the impact of a specific drug. The most frequently incriminated drugs include phosphate binders (calcium based, sevelamer, and lanthanum), numerous antibiotics such as fluoroquinolones, digoxin, iron supplements, morphine derivatives, azathioprine, mycophenolate mofetil, sirolimus, etc. In patients under immunosuppressive drug regimens, the suspected causal drugs should usually be temporarily replaced by an alternative immunosuppressive agent whenever feasible.

Upper GI Tract Disease More Prevalent in CKD Patients

Not surprisingly, in view of the high prevalence of diabetes in patients with CKD, diabetic gastroparesis is very common in CKD patients. Common symptoms are bloating, episodic vomiting, and early satiety. Delayed gastric emptying may adversely affect glycemic control as well as absorption of orally administered drugs. The ultimate diagnosis relies on nuclear medicine imaging of gastric emptying. Management is frequently difficult and includes the use of prokinetic agents such as domperidone, keeping in mind that many of such drugs prolong the QT interval and should not be combined with other drugs having the same characteristic (such as sotalol, fluoroquinolones, amiodarone, etc.)

21.2.2 Lower Gastrointestinal Tract

21.2.2.1 Bowel Movement Disturbances

In CKD patients, many drugs may cause either constipation, diarrhea, or an alternating cycle of these symptoms. These include various phosphate binders, both calcium based as well as non-calcium based (sevelamer and lanthanum) and calcium and magnesium combination. Other are the calcium and sodium-based potassium-binding resins and oral iron preparations. In a particular patient, a history of irregular bowel movements or constipation or diarrhea should trigger the question: is this drug-induced? A temporal relationship may often be disclosed by careful history taking. In case of doubt, temporary withdrawal of the suspected causal agent(s) may be very helpful.

Lower GI Tract Disease More Prevalent in CKD Patients

1. Ischemic colitis is more prevalent in CKD because of its association with multiple risk factors for atherosclerosis and vessel wall calcification. This diagnosis should be considered rapidly in a CKD patient with abdominal pain, diarrhea, and bloody stools. Computerized tomography can assist establishing the diagnosis.
2. Angiodysplasia is more prevalent in CKD patients than in the general population. Although the reasons for this higher prevalence are disputed, angiodysplasia is not uncommon throughout the GI tract from stomach to large bowel. When managing a lower GI tract hemorrhage, unexplained despite colonoscopy, a small bowel enteroscopy or an angiography (after appropriate preparation to minimize the toxicity of the contrast agent) will be the next step, if bleeding persists.

When facing GI tract bleeding, drugs known to interfere with hemostasis (aspirin, warfarin, NSAIDs, clopidogrel) should be temporarily withdrawn if possible and the search for the causal lesion started. The efficacy of hormone (estrogen-based) therapy for GI tract bleeding due to angiodysplasia is debated. Endoscopic treatment may be possible for some lesions, especially as most patients with angiodysplasia are elderly and surgical resection is associated with a high risk [26].

21.3 Conclusion

In the era of organ crosstalk, it is imperative to look for a single unifying diagnosis when faced with a challenging disease affecting multiple organs. Liver/GI tract and kidneys are intricately related to each other, where dysfunction of one organ system usually means trouble for the other. A clinician should consider the various etiologies of liver and kidney disease detailed in this chapter when faced with a patient presenting with malfunction of either one, or both, of these organ systems.

Before You Finish: Practice Pearls for the Clinician

- The onset of GI tract symptoms/signs (nausea, diarrhea, constipation) in a CKD patient should trigger the suspicion of a drug-related side effect. Numerous drugs may be incriminated, including phosphate binders, K-binding resins, antibiotics, and various analgesics.
- CKD patients have an increased prevalence of GI tract angiodysplasia. This should be kept in mind when investigating GI tract hemorrhage in CKD.
- Testing for both HBV and HCV should be included in the serological assessment of unexplained glomerulonephritis.
- Significant steatorrhea (not always clinically overt) may cause oxalate nephropathy. Thus, when facing unexplained CKD in a patient with diarrhea, oxaluria should be measured.
- Direct-acting antiviral(DAA)s are highly effective and well-tolerated for treatment of HCV in patients across all CKD stages, including those undergoing dialysis therapy and kidney transplant recipients, with no need for dose adjustment.
- HCV-infected patients with a typical presentation of immune-complex glomerulonephritis can be managed without a confirmatory kidney biopsy. However, a biopsy should be considered if there is worsening of GFR or proteinuria or if immunosuppressive therapy is considered.
- All patients with chronic HCV and glomerulonephritis should be treated with DAAs just as those without glomerulonephritis.

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Fluid and Electrolyte Problems in Chronic Kidney Disease

22

Gheun-Ho Kim

Before You Start: Facts You Need to Know

- Sodium is the most abundant ion in the extracellular fluid (ECF), and the ECF volume is determined by the total body sodium content.
- Total body water determines ECF osmolality which affects cell volume. Because sodium is the principal ion in the ECF, water balance disorders present as altered plasma sodium concentrations.
- Although potassium is mostly located in the intracellular fluid (ICF), normal plasma potassium is critical for heart, nerves, and skeletal muscle because the ratio between ECF and ICF potassium concentration is a determinant of transmembrane electrochemical gradients and neuromuscular excitability.
- With glomerular filtration rate (GFR) declining, renal excretion of sodium, water, and potassium is progressively reduced.

22.1 Introduction

Kidney handles sodium, water, and potassium excretion. Glomerular filtration and tubular transport harmoniously participate in these processes. With declining of glomerular filtration rate (GFR), less plasma sodium, water, and potassium are eliminated from the glomeruli. Therefore, sodium, water, and potassium balances are altered in chronic kidney disease (CKD). Typically, urinary excretion of sodium and water is regulated by tubular reabsorption, whereas urinary excretion of potassium is regulated by tubular secretion. These tubular transport processes are also modified in CKD to minimize the disturbed balances (Fig. 22.1).

Serum sodium is a function of total body sodium and water, and the kidney can retain its ability to excrete both sodium and water through advanced CKD because of tubular adaptation. Consequently, serum sodium concentration can remain within the normal range until the end stage kidney disease (ESKD). Serum potassium does not increase unless GFR declines below 50% of normal because of tubular secretion and transcellular shift [1].

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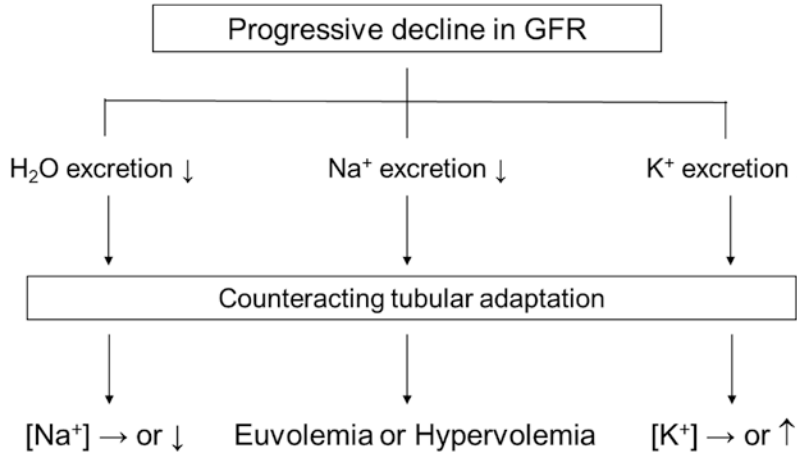

Fig. 22.1 Pathophysiology of fluid and electrolyte disturbances in chronic kidney disease. *GFR* glomerular filtration rate

22.2 Volume or Sodium Balance Disorders

Sodium is the most abundant ion in the extracellular fluid (ECF), which can be divided into plasma and interstitial fluid (ISF). The ECF volume is determined by the total body sodium content because thirst and the kidney's regulated excretion of water work together to maintain serum osmolality within a narrow range. Sodium content is derived from the balance between sodium intake and renal excretion of sodium. With progression of CKD and its accompanying reduction of renal sodium excretion, manifestations of ECF volume overload can occur such as edema and hypertension. Edema is caused by the expansion of ISF, which in turn increases plasma volume and exerts pressure on arterial blood.

22.2.1 Role of the Kidney in Sodium Balance Regulation

The kidney regulates sodium content by adjusting renal sodium excretion. As a result, it also regulates the ECF volume and controls the arterial blood pressure. In normal circumstances, kidneys balance sodium excretion with sodium intake, even though the daily intake of sodium is highly variable, owing to cultural, social, and personal factors [2].

Table 22.1 Regulatory systems for renal sodium excretion

System	Pathways
Sensors	Extrarenal baroreceptors: Arterial circulation, aortic arch, carotid sinuses, cardiac atria
	Renal: Juxtaglomerular apparatus
Effectors	Neurohormones: Sympathetic nervous system, renin, angiotensin II, aldosterone, atrial natriuretic peptide, prostaglandins, nitric oxide
	Direct effects on kidney: Changes in peritubular-capillary Starling forces
Kidney	Glomerular filtration rate
	Tubular sodium reabsorption

For modulation of renal sodium excretion, afferent sensor systems and efferent effector systems should be coordinated (Table 22.1). Baroreceptors located at arterial circulation, aortic arch, carotid sinuses, cardiac atria, and juxtaglomerular apparatus sense changes in intravascular volume and blood pressure caused by alterations in sodium balance. Carotid sinus volume receptors increase sympathetic outflow in response to hypotension. The increased sympathetic tone of the renal vasculature decreases sodium excretion. Renal sympathetic activation and catecholamines released from the adrenal medulla stimulate renin release. The juxtaglomerular apparatus senses renal perfusion and also stimulates renin release when the perfusion pressure is reduced. In addition to increasing circulat-

ing levels of angiotensin II, stimulation of these receptors leads to alterations in the local concentration of angiotensin, which profoundly decreases sodium excretion. Consequently, the renin–angiotensin–aldosterone system is activated by sodium depletion. Conversely, the atria contain secretory granules which, in response to an increase in ECF volume, release atrial natriuretic peptide (ANP), which increases sodium excretion and causes peripheral vasodilation [2]. Renal prostaglandins and nitric oxide can also increase renal sodium excretion in response to volume overload.

In addition, the balance of Starling forces between renal tubules and peritubular capillaries affects tubular sodium reabsorption. The increased arterial pressure raises peritubular hydrostatic pressure, leading to decreased tubular sodium reabsorption. When arterial pressure decreases, the decreased peritubular hydrostatic pressure will enhance tubular sodium reabsorption. This direct effect on the kidney may explain pressure–natriuresis relationship.

Neurohormonal effectors play the major regulatory role in renal sodium excretion. Plasma sodium is freely filtered at glomeruli, and more than 99% of filtered sodium is reabsorbed along the renal tubule. Approximately one-third of glomerular filtered sodium is reabsorbed in the proximal tubule, where Na^+/H^+ exchanger 3 (NHE3) acts as the major transcellular sodium transporter. The NHE3 activity is mainly regulated by angiotensin II in the proximal tubule. The thick ascending limb of Henle's loop is the second major site of sodium reabsorption, where 20–25% of glomerular filtered sodium is reabsorbed mainly via Na^+-K^+-$2Cl^-$ cotransporter 2 (NKCC2). The major effector on NKCC2 is vasopressin, which binds to arginine vasopressin (AVP) receptor 2 and activates the cAMP-protein kinase A pathway. Five to 7% of glomerular filtered sodium is reabsorbed in the distal convoluted tubule through Na^+-Cl^- cotransporter (NCC), and the remaining sodium can be reabsorbed along the collecting duct via epithelial Na^+ channel (ENaC). The distal convoluted tubule, connecting tubule, and cortical collecting duct are collectively called aldosterone-sensitive distal nephron (ASDN), and the final urinary sodium excretion is finely tuned by the action of aldosterone and angiotensin II in the ASDN. The ASDN plays an important role in independent regulation of sodium and potassium balance in response to varying intake of sodium and potassium [3].

22.2.2 Volume Overload in CKD

Volume overload is increasingly common in patients with advanced CKD. As GFR falls to less than 30 mL/min, the ability of renal sodium excretion can be compromised, leading to ECF volume overload [4]. However, a study by Hung and colleagues in patients with CKD stages 3–5 demonstrated that 48% were euvolemic according to bioimpedance assessment [5]. When the ECF volume was measured in CKD patients using chromium-labeled red blood cells, exchangeable sodium, bromide, or sulfate, it is usually normal, at least until GFR is profoundly decreased to <10 mL/min [6], because of tubular adaptation (Fig. 22.1). Other comorbidities such as heart failure, hypertension, and arterial stiffness will increase the prevalence of volume overload.

22.2.2.1 Clinical Diagnosis of Volume Overload

Clinical manifestations depend on the amount and relative distribution of accumulated fluid [2]. In severe cases, patients may experience dyspnea, peripheral edema, ascites, and pleural effusion, reduced exercise tolerance often accompanied by concomitant hypertension. On physical examination, left heart failure is associated with pulmonary venous congestion as manifested by pulmonary crackles. Secondary right heart failure is characterized by neck vein engorgement, peripheral edema, hepatic congestion, and ascites. Pleural effusions usually are a manifestation of combined right and left heart failure. Pitting peripheral edema usually requires 3 L of interstitial fluid excess [2].

Kidney disease can be diagnosed through urinalysis, azotemia, and renal imaging. Atrophic kidneys may suggest chronicity of kidney failure. An elevated brain natriuretic peptide (BNP) level

is seen in heart failure, and BNP may be the more appropriate biomarker to screen for cardiac dysfunction than NT-proBNP in CKD or cardiorenal syndrome because plasma BNP level is relatively independent of GFR [7].

22.2.2.2 Treatment of Volume Overload

To restore sodium balance in CKD patients with volume overload, sodium intake should be restricted and/or natriuresis can be enhanced by diuretics. Previous clinical trials have shown the effects of dietary sodium restriction on ECF volume, hypertension, and proteinuria in CKD patients. McMahon et al. conducted a double-blind placebo-controlled randomized crossover trial in 20 adult patients with hypertensive stage 3–4 CKD and found that a two-week sodium restriction (<100 mmol/day) for resulted in reduced blood pressure, ECF volume (assessed by body composition monitor), albuminuria, and proteinuria compared to a high sodium intake (additional 120 mmol sodium tablets) [8]. Saran et al. conducted a similar randomized crossover trial in 58 adults with stage 3–4 CKD to evaluate the effects of dietary sodium restriction (target <2 g sodium/day) over 4 weeks and found a reduction in blood pressure but no change in albuminuria [9]. It remains to be clear whether the blood pressure-lowering effect persists in the long term and whether the reduction in proteinuria is connected to the preservation of GFR. Interestingly, a post-hoc analysis of the HALT Progression of Polycystic Kidney Disease (HALT-PKD) clinical trials reported that dietary sodium restriction was also beneficial in the management of autosomal dominant polycystic kidney disease [10].

Diuretic therapy is the practical approach to correct volume overload because the effect of dietary sodium restriction is slow and adherence to a low-sodium diet is difficult. In CKD patients, diuretics can alleviate edema, control blood pressure, and potentiate the effects of other antihypertensive agents [4]. Three main classes of diuretics may be used in CKD; loop diuretics are the most potent and useful for patients with advanced CKD, thiazides and thiazide-like diuretics may also be used alone or in combination with a loop diuretic in CKD, and potassium-sparing diuretics may be useful for patients without hyperkalemia. In contrast, acetazolamide is a weak diuretic acting as a carbonic anhydrase inhibitor in the proximal tubule and should be avoided in advanced CKD patients.

Loop diuretics, such as furosemide, bumetanide, and torsemide, inhibit the NKCC2 in the thick ascending limb of the loop of Henle. The ceiling or maximally effective doses can lead to an almost complete block of sodium reabsorption in the Henle's loop, and fractional excretion of sodium increases up to 20–25%. Loop diuretics circulate bound to albumin and are secreted into the tubular fluid by organic anion transporter 1 (OAT1) in the proximal tubule. In CKD and nephrotic syndrome, these processes are compromised, and the target site (the thick ascending limb NKCC2) may not be intact. To overcome this diuretic resistance, higher doses of diuretics are required in CKD. For instance, CKD stages 4–5 patients should be started at a dose of 40–80 mg once daily and then titrated upward by 25–50% weekly depending on the desired effects on lowering ECF volume [11]. Torsemide has the advantage of a higher oral bioavailability and a longer half-life compared with furosemide. Intravenous furosemide has a rapid onset of action and is more potent than oral furosemide. The greatest natriuretic response is observed with intravenous doses of 160–200 mg of furosemide or equivalent doses of bumetanide (6–8 mg) and torsemide (80–100 mg) [12]. Because hypertension in CKD is usually volume-dependent, loop diuretics can play a role in the management of hypertension in advanced stages of CKD.

Thiazide diuretics, such as hydrochlorothiazide, inhibit the NCC in the distal convoluted tubule. Typically, the natriuretic effect of hydrochlorothiazide is dampened in patients with GFR <50 mL/min [13], and higher doses are needed if kidney function is compromised [14]. However, long-acting thiazide-like diuretics, such as metolazone, indapamide, and chlorthalidone, are associated with more sustained low-level diuresis and tend to be more effective in advanced stages of CKD than hydrochlorothiazide [15]. Agarwal

et al. recently reported that chlorthalidone (12.5–50 mg/day) improved blood pressure control and reduced albuminuria over 12 weeks in 160 patients with stage 4 CKD [16]. These responses were associated with decreases in ECF volume markers, and chlorthalidone should be used with caution in patients receiving loop diuretics, especially because of the increased risk of azotemia and electrolyte disorders [17].

Potassium-sparing diuretics can be classified into ENaC blockades and mineralocorticoid receptor antagonists (MRAs). The ENaC blockades such as amiloride and triamterene inhibit the ENaC in the collecting duct. The MRAs including spironolactone, eplerenone, and finerenone tend to have small effects on decreasing extracellular volume but may have antiproteinuric effects and cardioprotective benefits. In particular, finerenone was recently reported to reduce the risk of cardiovascular and kidney outcomes in CKD patients with type 2 diabetes [18]. However, these agents must be used cautiously in CKD patients because of the risk of hyperkalemia, and initiation of therapy with low doses is recommended along with slow-dose titration and frequent monitoring of potassium levels [11].

When edema is refractory to conventional diuretic therapy, the following stepwise strategy is recommended. First of all, dietary sodium restriction should be assessed by measuring 24-h urinary sodium excretion (< 100 mmol/day). When the ceiling dose of a loop diuretic is insufficient to induce a negative sodium balance, the combination of diuretics acting on separate nephron sites (e.g., thiazide-like agents) may be synergistic and lead to significant decreases in ECF volume [19]. In those patients with significant symptomatic volume overload and advanced CKD, continuous intravenous infusion of loop diuretics may confer additional benefits [20]. This can avoid post-diuretic sodium retention, which is accompanied with intermittent bolus loop diuretic injection. Moreover, continuous infusion of loop diuretics may be associated with lower peak plasma concentrations than high-dose intravenous dosing and may lead to fewer dose-related side effects, such as ototoxicity [4]. When these medical treatments are not effective in reducing volume overload, ultrafiltration is indicated with or without dialytic therapy according to the degree of uremia.

22.2.3 Volume Depletion in CKD

In general, ECF volume is depleted by fluid (sodium and water) loss through renal and nonrenal routes. Renal loss includes diuretic overuse, inherited sodium-wasting tubulopathies, tubulointerstitial nephritis, obstructive uropathies, and hypoaldosteronism. In this context, the CKD patients whose underlying disease has remarkable tubulointerstitial pathology are susceptible to becoming volume-depleted. Other CKD patients can also experience volume depletion when they are complicated by bleeding or extrarenal fluid loss due to diarrhea, vomiting, extensive burns, or excessive sweating.

22.2.3.1 Clinical Diagnosis of Volume Depletion

A detailed history will usually reveal the source of volume losses. The clinical manifestations of volume depletion depend on its magnitude, the rate at which it develops, and the type of fluid that was lost [2]. Thirst is common as the volume loss worsens. Whereas hypovolemic shock can occur with a rapid volume loss in severe cases, gradual volume loss with an intravascular volume contraction of less than 5% may be asymptomatic and associated with few physical findings. An intravascular volume contraction of 5–15% typically causes symptoms and signs, often including postural lightheadedness and weakness. Physical findings are not very helpful in diagnosing volume depletion. Findings such as reduced skin or eyeball turgor and dry mucous membranes are not reliable indicators of hypovolemia [2].

The classic urinary indices suggestive of volume depletion may be confounded by the preexisting CKD. Despite hypovolemia, urine osmolality may not increase to >800 mOsm/kg H_2O and urine sodium concentration may not decrease to <20 mmol/L due to accompanying tubular dysfunction. Similarly, the application of fractional excretion of sodium is limited in CKD

as a marker for hypovolemia. Preexisting azotemia is frequently aggravated by volume depletion. The rise of BUN out of proportion to that of serum creatinine may suggest renal hypoperfusion. Anemia of chronic disease is often associated with CKD, but bleeding episodes should be suspected when the hemoglobin level is acutely reduced. Serum sodium, potassium, and bicarbonate may change according to the components of lost fluids.

22.2.3.2 Treatment of Volume Depletion

Patients with CKD are unable to promptly conserve sodium in the face of volume depletion. However, the principles in treatment of volume depletion in CKD are the same as in general subjects. To restore hemodynamic integrity and tissue perfusion, the volume deficit should be replaced with isotonic fluids until the patient's heart rate, blood pressure, consciousness, and urine output are stabilized. Blood transfusions are necessary for hemorrhage, but the administration of colloids generally is no better than crystalloids for fluid resuscitation. At the same time, the underlying factors for fluid loss need to be found and corrected. Additionally, maintenance fluids are administered based on the ongoing losses. Because the patients with advanced CKD have limited capacity to excrete sodium and water, overshoot hypervolemia must be avoided.

22.3 Water Balance Disorders

Total body water determines ECF osmolality which affects cell volume. For normal cell volumes, human body fluid osmolality should be maintained between 280 and 295 mOsm/kg H_2O. This can be achieved by maintaining a water balance between water intake and renal water excretion. With progression of CKD, water may be retained by the kidney with a resultant decrease in ECF osmolality. Rarely, in patients with CKD and water deficit, the ECF osmolality may increase.

Water balance disorders present as altered plasma sodium concentrations (dysnatremia) because sodium is the principal ion in the ECF. Both urine concentrating and diluting mechanisms are impaired with progressive kidney disease. Therefore, CKD patients have limited abilities in water excretion and water conservation (Fig. 22.2) and are susceptible to both hyponatremia and hypernatremia.

22.3.1 Role of the Kidney in Water Balance Regulation

Vasopressin plays a pivotal role in regulation of water balance. Water intake is stimulated by thirst, and the kidney regulates water balance by adjusting renal water excretion, or urine concentration and dilution. When water intake is insuf-

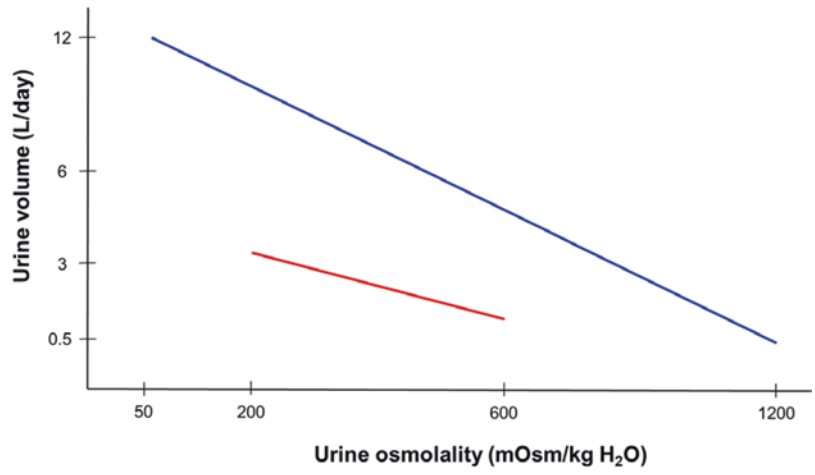

Fig. 22.2 Comparison of different ranges of urine osmolality and urine volume between advanced CKD (red, an assumptive case) and normal kidney function (blue). The range of obtainable osmolalities dwindles with declining GFR. Accordingly, the adaptive range of urine volume is limited in advanced CKD. *CKD* chronic kidney disease, *GFR* glomerular filtration rate

ficient, more water is retained by the kidney through the action of arginine vasopressin (AVP). The AVP produced in hypothalamus is released from posterior pituitary gland and acts on the renal tubules where urine concentration is promoted. First, AVP binds to the AVP receptor 2 in collecting duct principal cells and activates aquaporin-2 (AQP2) water channel to reabsorb water. Second, AVP binds to the AVP receptor 2 in thick ascending limb cells of the Henle's loop and activates NKCC2 to increase outer medullary interstitial hypertonicity. Finally, AVP upregulates urea transporter A2 in the thin descending limb to enhance inner medullary urea cycling. The latter two are critical components of countercurrent multiplication.

From these regulatory actions, urine concentration varies over a wide range. In normal humans, urine osmolality can increase up to 1200 mOsm/kg H_2O with increased circulating AVP (maximally concentrated urine). It also can decrease down to 30–50 mOsm/kg H_2O in the absence of circulating AVP (maximally diluted urine). These wide ranges of urine osmolality progressively dwindle in CKD, suggestive of impairment of both concentrating and diluting mechanisms [21]. The French NephroTest Cohort Study showed that baseline fasting urinary osmolality was strongly associated with measured GFR in 2084 adult patients with CKD stages 1–4 [22]. In a Korean CKD cohort, the urine osmolality obtained from the first voided urine in the fasting status was 400–500 mOsm/kg H_2O in CKD stage 3 and decreased below 400 mOsm/kg H_2O in CKD stage 4 [23]. Isosthenuria is defined as the specific gravity of urine becoming relatively fixed at 1.010, which is approximately the same as that of blood (~300 mOsm/kg H_2O). It is typically one of the constant signs of kidney failure [24].

22.3.2 Hyponatremia in CKD

Hyponatremia, which is defined as a plasma sodium concentration <135 mmol/L, can occur in CKD when renal water excretion is less than water intake. Rarely, depletional (hypovolemic) hyponatremia is induced in CKD patients when they are complicated with sodium (volume) losses and maintaining water intake. Typically, dilutional hyponatremia occurs in CKD patients because of impaired urinary diluting ability. As patients reach CKD stage 5, the urine osmolality hardly goes down to ~100 mOsm/kg H_2O in response to water load.

When hyponatremia was defined as a serum sodium concentration <136 mmol/L, its baseline prevalence was 13.5% in 655,493 US veterans with non-dialysis-dependent CKD [25]. However, over a mean 5-year period of observation, 26% of all patients developed at least 1 episode of hyponatremia. In this cohort, mortality increased with the severity of hyponatremia although it was not influenced by CKD stage.

Kidney failure is one of the major causes of hyponatremia because the reduced GFR accompanies a decrease in solute-free water clearance. Although both urine concentration and dilution are impaired in kidney failure, hyponatremia is more frequent than hypernatremia in CKD patients because glomerular filtration is the initial prerequisite for urine dilution. Three components are required for the production of dilute urine [4]: (1) there must be enough glomerular filtrate delivered to the distal nephron for dilution and excretion, (2) the diluting segments of the distal nephron must selectively reabsorb sodium and lead to a fall in urine osmolality, and finally, and (3) AVP levels must fall and the collecting duct must decrease its permeability to water reabsorption and allow water to be excreted (dilute urine). In addition to the decline in GFR, defects in the diluting segment should be additionally associated with CKD for development of hyponatremia [26]. In renal cortex, the distal convoluted tubule acts as the diluting segment because of the presence of NCC and ENaC and the absence of AQP2. Consistent with this, the risk of hyponatremia is increased by using thiazides and amiloride. The clinical phenotype of hyponatremia in CKD may be similar to that in syndrome of inappropriate ADH secretion (SIADH). Plasma AVP levels are elevated in patients with CKD because of reduction of its metabolic clearance rate [27].

22.3.2.1 Differential Diagnosis of Hyponatremia

Many CKD patients with hyponatremia are asymptomatic because the onset of hyponatremia is usually gradual. Mild to moderate symptoms include dizziness, headache, nausea, and vomiting. Severe neurologic manifestations are confusion, lethargy, seizures, and coma caused by brainstem herniation. Since most of the CKD patients are free of edema, hyponatremia in CKD can be classified as euvolemic. However, CKD patients may be edematous or hypervolemic when they are nephrotic or markedly uremic. Rarely, they can also be hypovolemic when they are complicated by fluid or blood loss.

Hyponatremia in CKD is hypotonic, but measured osmolality can vary from hypoosmolar to hyperosmolar according to the level of blood urea nitrogen (BUN). A high level of BUN will increase the measured osmolality, whereas tonicity or effective osmolality is not affected by blood urea. Urine sodium is also not very helpful in laboratory diagnosis because its concentration is typically >20 mmol/L in CKD. If tubular function is intact, urine sodium could be <20 mmol/L when remarkable volume depletion or edematous disorders such as nephrotic syndrome, liver cirrhosis, and congestive heart failure are coexistent.

22.3.2.2 Treatment of Hyponatremia

The treatment of hyponatremia in CKD patients follows the same principles as the treatment of hyponatremia in patients without CKD. Water restriction is the first measure to restore water balance although it is a slow acting approach to correct hyponatremia. When the patients are symptomatic and acute hyponatremia is suspected, 3% hypertonic saline can be infused to elevate the serum sodium level. Like cases without CKD, frequent monitoring of serum sodium levels is required to prevent overcorrection. Normal saline solution is the treatment of choice for hypovolemic hyponatremic conditions [26]. In cases with volume overload or hypertension, loop diuretics such as furosemide and torsemide are effective not only in relieving edema but also in elevating serum sodium levels. Tolvaptan, an oral AVP receptor 2 antagonist, may be added to furosemide in hyponatremic CKD patients when a greater diuretic effect is necessary [28]. Ultrafiltration therapy should be considered for patients with refractory edema that is not responsive to intensive diuretic treatment.

Results of a large epidemiologic study revealed the lowest mortality in patients with sodium levels of 140 mmol/L and adjusted hazard ratios for the group <130 and 130 to 135 mmol/L to be 1.93 and 1.28, respectively [25]. Therefore, gradual correction of plasma sodium levels to 135 mmol/L appears to be a reasonable target.

22.3.3 Hypernatremia in CKD

Hypernatremia, which is defined as a plasma sodium concentration >145 mmol/L, is infrequently noted in CKD patients when sodium or water balance is disturbed. If sodium intake exceeds the capacity of the kidneys to excrete sodium, it can result in sodium overload, leading to edema and hypernatremia. This usually derives from inadvertent salt overuse or iatrogenic causes such as intravenous hypertonic NaCl or $NaHCO_3$ infusion. The other more common etiology is water deficit caused by either insufficient water intake or enhanced water loss via renal and extrarenal routes. In any case, CKD patients are susceptible to hypernatremia because of impaired urinary concentration. To excrete the dietary solute load of 600 mOsm/day, as little as 0.5 L/day of highly concentrated urine (1200 mOsm/kg H_2O) would suffice. However, 2 L/day of urine output is necessary to excrete the dietary solute load of 600 mOsm/day when the urinary concentration is reduced to 300 mOsm/kg H_2O (Fig. 22.2). Thus, water deficit occurs if water intake is less than 2 L/day.

Hypernatremia increases osmolality of the ECF, causing an efflux of intracellular water and cellular shrinkage. As with hyponatremia, the symptoms of hypernatremia vary from asymptomatic to neurologically serious depending on the severity and rate of onset of hypernatremia. Altered consciousness is the typical manifestation, ranging from mild confusion and lethargy to deep coma [29].

On physical examination, edema can be found if sodium is primarily retained. In contrast with hyponatremia, measurement of serum osmolality is unnecessary for differential diagnosis of hypernatremia because hyperosmolality is naturally produced by hypernatremia and azotemia. In general, measurement of urine osmolality is useful in differentiating renal water loss from extrarenal water loss. However, its significance is limited in CKD because urine concentration is already disturbed by the associated tubular injury.

The treatment of hypernatremia in CKD patients follows the same principles as the treatment of hypernatremia in patients without CKD [30]. Simultaneously, efforts to seek and eliminate the underlying cause of water deficiency or sodium overload are mandatory. If hypernatremia is symptomatic, hypotonic fluids should be infused to lower serum sodium levels. Dextrose water is appropriate for treating pure water loss, and half-saline may be required for treating water and sodium loss. The rate and amount of daily water replacement should be based not on the calculated water deficit, but on the repeated measurements of serum [Na^+] to prevent under- or overcorrection. If hypernatremia is chronic (≥48 h) or of unknown duration, serum sodium correction should be gradual, not exceeding 8–10 mmol/L in the first 24 h to prevent cerebral edema [29]. More rapid serum Na^+ correction (up to 1 mmol/L per hour) may be appropriate if onset of hypernatremia is acute (<48 h).

According to the observational study from 655,493 US veterans with non-dialysis-dependent CKD, the prevalence of hypernatremia defined as a serum sodium concentration >145 mmol/L were 2% at baseline and 7% over a mean 5-year period of observation [25]. Thus, the prevalence of hypernatremia was much lower than that of hyponatremia but showed a significant increase with advancing stages of CKD, supporting the observation that the kidney's concentrating ability is affected to a greater extent by advancing CKD than its diluting ability [31]. Interestingly, the association between hypernatremia and mortality appeared to diminish linearly with more advanced stages of CKD [32]. This apparent "protective" effect of advanced CKD on hypernatremia-related mortality may be because of adaptation to increased extracellular (uremic) osmolality in patients with more advanced CKD [4].

22.4 Potassium Balance Disorders

Potassium is mostly (>98%) located in the intracellular fluid (ICF) and is required for normal cell function. In particular, the ratio between ECF and ICF potassium concentration is a determinant of transmembrane electrochemical gradient and neuromuscular excitability. Therefore, potassium balance is critical for the excitable tissues such as heart, nerves, and skeletal muscle, and the ECF potassium level should be maintained within a narrow normal range (3.5–5.0 mmo/L). Potassium also has a strong relationship with sodium, affecting plasma volume and blood pressure.

The potassium balance can be divided into internal and external. The internal potassium balance is determined by transcellular shift of K^+ across the cell membrane, which is mainly exerted by Na^+/K^+-ATPase. Insulin and catecholamines are the most important determinants of cell membrane potential and govern K^+ distribution into and out of cells. The external balance is resultant from dietary intake and fecal and urinary excretion. On a typical Western diet, daily potassium intake ranges from 90 to 120 mmol/day [30]. At steady state, the kidneys excrete 90–95% of dietary potassium, with the small remainder excreted in stool through the colonic secretion. With progression of CKD, renal potassium excretion may decrease, leading to an elevation in plasma potassium levels. Altered potassium secretion in the ASDN is the major component of dysregulated potassium homeostasis.

22.4.1 Role of the Kidney in Potassium Balance Regulation

The kidney is the major organ that regulates potassium balance. Although small amounts of potassium are excreted in stool and sweat, this

amount is essentially constant and is not regulated. Plasma potassium is freely filtered at glomeruli, but urinary potassium excretion can vary according to the status of total body potassium. Approximately 65% of glomerular filtered potassium is reabsorbed in the proximal tubule, where paracellular solvent drag and diffusion act as the major driving forces for potassium reabsorption [33]. In the thick ascending limb of Henle's loop, approximately 25% of the glomerular filtered potassium is reabsorbed mainly through the paracellular pathway. This is driven by the lumen-positive voltage promoted by apical K^+ recycling, which is resultant from the coupled action of NKCC2 and renal outer medullary potassium channel (ROMK).

Like sodium, the final urinary potassium excretion is finely tuned by regulation of potassium secretion in the ASDN. The major K^+ channels in the ASDN are Kir4.1 and Kir5.1 in the basolateral membrane and Kir1.1 (ROMK) and Ca^{2+}-activated big conductance K^+ channel (BK) in the apical membrane. Among these, the ROMK plays a major role by regulating potassium secretion in the later part of the ASDN. Usual fractional excretions of potassium range 15–20%. When potassium intake increases, fractional excretion of potassium can rise up to 80% [34] mainly caused by the increased potassium section in the principal cells. In cases of potassium depletion, H^+/K^+-ATPase in the α-intercalated cells activates to reabsorb potassium, and fractional excretion of potassium can be reduced down to 1.5% [35]. Because of the enhanced action of H^+/K^+-ATPase, urine ammonium excretion is increased and metabolic alkalosis may be associated [36].

In the ASDN, both sodium reabsorption through the ENaC and potassium secretion through the ROMK are regulated by aldosterone. However, the renal effects of aldosterone action are different between hypovolemia and hyperkalemia (aldosterone paradox) [37]. When aldosterone is stimulated by volume depletion or hyperreninemia, the aldosterone-regulated sodium transporters NCC and ENaC are activated to conserve sodium. Importantly, undesired potassium loss is prevented by the activated angiotensin II because of its inhibitory action on ROMK. When aldosterone is stimulated by hyperkalemia, the ROMK is activated to enhance potassium secretion and potassium balance can be restored. However, undesired sodium retention is prevented by downregulation of NCC because the NCC is dephosphorylated by hyperkalemia or dietary potassium loading [38]. Thus, aldosterone acts in the kidney to independently regulate sodium and potassium balance.

Kidneys can retain the ability to maintain potassium balance and normal serum potassium levels until very late stages of CKD. In response to oral potassium load, however, the increase in urinary potassium excretion is blunted in CKD patients compared with normal subjects [39]. Urinary potassium excretion gradually decreases with declining of GFR, but the fractional excretion of potassium increases (Fig. 22.3) because potassium secretion per nephron increases with progression of CKD [40]. In advanced CKD, potassium secretion increases in principal cells of the cortical collecting duct in association with increased activity of Na^+-K^+-ATPase [41]. In addition, as CKD progresses, intestinal potassium excretion also increases in concert with increased colonic Na^+-K^+-ATPase activity [42] and BK channel-mediated potassium permeability [43, 44].

22.4.2 Hyperkalemia in CKD

Hyperkalemia, defined as a plasma potassium concentration >5.0 mmol/L, is the most common electrolyte disorder in patients with advanced CKD. Decreased GFR and impaired sodium delivery to the distal nephron both hinder renal potassium excretion in patients with CKD [45]. The risk of hyperkalemia may increase when estimated GFR drops below 40 mL/min/1.73 m^2 [46], and the incidence of hyperkalemia increases as the CKD advances from stage 1 to 5.

The prevalence of hyperkalemia varies depending on the patient population studied and how it is defined. Overall, the prevalence of hyperkalemia in CKD is 14–20% [47], and Fig. 22.4 presents data from a Korean CKD

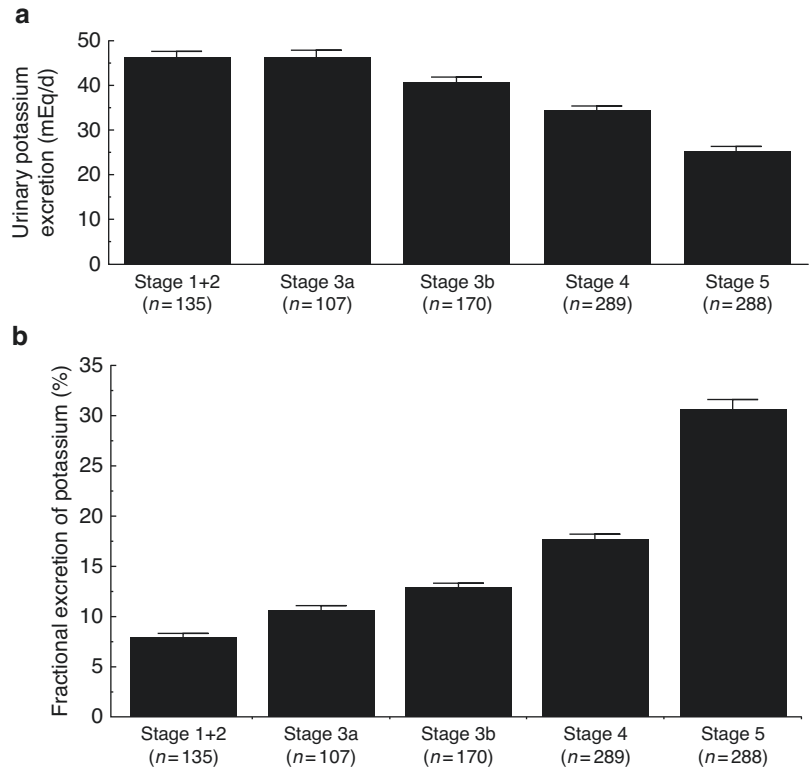

Fig. 22.3 Changes in urinary potassium excretion (**a**) and fractional excretion of potassium (**b**) according to different stages of CKD. *CKD* chronic kidney disease. (Reproduced with permission from the Korean Society of Nephrology: Ueda et al. [38])

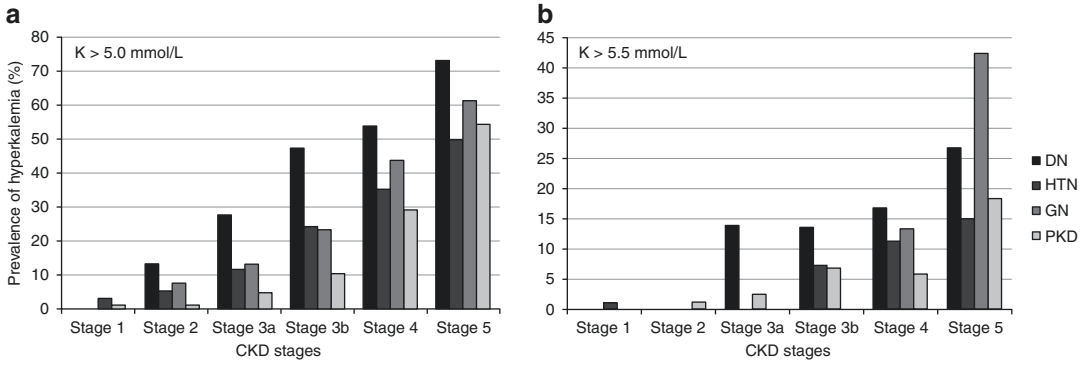

Fig. 22.4 Prevalence of hyperkalemia according to etiology of CKD in each CKD stage when hyperkalemia was defined as >5.0 mmol/L (**a**) and as >5.5 mmol/L (**b**). CKD, chronic kidney disease. (Adapted from the article of Kim et al. [48], according to the Creative Commons Attribution 4.0 International License)

cohort (n = 1788) with respect to different underlying diseases of CKD [48].

Even moderate levels of hyperkalemia are associated with unfavorable outcomes. Hyperkalemia is independently associated with significantly higher all-cause and cardiovascular mortality and with higher risk of ESKD [49]. Interestingly, the mortality associated with hyperkalemia is lower in patients with CKD compared with those with normal kidney function, probably due to the chronicity of hyperkalemia [50].

22.4.2.1 Differential Diagnosis of Hyperkalemia

The typical causes of hyperkalemia are similar in patients with and without CKD [51]. Excessive

dietary potassium intake can cause hyperkalemia in individuals with advanced CKD. When insulin deficiency, mineral acidosis, or hyperosmolality (e.g., hyperglycemia or contrast media) are associated, hyperkalemia is induced by the redistribution of potassium out of cells. The reduction of GFR < 15 mL/min/1.73 m^2 (or CKD stage 5) may be the major cause of decreased renal excretion of potassium [51], but hypoaldosteronism to impair potassium secretion in the ASDN may be a more important cause of hyperkalemia in earlier stages of CKD. The combination of hyperkalemia and hyperchloremic metabolic acidosis, or type 4 renal tubular acidosis is common in CKD and is most often attributable to either hyporeninemic hypoaldosteronism or obstructive uropathy. Hyporeninemic hypoaldosteronism can occur in patients with diabetic nephropathy and hypertensive nephrosclerosis, and many medications inhibiting the renin-angiotensin-aldosterone system (RAAS) in the kidney may result in hypoaldosteronism and hyperkalemia (Table 22.2). The RAAS inhibitors typically include angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockades (ARBs), and MRAs, and the combined use of more than one drug in this category increases the risk for hyperkalemia. Because RAAS inhibitors are commonly used in CKD patients who have diabetes mellitus and/or heart failure, these comorbidities put CKD patients at risk of hyperkalemia.

Table 22.2 Medications associated with hyperkalemia resulting from RAAS inhibition

Mechanism	Drug
Impaired release of renin	NSAIDs, beta-blockers, calcineurin inhibitors
Direct renin inhibitor	Aliskiren
ACE inhibitors	Captopril, enalapril, ramipril, perindopril
Angiotensin receptor blockers	Losartan, irbesartan, telmisartan, olmesartan
Impaired release of aldosterone	Heparin, ketoconazole
Mineralocorticoid receptor antagonists	Spironolactone, eplerenone, finerenone
ENaC blockers	Amiloride, triamterene, trimethoprim, pentamidine

ACE angiotensin converting enzyme, *ENaC* epithelial sodium channel, *NSAIDs* nonsteroidal anti-inflammatory drugs, *RAAS* renin–angiotensin–aldosterone system

Pseudohyperaldosteronism type II, also known as familial hyperkalemic hypertension or Gordon's syndrome is an inherited syndrome of hypertension and hyperkalemia. Other associated findings include hyperchloremia, metabolic acidosis, hypercalciuria, and suppressed plasma renin levels. These clinical features can be explained by the NCC hyperactivity in the distal convoluted tubule, caused by mutations of NCC regulator genes including *WNK1*, *WNK4*, *CUL3*, or *KLHL3*. A similar but more common acquired phenotype may occur when calcineurin inhibitors are administered to kidney transplant patients. Calcineurin inhibitors were reported to upregulate NCC, leading to a syndrome of hypertension and hyperkalemia [52].

Clinical manifestations of hyperkalemia vary widely from nonspecific muscle weakness to paresthesia, muscle paralysis, cardiac arrhythmias, and cardiac arrest. As hyperkalemia progresses, a series of abnormal electrocardiographic findings may occur: peaked T waves, prolonged PR interval, loss of P waves, widening of the QRS complex, and sine waves. However, these changes are not sensitive in detecting hyperkalemia, particularly in patients with advanced CKD. The reasons why the electrocardiographic changes are attenuated in hyperkalemic CKD patients are unclear, but variations in serum calcium concentration and the slow rate of rise in serum potassium have been proposed as possible explanations [53].

22.4.2.2 Treatment of Hyperkalemia

Acute treatment for severe hyperkalemia includes intravenous calcium, insulin, sodium bicarbonate, and inhaled β2-adrenergic agonists. Hyperkalemia may be classified as severe when the plasma potassium level is 6.5 mmol/L or higher, regardless of any associated ECG changes [54]. If no arrhythmia is associated, pseudohyperkalemia or spuriously high measurement of potassium must be ruled out. In vitro hemolysis is the major cause of pseudohyperkalemia and can be suspected by inspection of the serum. Clinicians may be advised to compare the serum and plasma potassium level because pseudohy-

perkalemia is a rise in serum potassium with concurrently normal plasma potassium concentration.

If ECG abnormalities are found, 1 g calcium gluconate (10 mL of 10% solution) or calcium chloride (3–4 mL of 10% solution) should be infused intravenously over 2–3 min with cardiac monitoring. Calcium reverses the depolarization blockade due to hyperkalemia by raising the action potential threshold and reducing excitability, without changing the resting membrane potential [29]. The infusion may be repeated because the electrical effect on cardiac excitation lasts for 30–60 min. To rapidly reduce the plasma potassium level, measures to translocate potassium from the extracellular space to the intracellular space are simultaneously necessary. Intravenous regular insulin 5 units plus 25 g glucose (50 mL of 50%) can be given with close monitoring of plasma glucose concentration. The effect begins in 10–20 min, peaks at 30–60 min, and lasts for 4–6 h. β2-Adrenergic agonists are also effective, and albuterol (salbutamol) 10 mg nebulized in 4 mL of normal saline is inhaled over 10 min. The effect starts at about 30 min, reaches its peak at about 90 min, and lasts for 2–6 h. Because tachycardia is a side effect, β2-adrenergic agonists should be used with caution in patients with cardiac disease [29]. Insulin and albuterol may have an additive effect on plasma potassium concentration. Conversely, intravenous bicarbonate has no role in the acute treatment of hyperkalemia because of its slow onset of action and low efficacy. It may be considered in hyperkalemic patients with metabolic acidosis but without volume overload. Intravenous bicarbonate (50 mL of 8.4% solution, containing 50 mmol each of Na^+ and HCO_3^-) can be given over 15 min [54]. If these medical treatments are unsuccessful, acute hemodialysis is indicated. For this, a vascular access is required, either a central venous catheter or a preexisting arteriovenous access.

Chronic treatment for mild to moderate hyperkalemia includes restriction of dietary potassium intake, avoidance of drugs that may induce hyperkalemia, augmentation of urinary potassium excretion, and enhanced fecal potassium elimination using cation exchange resins or potassium binders. If the CKD patients are hyperkalemic, dietary potassium needs to be limited to less than 75 mmol/day. Thus, plasma potassium levels should be monitored while restricting intake of potassium-rich foods such as vegetables, fruits, and nuts. Medications that may induce hyperkalemia (e.g., nonsteroidal anti-inflammatory drugs, nonselective beta-blockers, calcineurin inhibitors, and heparin) should be reviewed. They mostly interfere with potassium secretion from ASDN, and RAAS inhibitors including ACE inhibitors, ARBs, and MRAs are frequently used in patients with CKD and cardiorenal syndrome because of their cardiorenal protection. In cases of severe hyperkalemia, all agents that cause hyperkalemia should be discontinued. However, the benefit of RAAS inhibition may be considered in cases of mild hyperkalemia because potassium-lowering agents are available. Whether to stop or reduce RAAS inhibitors is an important issue, as it involves comparing the risk of hyperkalemia with the benefits of RAAS inhibition. The ongoing DIAMOND trial will show whether the use of novel potassium binders such as patiromer provides the long-term benefits for patients with heart failure and hyperkalemia who are taking RAAS inhibitors [55].

Loop diuretics, potassium binders, and dialysis are interventions used to remove potassium from the body. Loop diuretics with or without thiazides can be used to promote kaliuresis. These are beneficial for edematous patients, but caution needs to be paid to the risk of plasma volume depletion caused by overuse of diuretics. Fludrocortisone acetate may be prescribed to increase urinary potassium excretion in patients with aldosterone deficiency. However, larger doses (up to 0.4–1.0 mg/day) are required to effectively lower potassium level, and sodium retention, edema, and hypertension may be complicated [56]. Old potassium binders are cation exchange resins and include sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS). Novel potassium binders are patiromer and sodium zirconium cyclosilicate (ZS-9) and lack the intestinal toxicity. These agents have revolutionized the management of hyperkalemia

in users of RAAS inhibitors in CKD. The availability of safe, well-tolerated potassium binders allows for the continued use of RAAS inhibitors for cardiorenal protection [29]. However, the high cost currently limits the global use of novel potassium binders.

Sodium polystyrene sulfonate (SPS) is a cation exchange resin, which exchanges sodium for calcium, ammonium, and magnesium in addition to potassium. Thus, it is not very selective for serum potassium lowering and may lead to hypocalcemia and hypomagnesemia. Kayexalate was the commercial name given to the powdered form of SPS, first introduced in the 1950s [57]. Cation exchange resins seem to act on crypt enterocytes in the distal colon, which have the secretory pathway of potassium from basolateral NKCC1 cotransporter and Na/K-ATPase to apical BK channel [58]. Oral administration of SPS 15–60 g per day can be given in divided doses but without sorbitol because of the risk of intestinal necrosis [54]. The efficacy and safety of SPS were previously concerned, but the use of SPS may continue due to its clinical familiarity and lower cost [59].

Calcium polystyrene sulfonate (CPS) is another cation exchange resin, which exchanges calcium for potassium. Compared with SPS, CPS may have a higher potassium-selectivity at cation exchange [60]. Although CPS has been widely used for patients with advanced CKD in many countries, few studies have reported on its efficacy and adverse effects. Yu et al. conducted a retrospective analysis from 247 adult patients who were prescribed CPS for weeks to years [61]. They found that long-term use of small doses (5–15 g/day) of oral CPS was effective and safe for controlling mild hyperkalemia. Considering the similar action mechanisms, CPS could be used as an alternative to patiromer in countries where novel potassium binders are unavailable [62]. In a comparative study between CPS and SPS, serum potassium lowering was similar [60]. Unlike CPS, however, SPS significantly increased serum sodium and decreased serum calcium and magnesium concentrations.

Patiromer is a non-absorbable polymer consisting of smooth spherical beads approximately 100 μm in diameter. The active moiety of the polymer is composed of α-fluorocarboxylic acid that contains a calcium ion which dissociates in favor of a potassium ion to promote fecal potassium excretion in the distal colon [57]. Oral administration of patiromer can increase fecal potassium in a dose-related fashion, and doses of 15–30 g/day increased daily fecal potassium by approximately 15–20 mmol [63]. Randomized, controlled trials have evaluated the efficacy and safety of patiromer in hyperkalemic CKD patients already treated with RAAS blockers. Serum potassium lowering was demonstrated by daily doses between 8.4 and 30 g up to 52 weeks. Major adverse events were constipation and hypomagnesemia [64]. Based on these results, patiromer was approved by the Food and Drug Administration in 2015.

Sodium zirconium cyclosilicate (ZS-9) is a crystal that is highly selective for potassium ion trapping. Thus, it may act throughout the gastrointestinal tract and explain the rapid onset of action. ZS-9 was also tested for treating hyperkalemia in CKD, heart failure, or diabetic outpatients. Daily doses between 1.25 and 15 g up to four weeks were used in randomized, controlled trials and showed effective serum potassium lowering. Major adverse events were edema and diarrhea [64]. Based on these results, ZS-9 was approved by the Food and Drug Administration in 2018.

22.4.3 Hypokalemia in CKD

Hypokalemia, defined as a plasma potassium concentration <3.5 mmol/L, uncommonly occurs in CKD patients with inadequate potassium intake, increased intracellular potassium shift, and renal or gastrointestinal potassium loss. Overall, the prevalence of hypokalemia is 1–3% [47]. For hypertensive patients with CKD stage 1 and 2, a daily intake of 4 g of potassium per day (or 102 mmol) is generally recommended and dietary potassium restriction is not recommended until kidney disease is more advanced [49]. Frequent causes of potassium loss are diuretic overuse, metabolic alkalosis, vomiting, diarrhea, and hypomagnesemia.

Clinical symptoms and signs of hypokalemia vary depending on the rate of onset and severity [30]. These include muscle weakness, cramps, muscle paralysis and respiratory failure, cardiac arrhythmias, paralytic ileus, and rhabdomyolysis. In particular, hypokalemia is a major risk factor for both ventricular and atrial arrhythmias [29], including sinus bradycardia, atrioventricular block, paroxysmal atrial or junctional tachycardia, ventricular tachycardia, and fibrillation. ECG changes include broad flat T waves, emergence of U waves, ST depression, and QT prolongation. Hypokalemia also involves skeletal muscles, leading to weakness and even paralysis. Paralytic ileus may result from intestinal smooth muscle involvement. Hypokalemia is frequently associated with metabolic alkalosis because of enhanced renal proximal tubular ammoniagenesis.

22.4.3.1 Differential Diagnosis of Hypokalemia

Clinical settings are important clues for differential diagnosis. The history should focus on diet and dietary habits, medications including diuretics, laxatives, and antibiotics, and gastrointestinal problems such as vomiting and diarrhea [29]. On physical examination, it is important to differentiate whether the patient is hypertensive or hypovolemic. If hypokalemia is accompanied by hypertension, diuretic use should be sought first. When this possibility is excluded, following causes of mineralocorticoid excess need to be differentiated by measuring plasma renin activity and serum aldosterone: primary aldosteronism, renovascular hypertension, Liddle syndrome, and syndrome of apparent mineralocorticoid excess.

Urine potassium excretion or potassium-to-creatinine ratio is the mainstay for the differential diagnosis of hypokalemia. In CKD, however, the cut-off value suggestive of renal potassium wasting is unclear because of the associated tubular injury and dysfunction. Acid–base equilibrium can also be disturbed by impaired urinary acidification in CKD. In cases with normotensive hypokalemic metabolic alkalosis, measurement of urine chloride and urine calcium-to-creatinine ratio is useful for diagnosing vomiting, diuretic abuse, Gitelman syndrome, and Bartter syndrome. The chronic state of hypovolemia, hypotension, and hypokalemia in salt-losing nephropathy can lead to progressive declines in GFR.

22.4.3.2 Treatment of Hypokalemia

Management of hypokalemia in CKD patients involves correcting the underlying causes and cautious potassium replacement. Restriction of dietary potassium should be avoided in patients with hypokalemia. Adequate intake of fruits and vegetables is encouraged unless plasma potassium levels are increased. However, dietary salt intake needs to be restricted because increased distal sodium delivery would result in increased potassium excretion. Foods with a relatively high potassium content (>6.2 mmol/100 g) include spinach, broccoli, carrots, potatoes, kiwis, oranges, and mangos [49]. When potassium supplementation is indicated, small doses of potassium chloride are orally administered. If metabolic acidosis is coexistent, potassium citrate is preferred to elevate plasma bicarbonate. With severe and symptomatic hypokalemia, intravenous potassium chloride can be administered at a rate <10 mmol/h in half-saline. It should be diluted to <40 mmol/L for the peripheral venous route and <100 mmol/L for the central venous route [65]. The plasma potassium levels should be monitored more frequently than in patients without CKD to avoid excessive administration. Daily parenteral doses are typically limited to <60 to 80 mmol/day [66].

Hypokalemia is associated with poor outcomes including mortality and kidney function decline in CKD. Most studies have observed a U-shaped relationship between serum potassium and mortality, with the lowest risk observed in those with a serum potassium of 4–5 mmol/L [47]. Interestingly, prolonged hypokalemia is associated with CKD progression. When 820 patients with CKD were prospectively followed at four US centers for an average of 2.6 years, those with a serum potassium <4 mmol/L had a 69% higher ESKD risk compared to those with normokalemia, whereas ESKD risk was not higher for those with potassium ≥5.5 mmol/L [67]. In a separate

study from 1227 males with CKD, those with a serum potassium <3.6 mmol/L had greater annual loss of GFR (−0.23 mL/min per 1.73 m^2 per year) than those with a serum potassium of 3.6–5.5 mmol/L. In contrast, there was no significant difference in annual GFR loss for those with a serum potassium >5.5 mmol/L [68]. The association of hypokalemia with accelerated progression of CKD was postulated, at least in part, to be due to impaired renal angiogenesis and enhanced renal ammonia production with consequent intrarenal complement activation [69, 70].

Before You Finish: Practice Pearls for the Clinician

- CKD patients are susceptible to ECF overload when their GFRs are reduced to <10 mL/min or when tubular sodium reabsorption is enhanced by the activation of RAAS (e.g., congestive heart failure or nephrotic syndrome).
- Loop diuretics with or without thiazide-like agents are the mainstay for correcting volume overload in CKD. Dietary sodium restriction is a prerequisite for the maintenance of euvolemia.
- Dilutional hyponatremia may be caused by reduced free water clearance and impaired diluting segments in CKD patients and can be treated by restriction of water intake and administration of loop diuretics.
- Saline infusion is indicated when CKD patients are complicated by volume depletion caused by renal and extrarenal fluid losses.
- Hypernatremia is an infrequent electrolyte disorder in CKD, caused by the same etiologies in patients without CKD. Thus, the same treatment principles can be applied.
- Hyperkalemia is the most common electrolyte disorder in CKD patients taking RAAS inhibitors. The risk of hyperkalemia can be reduced by concomitant use of potassium binders.
- Hypokalemia uncommonly occurs in CKD patients with inadequate potassium intake, increased intracellular potassium shift, and renal or gastrointestinal potassium loss. Hypokalemia was known to be associated with accelerated progression of CKD.

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23 Pruritus and Other Dermatological Problems in Chronic Kidney Disease

Benjamin Gallo Marin, Cathy M. Massoud, and Leslie Robinson-Bostom

Before You Start: Facts you Need to Know

- Pruritus is one of the most common cutaneous symptoms in patients with chronic kidney disease on dialysis. Treatments offer minimal relief.
- Xerosis cutis, another common finding in chronic kidney disease, can be treated with emollients.
- Disorders in calcium and phosphorus metabolism are common in patients with chronic kidney disease and include calciphylaxis and metastatic calcinosis cutis.

23.1 Pruritus

Pruritus is commonly seen in patients with chronic kidney disease (CKD) on dialysis. In the past, prevalence was reported to be as high as 90% in patients with CKD; however, more recently, rates of 20–56% of patients have been described [1, 2]. It seems to be independent of sex, ethnicity, type of dialysis, and underlying kidney disease. Pruritus itself is not immediately threatening, but it is an independent predictor of mortality [3].

23.1.1 What Causes Pruritus in Chronic Kidney Disease?

The pathophysiologic mechanism of uremic pruritus is poorly understood, but hypotheses implicate immune system dysregulation that results in a proinflammatory state leading to itching [4]. The increase in levels of C-reactive protein and other inflammatory mediators, particularly interleukin-13, contributes to the intensity of itch [5, 6]. Additionally, the derangement in calcium and phosphate metabolism that occurs in CKD can cause accumulation of these substances in the skin, which can further exacerbate pruritus [3]. Some also postulate that changes in neurological perception that occur with chronic itching increase the perception and sensation of itch [3]. The middle molecule theory is based on the idea that non-dialyzable substances accumulate and cause pruritus. This explains why the itching resolves after renal transplantation [7].

23.1.2 What Are the Important Clinical Characteristics?

Pruritus has a negative impact on quality of life. It is frequently disabling and can have a significant

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effect on mental well-being contributing to daytime fatigue, agitation, and depression [3]. Patients may have complaints ranging from intermittent itching to persistent pruritus, usually affecting the back and usually worse at night. The arms, head, and abdomen are also affected [3, 4]. Recurrent itching or rubbing of the skin in the setting of chronic pruritus may lead to lichenification, a focal thickening of the skin that typically presents with exaggerated skin lines. Patients with CKD presenting with itching and white scale formation may be exhibiting uremic frost, a cutaneous finding that generally occurs at blood urea nitrogen levels of approximately 200 mg/dl and is indicative of profound renal failure [8]. Because uremic frost tends to occur in hair-covered areas in men, it may be confused with seborrheic dermatitis.

23.1.3 How Is Pruritus in CKD Treated?

Treatment for pruritus associated with CKD is limited. The evidence for the treatments described in the literature is mostly anecdotal or based on case series [9]. When approaching a patient with pruritus, a stepwise approach may be helpful. Treatment of xerosis with emollients is essential because pruritus can be worsened by dry skin (xerosis). A trial of emollients containing menthol or pramoxine can be beneficial [3]. Topical capsaicin is also cited as being beneficial for localized pruritus but has not been effective in our clinical practice. Studies have demonstrated a dramatic reduction in pruritus with the use of topical tacrolimus [3], but this treatment may not be as effective and is not practical in patients with more diffuse pruritus.

Systemic treatments like gabapentin have been shown to be effective in some case studies [4]. However, other studies have also failed to demonstrate any improvement with gabapentin [4]. In cases where it is effective, gabapentin was shown to decrease the mean pruritus score with a dosage of 300 mg three times a day. There is an increased risk of gabapentin toxicity in patients on dialysis; therefore, it is recommended to start with a low dose and gradually increase until the maximum dose is reached [4]. Other treatment options that have recently gained attention include difelikefalin [10], sodium thiosulfate [11], cannabinoid formulations [12], and dupilumab [13].

Fig. 23.1 Lichenification in a CKD patient with pruritus

Broadband ultraviolet B (UVB) phototherapy is another treatment option for pruritus in CKD and is regarded by many clinicians as the treatment of choice. UVB light decreases the level of proinflammatory cytokines, which, as mentioned previously, may play a role in the pathogenesis of itch. Case series and pilot studies have shown UVB to be effective [4, 9]. It is important to consider the risk of skin cancer associated with UVB exposure because CKD patients are immunosuppressed and thus are predisposed to malignancy. This is especially important to consider if they have light skin types and are candidates for renal transplantation (Fig. 23.1).

23.2 Xerosis

Xerosis is a common cutaneous manifestation of CKD and was shown in at least three different studies to be the most prevalent of skin changes observed [14–16].

It is characterized by dryness of the skin, ichthyosis, roughness, and poor skin turgor [17]. The effects of this condition can lead to compromised functional integrity of the skin barrier resulting in increased susceptibility to contact irritants and infection. Some studies have reported a difference in prevalence of xerosis between patients receiv-

ing dialysis and those that are not receiving dialysis, but others have not observed any difference between these two groups [18].

23.2.1 What Causes Xerosis in CKD?

The cause of xerosis is unknown; however, many theories exist to explain its occurrence. The skin is a primary site of water homeostasis and with dialysis treatment and the associated high-dose diuretic therapies, water balance can be disturbed leading to skin dryness [17]. Other theories cite the reduction in size of sebaceous glands and eccrine sweat glands as the cause for xerosis [19].

23.2.2 What Are the Important Clinical Characteristics?

Xerosis can be generalized or localized and is most often located on the extremities. Patients complain of dry "cracked" skin that can be superimposed on uremic pruritus [19]. An important diagnosis to exclude is ichthyosis vulgaris as the clinical characteristics of this entity can closely resemble those of xerosis.

23.2.3 How Is Xerosis in CKD Treated?

It is important to ensure the skin is adequately lubricated. Daily use of gentle skin care and emollients can be helpful in treating xerosis and its associated symptoms [3]. In xerosis, there is a known decrease in glycerol content in the stratum corneum leading researchers to test the efficacy of emollients containing glycerol and paraffin. Glycerol has a hydrating effect, while paraffin protects the skin from irritants therapy addressing two of the major components of xerosis [20]. A recent study found that application of a heparinoid-containing product for an 8 week period is effective in treating xerosis in patients undergoing dialysis [21]. Traditional soaps should be avoided in the setting of xerosis, primarily since these products alkalinize the skin and damage the skin's moisture barrier. Instead, synthetic detergents such as syndet cleansers are preferred since their lower pH resembles the acidic pH of the skin and do not disturb its barrier function [22]. Other recommendations include bathing with lukewarm water, the use of humidifiers, and refraining from excessive skin washing (Fig. 23.2).

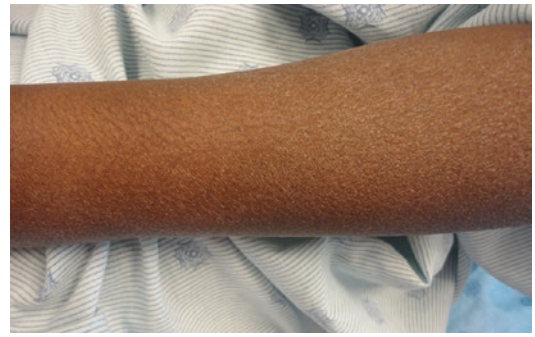

Fig. 23.2 Xerosis in a patient with CKD

23.3 Lindsay's (Half-and-Half) Nails

Lindsay's nails or half-and-half nails are a characteristic finding in patients with CKD. They are seen in patients with any degree of azotemia and present as a proximal white portion and distal reddish pink to brown portion of the nail. This specific nail finding is present in approximately one-third of patients with CKD [23]. Usually, this nail finding develops before patients need chronic dialysis, but it also is a frequent finding in patients on chronic dialysis [24]. A recent case series has reported the appearance of Lindsay's nails in patients with severe COVID-19 infection and without a history of known kidney disease [25].

23.3.1 What Causes Lindsay's Nails in CKD?

Although this condition is poorly understood, it is hypothesized that the distal brown band is the result of increased tissue concentration of beta-melanocyte-stimulating hormone due to its poor

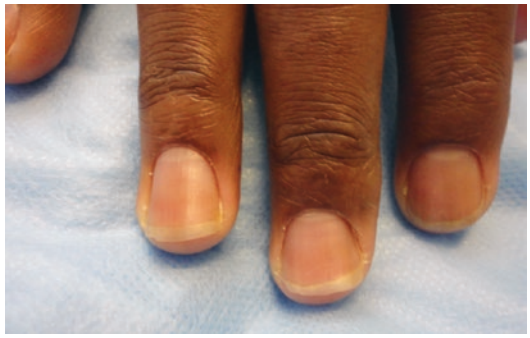

Fig. 23.3 Lindsay's (half-and-half) nails in a CKD patient. Note proximal white portion and distal reddish brown portion

dialyzability [19]. The white band, however, may result from long-standing anemia [26].

23.3.2 How Do you Treat Lindsay's Nails?

There are no treatments of Lindsay's nails, but the condition sometimes resolves with renal transplantation [19]. It has not been known to resolve with initiation of dialysis (Fig. 23.3) [27].

23.4 Acquired Perforating Dermatosis

This is an acquired pruritic disorder seen most commonly in patients with CKD with overlapping clinical and histologic features of primary perforating disorders including perforating folliculitis, Kyrle's disease, elastosis perforans serpiginosa, and reactive perforating collagenosis [28]. This disorder is characterized by hyperkeratotic follicular papules. It has also been described in the setting of diabetes mellitus (DM), copper deficiency, and PD-1 inhibitor therapy [29–31].

23.4.1 What Causes Acquired Perforating Dermatosis?

The pathogenesis of this disorder is not well understood, but a common finding is the transepidermal elimination of altered dermal substances [28]. The theory suggests that acquired perforating dermatosis may be caused by the accumulation of dermal microdeposits containing substances like calcium salts that cause a foreign body reaction [32]. Another hypothesis cites local trauma induced by excoriation and microvasculopathy causing extrusion of substances through the dermis as another cause for acquired perforating dermatosis [19].

23.4.2 What Are Important Clinical Considerations of Acquired Perforating Dermatosis?

It is important to remember that acquired perforating dermatosis is a spectrum of clinical disorders, and thus the specific underlying disease may vary with a similar presentation. Furthermore, the patient may also have pruritus associated with acquired perforating dermatosis or due to uremic pruritus. Koebnerization, or the development of new lesions induced by trauma, can occur with acquired perforating dermatosis; thus, adequate treatment of pruritus as well as counseling to decrease scratching is appropriate. Skin biopsy is required to make a diagnosis of acquired perforating dermatosis. While the histology of this condition varies, the main diagnostic feature is a central keratotic core overlying a focus of epidermal perforation [33].

23.4.3 How Do you Treat Acquired Perforating Dermatosis?

Topical and systemic retinoids, ultraviolet B phototherapy, psoralen and ultraviolet A (UVA), cryosurgery and photodynamic therapy, topical corticosteroids, and keratolytics should all be considered in the treatment of acquired perforating dermatosis [19]. Recent case reports have suggested that allopurinol may treat this condition [34]. Renal transplantation has also been known to clear acquired perforating dermatosis [32] (Fig. 23.4).

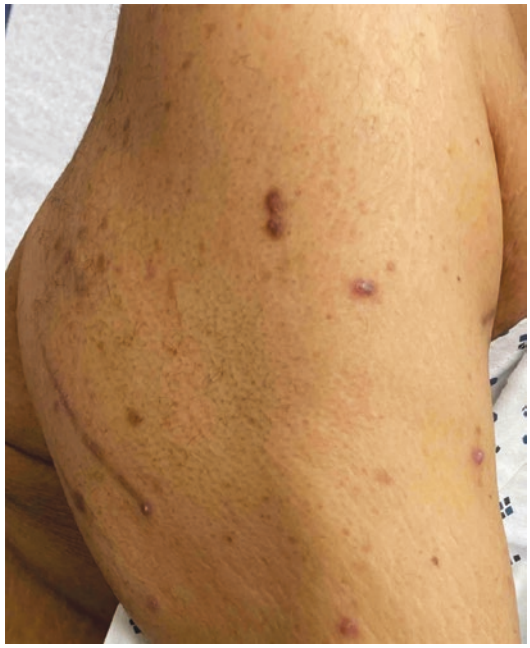

Fig. 23.4 Acquired perforating dermatosis with Koebnerization in a patient with CKD (Image courtesy of Deep Joshipura, MD)

23.5 Calciphylaxis

Calciphylaxis is also known as calcific uremic arteriolopathy and is a rare vasculopathy that typically presents in the setting of end-stage kidney disease (ESKD) associated with secondary hyperparathyroidism. It results from arteriolar deposition of calcium leading to evolving lesions of livedo reticularis (net-like erythema), livedo racemosa (a broken net-like pattern), and retiform purpura (purpuric patches with stellate borders) signifying necrosis of the deep dermis and subcutaneous tissues. It is particularly seen in patients on hemodialysis, but even in this population, it is only present in 1–4% [35]. Calciphylaxis is also seen in patients without uremia, specifically those with primary hyperparathyroidism. Additionally, calciphylaxis may occur in patients with both normal kidney and parathyroid function, these nontraditional patients may demonstrate a variety of comorbidities including: malignancy, connective tissue disease, osteomalacia, Crohn's disease, previous corticosteroid use, alcoholic liver disease, and protein C or S deficiency [35, 36]. Non-uremic calciphylaxis shows a predilection for obese postmenopausal people who are usually lupus anticoagulant positive [37].

23.5.1 What Causes Calciphylaxis?

The precise pathogenesis of calciphylaxis remains unknown, but small vessel endovascular fibrosis, fibrin thrombi, intimal proliferation, obliterative vasculopathy, tissue ischemia, calcification, panniculitis, and subcutaneous fat necrosis are all seen on histopathological examination [35]. CKD also leads to decreased clearance of phosphorus resulting in extraosseous calcification [19]. This calcification decreases lumen diameter and can predispose to sudden vascular occlusion, which leads to livedo reticularis and subsequent necrosis.

23.5.2 What Are Important Clinical Considerations of Calciphylaxis?

Patients may report exquisite tenderness overlying stellate or retiform purpura. These purpuric patches are typically symmetric and progress to deep stellate ulcers. The ulcers may become gangrenous and are most commonly located on the proximal thigh and lower abdomen or distally on shins, digits, or glans penis [19, 38]. In patients with ESKD, calciphylaxis should be suspected if they present with painful livedoid plaques and/or retiform purpura [39]. Skin biopsy may aid in diagnosis, yet excisional biopsy may be needed to obtain appropriate tissue depth. A negative skin biopsy does not preclude this diagnosis, and high clinical suspicion for calciphylaxis may guide empiric management. Imaging may aid in diagnosis, as these characteristic changes may be detected by ultrasound and plain radiograph [40, 41]. A high morbidity and mortality are associated with calciphylaxis, with death most commonly occurring secondary to sepsis. The medial survival rate after the appearance of lesions is

1 year [39]. Pain and palliative care consultations may be an underutilized resource for this patient population [42].

23.5.3 What Are the Treatments of Calciphylaxis?

Treatment for calciphylaxis includes both medical and surgical modalities. Sodium thiosulfate, ordinarily used to treat cyanide toxicity, can be given intravenously. There are no standard dosages but case reports citing efficacy of sodium thiosulfate administered dosages ranging from 5 to 25 g IV three times a week, usually after hemodialysis [35]. This treatment is thought to work because it acts as an antioxidant, vasodilator, and calcium chelator.

It is also important to normalize serum phosphate and calcium. Studies using bisphosphonates to treat calcium and phosphate disturbances seen in calciphylaxis have found that they reduce pain and promote ulcer healing [35]. They are thought to have an anti-inflammatory effect by suppressing cytokine release and inhibiting macrophages. There have also been numerous recent clinical trials investigating the utility of treating calciphylaxis with oral vitamin K supplementation, lanthanum carbonate, and SNF472 (hexasodium phytate) [39].

The role of surgical debridement in calciphylaxis is an issue that is debated. Some advocated for aggressive surgical debridement. Studies do show an association between surgical debridement and significant improvement in survival rates [35]. Still, others advocate for the use of hydrocolloid dressing and atraumatic debridement methods as any skin trauma can lead to new lesions. Other treatment methods including fish skin graft and cryopreserved human amniotic membranes have been reported [43, 44].

Parathyroidectomy is a potential surgical treatment for calciphylaxis in patients with hyperthyroidism, but there are variable outcomes and the evidence behind this treatment is not based on studies of large patient populations. Therefore, when considering this option, it is important to carefully consider the risk of post-surgical effects of parathyroidectomy [35].

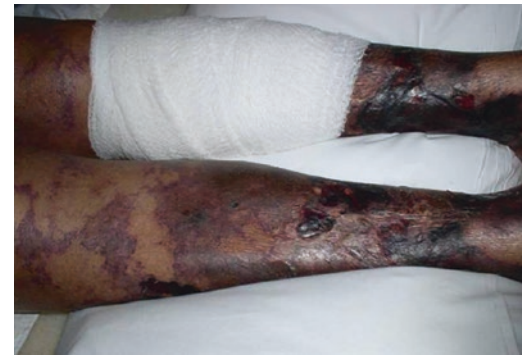

Fig. 23.5 Calciphylaxis in a patient with CKD (Image courtesy of Nathaniel Jellinek, MD)

Hyperbaric oxygen therapy has also been studied as a treatment for calciphylaxis. Its purported benefits include stimulation of fibroblast proliferation, conversion to myofibroblasts, stimulation of angiogenesis, and toxicity to various organisms that have the potential to cause serious infection and impair wound healing [35] (Fig. 23.5).

23.6 Metastatic Calcinosis Cutis

Metastatic calcinosis cutis (MCC), also referred to as benign nodular calcification, is a condition presenting with firm nodules and plaques in the skin and subcutaneous tissue. They are usually painless but occasionally periarterial depositions or depositions near joints can be painful [45].

23.6.1 What Causes Metastatic Calcinosis Cutis?

Increased serum calcium or phosphate levels or both cause MCC. When the levels of these substances are increased in blood, they precipitate into the skin and subcutaneous tissue causing palpable nodules and plaques [46]. Elevated calcium and phosphate are seen in kidney failure due to poor renal excretion of phosphate and secondary hyperparathyroidism that develops as a

result of poor intestinal absorption of calcium. Iatrogenic calcinosis cutis resulting from microtrauma and extravasation of intravenous calcium-containing fluids have also been reported [47].

23.6.2 What Are the Important Clinical Considerations?

Patients may present with skin-colored or pink, firm, tender papules, nodules, or plaques with well-defined borders [45]. These lesions can undergo secondary change resulting in ulceration. They may also become fluctuant and extrude contents, which are chalky in nature. Calcium and phosphate deposition can extend beyond the skin and may occur in other organs.

23.6.3 What Is the Treatment for Calcinosis Cutis?

MCC lesions usually resolve after serum normalization of calcium and phosphate [19]. The surgical treatments of MCC lesions are similar to the treatment of calciphylaxis lesions including parathyroidectomy for hyperparathyroidism.

23.7 Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is a generalized fibrotic disorder that can occur in patients with CKD who have been exposed to gadolinium (see Chap. 3). Acute or chronic kidney dysfunction in combination with inflammation contributes to the development of NSF [19]. Liver disease, erythropoietin, and acidosis are suspected contributors.

23.7.1 What Causes NSF?

Gadolinium exposure as a contrast agent in magnetic resonance angiography (MRA) or magnetic resonance imaging (MRI) was identified as a potential trigger for NSF [19]. Precipitates of gadolinium are produced and serve as activating substances for macrophages and fibroblasts. These precipitates may be endocytosed by fibrocytes resulting in a fibrotic expression in fibroblasts subsequently leading to an activation of kappa B pathway and transforming growth factor beta, thus promoting fibrosis that is seen in this condition [19]. Mice models have suggested that dysregulations in neutrophil elastase activity may facilitate the onset of NSF [48].

23.7.2 What Are the Important Clinical Considerations in NSF?

Consider the diagnosis of NSF if the patient reports a recent history of undergoing a procedure requiring MRI or MRA with contrast. This condition can present with indurated plaques or diffuse areas of skin induration but can also involve joints causing contractures [19].

23.7.3 What Is the Treatment of NSF?

No treatments have proven effective in curing NSF, so it is important to counsel patients to avoid the known trigger of this disorder. There is anecdotal evidence that improvement of this condition can be observed with topical or systemic steroids, cyclophosphamide, thalidomide, plasmapheresis, immunoglobulin infusion, imatinib mesylate, and rapamycin [19] (Fig. 23.6).

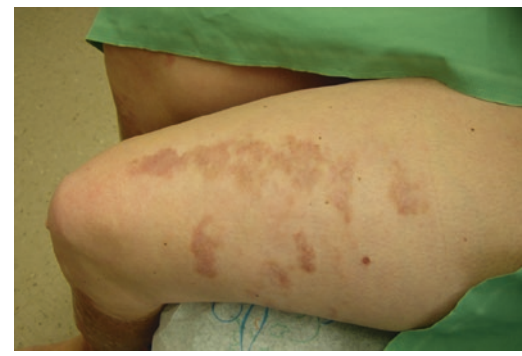

Fig. 23.6 Nephrogenic systemic fibrosis in a patient with CKD (Image courtesy of Seth Feder, MD)

23.8 Pseudoporphyria

Pseudoporphyria is a photodermatosis that is also known as bullous dermatosis of end-stage kidney disease. It is seen in patients with CKD or in patients undergoing long-term dialysis [19]. It has also been rarely reported in the setting of certain medications including voriconazole, furosemide, and olanzapine [49–51].

23.8.1 What Causes Pseudoporphyria?

The exact pathophysiology of pseudoporphyria is unknown, but ultraviolet (UV) light is thought to play a role in this entity given its association with UVA light exposure and medications that sensitize the skin to damage in UV light. Furthermore, in patients with CKD, risk of injury due to free radicals is higher due to low levels of glutathione in the blood and red blood cells [19].

23.8.2 What Are the Important Clinical Considerations in Pseudoporphyria?

This condition usually affects sun-exposed areas, usually the dorsal aspect of the forearms and hands. The patient may describe having fragile skin and blisters.

23.8.3 What Is the Treatment for Pseudoporphyria?

Photoprotection and sun avoidance are important aspects of pseudoporphyria treatment. N-acetylcysteine can also be used as it is thought to increase the production of plasma glutathione, thus reducing the risk of damage due to free-radical injury. These symptoms are slow to resolve and may recur with discontinuation of treatment.

23.9 Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is a disorder caused by a deficiency in uroporphyrinogen decarboxylase, a cytoplasmic enzyme involved in heme synthesis. This results in accumulation of heme substances in the blood causing skin changes on exposure to UV light. Scarring, fragility, hyperpigmentation, hypertrichosis, and milia are common changes seen in PCT [52]. PCT can occur in many disease states and has an estimated prevalence of 1.2–18% in CKD [52].

23.9.1 What Causes PCT?

As mentioned above, an accumulation of heme products in the blood leads to skin changes upon sun exposure. The cause of PCT in patients with CKD is not well understood but is likely multifactorial. Hypotheses implicate the distance of iron balance that can be seen in patients in dialysis.

23.9.2 What Are some Clinical Considerations?

There are two types of PCT: Type I (sporadic) and type II (familial). Patients presenting in their twenties likely have familial PCT, while those presenting in middle age are more likely to have sporadic PCT [19]. In addition to the skin changes mentioned above, patients may also have complaints of dark urine ("port wine urine") from porphyrin pigments and pruritus without abdominal pain unlike acute intermittent porphyria.

23.9.3 How Do you Treat PCT?

Photoprotection and avoidance of sun exposure are key components in the management of PCT. Patients are also advised to avoid triggering factors including alcohol, smoking, estrogen oral contraceptives, and supplemental iron.

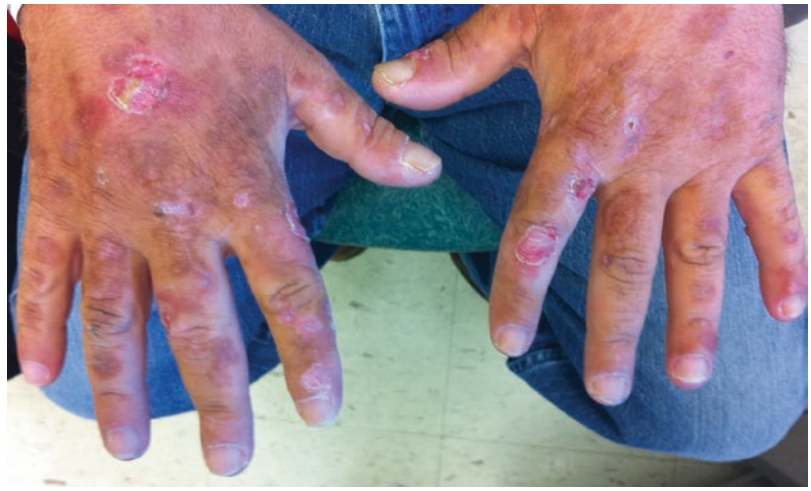

Fig. 23.7 Porphyria cutanea tarda in a patient with CKD (Image courtesy of Sandy Chai, MD)

Phlebotomy is an effective treatment of PCT and can be a treatment consideration in patients with CKD. However, some patients with CKD cannot tolerate the removal of 250–500 mL of blood twice a week. For these patients, small-volume phlebotomy is an option [53]. Research has also shown efficacy of deferoxamine treatment administered concurrently with dialysis. There is also a reported synergistic effect when deferoxamine is given with erythropoietin treatment [52] (Fig. 23.7).

Before You Finish: Practice Pearls for the Clinician

- There is no treatment for Lindsay's nails but sometimes it resolves with renal transplantation.
- Normalization of serum calcium and phosphate levels is the cornerstone of treatment in calciphylaxis and MCC.
- There are no effective treatments for NSF and therefore it is best to avoid gadolinium, a known trigger of the condition.
- Photoprotection is an important component of PCT and pseudoporphyria treatment. Deferoxamine and small-volume phlebotomy have also been effective in past studies.

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24 Pain Management in Chronic Kidney Disease

Sara N. Davison

Before You Start: Facts you Need to Know

- Pain is common in patients with chronic kidney disease (50–70% of patients depending on study) and is often not recognized.
- Pain is related to comorbidities and causes and complications of chronic kidney disease.
- Pain medication should be prescribed in a logical manner using a cautious stepwise approach.
- Pain adversely affects quality of life so must not be ignored.

24.1 Pain in CKD

Pain is common—we have all experienced it. Unlike most things treated in medicine, the experience of pain is entirely subjective. We can recognize situations where we expect pain, such as fractures, tissue damage due to surgery, ischaemia, etc., but each individual perceives the pain itself differently. Pain can therefore only be diagnosed if we ask patients whether they have pain and how this is affecting them. How pain is experienced depends on many factors including culture, social support, mood, as well as the pathology causing the pain.

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Pain is particularly common in patients with advanced chronic kidney disease (CKD). The mean prevalence of chronic pain reported by patients receiving chronic haemodialysis is approximately 60.5% and the mean prevalence of moderate or severe pain is 43.6% [1]. Patients with earlier glomerular filtration rate (GFR) categories of CKD suggest similar high prevalence rates of approximately 61% as do patients with end stage kidney disease managed with conservative kidney management (i.e., without dialysis) (59.8%) [1]. Often patients will not complain about chronic pain as they feel that this is part of their illness, that the healthcare team is not interested, or that any medication they have tried has been ineffective or has had adverse side effects. However, it is important to address pain as people living with chronic pain experience psychological distress, depressive disorders, disability, lower quality of life, conflicts in close relationships, reduced participation in many social aspects of everyday life, and increased hospitalizations and emergency department visits [2–5]. For haemodialysis patients, uncontrolled pain leads to shortened or missed treatments [6].

24.1.1 Causes of Pain

It is not surprising that patients with CKD have such a high pain burden. As shown in Table 24.1, pain can be due to the underlying kidney disease,

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https://doi.org/10.1007/978-3-031-42045-0_24

Table 24.1 Causes of pain related to CKD

Primary kidney disease	Some specific causes of kidney disease can be associated with significant pain, even at stages when kidney function itself is not impaired. Examples include:
	Polycystic kidneys
	Pain from bleeding into or rupture of cysts in kidney or liver
	Infection of cysts in kidney or liver
	Back pain from lumbar lordosis caused by abdominal distension from size of kidneys and/or liver
	Renal calculi—infection and obstruction
Comorbidity	Ischaemic heart disease—Angina
	Peripheral vascular disease—Claudication, ischaemic ulcers
	Diabetes—Peripheral neuropathy
	Malignancy
Complications of CKD	Renal bone disease
	Peripheral neuropathy
	Gout
	Calciphylaxis
Haemodialysis	Steal syndrome related to arteriovenous fistula access
	Cramps during dialysis
	Dialysis amyloid arthropathy
	Discitis secondary to access infection
	Femoral vein thrombosis following femoral vein access
Peritoneal dialysis	Abdominal pain related to dialysate inflow or outflow or distension
	Lower back pain related to increased intra-abdominal pressure
	Peritonitis
	Bowel obstruction secondary to encapsulating peritoneal sclerosis
Transplant	Surgery related
	Acute rejection
	Lymphocele

complications of poor kidney function, dialysis itself, and comorbidities [7–9]. Determining the cause of pain therefore requires careful history taking. Patients often have more than one cause of pain [7–9].

Increasingly, CKD is a disease of the elderly. Over 30% of people over 80 years old have impaired kidney function. The majority of patients attending a general CKD clinic is therefore elderly and will have the general features and complications of ageing. Many of these are associated with pain as shown in Table 24.2

Table 24.2 Causes of pain related to ageing

Musculoskeletal	Osteoarthritis
	Spinal stenosis
	Disc protrusion—sciatica
	Cervical spondylosis
	Vertebral fractures and collapse
Immobility	Decubitus ulcers

24.1.2 Types of Pain

It is important to differentiate between acute and chronic pain. *Acute pain* typically persists for less than 3 months and is often associated with tissue damage, e.g. after injury or surgery. Dialysis patients may also experience episodes of acute pain during dialysis, such as headaches and cramps. Acute pain can be episodic with periods without pain. It tends to last a predictable period, have no progressive pattern, and subsides as healing occurs. With acute pain it is therefore important to treat underlying causes to ensure long-term resolution.

In contrast, *chronic pain* is often defined as pain that persists for greater than 3 months. It is usually initiated by tissue injury but is perpetuated by neurophysiological changes within the peripheral and central nervous system leading to continuation of pain once healing has occurred. The severity of the pain is often out of proportion with the extent of the originating injury. Experience of chronic pain by the patient will be affected by psychosocial factors as well as the underlying pathology causing the pain.

For the purpose of management, it is helpful to categorize pain into:

- *Nociceptive*: Pain due to tissue damage. It may be described as sharp or like a knife and felt at the site of damage, e.g. joint pain from dialysis-related arthropathy or may be experienced as a dull, aching and poorly localized with stimulation of visceral nociceptors, e.g. gut ischemia. Nociceptive pain tends to respond to analgesics.
- *Neuropathic:* Pain due to nerve damage. It may be felt at a site distant from its cause, e.g. in the distribution of a nerve. Common descriptors include burning, shooting, and electrical-like sensation. It may also be associ-

ated with episodes of spontaneous pain, hyperalgesia, and allodynia; the presence of allodynia is pathognomonic, e.g. peripheral neuropathy. Neuropathic pain responds poorly to analgesics and typically requires adjuvant therapy.
- *Mixed nociceptive and neuropathic:* For example, pain of peripheral ischaemia.
- *Incident or movement related:* Caused by bone or joint damage; pain often absent at rest but more severe on movement.
- *Other specific causes:* Such as renal colic, bowel obstruction.

24.2 Screening and Assessment of Pain (Box 24.1)

Box 24.1 Screening and assessment of Pain in CKD

Key Facts

- Pain is perceived only by the patient, so can only be described by the patient.
- Perception of pain is affected by mood and the meaning of pain for the patient.

Pain is not assessed routinely by kidney care teams and is therefore frequently not recognized. Routine and proactive assessment of pain is important [8, 9]. There are three global symptom assessment tools in regular use, which have been adapted and validated specifically for use in those with CKD. These are the Edmonton Symptom Assessment System—revised: Renal (ESAS-r:Renal), the renal version of the Integrated Palliative Care Outcome Scale (IPOS renal), and the Dialysis Symptom Index (DSI). All three tools ask the patient about the presence and severity of common physical and psychosocial symptoms in patients with CKD [10–13].

Understanding the nature, severity, and need for treatment of pain is a challenge and takes time. Many patients do not discuss their pain if they feel that the healthcare team is not interested, is rushed, or that treatment is ineffective or carries too many adverse effects. A proper assessment of pain can greatly improve the relationship between patient and their doctor or nurse. It is also important that this is ongoing with repeat assessments to assess efficacy and the need for potential changes of management.

24.2.1 Obtaining a Pain History

A pain history should determine the site of pain, duration, whether constant or intermittent, what makes it worse or better, radiation, intensity, and nature of the pain. It is also important to determine the mood of the patient, particularly whether depressed or not, and the meaning of the pain to the person [14]. A full pain assessment is shown in Table 24.3.

Table 24.3 Scheme for pain assessment

	Useful questions
Site of pain	Where is pain?
Radiation	Does the pain go anywhere else?
History of pain	When did pain start?
	Was there anything that caused pain to start such as an injury, surgical procedure, and infection?
	Has the pain got better or worse over time or does it fluctuate?
	Is the pain worse during the day or at night?
	Does the pain keep you awake?
Nature of pain	What is the pain like? Is it burning, stabbing, sharp, colicky, dull, etc.?
	Note: *Nociceptive pain* is usually described as sharp; *neuropathic pain* is commonly described as burning, shooting, and stabbing
Aggravating factors	What makes the pain worse—Movement, position, eating, etc.?
Relieving factors	What makes the pain better—Position, eating, temperature, etc.?
Severity	How severe would you say the pain is—Mild, moderate, severe?
	Can you grade the pain on a scale of 1–10, with 10 being worst?
	Does the severity vary and if so how?

(continued)

Table 24.4 (continued)

	Useful questions
Impact of pain	How does the pain impact on daily activities, exercise, etc.?
	Does the pain stop you from sleeping?
	Do you ever feel down because of the pain?
Effect of treatment	What have you done to try and make the pain less?
	Do you take any painkillers, and if so what?
	Do you find the painkillers helpful?

24.3 Management of Pain

24.3.1 Barriers to Pain Management

A combination of clinician and patient factors contribute to poor pain recognition and management in patients. This is true for all patients, but probably happens more frequently for patients with CKD owing to the complexity of the causes of pain, the fact that many nephrologists are not trained in pain management, and the difficulty of prescribing analgesia with impaired kidney function. Table 24.4 lists potential clinician and patient factors and how these could be overcome.

Table 24.4 Potential barriers to pain management

Potential barriers	Overcoming barrier
Clinician factors	
Focus of care on management of medical problems—Kidney disease, dialysis, transplant, and comorbidity, so limited time for focus on other issues such as pain	Ensure that pain and its management in CKD is included in curriculum for all trainee kidney healthcare professionals
Lack of awareness of potential pain, so not asked about	Arrange local CPD and conferences about pain management
Not sure how to manage pain if any is reported	Make "kidney" pain-management guidelines available on wards and in clinics
Failure to monitor response to any treatment	Audit pain assessment and management as quality improvement project
Fear of drug toxicity because of impaired kidney function	
Fear of using opioids in noncancer pain	
More than one cause of pain so management complex	
Patient factors	
Underreporting of pain—Particularly if pain is chronic and thought by patient not to be related to kidney disease	Clinician should remember to ask patient about pain
Analgesia not taken because of fear of side effects	Routine symptom survey questionnaires that include pain—Though these must then be reviewed by clinical team and acted upon
Analgesia stopped because of side effects—And not reported to clinician	Availability of pamphlets about pain control in kidney disease
Anxiety about taking opioids because of fear of addiction	Availability of healthcare professional from kidney and/or palliative care team who can talk to patient about pain control and alleviate concerns
Delaying procedures that may relieve pain, e.g. amputation for ischaemic limbs	

24.3.2 Non-pharmacological Management

Pain perception and analgesic requirement vary between patients and with time in individual patients. Many factors can exacerbate pain including depression, loneliness, inactivity, fear, and anxiety about meaning of pain. Pain management therefore includes exploring psychosocial issues with patients and eliciting potential depression and anxiety which should then be appropriately managed with psychological support and/or medications such as antidepressants [7]. Other nondrug measures for pain relief may include:

- *Transcutaneous nerve stimulation* (*TENS*): The rationale for TENS is based on the gate theory for pain. TENS should only be used for chronic pain, including neuropathic pain—there is no evidence of benefit for acute pain. It should only be administered by

specialist pain clinics as how electrodes are placed makes considerable difference to efficacy.

- *Acupuncture*: Although evidence of benefit is equivocal, some patients find acupuncture beneficial for management of chronic pain. Theories for its mode of action include the production of endorphins.
- *Physiotherapy and manipulation*: Many people will try these methods, particularly for back pain, despite lack of evidence of benefit. Physiotherapy for patients with reduced mobility can also improve general well-being and mood, both of which may alleviate perception of pain.

24.3.3 Drug Management

The World Health Organization (WHO) analgesic ladder uses a stepwise approach to prescribing analgesics that selects initial analgesia according to the severity of the pain, starting at the lowest appropriate level and titrating as required to alleviate pain. This approach has been found to be useful and efficacious for cancer pain. It is now advocated for use in patients with non-malignant chronic pain and has been adapted for use for patients with advanced CKD and those on dialysis [15, 16]. An example of such an approach adapted for patients with advanced CKD is shown in Fig. 24.1 [4]. Table 24.5 out-

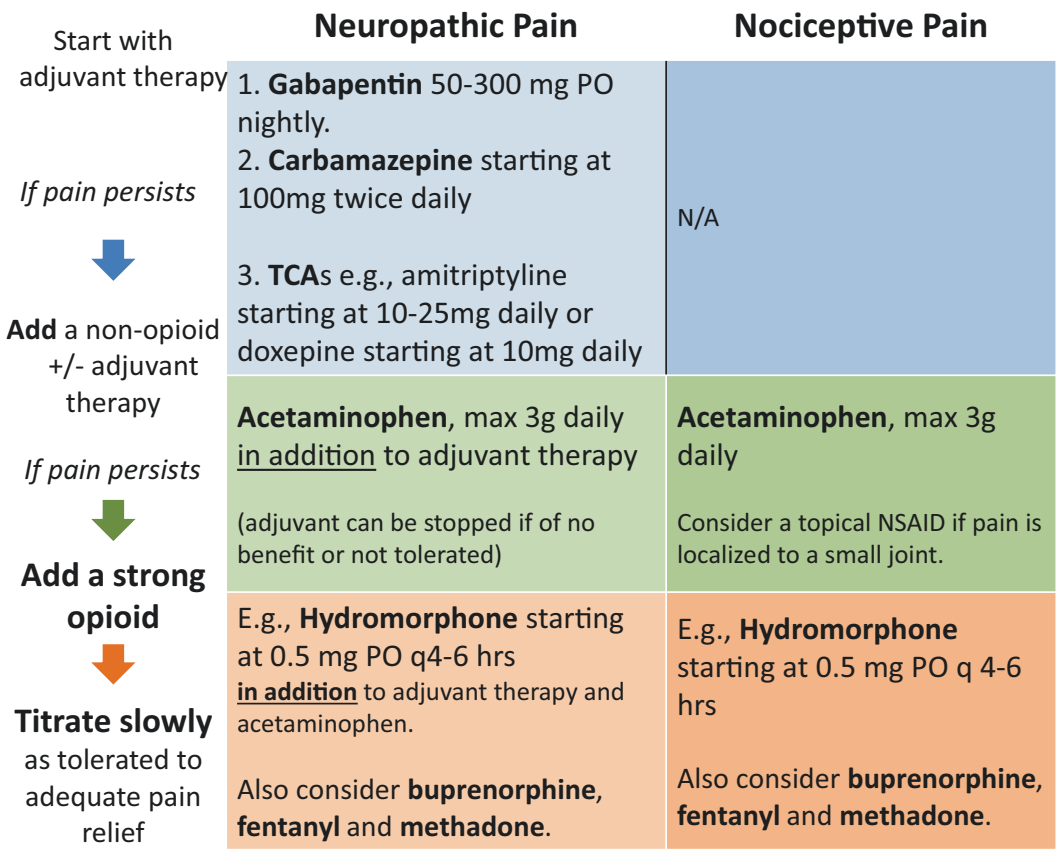

Fig. 24.1 Adapted analgesic ladder for patients with advanced chronic kidney disease

Table 24.5 Principles of pain management

By mouth	Use the oral or transdermal route whenever possible
By the clock	Where pain is continuous or predictable, analgesics should be given regularly. Additional breakthrough medication should be available on an "as needed" basis
By the ladder	Cautious stepwise approach using the modified WHO ladder starting with non-opioids and progressing to low-dose opioids. The analgesic should be used to its full-tolerated dose before stepping up to the next level. Adjuvant drugs can be added to all steps of the ladder. Non-opioid analgesics can be added to opioids
For the individual	There is no standard dose of strong opiates. The "right dose" is that which relieves pain without causing unacceptable adverse effects. Sensitivity to adverse effects varies between patients and must be monitored for closely. The impact on overall symptom burden, physical function, emotional state, cognition, and quality of life should be assessed
Attention to detail	Pain changes over time; thus, there is a need for ongoing reassessment. Side effects of opioids should be explained and managed actively, e.g. constipation and nausea, with anticipatory prescribing.

lines the five key principles to keep in mind when prescribing analgesics. Sustained-release preparations are generally not recommended in patients with advanced CKD.

Most analgesics, including opioids and their active metabolites, are cleared renally. The selection of analgesics for patients with advanced CKD is therefore challenging and must take into account the altered pharmacokinetics and pharmacodynamics, especially when eGFR is <30 mL/min. Table 24.6 outlines recommended analgesics in CKD [16]. Even for recommended analgesics, adverse effects are common so ongoing monitoring is important [17–20].

Acetaminophen is considered the non-narcotic analgesic of choice for mild to moderate pain in CKD patients. All of the opioids can cause sig-

Table 24.6 Analgesic use in advanced chronic kidney disease based on an adapted analgesic ladder

Recommended but use with caution	
Non-opioids	
Acetaminophen	Metabolized by the liver with only 2–5% excreted in the urine and does not require dose adjustment in CKD. Recommended maximum daily dose of 3.2 g/day. In high-risk patients (chronic stable liver disease, alcoholics, and malnourished patients), limit the maximal dose to 2.6 g/day
Opioids	
Oxycodone	Limited pharmacokinetic evidence for safety in advanced CKD with conflicting case reports. Although less than 10% is excreted unchanged in the urine, both the parent drug and the active metabolites appear to accumulate in CKD. The potential for drug interaction and unpredictable pharmacodynamic response is also relatively high. While not contraindicated, use with extreme caution and never use slow-release formulations. Consider a starting dose of 2.5 mg by mouth every 8–12 h
Hydromorphone	Extensively metabolized by the liver. Metabolites removed by dialysis, and if followed carefully, patients can tolerate well if doses started low and titrated slowly. Consider a starting dose of 0.5–1 mg by mouth every 6 h. active metabolites accumulate without dialysis therefore may not be an appropriate analgesic for patients with stage 5 CKD not on dialysis
Fentanyl patch	Rapidly metabolized in the liver, with only 5–10% excreted unchanged in the urine. Its metabolites are considered to be inactive. There does not appear to be clinically significant accumulation in advanced CKD and transdermal preparations have been used successfully. Not appropriate for opioid-naïve patients

Table 24.6 (continued)

Recommended but use with caution	
Methadone	Extensively distributed in the tissues where it accumulates. Slow release from the tissues can result in prolonged pharmacological action of up to 60 h. in advanced CKD it is excreted mainly in the faeces and does not appear to accumulate appreciably in plasma. It may be more effective for neuropathic pain than other strong opioids because of its N-methyl-D-aspartate receptor antagonism
Buprenorphine patch	Limited experience in advanced CKD, but the liver metabolizes it with little parent drug found in the urine. Pharmacokinetics appears minimally altered in CKD. Metabolites, however, accumulate in CKD but appear relatively inactive. It can be administered via a transdermal patch but might be difficult to antagonize with opioid antagonists. Additional care should be taken when used with benzodiazepines
Adjuvants	
Gabapentin	First-line therapy for neuropathic pain in advanced CKD. Titrate slowly. Doses up to 300 mg/day are generally safe but monitor for side effects (nystagmus, ataxia, tremor, somnolence, and reduced level of consciousness)
Carbamazepine	It requires no dose adjustment for patients with CKD and may have fewer adverse effects than gabapentin. Start at 100 mg twice daily and titrate slowly to a maximum of 1200 mg daily
TCA antidepressants (e.g. nortriptyline, desipramine)	Use may be limited due to anticholinergic, histaminergic, and adrenergic side effects resulting in symptoms such as dry mouth, orthostatic hypotension, and somnolence. Tachyarrhythmias are also a concern. Considered second-line therapy for neuropathic pain in CKD. Initiate at low dose, give in divided daily doses and titrate slowly

Table 24.6 (continued)

Recommended but use with caution	
Do not use	
Non-opioids	
NSAIDs	Risks include irreversible reduction in GFR for those with residual renal function, an increased risk of gastrointestinal bleeding and possible increased risk of myocardial infarction. Use is best reserved for specific indications of acute pain such as gout or renal colic. Use at the lowest effective dose and for the shortest duration, typically < 5 days.
Opioids	
Codeine	Metabolized by the enzyme CYP2D6 in the liver to its active metabolite morphine, which accumulates and can cause prolonged narcosis and respiratory depression. There is tremendous genetic polymorphism of the CYP2D6 gene and an individual's response is highly variable and can result in unpredictable toxicity with trivial doses or poor analgesic response with standard doses
Morphine, propoxyphene, meperidine (pethidine)	Neurotoxic metabolites are excreted renally and accumulate in patients with CKD. Patients are at high risk of neurotoxicity, including seizures

nificant toxicity, but some are less problematic than others (see Table 24.6). They should all be used cautiously, with both dose reduction, increase in the dosing interval, and regular monitoring. Patients requiring opioids can be managed effectively with short-acting hydromorphone that can be switched to transdermal fentanyl if the daily hydromorphone dose exceeds 12 mg.

24.3.4 Neuropathic (Nerve) Pain

Neuropathic pain is unlikely to respond to analgesics, including opioids alone. Adjuvants such as anticonvulsants and antidepressants have

proven successful in this regard, though studies specific to patients with advanced CKD are lacking. Opioids may be required in addition to adjuvant therapy. Methadone may be more useful than opioids for treating neuropathic pain. There are insufficient data or clinical experience with selective serotonin reuptake inhibitors (SSRI) and selective serotonin-norepinephrine reuptake inhibitors (SSNRI) for neuropathic pain in patients with advanced CKD to make a recommendation.

24.3.5 Other

Opioids can be abused so safe prescribing requires consideration of the risks associated with drug abuse and addiction. These issues need to be separated from physiological physical dependence, which is defined as the occurrence of withdrawal symptoms if the dose is abruptly reduced or after administration of an opiate antagonist. Experience suggests that less than 10% of patients have the biological characteristics that put them at risk of becoming addicted. Risk is highest in patients who have a personal or family history of alcohol or drug abuse. Such patients will benefit from careful monitoring by a specialist pain team.

24.4 Conclusion

Pain is common in patients with chronic kidney disease and can be caused by the kidney disease itself, complications related to kidney disease and comorbidities. It is therefore important that all patients should be asked about the existence and nature of any pain, that the cause of the pain is identified and that patients are given adequate and appropriate pain control. Management of pain also includes addressing psychosocial issues as pain can adversely affect quality of life, and this in turn can impact negatively on the perception of pain severity by the patient. Renal clinicians should be aware of the complex manner in which analgesic dosing is affected by kidney function and therefore become familiar with a few analgesics for each stage of the WHO pain-control ladder. Referral to palliative care or specialist pain services should be considered for management of complex pain or when drug abuse or addiction is suspected.

Before You Finish: Practice Pearls for the Clinician

- Regularly ask all patients with kidney disease about the existence of pain.
- Take a full pain history to determine nature, cause, and severity of pain and its psychosocial impact.
- Ask patients about existing analgesia to determine whether this is sufficient and/or appropriate for level of kidney function.
- Become familiar with one or two drugs in each analgesic class regarding dosage related to kidney function and likely side effects.
- Collaborate with your local specialist pain service and refer patients.
- Monitor for impact on overall symptom burden, physical function, emotional state, cognition, and quality of life.

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25 Depression and Other Psychological Issues in CKD

Nishank Jain and S. Susan Hedayati

Before You Start: Facts you Need to Know

- Depression, anxiety, and other psychological disorders are prevalent in patients with CKD.
- Patients with CKD commonly present with somatic symptoms, such as sleep disturbances, sexual dysfunction, low energy level, easy fatigability, and weight and appetite changes, which may be related to uremia and difficult to differentiate from depressive symptoms.
- Presence of depressive symptoms and major depressive disorder predicts adverse clinical and patient-centered outcomes in patients with CKD.
- Depression is a less commonly recognized problem in patients with CKD and ESKD.
- Often, depression is treated inadequately.
- Clinicians need to know the nuances in recognizing, diagnosing, and treating depression in patients with CKD in order to improve adverse clinical outcomes and quality of life.

Major depressive disorder (MDD) is a constellation of symptoms that a patient experiences for 2 weeks or more, comprised of either depressed mood or anhedonia plus at least 5 of the 9 *Diagnostic and Statistical Manual of Mental Disorders criteria* symptom domains [1] (Box 25.1). Patients with chronic kidney disease (CKD) and end stage kidney disease (ESKD) experience decreased energy, poor appetite, and sleep disturbance commonly that may not necessarily reflect an episode of MDD, but represent symptoms of uremia or burden of other comorbid illnesses, such as congestive heart failure. In addition, other symptom burdens, psychiatric conditions, or cognitive impairment experienced commonly by patients with advanced CKD or ESKD may be present, such as anxiety, chronic pain, erectile dysfunction, dementia, and delirium that need to be differentiated from a depressive disorder [2, 3]. It is even more challenging for clinicians to manage MDD in CKD and ESKD patients, as emerging data has shown pharmacologic treatment with antidepressants does not prove beneficial in abating depressive symptoms consistently and may be associated with increased side effects in these high-risk populations, which leads to only a minority of such patients getting treated appropriately and adequately [3–5]. More recently, CBT was shown to have potential benefit in reducing burden of depressive symptoms in ESKD patients [3, 4, 6]. This chapter discusses management and treatment of MDD in patients with CKD. Pain, sexual dysfunction, and quality of life (QOL) issues in patients with CKD are discussed in other chapters and will not be discussed here.

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Box 25.1 Clinicians Must Know the 9 Criterion Symptom Domains for Major Depressive Disorder Based on the Diagnostic and Statistical Manual of Mental Disorders

1. Depressed mood.
2. Loss of interest or pleasure (anhedonia).
3. Appetite disturbance.
4. Sleep disturbance.
5. Psychomotor agitation or retardation.
6. Fatigue and tiredness.
7. Worthlessness, feeling like a burden, or guilty.
8. Difficulty concentrating.
9. Recurring thoughts of death or suicide.

25.1 Prevalence of Depression in Patients with CKD

There is a high prevalence of depression in patients with chronic illnesses such as cardiovascular diseases (CVD) and ESKD. The point prevalences of depression in the general population and the primary care setting are estimated to be 2–4% and 5–10%, respectively [2]. Conversely, point prevalence of depression in patients with chronic diseases such as post-myocardial infarction (MI), congestive heart failure (CHF), and ESKD on chronic dialysis is much higher at 16%, 14%, and 25%, respectively [2].

A distinction must be made between the presence of depressive affect or depressive symptoms ascertained from patients by the use of self-report scales vs. a depressive disorder diagnosis (such as MDD) made by a physician using an interview. The majority of studies reporting prevalence of depression in patients with CKD and ESKD used self-report questionnaires to assess depressive symptoms instead of reporting a physician or interview-based diagnosis. Unfortunately, the estimates by self-reported rating scales may overestimate the presence of MDD, particularly in patients with advanced CKD or ESKD treated with maintenance dialysis, given the over-emphasis of the somatic symptoms of depression, such as appetite changes, sleep disturbance, and fatigue that are commonly present in such patients [7]. This was illustrated in a meta-analysis [7], where the prevalence of depression in ESKD patients on maintenance dialysis when ascertained by self-report scales was much higher at 39.3%, 95% confidence interval (CI) (36.8–42.0%) vs. by interview at 22.8%, 95% CI (18.6–27.6%). In addition, point prevalence estimates of interview-based depression were also high in CKD stages 1–5 patients not treated with maintenance dialysis at 21.4%, 95% CI (11.1–37.2), as well as in kidney transplant recipients at 25.7%, 95% CI (12.8–44.9), but not as precise as that for patients with ESKD, as reflected in the wide confidence intervals. This could be due to a lesser number of studies evaluating point prevalence of depression in lower stage CKD patients and transplant recipients.

25.2 Association of Depression with Adverse Clinical Outcomes

CKD or ESKD patients experiencing either depressive symptoms based on self-report scales or a clinical diagnosis of MDD are at a much higher risk of adverse clinical events as compared to similar patients without such symptoms or diagnosis (Box 25.2). These findings were not only reported in the kidney but also in the cardiovascular literature. Risk of death and hospitalization within a year double in ESKD patients on chronic dialysis with a clinical diagnosis of MDD compared to those without it [8–11]. In addition, a clinical diagnosis of MDD may increase cumulative hospital days and number of admissions to the hospital by 30%, independent

of other comorbidities (Box 25.2) [8–11]. Furthermore, MDD is an independent risk factor for recurrent cardiac events, re-hospitalization, and death in many chronic diseases including CVD and CHF, similar to its independent association with the risk of hospitalization, progression of kidney disease, initiation of dialysis, and death in patients with CKD and ESKD (Box 25.2) [8–11]. Noticeably, the strength of association of depression with adverse outcomes is as high as some of the other comorbidities including diabetes mellitus, peripheral vascular disease, and congestive heart failure. Studies reported greater risk of death within 90 days of dialysis initiation in depressed as compared with non-depressed patients [8–11]. Depression not only predicts adverse clinical outcomes, but also decreases QOL and aggravates sexual and physical dysfunction in patients with CKD and ESRD (Box 25.2) [12, 13]. It is, therefore, important to identify and manage levels of depression and functional impairment without which such problems fail to remit spontaneously in untreated CKD and ESKD patients.

Box 25.2 Clinicians Must Know that Depressive Symptoms and a Clinical Diagnosis of Major Depressive Disorder in CKD and ESKD Patients Are Independent Predictors of Adverse Clinical and Patient-Centered Outcomes

1. Death.
2. Hospitalization (increase cumulative hospital days and number of admissions).
3. Progression of kidney disease.
4. Initiation of dialysis.
5. Poor quality of life.
6. Sexual and physical dysfunction.
7. Fatigue.

25.3 Risk Factors for Depression in Patients with CKD

As depressive symptoms and MDD prognosticate poor clinical outcomes and decreased QOL in patients with CKD and ESKD, clinicians must be able to recognize risk factors for depression (Box 25.3 and Fig. 25.1). Several risk factors for depression in this high-risk population are similar to those in the general population and include younger age, female gender, low household income, lower education, and unemployment (Box 25.3 and Fig. 25.1) [2, 10, 12–14]. Although white race has been reported as a risk factor, a high level of depressive affect has also been reported among African American ESKD patients treated with maintenance hemodialysis [2, 10, 12–14]. Dialysis-related factors such as non-adherence to diet and interdialytic weight gain are associated with depression, but it is not clear whether they are risk factors for or result from the presence of depression [2, 10, 12–14]. Other clinical conditions such as diabetes mellitus, hypoalbuminemia, cerebrovascular and cardiovascular diseases, and comorbid psychiatric disorders, commonly associated with CKD and ESRD, add medical complexities and increase risk for depression (Fig. 25.1) [2, 10, 12–14]. This association between medical comorbidities and depression is similar to that in the general population. Depression makes social interactions and relationships more difficult for patients, leading to estrangement from spouse, family, work, community, and religious organizations (Box 25.3). Post-dialysis fatigue, time spent on dialysis, cognitive impairment, and comorbid illnesses may be further impediments to social interactions and impair ability to build relationships. An attempt should be made by clinicians to identify interrelated risk factors for depression in order to best manage their patients with CKD or ESKD diagnosed with depression.

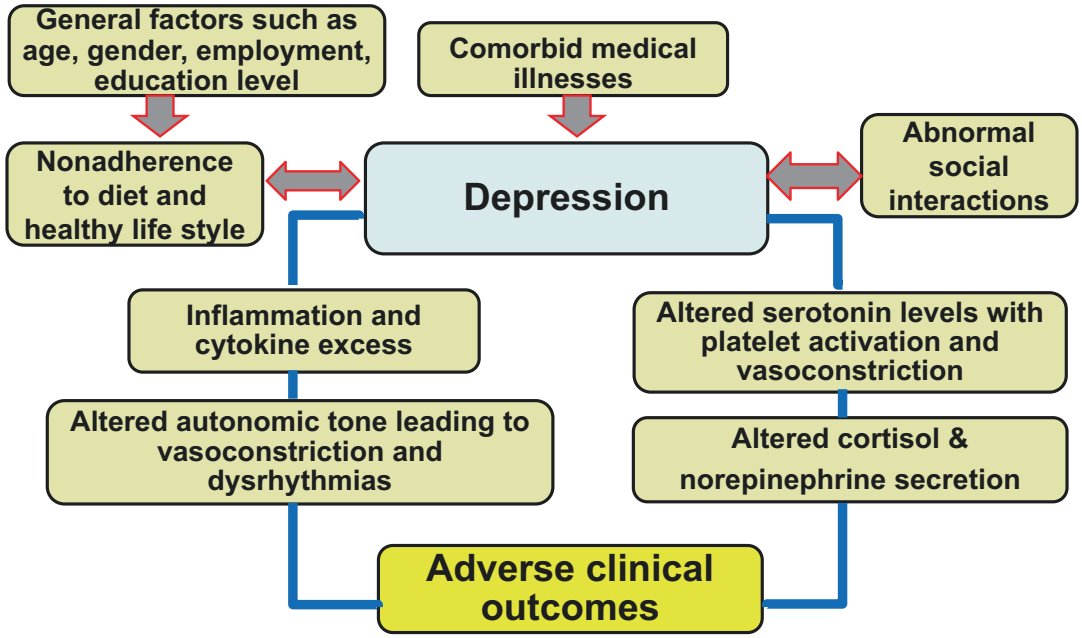

Fig. 25.1 Risk factors for depression and potential mechanisms that associate depression with adverse clinical outcomes

Box 25.3 Clinicians Must Be Able to Recognize Risk Factors for Major Depressive Disorder in CKD and ESKD Patients

1. General factors:
   (a) Younger age.
   (b) White race.
   (c) Female gender.
   (d) Low household income.
   (e) Lower education level.
   (f) Unemployment.
2. Dialysis-related factors:
   (a) Non-adherence to the recommended diet.
   (b) Non-adherence to interdialytic weight gain.
3. Other comorbid illnesses:
   (a) Diabetes mellitus.
   (b) Hypoalbuminemia.
   (c) Cerebrovascular disease.
   (d) Cardiovascular disease.
   (e) Other psychiatric disorders.
4. Psychosocial factors:
   (a) Impaired social interactions.
   (b) Estranged spouse.
   (c) Estranged family members.
   (d) Unemployment.

25.4 Potential Mechanisms for the Association of Depression with Adverse Outcomes

It is unclear whether depression itself has a direct mechanistic role in the development of cardiac events and other adverse clinical outcomes or whether it is merely a surrogate marker of comorbid illness (Fig. 25.1). However, specific biological factors were proposed and investigated as potential mechanisms by which depression may lead to cardiac events that are compelling. First, both depression and CVD appear heritable in

twin studies. In a study that included 2700 male twin-pairs from the Vietnam era, there was a correlation between genetic influences on depression and CVD, suggesting a common genetic link [2]. Second, depression leads to non-adherence with medications, unhealthy lifestyle, malnutrition, and loss of social network that can precipitate adverse events such as increase in peritonitis events noted in depressed chronic peritoneal dialysis patients compared to those who are not depressed [2]. Third, there are reports of altered autonomic tone, such as lower heart rate variability, in patients with recent MI with depression leading to coronary vasoconstriction and tachyarrhythmia. Therefore, autonomic dysfunction may be a potential pathophysiologic mechanism that can explain how depression leads to adverse clinical outcomes [2]. Fourth, several studies observed enhanced activity of the hypothalamic–pituitary axis, specifically increase in cortisol and norepinephrine secretion, in patients with CVD and MDD. It is hypothesized that increase in the levels of inflammatory cytokines due to depression may result in hyperactive hypothalamic-pituitary-adrenal axis and increase in cortisol and norepinephrine secretion. It is further postulated that increase in cortisol and norepinephrine levels may be important in decreasing the availability of tryptophan, an important precursor for neurocellular function, and, thus, precipitate depressive symptoms by decreasing the availability of neurotransmitters such as dopamine and serotonin [2]. Fifth, inflammation has been implicated, such as an increase in serum C-reactive protein (CRP) and decrease in omega-3-fatty acid serum concentrations. There is an association between inflammation and depression as shown in some patients treated with interferon alpha who show decrease in brain dopamine and serotonin levels that is treatable with paroxetine. To further support the role of inflammation, it was reported that depressed patients with psoriatic arthritis show improvement in their disease activity and depression when treated with etanercept [2]. Another proposed mechanism is the association of altered serotonin levels seen in depression, with resultant increased platelet activation and vasoconstriction that can then lead to coronary events [2]. However, all of the above are potential mechanisms to explain how depression predicts adverse clinical outcomes. Further studies are needed to confirm the mechanistic pathways involved in adverse clinical outcomes, such as higher rates of cardiovascular events, progression to ESKD, hospitalizations, and death, in patients with CKD and depression.

25.5 How to Identify Depression in Patients with CKD

Given one out of four or five patients with CKD or ESKD may be depressed, which puts them at increased risk for adverse clinical outcomes, poor QOL, and functional impairment, it is important for clinicians to screen such patients for depression. It is suggested that screening should be performed at the first outpatient evaluation of a patient in the CKD or dialysis clinic and then repeated annually or semi-annually. Self-report questionnaires [15, 16], that assess depressive symptom severity, perform well as screening tools with high sensitivity and average specificity (Table 25.1). These can be administered easily and consume no significant extra time during a patient visit. The 20-item Center for Epidemiological Studies Depression (CES-D),

Table 25.1 Validated screening tools to screen for and rate depressive symptom severity in patients with CKD and ESRD

Rating scale	Cutoff score in non-CKD patients	Cutoff score in CKD patients	Remarks
21-item BDI-II	≥10	≥11 in CKD	Higher cutoff of ≥14–16 is used in ESRD
16-item QIDS-SR	≥10	≥10 in CKD	Not validated in ESRD
20-item CES-D	≥16	≥18 in ESKD	Not validated in CKD
9-item PHQ-9	≥10	≥10 in ESKD	Not validated in CKD

BDI-II beck depression inventory II, *QIDS-SR* quick inventory for depression symptomatology self-report, *CES-D* Center for Epidemiological Studies Depression, *PHQ-9* patient health questionnaire-9 item, *CKD* chronic kidney disease, *ESKD* end-stage kidney disease

21-item Beck Depression Inventory (BDI-II), and 9-item Patient Health Questionnaire (PHQ-9) scales are screening tools that were validated against the Diagnostic and Statistical Manual of Mental Disorders to diagnose MDD in patients with ESKD (Table 25.1). Similarly, the BDI-II and 16-item Quick Inventory for Depression Symptomatology Self Report (QIDS-SR_{16}) are validated screening tools in patients with CKD (Table 25.1). Of the aforementioned questionnaires, there is no consensus regarding use of one tool over another for this patient population [3].

As compared to patients without kidney disease, those with ESKD requiring maintenance dialysis need to have higher cutoffs on the self-report rating scales to diagnose MDD, perhaps due to the presence of somatic symptoms associated with uremia or chronic disease. For example, the cutoffs on the 21-item BDI-II validated for the diagnosis of MDD in the general population, CKD, and ESRD are ≥10, ≥11, and ≥ 14–16, respectively [15, 16]. The 20-item CES-D cutoffs in the general population and ESKD are ≥16 and ≥ 18, respectively. There is no difference in the PHQ-9 and QIDS-SR_{16} cutoffs between the general population and patients with CKD (Table 25.1).

Given the co-existence of somatic symptoms of depression in CKD patients with uremic symptoms and other comorbid medical conditions, those who screen positive on self-report depressive symptom rating scales need to be further assessed with a structured interview to confirm a clinical diagnosis of depressive disorder, such as MDD. In research, clinician-administered structured interviews such as the *Structured Clinical Interview for Depression* (SCID) or the *Mini International Neuropsychiatric Interview* (MINI) have been used to establish diagnosis [15, 16]. These interviews take a significant amount of time (30–60 minutes) and require a certain level of training to administer. Therefore, in the clinical setting, eliciting the presence of 5 or greater of the depression symptom domains, including the presence of sadness or anhedonia, for a period of at least 2 weeks would confirm the presence of a depressive disorder (Box 25.1).

25.6 Differential Diagnosis of Depression in Patients with CKD

Of the psychiatric illnesses identified among the Unites States Medicare ESKD patients admitted to hospitals, presence of depression, dementia, substance, and alcohol abuse could be found in as high as 26%, 26%, and 15% of such patients, respectively [14, 17]. Therefore, it is important for providers to recognize the differential diagnosis of depression in an attempt to manage patients appropriately (Fig. 25.2).

Importantly, there is a need to simultaneously identify cognitive impairment commonly seen in CKD and ESKD patients. Persistent and/or progressive impairment in memory and other cognitive functions such as attention, language, orientation, reasoning, or executive functioning, and the cognitive skill necessary for planning and sequencing tasks, is defined as dementia [17]. A score of <24 on the Mini Mental State Examination (MMSE) is a commonly used screening tool to diagnose dementia, which has limited sensitivity and specificity in patients with CKD and ESKD. Prevalence of dementia may be as high as 16–38% in such patients. It should be appropriately recognized by clinicians, as it also predicts poor outcomes. In addition, cognitive dysfunction acts as an impediment to decision-making, adhering to complex medication dosing schedules, and self-care. Dementia is more insidious in onset, progressive in course over months to years, usually not reversible, and impairs consciousness in advanced stages. Interestingly, many of the risk factors associated with MDD are similar to those for dementia [17].

Delirium can masquerade dementia and depression and should be part of the differential [17]. Clinicians should recognize the fluctuating course of delirium that develops over a short period of time associated with lack of attention and consciousness. Usually, there is no complaint pertaining to loss of memory, and it occurs as a result of medical conditions (e.g. advanced heart failure, liver disease, hypertensive encephalopathy, infections, hypoglycemia, hyponatremia, and

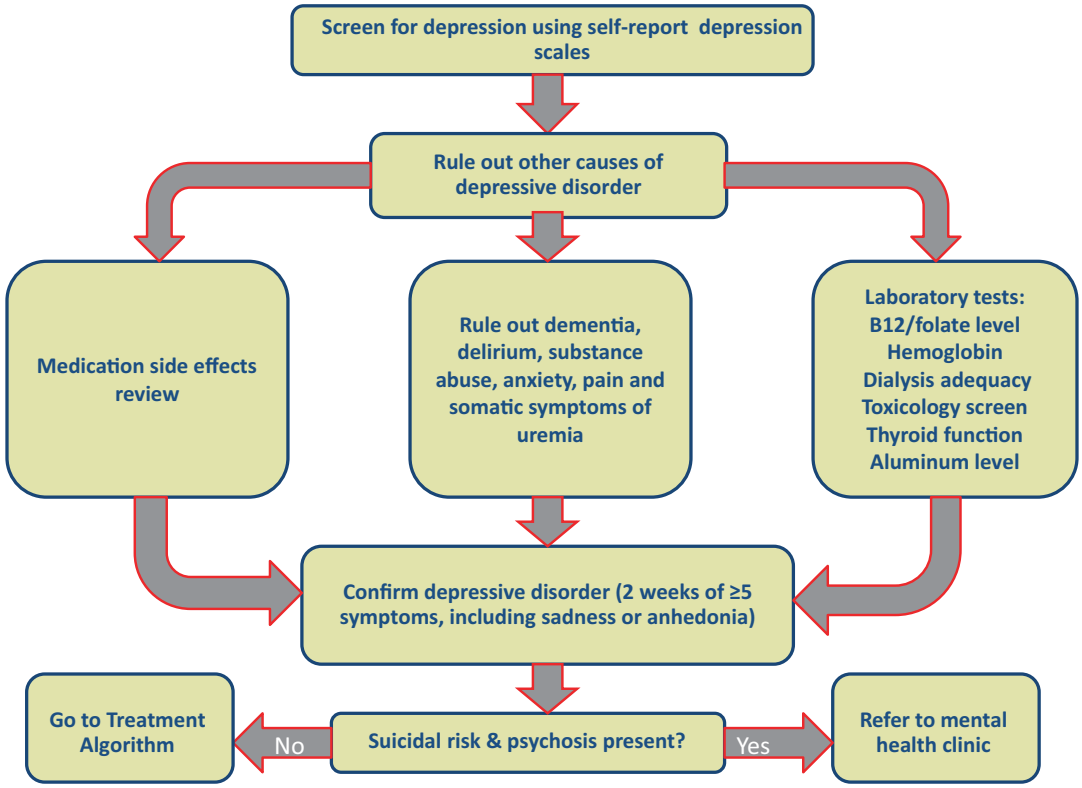

Fig. 25.2 Differential diagnosis of and an algorithm for screening/confirming depression in patients with chronic kidney disease (CKD)

hypercalcemia), side effects of certain medications (e.g. opioids, benzodiazepines, antihistamines, antipsychotics, and anticholinergics), or acute intoxications. Unlike dementia, delirium and depression are usually reversible. In addition, MDD is acute or chronic in onset and associated with intact consciousness, unlike delirium. Therefore, it is very important to differentiate dementia, delirium, and MDD so that management can be tailored accordingly. Box 25.4 shows important differences in dementia, delirium, and depression. Proper work-up for delirium and dementia includes a) medication review; b) obtaining laboratory data to rule out vitamin B12 and folate deficiency, thyroid dysfunction, acquired immunodeficiency syndrome, and substance abuse; c) obtaining brain imaging for presence of significant atherosclerotic cerebrovascular disease; d) assessing sleep disorders (such as restless legs and obstructive sleep apnea) by history and physical examination; and e) assessing dialysis adequacy, anemia, and aluminum toxicity in ESKD patients.

Box 25.4 Clinicians Must Be Able to Differentiate Delirium and Dementia from Depression [17]

1. Delirium:
   (a) Develops over a short period of time.
   (b) Lack of attention and consciousness.
   (c) No complaint pertaining to loss of memory.
   (d) Occurs as a result of.
      - Medical conditions.
      - Side effects of certain medications.
      - Intoxications.
   (e) Reversible.

2. Dementia:
   (a) Develops over months to years insidiously.
   (b) Progressive; altered consciousness in advanced disease.
   (c) Loss of memory common, along with loss of at least one other cognitive function such as:
      • Attention.
      • Language.
      • Orientation.
      • Reasoning.
      • Executive functioning.
      • Cognitive skill necessary for planning and sequencing tasks.
   (d) Usually permanent and irreversible.
3. Depression:
   (a) Develops over months to years.
   (b) Not associated with lack of consciousness.
   (c) No loss of memory.
   (d) Reversible.

Apart from delirium and dementia, generalized anxiety is quite common in patients with kidney disease and should be distinguished from depression by identifying patients who worry excessively on more days than not about a number of topics, that has persisted for more than 6 months, with the presence of self-perception that they are worried and lack control to modify its intensity and frequency [1]. This accompanies 3 of the 6 criterion symptom domains including fatigue, irritability, muscle tension, sleep disturbances, psychomotor agitation, and disturbed concentration [1]. Similarly, somatic symptoms such as sleep disturbances, sexual dysfunction, poor QOL, low energy level, easy fatigability, and weight and appetite changes can be present with uremia and make the diagnosis of MDD difficult. Alcohol and other substance abuse related disorders should be excluded, as these are commonly associated with depression (Fig. 25.2). Finally, fatigue, a common symptom of MDD, can also be present due to coexisting comorbidities in CKD/ESKD patients which should be carefully evaluated [18].

25.7 Treatment of Depression in Patients with CKD

A diligent clinician should recognize MDD, identify its risk factors, triage patients at risk of suicide, and tailor management based on the needs of the specific patient and the resources available. Screening tools enable clinicians to identify patients who are at risk for suicide. It is important to differentiate "thoughts for suicide" from "thinking about death" in patients with end-stage and terminal diseases such as ESKD and cancer in order to triage patients appropriately. Given a majority of patients with kidney disease are elderly, "thoughts of death" may be common without depressive symptoms or thoughts of suicide (Box 25.5). Furthermore, those who screen positive for suicidal thoughts should be queried for presence of active suicidal intent or plan (Fig. 25.2). Those with suicidal intent or plan should be referred to an emergency department or urgent care facility that can provide further urgent psychiatric clinical assessment, triage, and management (Fig. 25.2).

Box 25.5 Clinicians Must Be Able to Recognize those at Risk for Suicide so that Time-Dependent Interventions Can Be Implemented

1. In those with thoughts of suicide or death, ask about suicidal intent or plans:
   (a) How often do you think about suicide?
   (b) Have you made any plans?
   (c) Have you tried taking your life before?
   (d) How do you plan to end your life?
   (e) What will hold you from taking your life?
2. Those patients who have suicidal intent should immediately be referred to an emergency department or urgent care for further evaluation and management. Appropriate steps should be taken to organize support groups from family, friends, community, religious and social organizations based on the availability of resources.

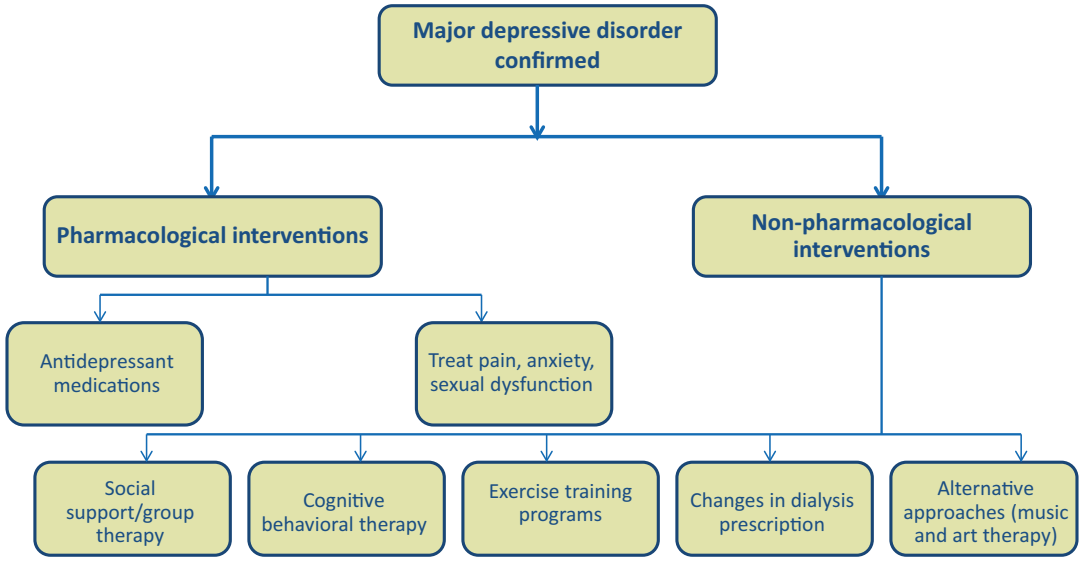

Fig. 25.3 Treatment options for depression in patients with chronic kidney disease (CKD)

Pharmacologic and non-pharmacologic interventions can be implemented to treat MDD in CKD and ESKD patients (Fig. 25.3) [19]. Unfortunately, there is a paucity of data to establish the safety and efficacy of antidepressant medications and other interventions for the treatment of depression in CKD and ESRD patients [19]. Second, high medication discontinuation rate is commonly observed in depressed patients with kidney disease [19]. Third, safety concerns of adverse events drive clinicians to either undertreat MDD or under-dose antidepressants in CKD and ESRD patients (Box 25.6) [19]. Encouraging results of efficacy for the use of antidepressants in treating MDD associated with chronic diseases such as CVD come from a double-blinded placebo controlled randomized trial, the *Sertraline Antidepressant Heart Attack Trial (SADHART)*, that showed sertraline to be safe and efficacious in patients with acute coronary syndrome. Based on these results, sertraline may be considered for treating MDD in CKD and ESKD individuals [19]. The *Chronic Kidney Disease Antidepressant Sertraline Trial (CAST)* evaluated efficacy and safety of sertraline treatment, dose-escalated to a maximum dose of 200 mg daily, compared with placebo in a randomized controlled trial (RCT) in patients with non-dialysis stages 3b-5 CKD and MDD [5]. This RCT demonstrated improvement in depressive symptoms at 12 weeks from baseline in the sertraline and the control arms. However, there was no additional benefit with use of sertraline over placebo in the study participants, and sertraline was associated with increased gastrointestinal side effects as compared with placebo. In ESKD patients receiving hemodialysis, similar improvements in depressive symptoms were observed in the treatment and the placebo arms of recent RCTs. A more recent RCT in ESKD patients with MDD showed a marginal benefit of open-label sertraline as compared with CBT, but there was no control group [4]. There are no RCTs to evaluate safety and efficacy of antidepressants in ESKD patients receiving peritoneal dialysis and kidney transplant recipients [3]. Despite these findings, the European Renal Best Practice guidelines recommend use of antidepressants in patients with CKD stages 3–5 as summarized in Box 25.7 [20].

Box 25.6 Clinicians Face Day-to-Day Challenges in Treating MDD because of Limited Data Regarding Safety and Efficacy of Antidepressant Use in Patients with CKD and ESKD

1. Lack-luster performance of sertraline in recent RCT which demonstrated reduction in depressive symptoms at 12 weeks in the sertraline-treated and the placebo-treated arms, with no added benefit of sertraline over placebo in patients with advanced non-dialysis CKD, e.g. stages 3b-5.
2. Limitations of some studies including small sample sizes and under-dosing of antidepressant medications.
3. High rate of medication discontinuation seen in small studies.
4. Safety concerns related to adverse events from antidepressant medications, thought to be due to:
   (a) Renally excreted active metabolites and risk of accumulation to toxic levels.
   (b) Risk of drug–drug interactions given the presence of other comorbid conditions and high pill burden.
   (c) Cardiac side effects of several classes of antidepressants that may worsen the disproportionate burden of cardiovascular disease seen in CKD and ESKD patients.
   (d) Increased risk of bleeding in the setting of uremic platelet dysfunction.
   (e) Side effects of nausea and vomiting that may exacerbate uremic symptoms.
   (f) CNS depression that may increase risk of cognitive dysfunction or delirium.

Box 25.7 What the Guidelines Recommend for the Use of Antidepressant Medications in Patients with CKD Stages 3–5 [20]

1. KDIGO Controversies Conference on Supportive Care in CKD developed a roadmap to improving quality care. This executive summary concluded that the current evidence is sufficient to support the development of clinical guidelines to help a systematic approach to depression in CKD [22].
2. Active treatment should be started for patients with CKD stages 3–5 who meet criteria for major depressive disorder. Level of evidence and recommendation: 2D.
3. Treatment effect should be re-evaluated after 8–12 weeks of treatment with antidepressant drug therapy. Level of evidence and recommendation: 2D.
4. Selective serotonin reuptake inhibitors should be the first line of therapy if pharmacological intervention is considered for patients with CKD stages 3–5. Level of evidence and recommendation: 2C.

Table 25.2 describes potential side effect profiles of several classes of common antidepressants that can occur at increased frequency in CKD and ESKD patients as compared to those with no kidney disease [19]. Although there is a lack of significant data on the safety and efficacy for the use of antidepressant medications in patients with advanced CKD stages 3–5 and ESKD, this should not discourage clinicians from treating depression appropriately until more data become available because some individuals may still find it beneficial. Management strategies require discussion of risks vs. benefits of antidepressant medications with patients, use of a class of antidepressant with the least possible drug–

Table 25.2 Safety profiles and dose adjustments recommended for different classes of antidepressants in the setting of CKD or ESKD

Medication	Dose in mg/day	Metabolism	Potential side effects	Dose adjustments
Selective serotonin reuptake inhibitors				
Sertraline	50–200	Active metabolite is excreted by kidney and can accumulate	Increased risk of bleeding; GI side effects: Nausea and diarrhea; hyponatremia; sexual dysfunction	Start at lower doses and escalate slowly
Paroxetine	10–40	Prolonged half-life	Same as the class side effects	Lower maximum dose recommended
Fluoxetine	20–80	Prolonged half-life	Same as the class side effects	Use with caution
Citalopram	10–40	Active metabolite can accumulate	Higher doses prolong QTc and increase risk of torsades de pointes	Not recommended for eGFR <20 mL/min
Escitalopram	10–20	Active metabolite can accumulate	Same as the class side effects	Use with caution in severe kidney disease
Dopamine/norepinephrine reuptake inhibitors				
Bupropion	200–450	Active metabolite can accumulate	Cardiac dysrhythmias, wide QRS complex, nausea, insomnia, and dizziness	Reduce frequency or maximum dose
Noradrenergic and serotonergic agonists				
Mirtazapine	15–45		CNS side effects include somnolence and weight gain	Reduce by 30% if CrCl 11–39; by 50% if CrCl <10
Tricyclics (TCAs)				
Amitriptyline	75–150		QTc prolongation, arrhythmias, orthostatic hypotension, CNS, and anticholinergic side effects	None; avoid in CKD and ESKD
Serotonin/norepinephrine reuptake inhibitors				
Venlafaxine	75–225	Accumulation of toxic metabolite	Hypertension, neuroleptic malignant syndrome, serotonin syndrome, sexual dysfunction	Reduce dose by 25–50% in mild-moderate CKD
Serotonin modulators				
Trazodone	150–400		Cardiac dysrhythmias, priapism, liver failure, Stevens-Johnson syndrome	Reduce dose and use with caution in advanced CKD and ESKD

CrCl creatinine clearance, *GI* gastrointestinal, *CNS* central nervous system, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *ESKD* end-stage kidney disease

drug interactions, starting antidepressants at a lower dose than that recommended for patients without kidney disease, and close follow-up to monitor treatment response, side effects, and a need for dose adjustment. Providers should pay special attention to drug–drug interactions that are highly likely in chronic hemodialysis patients due to polypharmacy. Typically, antidepressants should be started at low doses and dose escalation should be based on response and tolerability after at least 1–2 weeks of treatment on a particular dose.

Non-pharmacological interventions hold promise for the management of MDD in CKD and ESKD patients without increasing pill burden or raising concerns regarding adverse events and drug–drug interactions (Fig. 25.3) [19]. Such interventions include changes in dialysis prescription, exercise, and CBT (Box 25.8) that were shown to be efficacious in the general population. The *Following Rehabilitation Economics and Everyday-Dialysis Outcome Measurements (FREEDOM)* cohort observational study reported improvements in the depressive symptom severity scores measured by the BDI-II scale and health-related QOL measured by the Short Form-36 (SF-36) scale with six times weekly hemodialysis (Box 25.8) [19]. However, although in the *Frequent Hemodialysis Network (FHN)* trial, frequent hemodialysis (6 times a week as com-

pared with 3 times a week) was associated with significant benefits with respect to both co-primary composite outcomes of death or increase in left ventricular mass and death or a decrease in the physical-health composite score, there were no significant effects of frequent hemodialysis on cognitive performance or self-reported depression [21]. To date, clinical trials suggest that in-person or tele-CBT is not only feasible in patients, but also effective in managing depressive symptoms.

Weekly chairside CBT, administered by a trained professional during hemodialysis over 12 weeks, was reported to improve depressive symptom severity on the BDI-II scale, overall QOL on the Kidney Disease QOL Questionnaire-Short form (KDQoL-SF), and interdialytic weight gain in patients with ESKD [6]. A trained psychologist attempts to restructure negative thoughts and encourage logical thinking so as to modify behavior and mood. Those who ineffectively handle problems and/or make poor decisions are able to better cope with adversities and improve their depressive symptom severity [19]. This technique administered by trained social workers to the ESKD patients after Hurricane Katrina showed encouraging results in assuaging depressive symptoms. However, the duration and structure of CBT remains unclear and is an area of great research interest. Other psychotherapies such as mindfulness, cognitive restructuring, and stress management have also been explored as possible non-pharmacologic interventions for this patient population. Furthermore, some elements of CBT such as goal setting and problem solving and social support have also been explored for this patient population [3]. However, psychotherapies and elements of CBT remain to be fully established for their effectiveness in patients with kidney diseases [3]. Combined pharmacological intervention and CBT may be also considered, as the combination works better in the general population (Box 25.8) [3]. However, the combination approach remains to be investigated in patients with kidney disease.

Decreased functional capacity is common in patients with ESKD and is associated with poor QOL measures. Resistance exercise training by ankle weights was reported to improve QOL in patients on chronic maintenance hemodialysis (Box 25.8) [19]. Similarly, aerobic exercise over 10 months was effective in reducing heart rate variability, improving depressive symptom severity and QOL measures in a small group of chronic hemodialysis patients (Box 25.8). Therefore, exercise training can potentially function as a non-pharmacological intervention that clinicians can prescribe to treat MDD in CKD and ESKD patients given little harm and the multifaceted benefit of such an intervention. Other potential approaches to treat MDD in CKD and ESKD patients focus on pain management, improving sexual dysfunction, and management of anxiety (Box 25.8) [19]. Further research is required to evaluate if community and religious organizations may intervene and ameliorate depressive symptoms of CKD and ESKD patients by improving their social interaction skills. This may also help in addressing and overcoming marital and family discord that is commonly found in this patient population. Music and art therapy is an exciting field that remains to be more fully explored in patients on chronic hemodialysis while they remain idle on the dialysis machine for a long period of time. It remains to be investigated whether treatment of depression in patients with CKD can result in improvements in QOL and survival.

Box 25.8 Clinicians Should Be Aware of the Non-pharmacological Interventions that Can Be Used to Treat Major Depressive Disorders in Patients with CKD and ESKD Patients

1. Alterations in dialysis prescription.
   (a) Frequent dialysis, six times vs. three times per week.
2. Cognitive behavioral therapy (CBT).
   (a) Trained psychologist to administer therapy.
   (b) Trained social worker to administer support and therapy.

3. Combination of antidepressants and CBT.
4. Exercise training therapy.
   (a) Resistance training exercises (e.g. ankle weights).
   (b) Aerobic exercises.
5. Treatments for anxiety, pain, sleep disorders, and sexual dysfunction.
6. Alternative approaches.
   (a) Music and art therapy.
   (b) Involving community and religious organizations.
   (c) Social interventions to mend support from family and friends.

25.8 Recommendations and Conclusions

Depression is common in patients with kidney disease but less frequently recognized and inadequately treated. It is well-established that a diagnosis of current MDD or depressive symptoms independently predicts adverse clinical outcomes in patients with kidney disease. Therefore, it becomes imperative for clinicians who are involved in the care of such patients to screen for and diagnose depression accurately. Several quick and easily administered self-report scales are validated to screen for depression in these patients. However, those who screen positive for depression on screening need to be further evaluated so that dementia, delirium, anxiety disorders, medication side effects, and other medical conditions, such as underlying sleep disorders, thyroid dysfunction, or dialysis inadequacy, can be excluded. Finally, appropriate management strategies should be implemented to maximize efficacy and safety of depression treatment using available pharmacological and non-pharmacological interventions that are acceptable to specific patients. The ultimate goal of a clinician should be to assuage depressive symptoms and potentially achieve complete remission of depression.

Before You Finish: Practice Pearls for the Clinician

- Clinicians should understand the differences between depressive symptoms and a clinical diagnosis of major depressive disorder.
- Screening for depression should be performed at the first outpatient evaluation of a patient in chronic kidney disease or dialysis clinic and then repeated annually.
- Validated self-report tools exist that can be easily administered to screen for depression. Subsequently, confirmation of a current major depressive disorder should be done by a clinician interview for those who screen positive.
- Those at risk for suicide should be differentiated from those who often think about death based on religious and cultural beliefs, old age, or terminal illness.
- A broad differential diagnosis should be considered before a diagnosis of major depressive disorder is confirmed, based on appropriate physical examination, mini-mental examination, and laboratory data.
- Clinicians should be able to recognize the risk factors for depression.
- Once a diagnosis of major depressive disorder is confirmed, a thorough review of risks vs. benefits of pharmacological and non-pharmacological interventions should be discussed with patients to tailor individualized management strategies.
- To start an antidepressant medicine, the lowest possible dose should be initially prescribed, followed by frequent monitoring and gradual dose escalation every 1–2 weeks based on patient's response to and tolerability of the medication.
- Any adverse effects of antidepressant medications should be monitored closely.
- Non-pharmacologic treatments such as cognitive behavioral therapy and exercise should also be considered.

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Sexual Dysfunction in Chronic Kidney Disease

26

Domenico Santoro, Guido Gembillo, Ersilia Satta, and Guido Bellinghieri

Before You Start: Facts you Need to Know

- Physiology of erectile function is dependent on a balanced vascular, neurologic, hormonal, and psychological system.
- Prevalence of erectile dysfunction (ED) in the Western industrialized countries amounts to 20–30% in the general male population and probably higher, about 75% in patients at high risk for cardiovascular disease.
- Sexual dysfunction (SD) in patients with CKD should be thought as a multifactorial problem that is caused by a variety of physiological and psychological factors, as well as by comorbid conditions. For example, diabetes and vascular disease (commonly encountered in patients with CKD) can impair the ability of male patients to achieve an erection and of female patients to become sexually aroused.
- Drugs that sustain cyclic-GMP-mediated smooth muscle relaxation in the corpus cavernosum, such as sildenafil, vardenafil, avanafil, and tadalafil, can improve erectile function in male patients.

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26.1 Introduction

Sexual dysfunction (SD) is a common problem in people with chronic kidney disease (CKD). SD should be considered a multifactorial problem in these patients, caused by a variety of physiological and psychological factors as well as comorbid conditions [1]. Male patients with CKD suffer from decreased libido, erectile dysfunction (ED), and difficulty achieving orgasm. This population has diffuse atherosclerotic disease of the penile arteries and hypoxic changes in the contractile and structural components of the corpus cavernosum.

In women with CKD, dyspareunia, amenorrhoea, decreased libido, and delay in sexual development are frequently observed, with a tendency to reach menopause 5 years earlier than the general population (Table 26.1) [1, 2]. In 1972, the first epidemiological study of sexual function in patients with CKD was conducted. Since then, several studies have confirmed that SD is highly prevalent in CKD patients.

SD is reported in 74% of women with ESRD, while in men with ESRD the prevalence of ED is 71%, 59% in kidney transplant recipients, 79% in haemodialysis (HD), and 71% in peritoneal dialysis (PD) patients. In addition, ED is common in ESRD patients regardless of the type of renal replacement therapy [3]. It should be emphasised that SD is also closely related to HD adequacy. Inadequate dialysis leads to poorer sexual

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Table 26.1 Clinical manifestations of SD in CKD patients

Women	Men
Premature menopause	Erectile dysfunction
Genito-pelvic pain/penetration disorder	Premature ejaculation and delayed ejaculation
Decreased libido	Decreased libido
Sexual aversion disorder	Oligospermia
Hypoactive sexual desire	Decrease in muscle mass
Endocrine abnormality: Decrease in oestrogen production, vaginal dryness, dyspareunia	Azoospermia, infertility
Irregular menstrual cycles, anovulatory cycles, infertility depression, anxiety	Depression, anxiety

function and higher levels of depression and anxiety [4]. In both men and women with ESRD, renal transplantation improves sexual function [5, 6].

Although it is an important factor influencing quality of life in ESRD in both sexes, very little attention is paid to SD by the treating medical team in dialysis patients. Despite its importance, only 25% of patients talk to their doctors about SD [7–9].

26.2 Male Sexual Dysfunction

Various sexual health changes are common in patients with CKD, such as testosterone depletion, testicular damage, hypothalamic-pituitary-gonadal axis dysfunction, hyperprolactinaemia, but most common is ED [10].

Erection is a neurovascular event. During sexual stimulation, vasodilation and relaxation of trabecular smooth muscle allow blood flow into the cavernous sinusoids and increase intracavernous pressure (ICP) [1, 11]. Erection is maintained by compression of the subtunical venules against the tunica albuginea. Relaxation of the smooth muscle of the corpus cavernosum is the crucial physiological event in penile erection. The nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway has been recognised as the classical pathway for mediating the relaxation of the smooth muscle of the corpus cavernosum. Activation of the cavernous nerve results in the release of NO from the nerve endings in the corpus cavernosum. In addition, NO is released from the endothelium in response to shear stress. NO is synthesised by neuronal nitric oxide synthase (nNOS) in the nerve endings of the corpus cavernosum and by endothelial oxide synthase (eNOS) in the endothelium, which uses L-arginine and oxygen as a substrate to produce NO. Subsequently, NO activates soluble guanylate cyclase (GC) and increases cGMP levels in smooth muscle cells.

The increase in blood flow required for erection is comparable to that required by the heart for vigorous exercise [11, 12]. ED is the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual intercourse [12, 13]. ED may mask previously undiagnosed comorbidities such as cardiovascular disease and diabetes. Regardless of the aetiology, ED is almost always accompanied by psychological symptoms when the man is “bothered” by his condition (performance anxiety).

The risk factors for ED can be divided into age-related, vascular and non-vascular causes. Vascular Causes for ED include diabetes, dyslipidaemia, and hypertension, while non-vascular causes ED include surgery for prostate cancer and central nervous system (CNS) disorders. Ageing is one of the most important and well-defined risk factors for ED, affecting it in both vascular and non-vascular ways. The increasing incidence of atherosclerosis with age is accompanied by the negative effects of age on sexual desire and libido. So these categories are not mutually exclusive; in fact, there is a high degree of overlap. It is well documented that hormonal changes characterised by prolactin, gonadotropins, and gonadal hormonal changes occur in both men and women [11]. ESRD patients often have hyperprolactinaemia, which is due to hormonal overproduction and a reduced metabolic clearance rate [14].

Male CKD patients have abnormalities in testicular structure and function. Common histological findings show damage to the testes in the seminiferous tubules, interstitial fibrosis,

calcifications, thickening of the basement membrane, and arrested germ maturation, but also decreased ejaculate volume, low or complete azoospermia, and low percentages of motility and infertility [1].

Hormonal and metabolic changes occur early in CKD: Patients with renal failure have a much higher incidence of elevated prolactin levels than healthy men, which is responsible for decreased libido and ED. In this population, testosterone levels are also decreased, which is related to Leydig cell dysfunction. The molecular mechanism of testosterone and its role in the development of cardiovascular disease plays an important role in ED. Recent studies have been conducted to correlate blood levels of testosterone in patients with ED with different degrees of CKD (stages I– IV) [11]. Alterations in the autonomic nervous system are a common cause of SD in CKD; the integrity of this system may reduce sensations and arousal during sexual activity. Anaemia, a common complication of CKD, has been associated with a reduction in libido and ED [12, 13]. The lack of oxygen associated with the reduction in haemoglobin levels has been linked to a decrease in NO synthesis and an increase in endothelial contractile factor, which inhibits erectile function. Recombinant human EPO therapy has been shown to improve erectile function and sexual performance in some, but not all, patients with CKD [15].

26.3 Female Sexual Dysfunction

In women with CKD, a decrease in libido, amenorrhoea, and irregular menstrual and anovulatory cycles are caused by increased levels of follicle stimulating hormone (FSH) and luteinising hormone (LH). In these patients, oestradiol levels do not reach an adequate peak during the luteal phase. The mid-cycle surge LH cannot be alleviated by administration of endogenous oestrogen, confirming central hypothalamic dysfunction. Clinical manifestations of SD in women include premature menopause, skin wrinkling, urinary incontinence, hot flushes, sleep and cognitive disturbances, and cardiovascular disease. Decreased libido is often observed, while pregnancy is rare (spontaneous abortion is a common occurrence). In women with ESRD, all these changes lead to a ten-fold reduction in fertility [16]. Few studies have carefully examined ovarian function in women with CKD; this lack of data probably reflects the complexity of studying the reproductive system in women [11]. The high prevalence of SD in ESRD patients highlights the need to study the impact of SD at all stages of CKD [17, 18]. In addition, 30–80% of women on dialysis report sexual symptoms [19]. Psychosocial factors can have a significant impact on sexual function in patients with CKD. Several studies have found that 20–30% of patients with CKD have clinical depression. Studies have also shown an association between SD and several other quality of life parameters, such as the mental and physical components of the 36-Item Short-Form Health Survey (SF -36) and depression scores [11].

26.4 Diagnosis and Evaluation of Sexual Dysfunction

The first step in assessing SD in patients with CKD is to take a detailed sexual history of sexual desire, arousal and orgasmic ability, fertility, and ED in men. Changes in the frequency of sexual intercourse must also be determined. Patients are often very reluctant to raise such concerns. Doctors should determine the timing of the onset of these problems in relation to the stage of CKD. In addition, the history should focus on the patient's past and current medical conditions, i.e. chronic/medical conditions such as diabetes, anaemia, neurological conditions or lumbosacral disc disease, endocrinological conditions such as hypogonadism, hyperprolactinaemia, and thyroid disease, and atherosclerotic vascular risks such as diabetes, hypercholesterolaemia, hypertension, hyperhomocysteinaemia, smoking habits, or a family history. Current drug therapy should also be reviewed in detail. Medications such as cimetidine, tricyclic antidepressants, phenothiazines, and metoclopramide are often associated with ED. Finally, it is important to screen patients for

the presence of psychosocial problems (depression, psychiatric illness) and current stressors (loss of job or home, etc.).

26.4.1 In Men

Physical examination is important to assess the sexual function of the male patient. This assessment should include vascular disease, autonomic disease, autonomic dysfunction, and hypogonadism [1, 11].

Absence of secondary sexual characteristics and decreased testicular function indicate male hypogonadism. This condition occurs in patients with congenital and acquired disorders who often have inadequate function of the hypothalamic-pituitary axis. These altered mechanisms result in a deficiency of androgens and/or impaired sperm production. The nocturnal penile swelling (NPT) test can be used to differentiate between organic and psychological causes of impotence. A patient with normal nocturnal erection during rapid eye movement sleep (REM) may benefit from psychological testing and evaluation [20].

For this purpose, the Erectile Hardness Score (EHS) [21] can be used to assess penile rigidity or the Beck Depressive Inventory (BDI) [22] if a depressive status is suspected to affect sexuality.

Depending on the patient's specific complaints, laboratory testing of hormone levels (testosterone, oestrogen, FSH, LH, TSH, PTH, prolactin levels) and zinc levels should be considered. The test to distinguish between a neurogenic and a vascular cause of impotence includes Doppler examinations to measure blood flow in the penis, measurement of blood pressure in the penis, and palpation of the penile pulse. The NIH Consensus Panel on ED outlined several goals for basic and clinical research on ED. One of these goals was to create a staging system for quantitative and qualitative classification of ED. Such a system would support research and patient treatment by:

1. Quantifying the specific patient population to be enrolled in a clinical trial.
2. Determining and comparing response rates for different treatments.
3. Improving clinical decision-making and patient care.
4. Supporting educational initiatives.
5. Supporting applications for reimbursement.

The EF domain of the International Index of Erectile Function (IIEF) was considered for this purpose. This subscale in particular showed a high degree of reliability and excellent sensitivity and specificity for treatment effects in validation studies [15]. The IIEF was developed in conjunction with the sildenafil clinical trial programme and has since been considered the "gold standard" for assessing efficacy in clinical trials of ED. Overall scores of 22–25 indicate normal EF, while lower scores indicate ED (mild ED, 17–21; mild to moderate ED, 12–16; moderate ED, 8–11; and severe ED, less than 8 points). The Arizona Sexual Experiences Scale (ASEX) is a five-point rating scale that assesses sex drive, arousal, vaginal lubrication or penile erection, ability to achieve orgasm, and post-orgasmic satisfaction. The possible total scores range from 5 to 30, with higher scores indicating more SD. Its reliability has been positively evaluated for use with dialysis patients [15].

The Mell-Krat scale is widely used in Poland and the Czech Republic as a validated instrument helpful in complex assessment of sexual function and quality of sexual life. The version for men includes 13 and the one for women 20 questions with answers ranging from 0 to 4. The higher the score, the better the sexual function. Optimal scores for men are 38 points or higher, for women 55 points or higher. The Beck Depression Inventory (BDI) is one of the most commonly used instruments to measure the severity of depression. It consists of 21 questions, scored from 0 to 3, each capturing a specific symptom that is common in people with depression. A total score of 10 or higher indicates depression (10–18 for mild depression, 19–29 for moderate depression, and more than 30 points for severe depression).

26.4.2 In Women

Assessing sexual function in women may be more difficult than in men, which may explain the lack of studies on SD in women with CKD [1, 11]. Domains of sexual function in women include pleasure, arousal, pain, and satisfaction. These can be assessed with the 9-item FSFI. Several validated screening tools address hypoactive sexual desire disorder (HSDD), which is the most common sexual problem in women of all ages. The usefulness of these screening tools will depend on your clinical specialty and the patient population you manage (Box 26.1). Menstrual abnormalities are common in CKD and many women are anovulatory, have infertility, menstrual irregularities, and premature menopause [23]. The hormonal changes that lead to premature menopause in women with CKD likely contribute to SD and are at least partly responsible for the higher prevalence of sexual dysfunction in women with CKD compared to the general population. Ovarian failure in women with CKD may be associated with abnormalities in the hypothalamic-pituitary-ovarian axis [17, 20, 24].

Box 26.1 Screening Tools for Female SD

- Decreased Sexual Desire Screener (DSDS): 5 questions, self-completion; tests for generalised acquired HSDD [25].
- Female Sexual Function Index (FSFI): 19 questions, self-assessment; assesses all dimensions of female sexual function including sexual satisfaction [26].
- Sexual Interest and Desire Inventory-Female (SIDI-F): 13 questions, administered by a clinician; assesses the severity of female HSDD [27].
- Brief Hypoactive Sexual Desire Disorder Screener: 4 questions, for self-assessment of HSDD in postmenopausal women [28].
- Brief Profile of Female Sexual Function (B-PFSF): 7 questions, self-assessment of HSDD in postmenopausal women [29].
- Female Sexual Distress Scale-Revised (FSDS-R): 13 questions, for self-assessment of distress related to female SD [30].
- Elements of Desire Questionnaire (EDQ), a 9-item questionnaire assessing sexual desire (PRO) [1].
- Women's Inventory of Treatment Satisfaction (WITS -9): nine items on a 7-point numerical rating scale to assess satisfaction with treatment and sexual relationships in the past 4 weeks.

26.5 Management of Sexual Dysfunction in Men and Women

26.5.1 In Men

Various strategies can be used to treat SD in men. Both psychological and physical variables can lead to this condition. The aetiopathogenesis of the disorder and the patient's comorbidities are critical in choosing between pharmacological, non-pharmacological, or an approach that incorporates both treatments.

In the general population, medications that support cyclic GMP-mediated smooth muscle relaxation in the corpus cavernosum, such as sildenafil, vardenafil, and tadalafil, can improve ED in male patients. The introduction of sildenafil has completely changed the approach to the assessment of patients with SD, as this drug is considered an effective and well-tolerated treatment for men with ED (Table 26.2). It is important to avoid the use of PDE5 inhibitors in selected conditions (Box 26.2).

Table 26.2 Common adverse effects of drug treatment of SD

PDE5 inhibitors	Testosterone
Headache	Decrease in high-density lipoprotein, fibrinogen, lipoprotein (a)
Nasal congestion	Increase prostate volume, prostate cancer, exacerbating symptoms of benign prostate hypertrophy
Gastric reflux/ dyspepsia	Alterations in liver function
Myalgia/back pain	Polycythaemia
Flushed face	Exacerbation of sleep apnea

Box 26.2 Precautions to the Use of PDE5 Inhibitors

- Nitrates and PDE5 inhibitors should not be taken together.
- Amyl nitrate should not be used with sildenafil.
- Any treatment for ED is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors.
- These medications must be used with caution when co-administered with antihypertensive agents.
- PDE5 inhibitors are contraindicated because of the risk of excessive vasorelaxation with nicorandil.
- Sildenafil should be used at a dose of 25 mg in patients with a ClCr <30 ml/minute.
- Vardenafil should be started at a dose of 5 mg in patients with a ClCr <30 ml/minute, increasing to 20 mg if necessary.
- Tadalafil should be started at a dose of 5 mg in patients with mild (creatinine clearance 51–80 ml/minute) or moderate (creatinine clearance 31–50 mL/min) renal disease, increasing the dose to 20 mg if needed.
- Avanafil should also be used with caution. In patients with mild renal impairment (creatinine clearance ≥50, < 80 mL/min) and (moderate creatinine clearance ≥30, <50 mL/min), the pharmacokinetics of a single dose of 200 mg avanafil are not altered.
- PDE5 inhibitors are poorly excreted by dialysis and must be used with special caution in patients with end-stage renal disease.
- Blood levels of PDE5 inhibitors may increase with concomitant use of medicinal products that inhibit the CYP34A pathway.

In the past, we have proposed an algorithm for CKD patients with the possibility of investigating the previously mentioned factors using some instrumental interventions such as the NPT test, penile echo colour Doppler, nerve conduction velocity or erectile tissue biopsy in order to prescribe the necessary surgical or medical interventions [12, 13]. The complexity of the proposed algorithm requires many diagnostic procedures and a lot of time and economic resources to locate the pathological lesions responsible for the ED. Given the proven efficacy of PDE5i use, we propose an algorithm to test the possibility of obtaining an erection and classify patients as responders or non-responders to PDE5i therapy (Fig. 26.1). In non-responders, it is necessary to investigate other factors (hormonal, psychological, neurological, vascular, cavernous changes, or certain medications) involved in triggering or maintaining ED [13] (Box 26.3). Low-intensity shock wave therapy (LI-SWT) has been shown to be useful in vasculogenic ED [31].

In patients who do not respond to PDE5i, sublingual administration of apomorphine may be an alternative. Results with this agent are promising and it is the only approved oral drug for ED that is not absolutely contraindicated with the use of nitrates [32].

Testosterone therapy is indicated in adult men diagnosed with hypogonadism (total testosterone <12 nmol/L). Clomiphene citrate has also been used empirically to increase testosterone levels, but neither its efficacy nor its safety has been

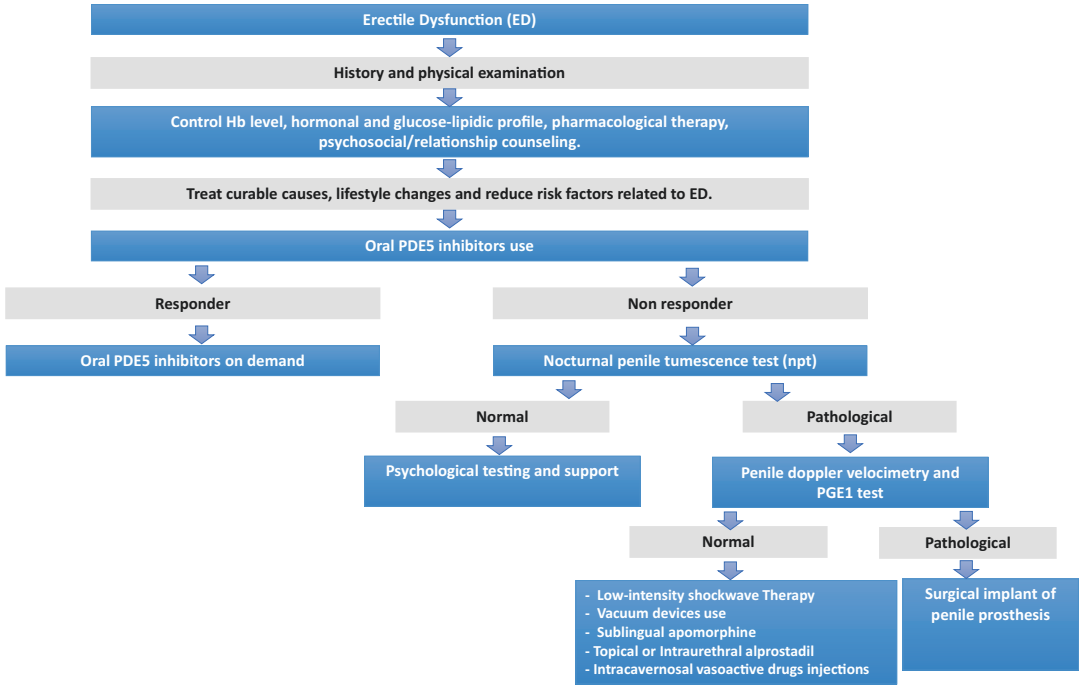

Fig. 26.1 Diagnostic and therapeutic algorithm for the evaluation of ED in CKD patients

demonstrated in randomised trials [33]. Oral testosterone and testosterone derivatives are not used due to their lack of efficacy and adverse effects on liver function and lipid profile. They are therefore used as parenteral and transdermal preparations (Boxes 26.4 and 26.5). There are few studies on the use of testosterone in patients with CKD, and several studies suggest that ED does not improve with testosterone in CKD (Table 26.2; Boxes 26.4 and 26.5) [20, 34–37].

Box 26.3 What the Guidelines Say you Should Do: Workup on ED [38]

- Sexual history and physical examination are needed in the initial assessment of ED to identify underlying medical conditions associated with ED.
- Clinical use of a validated questionnaire related to ED may help assess all sexual function domains.
- Routine laboratory tests, including glucose–lipid profile and total testosterone, are required to identify and treat any reversible risk factors and modifiable lifestyle factors.
- Specific diagnostic tests are indicated in selected cases: nocturnal penile tumescence and rigidity testing using RigiScan, intracavernous vasoactive drug injection, duplex ultrasound of the cavernous arteries, dynamic infusion cavernosus arteries, dynamic infusion cavernosometry, and cavernosography.

Box 26.4 What the Guidelines Say you Should Do: Treatment of ED [1, 38]

- Lifestyle changes and modification of risk factors must precede or accompany treatment of ED.
- The first-line treatments are pharmacological therapies and vacuum devices.
- Vacuum erection devices use a tape at the base to draw blood into the penis to keep the blood in and induce an erection.
- The American University of Physicians recommends that clinicians initiate therapy with a PDE-5 inhibitor in men seeking treatment for ED who do not have a contraindication to taking PDE-5 inhibitors.
- Clinicians need to base the choice of a particular PDE-5 inhibitor on the individual preferences of men with ED, including ease of use, cost of the drug, and side effect profile.
- LLI-SWT can be used in vasculogenic ED and in patients who do not respond satisfactorily to pharmacological therapy.
- Data are insufficient to compare the efficacy and adverse effects of different PDE-5 inhibitors for the treatment of ED, as few head-to-head studies are available.
- Pro-erectile treatments need to be given as soon as possible after radical prostatectomy.
- Testosterone replacement restores efficacy in hypogonadal patients who do not respond to PDE5-Is.
- Apomorphine can be used in mild to moderate ED, psychogenic ED, or in patients with contraindications to PDE5-Is or non-responders.
- Intracavernosal injection is a second-line therapy.
- Penile prosthesis represents a third-line therapy, both inflatable and non-inflatable.
- Intraurethral suppositories are another alternative. These are devices that are inserted into the meatus of the urethra and induce an erection.

26.5.2 In Women

Few studies address decreased libido and sexual function in women with CKD. Quality of life surveys suggest that discussion of sexual function and other reproductive issues is an important component of psychosocial assessment and that there is a great need for education about sexual function in the context of CKD (Box 26.5). Pharmacological therapy with oestrogen/progesterone and androgens is important along with correcting anaemia, ensuring adequate dialysis performance and treating underlying depression [1, 9]. In women requiring haemodialysis, dialysis adequacy and depression are significantly related to SD [39]. Lifestyle changes such as smoking cessation, strength training, and aerobic exercise can reduce depression, improve body image, and have a positive impact on sexuality. Women with CKD who suffer from chronic anovulation and lack of progesterone secretion can be treated with oral progesterone at the end of each menstrual cycle to restore a regular cycle. It is not clear whether uncontrolled oestrogen stimulation of the endometrium (due to anovulatory cycles) predisposes women with CKD to endometrial hyperplasia or endometrial cancer.

The synthetic steroid tibolone, used for postmenopausal symptoms, has been shown to have a positive effect on sexual symptoms and to improve genital blood flow and vaginal pulse amplitude [40]. In these cases, routine gynaecological follow-up is recommended, and some women may also benefit from taking a progestogen several times a day to mitigate the effects of oestrogen on the endometrium (Boxes 26.5 and 26.6) [41, 42].

Box 26.5 Relevant Guidelines on Sexual Dysfunction

1. European Association of Urology for diagnostic workup and treatment of ED in general population [35].
2. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians [43].
3. Practice guidelines on sexual dysfunction in women from American College of Obstetricians and Gynecologists (ACOG) [41].
4. British Society for Sexual Medicine (BSSM). Guidelines on the management of sexual problem in women: the role of androgens [42].
5. European Association of Urology Guidelines on Sexual and Reproductive Health-2021 Update: Male Sexual Dysfunction [44].

Box 26.6 What the Guidelines Say you Should Do: Treatment of SD in Women and the Opportunity for Psychosexual and/or Couples Counselling [41, 42]

- Low-dose vaginal oestrogen therapy is the preferred hormone treatment for female sexual dysfunction due to the genitourinary syndrome of menopause.
- Low-dose systemic hormone therapy with oestrogen alone or in combination with progestogen may be recommended as an alternative to low-dose vaginal oestrogen in women suffering from dyspareunia associated with the genitourinary syndrome of menopause as well as vasomotor symptoms.
- The general use of testosterone in women is not approved in the international guidelines due to insufficient indications and lack of long-term data. However, postmenopausal women suffering from their decreased sexual desire and other identifiable causes may be candidates for short-term testosterone therapy.
- Flibanserin may be used for hypoactive sexual desire in premenopausal women.
- The selective oestrogen receptor modulator ospemifene may be used as an alternative to vaginal oestrogen for the treatment of dyspareunia due to the genitourinary syndrome of menopause.
- Hypogonadal women may also use androgens due to premenopausal pituitary problems.
- For the treatment of HSDD, the most recommended therapy is transdermal testosterone in high physiological doses in combination with oestrogen in postmenopausal women and in women of late reproductive age. For women of reproductive age, there is not yet sufficient data.
- Transdermal patches and topical gels or creams are preferred to oral products because hepatic first-pass effects have been demonstrated with the oral formulation.
- Although there is no consistent correlation between sexual function and androgen levels (free and total testosterone, androstenedione, dehydroepiandrosterone, and SHBG) across a wide age range, androgen therapy may improve sexual desire in some women.
- The main side effects of androgens are hirsutism and acne, but also adverse events during possible pregnancy, such as the androgenising effect on a female foetus. If testosterone supplementation does not lead to discernible benefits, its discontinuation after 6 months should be considered.

Low oestradiol in amenorrhoeic women on dialysis leads to vaginal atrophy and dyspareunia. Topical oestrogen cream and vaginal lubricants may be helpful in this situation. Women with CKD who have menstrual cycles should be encouraged to use contraception. Restoring fertility is not an advisable therapeutic goal because of poor pregnancy outcomes. HSDD is the most common sexual problem reported by women with CKD. Testosterone replacement therapy to treat HSDD has been shown to be effective in some women without CKD. However, there are very few data on the long-term safety of androgens in women with CKD and ESRD [36, 37, 45].

Before You Finish: Practice Pearls for the Clinician

- A detailed history of menstrual behaviour should be obtained in women and ED in men.
- Laboratory dosing of hormone levels (testosterone, oestrogen, FSH, LH, thyroid stimulating hormone, PTH, and prolactin levels) should be considered.
- In male and female patients, it is important to address the psychosocial factors that may contribute to SD.
- Phosphodiesterase inhibitors are recommended as first-line therapy because of their efficacy, ease of use, and good side-effect profile.
- Sildenafil, vardenafil, avanafil, and tadalafil appear to be equally effective. ED patients who prefer higher efficacy need to use sildenafil, while those who optimise tolerability should use tadalafil first [46].
- Tadalafil is also preferable because of its longer duration of action.
- In patients with mild vasculogenic ED and PDE5Is that do not respond, LI-SWT may be a good alternative.
- As second-line therapy, intraurethral/intracavernosal injectables such as alprostadil are recommended, depending on patient preference.
- As third-line therapy, surgical implantation of a penile prosthesis is reserved for patients who cannot use or have not responded to first- and second-line therapies.
- Androgen replacement therapy is indicated only in cases of proven hypogonadism.

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Sleep Disorders in Chronic Kidney Disease

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Before You Start: Facts you Need to Know

- Sleep disorders are common in patients with chronic kidney disease (CKD) and affect nearly all patients in end-stage kidney disease (ESKD) on dialysis treatment.
- The worst sleep quality and quantity occur in the night of the longest interdialytic interval and in patients awaiting morning dialysis. However, sleep disorders in CKD and ESKD are largely under-recognized, overlooked and their treatment is far from optimal.
- The interest for the quality and quantity of sleep in patients with ESKD emerged immediately after the introduction of dialysis therapy and has grown extensively as indicated by the number of papers on the topic. We know that 80–100% of patients with ESKD on maintenance dialysis lack the benefits of a refreshing sleep. They sleep poorly and their sleep is characterized by delayed sleep onset (DSO), frequent awakenings (FA), excessive daily sleepiness (EDS), restless leg syndrome (RLS), sleep disordered breathing (SDB), nightmares (NM), and sleepwalking (SW).
- Insomnia is the first prioritized symptom in dialyzed patients who experience day–night reversal.
- The disordered sleep occurs with impaired neurocognition, depression, pain, cardiovascular events, low quality of life (QoL), and mortality and is associated with lower health related quality of life (HRQoL).
- A disordered sleep is also observed in children and adolescents treated with various dialysis modalities.
- Even successful renal transplants do not fully cure sleep disorders because of the impact of steroids, overweight, obesity, fluid and sodium retention, and diabetes.
- Many toxins including urea, phosphate, anemia, and PTH have been incriminated.
- The worst sleepers are the patients on dialysis with medically intractable hyperparathyroidism needing surgery. Their sleep significantly improves after parathyroidectomy.
- Hypertension and the use of antihypertensive drugs have an independent role in the genesis of poor sleep.
- The diagnosis of poor sleep is now included in the work-up of patients on maintenance dialysis. Polysomnography (PSG) has emerged as the gold standard but questionnaires still play a role. Actigraphy is coming of age because of its simplicity.
- Sleep disorders because of their impact on functional capacity are still an important med-

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ical burden in patients with ESKD and cause more health services utilization, thus increasing the expenditures for a disease already plagued by high costs.
- Therapy is still in its infancy but cognitive behavioral therapy (CBT) is coming of age.

27.1 Introduction

Sleep is a recurrent dynamic process that affects every body function for nearly one-third of the day and has a housekeeping role. It regulates metabolism and immunologic functions [1].

Sleep has been studied extensively since antiquity [2, 3] starting with *Homeric Poems* (750–723 BC). In *Iliad* (XIV, 270) sleep was located in the Isle of Lemnos where even Juno flew to visit the brother of death to induce sleep to Zeus. Hesiod (floruit c.700 BC), wrote: "*Nix bore hateful Moros (doom) and black Ker (destiny) and Thanatos (death) she bore Hypnos and the tribe of Oneroi*" (*Theogony* 211–212). For Heraclitus of Ephesus (floruit 504–1 BC): "in sleep sense-channels are closed, so that the mind is prevented from growing together with what stays outside." For Parmenides of Elea (c515/510 BC-450 BC): "sleep was due to a reduction of organic heat," whereas for Diogenes of Apollonia (floruit 440–430 BC) sleep was "caused by a moistening of the air-soul." Alcmeon of Croton (510–440 BC) thought that it was caused "by confinement of blood to large blood vessels, whereas waking is brought about by re-diffusion." For Anaxagoras (500/497–428 BC): "sleep was a process unrelated to the soul and entirely due to the body exhaustion of physical energy." For Empedocles (492–432 BC): "Sleep depends on a moderate cooling of the warmth in the blood, it depends on the separation of the element fire." For Plato (429–347 BC): "Sleep begins when the light is turned off. The dark supervenes, the eyes are shut and keep internally the fire of the light. Light meets with its dissimilar, the darkness." Whereas for Aristotle (384–322 BC): "Sleep was a deprivation of waking, and there was no perception (*De somno et vigilia)*."

The problem of how long one can sleep is well recorded in the Quran (610 AD), Surah XVIII, 8–26. The narrative addresses the Seven Sleepers of Ephesus and the famous Grotto. "*Dost thou consider that the Companions of the Cave, and al Rakim, were one of our signs and a great miracle? they said, O Lord, grant us mercy from before Thee, and dispose our business for us to a right issue. Wherefore we struck their ears so that when the young men took refuge in the Cave, they slept in the Cave for a great number of years: then we awakened them … that they might ask questions of one another. One of them said, How long have ye tarried here? They answered, We have tarried a day, or part of a day. Others said: Your Lord best know the time ye have tarried And they remained in their Cave 300 years and 9 years over.*"

Poor sleep of short duration may cause obesity, diabetes mellitus, hypertension, myocardial infarction, ictus as well as loss of attention and memory. Sleeplessness (5 h or less per night) is associated with a 30% reduction of estimated glomerular filtration rate (eGFR) and incident CKD (eGFR <60 mL/minx 1.73 m^2 of BSA [4, 5]. In the last 30 years, several studies have demonstrated that 20–80% of patients with end stage kidney disease (ESKD) have sleep disturbances [6, 7] that are partly corrected by kidney transplantation, the cheapest, most successful, and long-lasting treatment. Sleep disorders in ESKD include insomnia (I), restless leg syndrome (RLS), periodic limb movements in sleep (PLMS), and obstructive sleep apnea (OSA). A recent systematic review [8] and meta-analysis of 3708 articles published in the period between January 1, 1990 and September 18, 2018 on a total of 45,716 patients either on CKD or treated with hemodialysis (HD), peritoneal dialysis (PD), and transplantation (TX), identified 93 articles (62 on poor sleep, related to 21,180 patients and 31 on insomnia related to 17,010 patients. Prevalence of poor sleep was 59% in CKD, 68% in HD, 67% in PD, and 46% in TX. Correspondent prevalence for insomnia was 48% in CKD, 46% in HD, 61% in PD, and 26% in TX (Fig. 27.1).

The first report on sleep disorders in CKD was published by the group of Charles Mion in

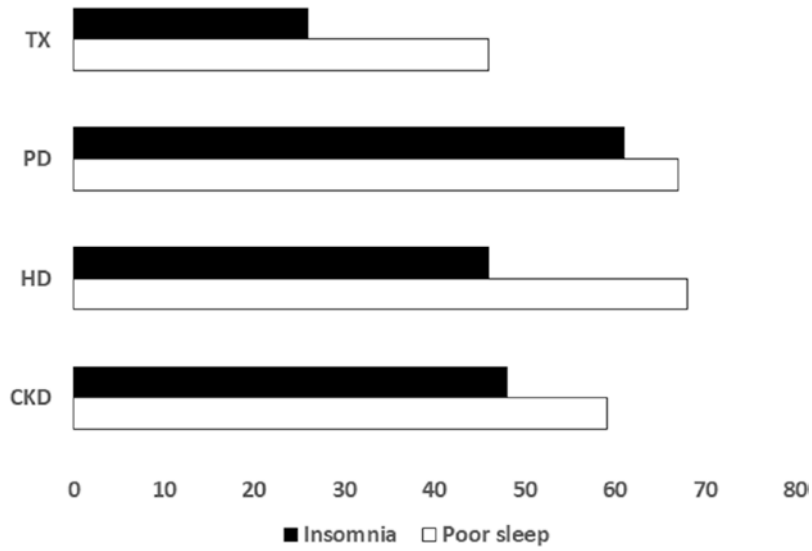

Fig. 27.1 Sleep disorders in CKD. A global perspective. Compiled from data of Tan L-H et al. [8]

Montpellier. A disorder of the sleep architecture was present in all stages. The early studies were not published in nephrological journals. However, in 1981 the term "Psychonephrology" was coined by Norman B. Levy [9, 10].

27.2 Sleep Disorders and their Effects in CKD

Sleep disorders (SD) in chronic kidney disease (CKD) are insomnia (I), sleep apnea syndrome (SAS), central sleep apnea (CSA), restless leg syndrome (RLS), and periodic limb movements (PLMS). They cause fatigue (FA), excessive daytime sleepiness (EDS), impaired day time function (DTF), impaired health-related quality of Llife (HRQoL), increase morbidity and mortality.

In the general population the prevalence of insomnia (difficulty in falling asleep and staying asleep and early morning awakenings) is 4–29%. Sleep disorders are common in chronic kidney disease (CKD) needing dialysis and were described for the first time in 1970, just 7 years after Belding Hibbard Scribner (1921–2001) made maintenance hemodialysis (HD) possible. A 41–85% prevalence of SD has been demonstrated in adult patients on HD and on peritoneal dialysis (PD). However, some recent data point to a higher prevalence (80–100%).

In the study of Merlino et al. [11]—a major study in the history of sleep disorders in end stage kidney disease—enrolling 832 HD and PD patients, SD were present in 80.2%, as insomnia (69.1%), RLS (18.4%), SAS (23.6%), excessive daytime sleepiness (EDS) (11.8%), possible narcolepsy (1.4%), sleepwalking (2.1%), nightmares (13.3%), and possible rapid eye movement (REM) behavior disorder (RBD) (2.3%) as shown in Fig. 27.2.

The worst sleep is experienced by aged patients and is typical in the nights during the longest dialytic interval and in the early morning shift. Insomnia may be associated with pain, itching, poverty, and dialysis vintage. It causes anxiety and stress, depresses the immune system, and is a risk for cardiovascular disease.

Sleep quality and quantity were linked to dialysis shift in 1997 [12]. We were able to characterize this link by means of a 14-day questionnaire compiled by patients treated three times a week by hemodialysis either in the morning or in the afternoon [13]. It was possible to demonstrate that early shifts are associated with poor sleep. We also characterized the sleep of 4 representative nights (A, B, C, D): Night A (after dialysis), night B (before dialysis), night C (neither pre-

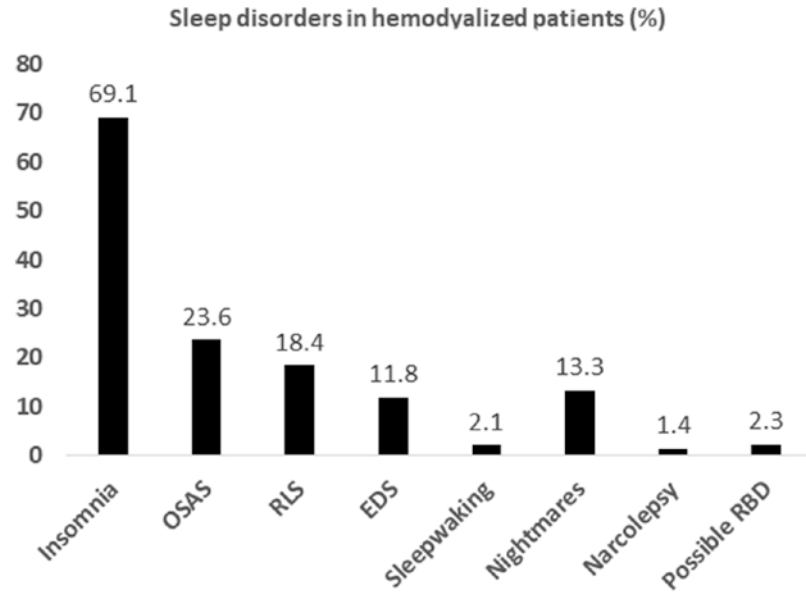

Fig. 27.2 Prevalence of sleep complaints in the historical study of Merlino G et al. [11]

ceded nor followed by dialysis). For example, Saturday night for those dialyzed on Monday–Wednesday–Friday), night D (the night of the longest interdialytic interval, for example, Sunday for those dialyzed on Monday–Wednesday–Friday). Sleep duration declined significantly from night A to night B, to nights C and D, more for those dialyzed in the morning. Sleep efficiency declined also from night A to night B, to nights C and D.

Pain is common in ESKD and is a burden even in early stage CKD. Its prevalence is in the range of 41.4–69% and is associated with higher prevalence of insomnia and of depression, burden of illness and life satisfaction, and, in addition, the Pittsburgh Sleep Quality Index (PSQI) correlates negatively with bodily pain.

PTH has been variably associated with sleep disorders since it causes bone disease and pain. In our experience patients with medically intractable hyperparathyroidism are among the worst sleepers. Sleep ameliorates following parathyroidectomy (Tables 27.1 and 27.2) [14].

Sleep disorders in HD patients predict quality of life and mortality risk, as it emerged in the DOPPS study where poor sleepers, in comparison with good sleepers, had a 16% higher relative risk of death [15]. It seemed safe to explain everything in terms of losses and dependencies associated with dialysis [16] as outlined in Table 27.3. However, SD were not cured by a successful kidney transplantation [17].

Table 27.1 Sleep disorders in hemodialyzed patients of comparable age, women/men ratio, BMI, dialysis vintage, Kt/v, needing and not needing parathyroidectomy. Compiled from data in R.M. De Santo et al. [14]

Category	Needing PTX	Not needing PTX	*p*
PTH, pg/mL	1300 ± 248.5	253 ± 52.4	<0.001
Serum phosphate, mg/dL	6.53 ± 0.46	5.03 ± 0.58	<0.001
SBP, mmHg	139 ± 4	131 ± 8	<0.001
DBP, mmHg	83 ± 4	73 ± 5	<0.001
On antihypertensive drugs %	100	63.8	<0.001
Charles comorbidity index	6.55 ± 0.62	5.27 ± 8.3	<0.001
PSQI	11.9 ± 1.4	6.91 ± 1.7	<0.001
Sleeping hours	5.08 ± 1.4	7.1 ± 0.8	<0.01
Daily naps	1.9 ± 1.6	3.6 ± 1.3	<0.01
Insomniacs, %	72.7	38.6	<0.001
No disturbances, %	4.54	28.4	<0.01

Table 27.2 Effects of parathyroidectomy on sleep disorders in hemodialyzed patients. Data before surgery (no. 40) and 3 years after (no. 36). Compiled from data in R.M. De Santo et al. [14]

Category	Before PTX	Three years after PTX	*p*
PTH, pg/mL	1278 ± 230	45 ± 2	<0.001
SBP, mmHg	138.1 ± 10.4	130.4 ± 6.8	<0.01
DBP, mmHg	83.1 ± 10.4	79.6 ± 8.9	<0.01
PSQI	11.9 ± 1.6	7.0 ± 1.2	<0.01

Table 27.3 Uremia associated losses and dependencies. Based on data of M Fabrazzo and RM De Santo [16]

Losses
Loss of urinary function
Loss of the capacity to concentrate
Loss of workplace
Loss of the freedom to select or to find a job
Loss of the role in the family
Loss of the family dynamics
Loss of the role in social relationship
Loss of quality of life
Loss of the sense of femininity
Loss of menstruation
Loss of the capability of having an orgasm
Loss of the sense of masculinity
Loss of erectile function
Loss of libido
Loss of capability to set constructive goals
Loss of good mood
Loss of life expectancy
Loss of capability of practicing a sport
Loss or limitation in mobility
Loss of freedom in selecting beverages
Loss of body weight
Loss of muscle mass
Loss of body imaging
Loss of skin color
Loss of weight stability
Loss of sleep hours
Dependencies
On dialysis staff
On physicians
On medications
On family
On a machine
On dialysis shifts
On dialysis calendar

27.3 Sleep Disorders in CKD Not Needing Dialysis

In predialysis CKD (creatinine clearance 29.96 ± 10.93 mL/min) Iliescu et al. 2004 were the first to disclose a 53% prevalence of disordered sleep by means of Pittsburgh Sleep Quality Index (PSQI). The prevalence matched that for hemodialysis patients studied at that time. The paper did not disclose any difference between patients with creatinine clearance lower or greater than 17.8 mL/min but identified depression as the only significant predictor of poor sleep [18].

The prevalence of poor sleepers was 14% at eGFR of 25.5 mL/min in the study of Kurella et al. [19]. In the latter study 34% of subjects with ESKD, 27% of subjects with advanced CKD, and 14% of subjects with mild to moderate CKD had sleep maintenance disturbances ($P = 0.05$). Thirteen percent of subjects with ESKD, 11% of subjects with advanced CKD, and no subjects with mild-moderate CKD had complaints of daytime somnolence ($P = 0.03$). The conclusion was that sleep disorders are common in CKD and ESKD particularly in those with lower eGFR.

In a study of Parker et al. [20], a total of 8 CKD patients were studied. The estimated GFR was 14.5 ± 7.2 mL/min (range 5.4–28.8 mL/min). They were compared to patients on HD who had less total sleep time, less REM sleep, longer sleep latency, more arousal, more apneas, and more PLMD. CKD patients had normal sleep latency but poorer functional and psychological status. It was concluded that sleep disorders in CKD have etiologies that are different from those on HD. Functional and psychological factors probably prevail in CKD, intrinsic disruption in HD treatment.

Sleep disorders, however, occur very early [21, 22] in CKD. In a study on sleep disorders in people with newly diagnosed CKD (eGFR 58.6 ± 44.4 mL/min), the prevalence of sleep disorder was 89.5% [21]. The prevalence of reported sleep complaints—shown in Fig. 27.3—was not associated with factors considered responsible for sleep disor-

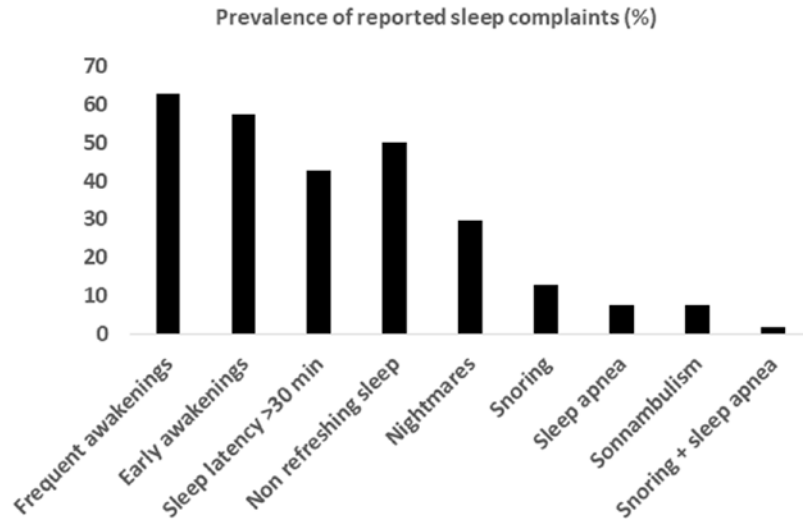

Fig. 27.3 Prevalence of sleep complaints at the time of CKD diagnosis. Compiled from data of De Santo RM et al. [21]

ders in maintenance hemodialysis [21]. The data suggested that the intrusion of a chronic disease in the life of patients with early CKD might be the triggering event for sleep disorders. Conversely, stress must be regarded as a more common precipitating factor than insomnia since more than seven out of 10 poor sleepers recall specific stressful experiences and also point to an inefficient coping mechanism. The lack of an association between comorbidities and sleep disorders suggested that in early CKD, sleep disorders are a marker of insufficient elaboration of coping with a chronic disease, usually viewed as associated with life-long constraints. From studies utilizing the narrative in CKD patients it has emerged that initial discovery of kidney disease is a disrupting event, so as Kjeerans and Maynooth say [23] the patients need "to create meaning and to re-establish cohesion in their lives. It means that discovering that you are affected by a chronic disease with unpredictable time course, with many potential comorbidities, is a deconstructing event. Thus, people who during their healthy days do not care where their kidneys are, start asking questions to physicians, friends, neighbors and patients on dialysis or receiving a kidney transplant. Thus, they learn that they will be needing a lot of medication and will probably end up attached to a machine and less probably receive a transplant. The latter appears a remote possibility, an impossibility" [21]. Indeed, the moment dialysis becomes essential [5, 6] a patient is faced with the irrefutable fact that recuperative powers have limits and there awaits a bleak future with loss of autonomy. Dialysis creates a radical shift of focus from the inside to outside oneself. The unpredictability of kidney disease which is made clear at the time of diagnosis has been appropriately defined as an act holding someone hostage. So it is important that the narrative be focused and extensive in the early days of the disease [22].

A 3-year longitudinal study by Sabbatini et al. [24] suggested that progression of kidney disease is accompanied by a progressive worsening of SD, but an independent association was not demonstrated. By contrast, in our laboratory, hypertension was associated with SD in HD and CKD patients. The association disappeared in the 4-year longitudinal study where systolic and diastolic blood pressure, under a tight control, fell within target values in CKD. In that study depression correlated with sleep quality in logistic regression analysis [25].

27.4 Restless Leg Syndrome and Periodic Limb Movements of Sleep

It is a common neurological sensory-motor disorder manifesting with unpleasant nocturnal sensation in the lower limbs that is relieved by

movements. It may be felt in the muscle mass or in the skin. It affects 5–15% of the general population. The condition is characterized by an urge to move the legs (rarely also the arms) and by a peculiar and unpleasant sensation of paresthesias, deep in the legs.

The sensation appears during periods of rest or inactivity, particularly in the evening and at night and is typically relieved by movement. Paresthesias may be exceedingly unpleasant and give rise to severe sleep disturbances with sleep fragmentation, daytime sleepiness, and fatigue. The deep sensation is felt within the lower extremities. It has been defined as aching, burning, cramping, crawling, creeping, itching, pulling, and tingling. The sensation may also be felt in the thighs and sometimes in the feet. The disagreeable long-lasting sensation is usually felt prior to sleep onset and causes an almost irresistible urge to move legs and causes disrupted sleep and excessive daytime sleepiness. RLS may be unilateral but commonly is bilateral and symmetrical, RLS may be continuous or intermittent. Patients walk to get relief (Night-walker's syndrome [26]).

Patients affected by RLS have higher scores for major depressive disorders, dysthymic disorders, anxiety, depression, minor depressive disorders. They have worse scores for day time sleepiness, sexual dysfunction, and social functioning as well. RLS is associated with impaired neurocognition and attention and higher mortality. It may appear at any age between 5 and 80 years but is more frequent in people aged 45 years or more with a family history of the disease. In 50% of the patients there is a positive family history. Physical examination is normal [13, 27].

Eighty to ninety percent of patients with RLS have Periodic Limb Movements of Sleep (PLMS). The latter is a distinct entity positively associated with age. As pointed out by the American Sleep Disorder Association, 34% of the cases occur in patients older than 60 years. The prevalence of PLMD may be as high as 70% [28] and as important as RLS in terms of sleep disorder. Brain iron deficiency has been identified as a causative factor since iron is a cofactor for dopamine production in the brain.

Diagnosis is based on polysomnography, the levodopa/carbidopa test (25 mg of levodopa/100 mg carbidopa) and by the Criteria of the RLS Study Group that includes the urge to move legs, an uncomfortable sensation, improved by motion and exacerbated by lying down. Treatment includes use of dopamine agonists effective but not long-lasting, gabapentin or pregabalin (calcium channel alpha-2-delta ligands that require renal adjustment). Acupuncture, pneumatic compression, near-infrared light may be helpful. RLS is very common in CKD patients requiring hemodialysis (prevalence 6–62%). In a recent study by Lamanna et al. [28], the prevalence of RLS was 31% and was associated with risk of cardiovascular events and deaths. Nocturnal hypertension and inflammation were discussed as potential independent risk factors.

In nondialyzed patients (eGFR 26.8 ± 9.2) a prevalence of RLS of 37.1% was reported by Markou et al. [29]. In patients with eGFR >15 mL/min it was 25%, whereas in those with eGFR<15 mL/min it was 45.4%. Daytime sleepiness was worst in patients with RLS [29].

In a case control study of Merlino et al. [30] in CKD patients not needing dialysis, the prevalence of RLS was 10% and 3.3% in controls. In a study by Lee et al. [31] in patients with eGFR>60 mil/min, CKD patients with eGFR <60 mL/min and patients on dialysis RLS emerged common and important source of sleep disruption in the whole spectrum of kidney disease. In fact, the prevalence of RLS was 18.9% in patients with eGFR>60 mL/min, 26% in CKD patients with eGFR <60 mL/min, and 26% in patients on maintenance hemodialysis (Fig. 27.4).

RLS in CKD patients has been associated with a statistically significant increase in sleep latency, non-refreshing sleep, leg movements during sleep, poor memory and with a poor sleep as indicated by a PSQI >5. CKD patients with RLS have difficulties in initiating and maintaining sleep. However, RLS is associated with kidney disease, but not with the severity of the disease and in multivariate analysis was predictor of poor sleep.

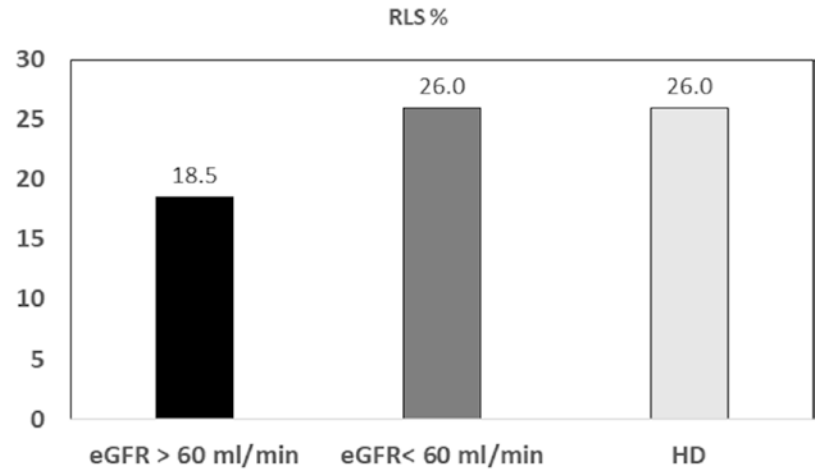

Fig. 27.4 Prevalence of RLS in the whole spectrum of kidney disease. Compiled from data of Lee J et al. [31]

The study did not disclose differences in daytime sleepiness between mild and severe CKD groups.

Transplantation normalizes RLS, but it deteriorates again with graft failure. In many studies the prevalence of RLS after transplantation falls in the range of the general population. However, many studies have reported a high prevalence of RLS in patients receiving a kidney graft.

27.5 Sleep Apnea

Sleep apnea syndrome (SAS) is a chronic sleep disorder causing repeated cessation of breath for 10 s or more, during sleep. It is characterized by loud snoring, breathlessness, waking, and daytime sleepiness. Hypopnea is a 50% reduction in airflow for 10 s or more or a decrease of 30% of airflow associated with increased desaturation or arousal from sleep. The apnea–hypopnea index (AHI) is calculated by dividing the number of apnea-hypopneic episodes for the hours of sleep. An index of 5–10 indicates mild apnea, an index of 15–30 indicates moderate apnea, and an index >30 indicates severe apnea.

The prevalence of SA in the general population is 3–10% in women and 10–17% in men. Prevalence may be higher in persons with obesity and diabetes.

Sleep apnea may be obstructive, central, mixed. Apnea accompanied by respiratory effort—obstructive sleep apnea (OSA)—is typical in CKD, whereas central sleep apnea (CSA) without respiratory effort is underreported. It causes cognitive impairment, decreased daytime functioning and is associated with depression, hypertension, left ventricular hypertrophy, cardiovascular morbidity and mortality. In CKD it is caused by (1) increased ventilatory threshold and/or higher sensitivity to hypercapnia and (2) a rostral fluid shift in reclined position of fluid from legs to the neck that increases collapsibility of the upper way. There is correlation between leg fluid volume and neck circumference.

OSA increases the risk of kidney injury and impairs kidney function. It is found in 1 out of 4 patients with eGFR <60 mL/min, in 4 out of 10 with ESKD, and in more than 6 out of 10 patients on HD or continuous ambulatory peritoneal dialysis (CAPD). The prevalence of CSA is in the range of 9–75%. Nocturnal hemodialysis and cyclic-assisted nocturnal peritoneal dialysis cure OSA that also benefits of compressive stockings.

The link between CKD and OSA is driven by (1) chemoreflex responsiveness and (2) pharyngeal narrowing [32, 33], as reported in Fig. 27.5. Metabolic acidosis causes hyperventilation and hypocapnia. The latter enhances chemoreceptor sensitivity that (1) destabilizes respiratory control during sleep, (2) reduces PCO2 below the apneic threshold, and (3) impairs chemoreflex control. Pharyngeal narrowing is brought about

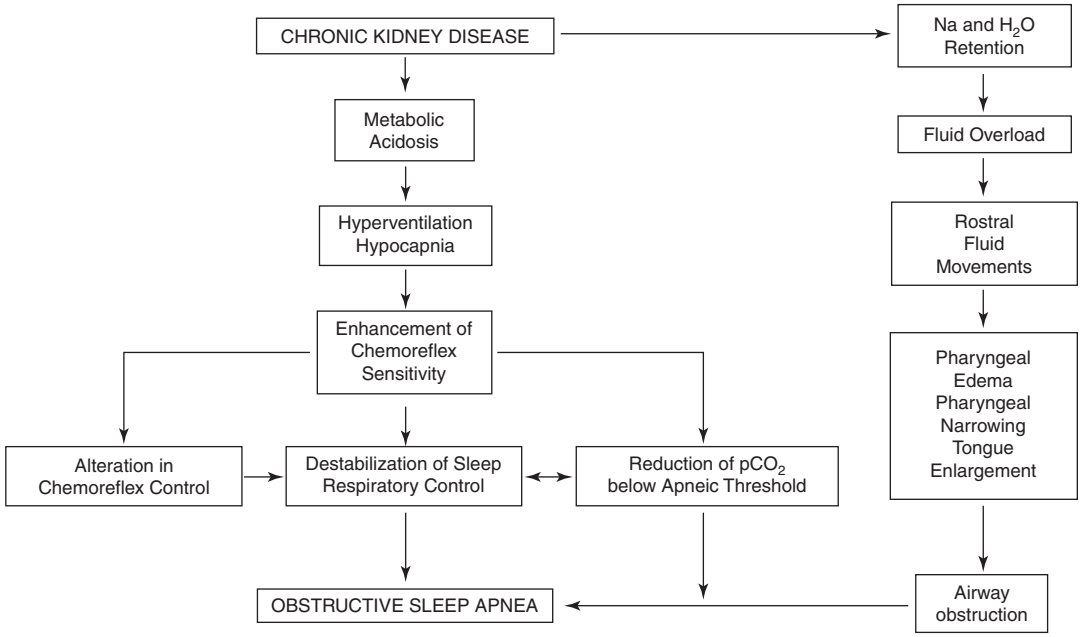

Fig. 27.5 Relation between CKD and OSA. Modified from Abuyassin B et al. [32]

by sodium and water retention and fluid overload and is characterized by narrowing and/or increased thickness of pharyngeal musculature and by tongue enlargement that leads to significant reduction of naso-pharyngeal volume, oropharyngeal volume, and hypopharyngeal volume.

The link between OSA (Fig. 27.5) and CKD is driven by hypoxia, leading to RAAS activation, increased sympathetic tone, hypertension, inflammation, oxidative stress, and excessive negative intrathoracic pressure. Hypoxia causes renal tissue hypoxia that leads to tubulointerstitial injury, renal vasculature damage, and apoptosis that are associated with functional impairment. CKD is the end effect. Oxidative stress causes an increase in asymmetric dimethylarginine that by inhibiting nitric oxide synthase reduces nitric oxide availability. Hypoxia also activates the RAAS and causes endothelial dysfunction, increases the sympathetic tone, causes hypertension, increases insulin resistance, and the atherogenic milieu and ends in CKD. CKD is also mediated by increased right atrial pressure, increased atrial natriuretic peptide that leads to hyperfiltration.

Volume overload has a pivotal role in edema formation in upper airway, leading to oropharyngeal narrowing. Hypervolemia also causes an increase in quantity of overnight rostral fluid shift from the legs during sleep. This is valid for the general population and much more for fluid retaining condition like heart failure and ESKD and causes changes in neck circumference as well as of apnea-hypopnea time (AHT) as demonstrated by Elias [34].

In a study by Sakaguchi et al. in non-obese CKD patients—mean eGFR of 31 mL/min per 1.73 m^2, the decline in GFR was three to fourfold faster in persons with mild-to-severe nocturnal hypoxia (NH), than in persons with no or mild NH (Fig. 27.6). That longitudinal study points to NH as an independent risk factor for fast GFR decline in CKD [35].

There were great expectations on the impact of kidney transplantation on OSA following the papers by Langevin et al. and Auckley et al. [36, 37]. But it soon became evident that transplanta-

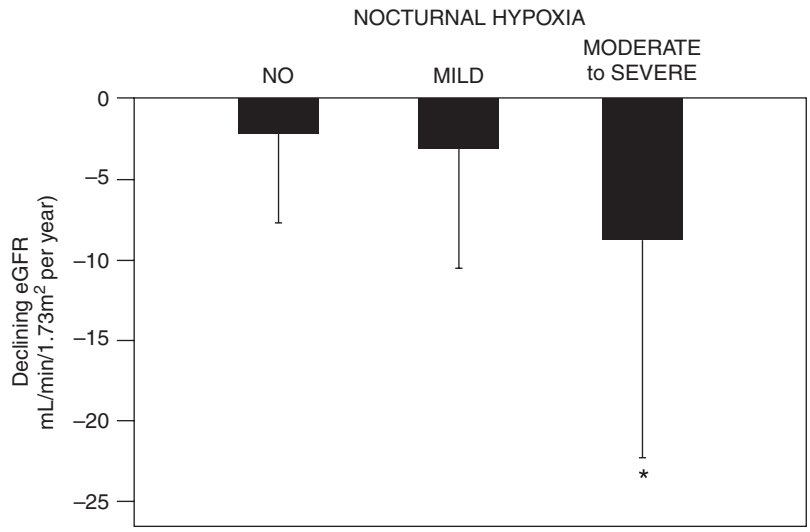

Fig. 27.6 eGFR losses caused by nocturnal hypoxia. (Modified from Sakaguchi Y et al. [35])

tion improved but did not normalize sleep disturbances [37]. Recent studies confirm partial benefits as attested in the study by Valentina Forni Ogna [38]. In kidney transplanted patients with sleep disordered breathing, a strong association was found with 24 h, daily and nocturnal systolic blood pressure by Mallamaci et al. [39]. The group in Reggio Calabria demonstrated that those hypertensive patients were not at higher risk of mortality. They may have been protected by the denervation.

27.6 Sleep Apnea Syndrome as a Trigger of CKD

The relation of OSAS and CKD is bidirectional (Fig. 27.7), there is high frequency of OSAS in CKD but also high prevalence of CKD with OSAS. The link is explained by the chronic hypoxia hypothesis introduced in 1998 by Fine, Orphanides, and Norman that is in good keeping with population and experimental data in humans [40–42]. The hypothesis explains how glomerular injury is transferred to the interstitium and causing scarring and loss of renal function. The primary glomerular disease leads to restriction of postglomerular flows in affected glomeruli and injury of peritubular capillaries causing a hypoxic milieu that maintains inflammation and the fibrotic response of tubulo-interstitial cells that extends to unaffected capillaries, nephrons, and glomeruli. The end effect is a reduction in the number of peritubular capillaries (the hallmark of chronic kidney disease) through enhancement of antiangiogenic factors and the contemporary suppression of proangiogenic factors.

Persons with OSAS carry an increased cardiovascular risk (systemic hypertension, atrial fibrillation, coronary artery disease, stroke). In addition, they may have mild CKD and/or proteinuria that is more common at night. There is a relation between severity of OSAS and loss of kidney function that is independent of hypertension although nearly 50% of people with OSAS may have hypertension. Renal biopsy has disclosed glomerulomegaly and focal segmental glomerulosclerosis [42–45].

Continuous positive airway pressure (CPAP) administered to patients with obstructive sleep apnea syndrome reduces renal plasma flow, filtration fraction, renal vascular resistance, activity of RAAS, and proteinuria. RAAS inhibition is superior to CPAP in reducing BP but not in improving excessive daily sleepiness. Administration of an aldosterone antagonist may reduce fluid retention and supine enlargement of neck circumference and remain a therapeutic

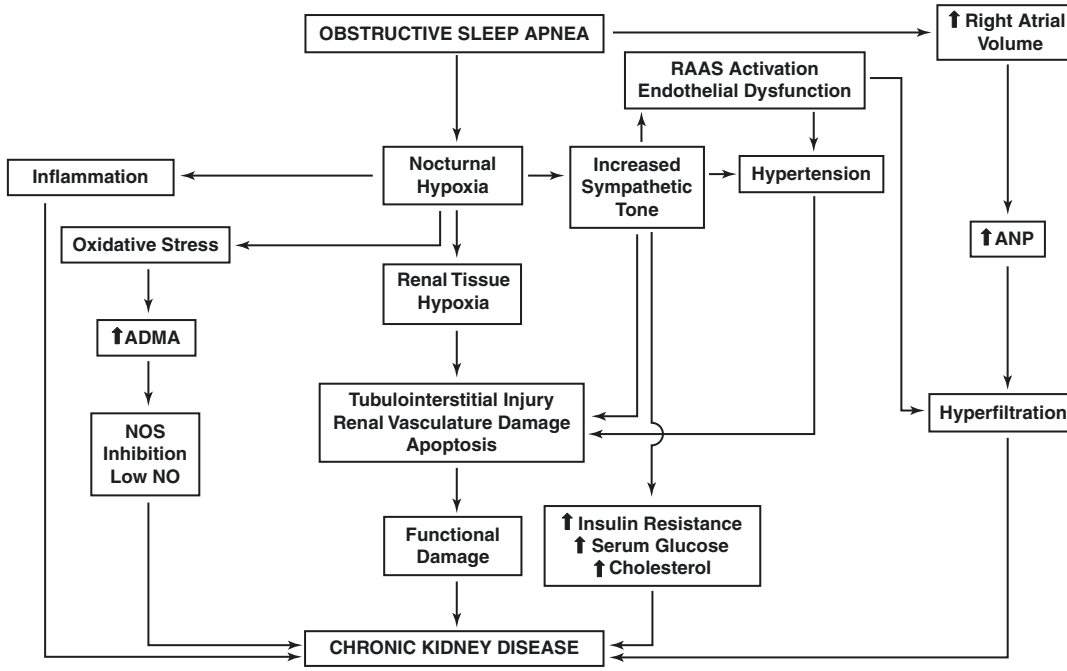

Fig. 27.7 Bidirectional relation of OSA and CKD. Modified from Abuyassin B et al. [32]

option when CPAP is not feasible. An association of CPAP and anti-aldosterone drugs is a possibility that deserves to be explored.

27.7 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) that affects 10–12% of the general population is more prevalent (60–70%) in dialyzed patients. It is characterized by inability to stay alert during the day resulting in sleepiness or unintentional dosing during active and passive daily activities, thus indicating that there is a day/night sleep reversal that is a principal indicator of the uremic status.

The pathogenesis is multifactorial and includes: (1) uremia per se, (2) subclinical encephalopathy, (3) abnormal melatonin metabolism, (4) tyrosine deficiency (dopamine production), (5) production of inflammatory cytokines, (6) changes in body temperature rhythm caused by dialysis, (7) effect of dialysate temperature on sleep, (8) coexistence of sleep apnea. It is improved by nocturnal hemodialysis and by transplantation.

27.8 Alexithymia and Sleep Disorders in CKD

Alexithymia is a personality trait that reflects difficulties in affective self-regulation that was introduced to medical literature by Peter E. Sifneos in 1996 [46]. A major contribution to our understanding of alexithymia comes from studies carried out by Fukunishi starting in 1989 [47]. As reported by R.M. De Santo et al. in 2010 [14], alexithymia incorporates difficulties in distinguishing between feelings and the physical sensations of emotional arousal, limited marginal process, and an externally oriented cognitive style. It has been associated with physical and mental health problems, substance abuse disorders, and mortality in the general population where a prevalence of 4–13% has been reported. It is considered a potential way of dealing with disease-generated stress. Alexithymia scores are correlated with sleep complaints in community samples. The correlation is dependent on depression because it disappears when the contribution of depression is partialled out by multiple regression [14]. That study was one of the 3 prospective

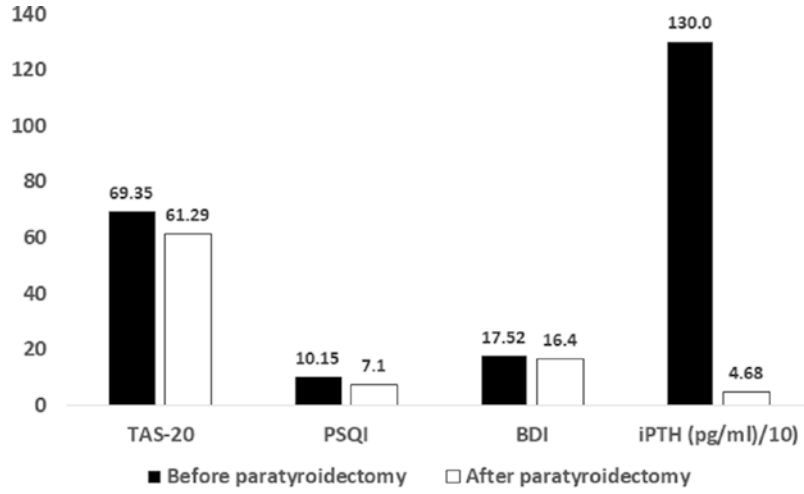

Fig. 27.8 Alexithymia, sleep disorders, PTH, and depression in patients with insuppressible hyperparathyroidism before and after parathyroidectomy. Compiled from data De Santo RM et al. [14]

studies characterized as bearing many strengths and no limitations among 23 studies amenable to meta-analysis in hemodialysis patients [48] and 1 of the 24 papers subjected to systematic review and peer analysis on the more general problem of sleep complaints and alexithymia [49].

De Santo et al. [14] performed a study on 80 HD patients not requiring parathyroidectomy (iPTH 353 ± 52.4 pg/mL) and 40 HD patients with insuppressible hyperparathyroidism needing parathyroidectomy (iPTH 1299.6 ± 248.5 pg/mL). They measured the degree of alexithymia with the Toronto alexithymia scale (TAS-20), sleep disorders with the 19-item Pittsburgh sleep quality index (PSQI) that identifies good sleepers and poor sleeper. The Beck depression inventory (BDI) was used to measure depression, comorbidities were evaluated by the Charles comorbidity index (CCI). Patients with insuppressible hyperparathyroidism had significantly higher TAS-20, higher PSQI, CCI, systolic and diastolic blood pressure, and higher BDI. In 40 patients needing parathyroidectomy, 32 had a BDI score ≥ 15 and BDI correlated directly with iPTH. Patients with insuppressible hyperparathyroidism after surgery had significantly lower TAS-20, PSQI, iPTH, and BDI, as indicated in Fig. 27.8.

There is a renewed interest in detecting alexithymia in CKD patients because it carries the risk of lack of adherence to dietary and medication plans. Inflammation has been assigned a causative role [50, 51] in a study on 170 HD patients probably malnourished (68.9% were poor sleepers, 65.3% alexithymia, 28% depressed, 21% with excessive daytime sleepiness).

27.9 Putative Determinants of Sleep Disorders in CKD

A list of nearly fifty putative determinants for SD in chronic kidney disease needing or not HD therapy [13, 52] have been grouped in: 1. Demographic factors, 2. Lifestyle related factors, 3. Disease related factors, 4. Psychological factors, 5. Treatment related factors, and 6. Socioeconomic factors. Important factors emerged: Age in group 1; cigarette smoking and obesity in group 2; GFR, anemia, PTH, calcium concentrations, neurotransmitters production, hypertension and antihypertensive drugs, bone pain, hypoxemia, and pruritus in group 3; depression, perceived quality of life, and disease intrusiveness in group 4; the dialysis team, the shift, the day of the weekly treatment schedule, albumin and C-reactive protein concentrations, comorbid conditions, losses and dependencies of a dialysis-dependent life emerge in group 5; poverty and living in urban environment emerge in the last group (Fig. 27.9).

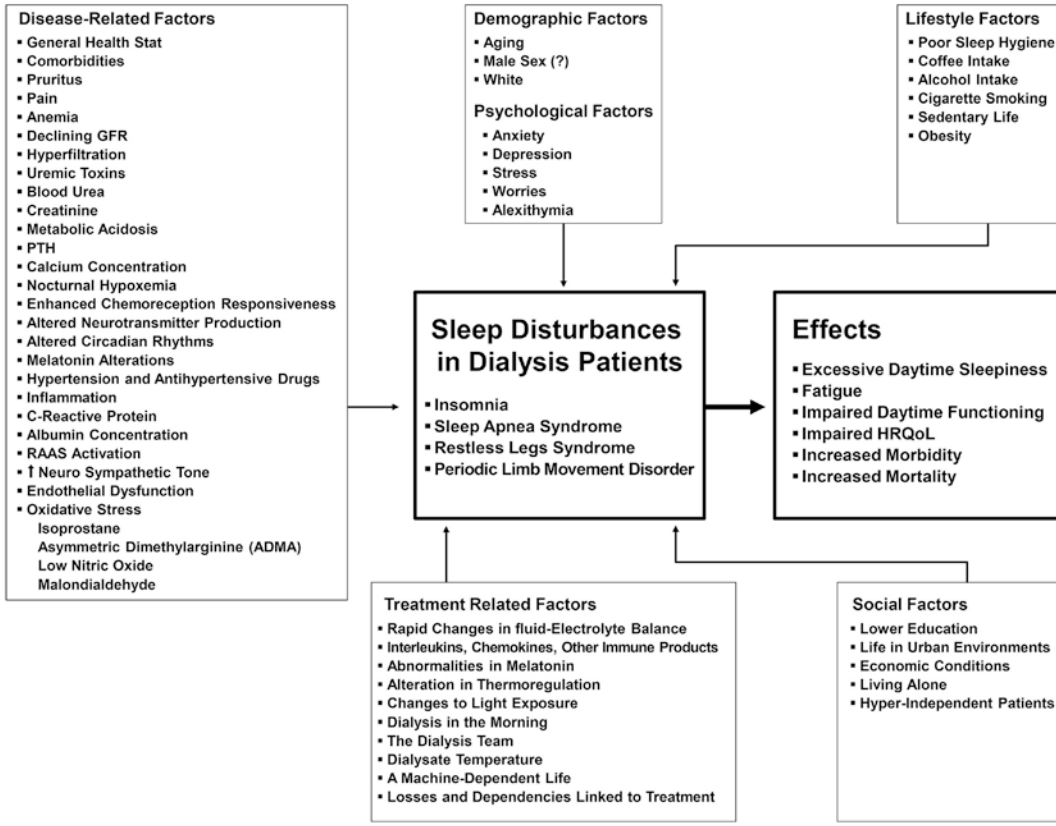

Fig. 27.9 Putative determinants of sleep disorders in CKD. Modified from Parker KP [52] and De Santo RM et al. [13, 22]

27.10 Mild Cognitive Impairment and Sleep Disorders in CKD

27.10.1 Mild Cognitive Impairment

The term mild cognitive impairment (MCI) was introduced to medical literature in 1988 by Reisberg et al. [53], and it took 11 years to become a very important syndrome that it now is [54]. According to De Carli it can be considered the transition phase between healthy cognitive aging and dementia [55] and is a syndrome defined by a "cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life" [56]. It affects attention, memory, language skills, visuospatial performance, executive functions, and inhibitory control.

As soon as dialysis became a widespread procedure worldwide, intellectual and emotional patterns were found to be impaired in hemodialyzed patients [57]. Dementia incidence rates (DIR) were progressively higher with lower eGFR: from 6.56/1000 person-years in persons with eGFR 90–104 mL/min to 30.28/1000 person-years in those with eGFR <30 mL/min. As many as 10% of dementia cases could be attributed to eGFR <60 mL/min/1.73m^2, a proportion higher than that attributed to other dementia risk factors such as cardiovascular disease and diabetes [58]. However, in the last few years MCI and dementia became the most important topic related to quality of life in CKD patients including those in ESKD, those receiving a kidney transplantation or just presenting with albuminuria.

Albuminuria associated with worse score of executive functioning and increased white matter hyperdensity volumes in older persons [59]. Albuminuria is a risk factor for MCI and dementia as demonstrated by cross-sectional and long-term studies. It is speculated that kidney and brain have in common microvascular similarities that render them prone to endothelial dysfunction driven by oxidative stress and inflammation. In a recent review [60] it was stressed that although the exact substrate of MCI and dementia is still under investigation, available experimental data indicate that elevated albuminuria and low glomerular filtration rate are associated with significant neuroanatomical declines in hippocampal function and gray matter volume. Thus, albuminuria may be critical in the development of MCI and its progression to dementia [60].

Furthermore, low eGFR as well as albuminuria has been associated with decreased volumes of hippocampus and gray matter and decreased cortical thickness in human and experimental studies in mouse. The association between MCI may be driven by elevated systolic blood pressure, increased arterial stiffness, older age, oxidative stress [61, 62].

The high prevalence of MCI (Table 27.4) is already present in the early stage of CKD (stage 3) and is nearly doubled (62%) in advanced stages of CKD (stage 4 and 5) [61–65]. In patients treated with hemodialysis, few have normal cognitive function [61, 62, 66]. Peritoneal dialysis seems to offer some advantages [61, 62, 67, 68]. Even kidney transplantation, the best treatment in terms of quality and quantity of life and costs for the society does not normalize cognition scores [69] but improves it significantly. The prevalence of cognitive impairment was 58.0%. Multivariable linear regression demonstrated that older age, male sex, and absence of diabetes were associated with lower Montreal Cognitive Assessment (MoCA) scores. Estimated GFR was not associated with level of cognition. The logistic regression analysis confirmed the association of older age with cognitive impairment. In other studies, transplanted patients did not score better than on HD patients [69–71].

It should be added that patients with sleep disordered breathing (SDB) have poor cognition scores for global cognitive function, immediate and delayed verbal memory, working memory, attention, and psychomotor speed. However, it has been shown that improvements are obtained with CPAP [68]. Table 27.1 also shows that in all categories the risk of dementia in MCI-CKD was very much higher than in the general population.

Finally, it should be stressed that few studies that have explored cognitive function in Stage 1 and 2 in elderly CKD have disclosed that these stages are not asymptomatic and are associated with significant impairment of speed of processing and attention [69].

In recent but classical study, Viggiano et al. [61, 62] reviewed the morphological, functional, and pathogenetic features of MCI-CKD. In MCI-CKD tractography disclosed internal capsule demyelination, whereas MRI disclosed deep white matter demyelination, EEG showed impaired cortical synchronization at delta frequencies. They also disclosed that animal models of CKD with MCI show sleep disorders but normal cerebral architecture, however difference exists between MCI in the general population and

Table 27.4 Data point out the burden of MCI and dementia in chronic kidney disease. Mainly based on recent but classical works of D Viggiano et al. [61, 62]

Population	Prevalence of MCI	Prevalence of dementia	References
Healthy	11–26%	13%	[61, 62]
Early CKD, stage 3	15.6–31%	Unknown	[61, 62]
Late CKD, stage 4, 5	25–62%	Unknown	[61–65]
Hemodialysis	26–73.6%, 87.7%	8–37%	[61, 62, 66]
Peritoneal dialysis	28.6–68.6%	4–33%	[61, 62, 67, 68]
Transplantation	58%	7–22%	[61, 62, 69]

MCI-CKD, the latter identified as a distinct "renocerebral syndrome" not overlapping with the former.

Two hypotheses have been proposed to explain MCI and dementia in CKD [70]. A vascular hypothesis based on cardiovascular risk factors (diabetes mellitus, hypertension, cerebrovascular disease) and a neurodegenerative hypothesis based on uremic toxins. Probably the explanation is in a combination of both. Risks include general factors, cardiometabolic factors, neuropsychiatric comorbidities, impairment of the glymphatic system, the uremic factors including toxins, genetic factors, factors causing endothelial dysfunction, neuroinflammation, neurodegeneration, dialysis driven factors causing cerebral edema or associated with drop in mean blood pressure and cerebrovascular flows (Table 27.5).

Diagnosis is based on polysomnography (EEG for characterizing NREM and REM sleep, electrooculography, electromyography, respiratory patterns, pulse oximetry) and by respiratory cannula on the assessment of sleep apnea. The use of an accelerometer allows assessment of hands tremor.

Actigraphy allows monitoring of motor activity and posture. Examination of retinal vessels might be of immediate clinical value for sleepiness but there is no agreement on its value.

A lot can be learned by assessing KDQoL-CF (as screening), Pittsburgh Sleep Quality Index, the Montreal Cognitive Assessment (MoCa) that has a sensitivity of 80–100% and a specificity of 50–76% and by single leg standing Time (SLST).

Sequential MRI and spectroscopy of the left hippocampal area, brain tractography (diffusion tensor imaging) to investigate demyelination of

Table 27.5 Risk factors and molecular mechanisms for MCI and dementia in CKD. Modified from DM Kelly, M Rothwell [71], and D Viggiano et al. [61, 62]

A. Risk factors for MCI and dementia
General factors
Advanced age
Education
Occupational attainment
Smoking
Cardiometabolic risk factors
Hypertension
Stroke
Small vessel disease
Diabetes mellitus
Obesity
Neuropsychiatric comorbidities
Depression
Sleep disorders
Beta-amyloid deposition
Genetic factors
Dialysis factors
1 Toxins causing brain edema
(a)Urea
(b) Newly generated osmolytes
2 Altered cerebral blood flow
(a) Reduced cerebral blood flow with "cerebral stunning"
(b) Drop in mean arterial pressure

Table 27.5 (continued)

B. Mechanisms for MCI and dementia
Reduction of brain extracellular spaces (glymphatic system) mediated by
Diabetes
Hypertension
Sleep disorders
Endothelial dysfunction mediated by
Asymmetric dimethyl arginine (ADMA)
FGF23
Hippuric acid
Neuropeptide Y
Neuroinflammation mediated by
CRP
Fibrinogen
IL-6
IL-1ℓ
TNF
Indoxyl sulfate
P-cresyl sulfate
Neurodegeneration mediated by
IL-1ℓ
Summary of uremic (neuro)toxins possibly involved in MCI
Uric acid
Phosphate
PTH
Homocysteine
Indole-3-acetic acid
Asymmetric dimethyl arginine (ADMA)
FGF23
Hippuric acid
Neuropeptide Y
CRP
Fibrinogen
IL-6
IL-1ℓ
TNF
Indoxyl sulfate
P-cresyl sulfate

Box 27.1 Mild Cognitive Impairment (MCI) in CKD

- MCI-CKD is a distinct "renocerebral" entity not overlapping with MCI in general population [61, 62, 71].
- Tractography discloses internal capsule demyelination, MRI deep white matter demyelination, EEG impaired cortical synchronization at delta frequencies.
- The patient is not aware of her/his MCI and may be reported by caregivers/family or may be suspected when a patient becomes confused with prescriptions and misses dates for consultation or therapies.
- MCI-CKD may be a cause of exclusion from unattended dialysis programs.
- Explore QoL indices, assess the Pittsburgh Sleep Quality Index, explore the Montreal Cognitive Assessment, workup the existence of sleep disorders by Polysomnography, explore the neurotoxin status and biomarkers of inflammation.
- No specific therapy exists but all suggestions for optimization of usual therapy should be followed up.

the internal capsule, CT/MRI imaging of white matter, fMRI for cerebral blood flow may help to follow up MCI starting with CKD stage 3.

Nephrologists should know that 90% of CKD patients are not aware of their MCI and a lot may be learned through patient's own narratives and by reports of spouses, family members, and caregivers. They should also be aware that MCI may interfere with taking medicines and may cause inability for programs of unattended dialysis (Box 27.1).

27.10.2 Cognitive Dysfunction and Sleep Disorders in CKD

It is now evident that the prevalence of sleep disorders and cognitive impairment is very high in CKD patients needing dialysis or not and affects their lives. The prevalence of cognitive impairment is 10–40% in CKD, 70–87% in HD patients, and 27–67% in peritoneal dialysis. The association of sleep disorders and cognitive impairment represents a further burden. Cognitive impairment (verbal memory, working memory, attention) has been associated with a sleep disordered breathing in CKD stages 4–5. In addition, memory problems have been disclosed in HD patients in whom cognitive impairments predict mortality. In a prospective study—not utilizing polysomnography—in PD patients [20], the prevalence of sleep disorders was 65.5% and that of possible narcolepsy 4.7%. Sleepwalking and nightmares in the same cohort were identified as risk factors for impaired delayed memory.

Presently cognitive impairment and sleep disorders may be seen as manifestations of brain dysfunction driven by an incompletely mosaic of factors that includes anemia, uremic toxins, PTH, inflammation, malnutrition, instable hemodynamics, and derangements in fluid volume and electrolytes. The structural equivalents are represented by lesions of hippocampus, small-vessels ischemic brain disease and deep and white matter demyelination.

Older patients or those with cerebrovascular lesion should be screened using the Montreal Cognitive Assessment to explore executive functions. If cognitive impairment is present, more specialized tests should be used under guidance of a geriatrist or a neurologist and/or a specialist of imaging [71]. For accurate evaluation refer to strategies employed in research [71–73]. In mild-moderate CKD with albuminuria, using angiotensin converting enzyme inhibitors and angiotensin receptor blockers and achieving strict blood pressure control are recommended. In dialyzed patients cooling dialysate temperature and more efficient removal of small molecules have not provided benefits. New experimental strategies are coming of age [72].

Physicians must be aware that [61, 62, 71]:

- No therapy exists.
- Treating the cardiovascular risks is mandatory but not enough.
- Mediterranean diet provides unproved benefits although people on Mediterranean diet score better on cognitive function.

- Supplementation of vitamin B, folate, vitamin D, vitamin E is ineffective but necessary if their levels are below normal.
- Use of polyunsaturated fatty acids did not meet expectation.
- Hemodialysis is ineffective.
- Peritoneal dialysis is probably better, transplantation improves the outcome.
- Obesity and isolation should be reduced if present.
- Physical activity should be optimized, and cognitive training prescribed.
- CPAP is mandatory in the presence of sleep apnea.
- Control of hyperparathyroidism is crucial both for sleep improvement and the toxin burden.
- Anti-inflammatory drugs have great promise (use of colchicine improved MCI).
- Use of plasma exchange + albumin supplementation reduced dementia progression by 61% in 1 year.
- Use of everolimus—a protein kinase inhibitor of m-TOR—may protect the glymphatic functions.
- Use of erythropoietin is certainly beneficial.

Transplantation is a great option since it improves the cognitive impairment that becomes evident within 1 year and is stable over the years. The improvement is due to restoration of kidney function that also favors optimal clearance of drugs and avoids the stress of dialysis and its associated hemodynamic changes and the risk of coagulation. In patients with cognitive impairment physicians should favor more frequent medical control and family shared decision, avoid polypharmacy and sedative medications, improve sleep hygiene, treat depression, increase social support, favor mental stimulation and exercise [70].

27.11 Impairment of the Melatonin Clock in CKD

Among the many factors associated with the disordered sleep in CKD, melatonin has been studied extensively also because of its circadian rhythm and the efficacy of its use in clinical practice.

Melatonin, a pineal hormone, is a determinant of the sleep-wake rhythm. It is nearly undetectable in blood during daytime and starts rising in the evening and the secretion peaks at night. In CKD, Koch et al. [74] were the first to show a correlation between impaired GFR and decrease in melatonin rhythm and production (Fig. 27.10) that is blunted at night.

These authors promoted the use of melatonin at bedtime (3 mg) that is well tolerated, free of untoward effects, and effective in improving the disordered sleep. Melatonin improves sleep quality by reducing sleep onset latency, increasing total sleep time and sleep efficiency, and reducing sleep fragmentation that in turn results in a more refreshing sleep. However, the favorable effect was not confirmed after a long-lasting use (3 years). But there might be reasons for this and some have been reviewed by Russcher et al. [2] who suggested melatonin accumulation in CKD as well as a possible downregulation of the melatonin receptor.

There are many reasons for utilizing melatonin in CKD: (1) the antioxidant properties, (2) the anti-inflammatory action, (3) the improvement of the dipping profile in essential hypertension, (4) the excessive daytime sleepiness in uremia, (5) the impairment of the beta-adrenergic system, (6) anemia, (7) the lack of erythropoietin [74, 75].

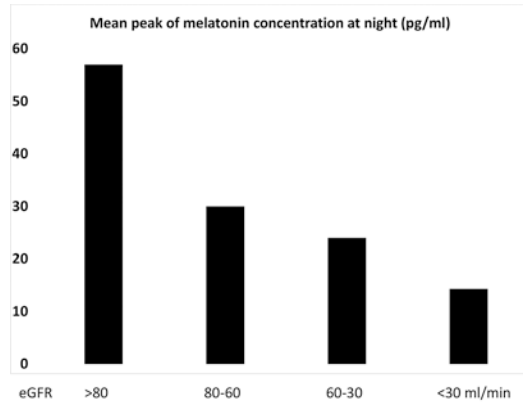

Fig. 27.10 Peak melatonin concentration at night. Modified from Koch BC et al. [74]

27.12 Management of Sleep Disorders in CKD

Treatment of pruritus and pain is preliminary. Pruritus affects up to 84% of dialysis patients but also patients with CKD. It may be continuous, discontinuous, may last months or years, and affect symmetrical areas of the body especially at night. It shall be treated topically by hydrating skin 2–3 times a day. Phototherapy (Type B UV light) has been used with success, but it did not pass the test of a controlled trial. Gabapentin (100 mg/after dialysis) has achieved good results. Promising results have achieved with oral and intravenous opioids and sertraline. There is no place for antihistamines since the central transmission of itch occurs via a non-histaminergic path [76].

27.12.1 Insomnia

Pharmacological approaches are the first line paying strong attention to sleep hygiene that reflects healthy habits, behaviors and environmental factors that promote improved sleep: going to bed just to sleep, avoiding caffeine, and reading in bed. If insomnia is chronic, cognitive behavioral therapy (CBT-I) is added.

Benzodiazepine receptor agonist of the non-benzodiazepine class is used for insomnia. They are known as the Z drugs (eszopiclone, zaleplon, zolpidem, zopiclone) that usually do not require adjustment for kidney failure. Treatment shall start with low dose and titrated monitoring adverse effects. Zaleplon has been investigated in a randomized double-blind placebo controlled study with amelioration of sleep quality [76].

Melatonin (3 mg before sleep) improved the quality of sleep in dialysis patients in short-term and long-term studies. Cooling the dialysate reduces sleep latency. More frequent hemodialysis improves sleep apnea [76].

27.12.2 Restless Leg Syndrome

Lifestyle changes include avoiding caffeine, nicotine, and alcohol, promoting exercise and resistance training. Pharmacological treatment starts with drugs affecting the dopamine pathways. Levodopa has been shown to be effective in reducing RLS but has been without effect on sleep quality and quantity. The non-ergoline dopamine receptor agonists ropinirole, pramipexole, and rotigotine (transdermal) have been used with success in short-term studies although associated with fatigue, lightheadedness, and nausea and frequently associated with augmentation (worsening of symptoms). Ropinirole has been proved effective in decreasing RLS and ameliorating sleep quality. Pramipexole also reduced the severity of RLS without adverse effects. Identical benefits have been achieved by transdermal rotigotine [76].

Second line drugs for RLS are gabapentinoids. Gabapentin (inhibitor of glutamate release) given at a dose of 100–300 mg after dialysis thrice a week reduced RLS severity, ameliorated general health, and reduced pain and was more effective than levodopa and significantly reduced pruritus [76]. Opioids too are coming of age. There are reasons to give intravenous iron that have not been confirmed. Aerobic exercise associated with low dose of the dopamine agonists ropinirole during dialysis gave very favorable results in reducing RLS [76].

27.12.3 Sleep Apnea

CPAP is the cost-effective mainstay of medical treatment for OSA [77]. It holds the potential for preventing and treating OSA in CKD.

Six months CPAP in obese patients with OSAS significantly improved eGFR (+20 mL/min/1.73 m^2) from 84 ± 13.1 mL min to 104.2 ± 19.0 mL/min ($p < 0.00001$). In addition, AHI was the most important independent predictor of eGFR [78]. However, a year of CPAP failed to improve CKD patients with eGFR at 38.4 + 1.5 mL/min × 1.73m^2, but the study provided some evidence that CPAP slowed the decline in eGFR in patients with a lower risk of CKD progression [3]. Thus, many studies are ongoing to address its effectiveness.

CPAP has been used successfully in patients with sleep apnea on hemodialysis since 1991, has

been effective in peritoneal dialysis, and has been recognized as an effective method [79] and recognized "the first line treatment in HD patients with OSA" [80, 81].

27.13 Assessing Effectiveness of Interventions

In a study aiming to assess the effectiveness of interventions to improve sleep quality in adults and children with CKD, or with ESKD treated with dialysis, or with transplantation [82], the real value of the whole armamentarium at our disposal was analyzed. Table 27.6 lists 15 intervention procedures utilized in clinical practice to improve CKD-related sleep disorders.

For relaxation there is very little evidence for effects on sleep quality and anxiety, depression, fatigue, and evidence for quality of life. Exercise improved sleep quality (very low certainty evidence), decreased fatigue and depressive symptoms according to Zung Self-Rating Depression Scale (moderate certainty evidence). Acupressure improved sleep latency scale, sleep efficiency and fatigue (moderate certainty evidence), total sleep time (low certainty evidence), sleep quality and depression (very low certainty evidence). Cognitive behavioral therapy improved sleep quality (very low certainty evidence). Single studies showed improved total sleep time, sleep efficiency, anxiety, quality of life. Effects on depressive symptoms were also observed (moderate certainty evidence). Sleep hygiene education improved sleep latency (very low certainty evidence), total sleep time, sleep efficiency, and sleep disturbance (moderate certainty evidence) but had no effect on fatigue, pain, and quality of life.

Table 27.6 Interventions for improving sleep quality in CKD [82]

1. Relaxation, progressive muscle relaxation, nurse-led breathing, mindfulness, Benson relaxation technique
2. Exercise (aerobic exercise, exercise during hemodialysis, yoga-based exercise, resistance exercise)
3. Acupressure
4. Cognitive behavioral therapy
5. Sleep hygiene education
6. Telephone support
7. Reflexology
8. Music at bedtime and during hemodialysis
9. Massage
10. Light therapy
11. Aromatherapy
12. Dopaminergic agonists (rotigotine and ropinirole)
13. Gabapentin
14. Melatonin
15. Dialytic modalities (CAPD, APD, nocturnal dialysis)

Telephone support improved [83] sleep quality, but had no effect on fatigue, pain, and quality of life. Reflexology caused slight improvement of sleep quality (moderate certainty evidence). However, Unai, Balci, and Akpinar showed improvement of fatigue [84]. Music during hemodialysis [85] improved sleep quality, total sleep time, and sleep disturbance. Music at bedtime outperformed music during hemodialysis at improving sleep latency, total sleep time, and sleep disturbance. Abdominal massage improved sleep quality, pain, and quality of life. Light therapy improved sleep latency but had no effect on sleep efficiency or depressive symptoms, whereas aromatherapy improved sleep quality, total sleep time, sleep efficiency, and sleep disturbance [86].

Rotigotine and ropinirole were also studied. When giving Rotigotine to patients requiring hemodialysis, Dauvilliers (2016) found improvement of total sleep time and sleep efficiency. Rotigotine also improved periodic limb movements and RLS symptoms [87]. Ropinirole and levodopa were given to 11 patients on maintenance hemodialysis with RLS in the course of an open randomized control trial. Levodopa improved RLS scores by 33%. Ropinirole was superior since it ameliorated RLS scores by 73.5% [88].

Gabapentin was compared with dopaminergic agonist levodopa. Improvement was observed for sleep latency and sleep disturbance with gabapentin. Melatonin for 30 weeks improved sleep quality [89].

No difference in sleep quality was seen between patients treated with continuous ambulatory peritoneal dialysis and with automated peritoneal dialysis. However, nocturnal dialysis is associated with poor sleep quality.

The study was unable to find suitable data for children and to provide evidence for adverse effects of therapies.

Before You Finish: Practice Pearls for the Clinician

- Sleep disorders in CKD are amenable to cures.
- Optimal blood pressure control must be achieved.
- Sleep hygiene should be optimized.
- Pharmacological therapy is feasible for insomnia and restless legs syndrome.
- Melatonin has a role in the therapy of insomnia, but in chronic treatments can lose efficacy.
- Compressive stockings may reduce fluid rostral movements at night.
- CPAP is the mainstay for OSA.
- Nocturnal hemodialysis and automated cyclic peritoneal dialysis are feasible options.
- Cognitive behavioral therapy is coming of age.

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28 Neuropathy and Other Neurological Problems in Chronic Kidney Disease

Ria Arnold and Arun V. Krishnan

Before You Start: Facts you Need to Know

- Neurological complications are highly prevalent in CKD and are a major contributor to patient morbidity and mortality risk.
- The uremic state can potentially affect all levels of the nervous system, from central nervous system disorders such as encephalopathy and cognitive dysfunction, to peripheral disorders such as myopathy, autonomic and peripheral neuropathies.
- Neurological complications often become clinically apparent with severe kidney disease; however, detection and management of these conditions in earlier stages of CKD may reduce their impact at later stages.

28.1 Neuropathy in CKD

Neurological complications are highly prevalent with CKD. The systemic nature of uremia causes a variety of neurological disorders potentially affecting all levels of the nervous system (Fig. 28.1). These may include central nervous system disorders such as cognitive dysfunction and encephalopathy, to peripheral disorders such as myopathy, autonomic and peripheral neuropathies (Table 28.1). These complications have profound quality of life implications and increased mortality is also a significant concern, particularly where there is severe encephalopathy causing coma, cardiac autonomic neuropathy predisposing to sudden cardiac death or advanced peripheral neuropathy, which may lead to foot lesions, ulceration, and amputation. Less common causes of CKD may also affect the central and/or peripheral nervous system independent of uremia such as amyloidosis, systemic lupus erythematosus, hepatic failure, Wilson's disease, and Fabry disease. Recent studies have demonstrated high prevalence of chronic neurological disorders such as peripheral neuropathy and cognitive impairment in stages 3 and 4 CKD highlighting the opportunity for early detection and management of these conditions in earlier stages of CKD which may reduce their impact at later stages.

28.1.1 Peripheral Neuropathy

Definition: Peripheral neuropathy, also known as uremic neuropathy, is the most common neurological complication of CKD and a significant cause of morbidity. This condition typically pres-

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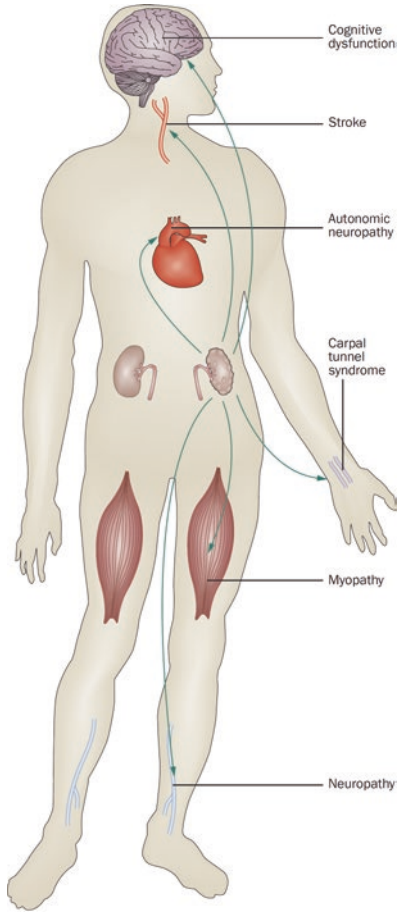

Fig. 28.1 The spectrum of neurological complications in chronic kidney disease (Reprinted from Krishnan and Kiernan [9])

ents as a distal symmetric polyneuropathy with damage to distal portions of the longest nerves first (toes and feet) with initial preferential involvement of the sensory axons and progressive 'dying back' of peripheral nerves.

Prevalence: Recent studies in patients with stages 3–4 CKD have demonstrated a prevalence of neuropathy of ~70% [1]. The increasing incidence of diabetic nephropathy introduces a highly susceptible patient cohort that is likely to have pre-existing neuropathy. Recent evidence demonstrates that this results in more severe neuropathy that progresses more rapidly than people with either diabetes or CKD alone [2].

Clinical Presentation: Peripheral neuropathy typically manifests as a slowly progressive symmetrical length-dependent neuropathy of insidious onset. There is preferential involvement of distal nerves and more severe involvement of the lower limbs than upper limbs [3]. Clinical examination in early stages reveals symptoms and signs confined to the lower limbs, including distal sensory loss to pinprick and vibration and reduced, or absent, ankle deep tendon reflexes [4]. With more severe disease, sensory involvement progresses proximally, and upper limb involvement may occur in a 'stocking-and-glove' distribution. In advanced cases motor nerve involvement can develop resulting in muscle atrophy and weakness, which is again most prominent distally (Fig. 28.2). Assessment of power in intrinsic foot muscles, such as extension of the big toe, may provide clues to early motor involvement. While damage to large motor and sensory fibres is typical of uremic neuropathy, small fibre neuropathy may also occur. In diabetic patients, small fibre symptoms may dominate with patients experiencing severe burning and shooting pain and altered temperature and pain perception [4].

Diagnostic Investigations: Clinical diagnosis of uremic neuropathy requires exclusion of alternate causes and types of peripheral neuropathy. The presence of glucose dysmetabolism is a critical factor given the likelihood of pre-existing neuropathy and greater severity of neuropathy seen in people with diabetic-CKD. Causes such as vitamin B12 deficiency, prolonged excessive alcohol use, or hereditary neuropathies are also important differential diagnoses.

Connective tissue disorders may be associated with a rapidly progressive neuropathy due to peripheral nerve vasculitis. Other causes of rapidly progressive neuropathy in CKD include inflammatory demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy, which have been described in the context of CKD due to nephropathy [5]. Unlike typical length-dependent uremic neuropathy which presents with sensory features, inflammatory neuropathies are often characterised by marked motor involvement even at the onset of the disease. Demyelinating neuropathies require early recognition, as prompt treatment

Table 28.1 Neurological disorders in patients with CKD

Neurological disorder	Prevalence	Clinical features	Management
Uremic neuropathy	~70% of patients with stage 3–4 CKD ~90% of patients on dialysis	Sensory loss, weakness, and wasting, maximal distally; absence of ankle jerks; lower limbs more severely affected than upper limbs	Neuropathic pain therapy. Other options: Vitamin supplementation; potassium restriction; glycaemic control, erythropoietin; exercise programs
Autonomic neuropathy	50–60% of patients with CKD	Impotence; postural hypotension; cardiac arrhythmia; symptomatic intradialytic hypotension	Sildenafil to treat impotence Midodrine to treat severe orthostatic hypotension
Cognitive dysfunction	27–62% of patients with stage 1–4 CKD	Impairments in cognitive and behavioural executive function, action speed, language, and episodic memory	Management of traditional risk factors renal transplantation erythropoietin
Encephalopathy	–	Sensorial clouding, apathy, irritability; confusion, disorientation, coma motor disturbances, tremor, asterixis, myoclonus	Dialysis seizure treatment: Phenytoin, sodium valproate, or carbamazepine
Carpal tunnel syndrome	5–30% of patients with CKD	Hand paraesthesia and numbness; weak thumb abduction	Splinting; local steroid injection; surgical decompression
Myopathy	~50% of patients with CKD	Proximal weakness of the lower limbs	Exercise programs; adequate nutrition, erythropoietin; l-carnitine

CKD chronic kidney disease
Source: Adapted with permission from Krishnan and Kiernan [9] Macmillan Publishers limited

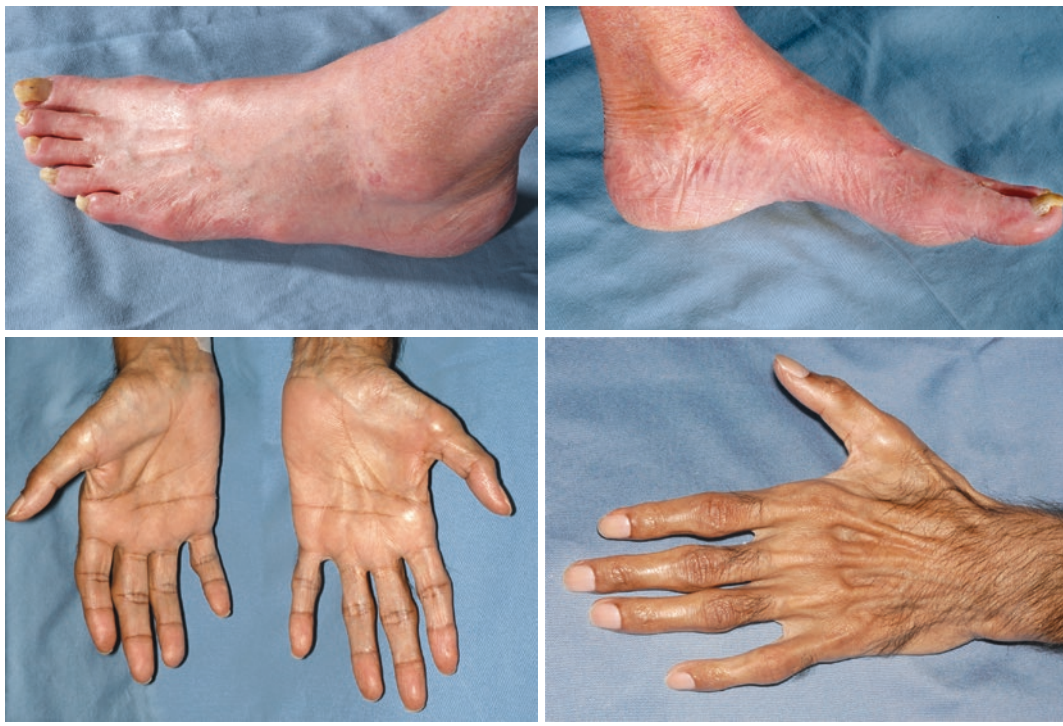

Fig. 28.2 Wasting of the intrinsic distal muscles in two patients with uremic neuropathy. In addition to weakness, the patients complained of numbness and had impaired joint position sense (Reprinted from Krishnan [3])

with immunotherapy may lead to clinical improvement.

Nerve conduction studies are the gold standard for the diagnosis of neuropathy. Nerve conduction studies in CKD patients with neuropathy reveal reduced sensory amplitudes and to a lesser extent motor amplitudes with relative preservation of motor and sensory conduction velocities, findings consistent with a generalised neuropathy of the axonal type (Fig. 28.3). In contrast to axonal neuropathies, demyelinating neuropathies demonstrate significant reductions in nerve conduction velocities.

Treatment Approaches: Treatment of peripheral neuropathy is determined by the underlying cause as well as pain management as required. However, disease modifying pharmacological interventions remain elusive. Cumulative evidence in CKD highlights the importance of a multidisciplinary approach for long-term risk reduction and management with nutrition, lifestyle factors, and foot health. Recent studies in CKD have demonstrated that hyperkalaemia has a detrimental effect on nerve function and a 2 year randomised controlled trial of potassium restriction in stage 3–4 CKD showed a significant positive effect on neuropathy and physical function, highlighting the importance of maintaining normokalaemia in CKD patients [6]. For those with diabetes, glycaemic control remains an important preventative strategy which is more effective in type 1 diabetes than type 2 diabetes [7]. In the absence of disease modifying pharmacological interventions, lifestyle interventions including reducing body weight and increasing physical activity levels are increasingly advised given their association with improved neuropathy and pain outcomes. Attention to foot care is an integral part of managing neuropathy in both CKD and diabetes. Reducing the risk foot ulcers and infective complications requires assessment of predisposing factors such as routine foot checks, correction of ill-fitting shoes, and education which may require the involvement of a podiatrist [8].

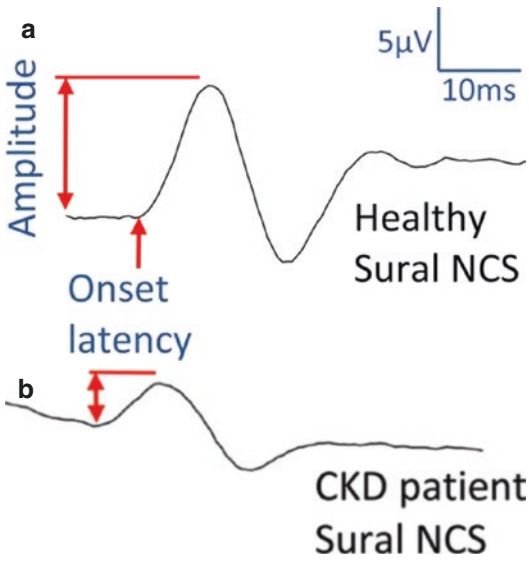

Fig. 28.3 Sensory nerve conduction results of the Sural nerve, a lower limb sensory nerve, for a healthy control subject (**a**) and a chronic kidney disease patient (**b**). Results in the chronic kidney disease patient demonstrate a reduction in amplitude of the sensory nerve amplitude consistent with a sensory neuropathy

Painful neuropathy may be managed with use of membrane-stabilising neuropathic pain treatments, including a range of tricyclic antidepressants (e.g. amitriptyline) and anticonvulsants (e.g. sodium valproate, carbamazepine, pregabalin, and gabapentin) [4]. However, these medications have a constellation of potential side-effects and anticonvulsants typically require dosing restrictions for patients with CKD [4]. Tricyclic antidepressants are often used as first line treatment for painful neuropathic symptoms due to ease of once-daily dosing which may help improve compliance [4]. Treatment with these agents may be poorly tolerated by older patients and should therefore be used with caution in patients with cardiac arrhythmias, congestive heart failure, orthostatic hypotension, and urinary retention [4]. Alternative treatments include anticonvulsant medications such as pregabalin or gabapentin although both have dosing restrictions in patient according to creatinine clearance [4]. Symptoms of neuropathic pain in CKD may also be reduced by vitamin supplementation with pyridoxine and methylcobalamin [9].

Demyelinating neuropathies are typically treated with intravenous immunoglobulin; however, the risk of nephrotoxicity with this treatment must be carefully considered in patients who have residual kidney function [3]. Potential alternative treatments include plasma exchange or corticosteroid treatment.

In advanced CKD the commencement of dialysis has little effect on peripheral neuropathy and long-term studies have revealed progression continues over 4 years with no differential effect of high-flux haemodialysis compared to hemodiafiltration [10]. Renal transplantation comes with a range of post-transplant conditions such as new onset diabetes after transplant (NODAT) and immunosuppressive regimens including calcineurin inhibitors may induce or worsen existing peripheral neuropathy, emphasising the need for prevention [11].

28.1.2 Autonomic Neuropathy

Definition: Autonomic neuropathy is another highly prevalent complication of CKD with potentially life-threatening consequences such as cardiac arrhythmia, silent myocardial ischemia, and sudden cardiac death [4]. It also encompasses a range of conditions that have a debilitating impact on quality of life such as altered thermoregulation, digestion, bowel, bladder and sexual dysfunction as well as a complex link to renal mechanisms of blood pressure control that may exacerbate renal decline [12]. Broadly, autonomic neuropathy is reported to occur in approximately 60% of patients with stage 5 CKD and studies of non-dialysis diabetic-CKD have demonstrated prevalence rates of 20–80% [13]. However, few studies have systematically evaluated prevalence in early stages of CKD and thus prevalence in contemporary cohorts is unclear [14].

Clinical Presentation: The most common symptom of autonomic neuropathy is impotence which develops in the majority (~70%) of male patients [15]. Other clinical manifestations may include bladder and bowel dysfunction and evidence of altered sudomotor function manifesting as dry skin and impaired sweating. Cardiovascular autonomic dysfunction may present with orthostatic intolerance, reduced exercise tolerance, and palpitations or loss of consciousness due to cardiac arrhythmia [4].

Diagnostic Investigations: Clinical assessment of autonomic function may be undertaken using a variety of techniques such as assessment of cardiac and pupillary reflexes, sweating, and blood pressure control. Sexual dysfunction is self-reported and generally under-recognised [15]. Assessment of cardiac autonomic neuropathy requires a battery of tests including heart rate variability, Valsalva manoeuvre, and changes in heart rate with standing [4].

Treatment approaches: Erectile dysfunction responds to treatment with sildenafil and is well tolerated [15]. The optimal management for cardiac autonomic neuropathy remains unclear. While some evidence has suggested that angiotensin-converting enzyme inhibitors may be helpful in reducing heart rate variability, others have demonstrated either no benefit or a potentially deleterious effect of these medications [4]. The use of beta-blockers in CKD patients has been limited due to concerns for potentially higher rates of adverse effects, including hyperkalaemia and glycaemic abnormalities [4]. However, recent studies have shown that beta-blockers may provide cardiovascular protection in patients with advanced CKD. The combined alpha/beta-blocker carvedilol is metabolically neutral and may provide the beneficial effects of beta-blockade on cardiovascular events with a better side-effect profile [4]. In patients with diabetic-CKD, adequate glycaemic control remains an important step in preventing the progression of both autonomic and peripheral neuropathy [4]. With instances of severe orthostatic hypotension resulting from autonomic dysfunction, treatment with midodrine may improve symptoms. Current recommendations in dialysis for those experiencing intradialytic hypotension, however, suggest it should be used as a last resort [16].

28.2 Carpal Tunnel Syndrome

Definition and Clinical Importance: Carpal tunnel syndrome (CTS) is the result of compression of the median nerve at the wrist. CTS is the most common mononeuropathy in CKD affecting up to 30% of dialysis patients [3]. Patients with CTS experience sensory symptoms in the hands including paraesthesia, numbness, and pain with a characteristic feature of nocturnal exacerbation [3]. The prevalence of CTS in CKD can be attributed to various factors. The presence of fistulae has been implicated in the development of CTS related to higher prevalence limbs with fistulae ~30% compared to ~12% on the contralateral side [17]. The presence of amyloidosis or poor clearance of β2 microglobulin may lead to localised deposition of amyloid in soft tissues leading to compression. Symptoms are often more severe in the dominant hand and may involve any part of the hand, even extending to more proximal regions of the arm in some cases. Longstanding disease can result in motor involvement causing weakness and wasting of muscles innervated by the median nerve, particularly abductor pollicis brevis.

Diagnosis: Diagnosis of CTS is made on clinical grounds and exclusion of other pathologies such as cervical spondylosis or generalised neuropathy. Neurological examination may demonstrate reduction in sensation in the median nerve territory or weakness of median-innervated muscles. Phalen's test may also aid in diagnosis. This test is conducted by placing the wrist into end-of-range palmar flexion for 1 min and aims to increase intra-tunnel pressure and thereby reproduce symptoms [3].

Management: Most patients with CTS should initially receive a trial of conservative treatment, with splinting of the wrist or a subcutaneous corticosteroid injection at the wrist. Injection of steroid should be avoided where CTS develops in the fistula arm. In patients who are refractory to conservative treatment or in those in whom there is significant loss of muscle power or severe abnormalities of median nerve conduction, referral to a hand surgeon may be appropriate for endoscopic decompression of the nerve. While clinical improvement typically occurs with surgical decompression, outcomes are less favourable if the patient had fixed motor and sensory deficits prior to surgery. In cases where amyloid deposition is suspected, biopsy specimens from the flexor retinaculum should be obtained during surgery.

28.3 Myopathy

Definition and Clinical Importance: Uremic myopathy is characterised by proximal muscle weakness and wasting, predominantly affecting the lower limbs. Reduced exercise capacity, limited endurance, and motor fatigue are also prominent features resulting in substantial functional limitations and morbidity. Prevalence data is lacking in early CKD where it is considered rare and historical evidence suggest it affects ~50% of stage 5 CKD patients [18]. The pathophysiology remains unclear though uremic myopathy typically appears with glomerular filtration rates less than 25 mL/min and progression tends to parallel decline of kidney function [19]. Possible aetiologies include hyperparathyroidism, metabolic bone disease with vitamin D deficiency, impaired potassium regulation, accumulation of uremic toxins, carnitine deficiency, and muscle mitochondrial alterations [9]. A clear association between malnutrition, specifically protein deficiency, and uremic myopathy has been demonstrated in elderly patients [19] . Furthermore, rates of uremic myopathy are higher in patients with diabetic-CKD leading to a suggested role for insulin resistance in the development of this condition.

Diagnosis: The diagnosis of uremic myopathy is based on the demonstration of weakness in proximal hip girdle muscles [19]. There are no specific tests for uremic myopathy and electromyography and creatine kinase levels are typically normal. Muscle biopsy reveals non-specific features such as type II fibre atrophy and fibre splitting, although the procedure is not undertaken routinely due to its invasive nature and should be considered only after neurological referral.

Management: While no specific treatment exists for uremic myopathy, management requires

treatment of potential contributing factors. Adequate management of hyperparathyroidism and vitamin D deficiency must be achieved. Nutritional supplementation, anaemia correction with erythropoietin, and exercise programs have been shown to improve exercise tolerance and neuromuscular function [19].

28.4 Cognitive Disorders and Dementia

Definition: Cognitive impairment is defined as a new deficit in two or more areas of cognitive function. Mild cognitive impairment (MCI) is detectable by clinical assessment but does not impact daily functioning, while dementia is characterised by cognitive impairment and behavioural disturbance that interfere with independence and daily functioning [20]. Both conditions are characterised by deficits in memory, attention, and executive function which can be a major cause of chronic disability and poor adherence to treatment plans [21]. CKD is a risk factor for progressive cognitive impairment and dementia independent of vascular and demographic variables [22].

Prevalence and Pathophysiology: Cognitive impairment is present across the spectrum of CKD with both the prevalence and rate of progression inversely associated with level of kidney function [22]. Mild cognitive impairment affects 27–62% of people with stage 1–4 CKD, 5–10% of which will progress to dementia [23]. In stage 5 CKD, studies have shown ~70% of patients demonstrate moderate to severe cognitive impairment and the prevalence of dementia ranges from 8 to 37%. However, less than 5% of patients have cognitive impairment documented as a comorbid condition in medical records, suggesting the condition is under-recognised in routine clinical practice [22]. Dementia is a more powerful predictor of mortality than heart failure or stroke in stage 5 CKD patients and thus presents an important clinical complication [22].

The pathology of MCI and dementia in CKD is likely multifactorial with both vascular and uremic mechanisms of damage. Given that individuals with CKD often have several comorbid conditions associated with a range of traditional risk factors such as advanced age, hypertension and diabetes, vascular pathology plays an important role [21]. There has been renewed interest in the 'kidney–brain axis' given the shared physiology of these organs as low vascular resistance systems which renders the microvasculature of both particularly susceptible to hypertensive injury [24]. Additionally, patients in whom vascular nephropathy is the cause of CKD have a heightened risk of silent white matter disease. A vascular aetiology for cognitive dysfunction is further supported by association between clinically silent cerebrovascular disease and degree of kidney impairment [9].

The impact of non-traditional kidney related factors remains important as CKD is a risk factor for cognitive dysfunction independent of vascular and demographic variables. This is emphasised by the relationship between cognitive and uraemia as well as improvement observed with transplantation [25]. Consideration should also be given to secondary hyperparathyroidism and anaemia as potential risk factors for cognitive impairment in CKD. Excess parathyroid hormone levels in patients with CKD are postulated to interfere with neurotransmission in the CNS by increasing brain calcium content [26].

Clinical Presentation: The onset of cognitive decline is subtle and overt cognitive impairment often becomes clinically apparent at more severe stages. Cognitive impairment tends to be poorly recognised by healthcare providers and correlates poorly with subjective complaints, while caregivers and family members often notice deficits sooner [25]. Careful history taking and screening are the most accurate method of early detection; however, sleep disturbance, depression, unexplained falls, or confusion about medications may provide early warning signs of cognitive impairment [25]. The pattern of cognitive impairment in CKD is not substantially different from that of vascular dementia or Alzheimer's disease. However, there is a prominence of cognitive and behavioural executive function and action speed impairments, followed by language and episodic memory [25].

Diagnosis: Cognitive assessment should be undertaken in individuals with cognitive complaints and when family or caregivers report symptoms, especially in conjunction with difficulties of daily living [25]. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are the most widely used methods of assessment for cognitive impairment [20, 25]. The MMSE provides a score of global cognitive function and a score of <24 typically indicates cognitive impairment. The instrument has low sensitivity for mild cognitive dysfunction [20] and is focussed largely on memory and attention at the expense of other cognitive domains such as executive function which are particularly relevant to CKD. The MoCA provides a potentially superior alternative that includes both global cognitive and executive function assessment with a sensitivity of ~80% with age corrected values. Scores gained on the MMSE and MoCA may be influenced by a subject's educational and cultural background and the clock drawing test may provide a quick easy to administer alternative. For patients in whom scores are normal but where clinical suspicion for cognitive impairment is high, referral to a neuropsychology service is recommended for more intensive cognitive assessment. In all patients, cerebral imaging with computerised tomography scans (CT) or magnetic resonance imaging (MRI) is also recommended to exclude space-occupying lesions that may represent a treatable cause of cognitive impairment. Screening blood tests are also recommended to exclude other causes of cognitive impairment, including B12 deficiency and hypothyroidism.

Treatment: There are no specific treatments for cognitive dysfunction in CKD and thus early recognition and prevention are key strategies to combat CKD related cognitive decline [21]. Pharmacological interventions have not been widely tested in people with CKD and are not routinely recommended. Management approaches include general strategies control traditional risk factors with evidence extrapolated from general populations [21]. A recent RCT has shown intensive blood pressure control reduced risk of mild cognitive impairment and probable dementia in CKD though this was not the primary outcome further investigations are warranted [27]. Expert opinion suggests avoidance of sedating medications and polypharmacy are important factors to consider, as are practical measures such as strengthening support mechanisms and family/carer involvement, strategies to improve treatment adherence such as frequent follow-up, written instructions, and integrated multidisciplinary care [21]. For advanced CKD, several cohort studies have demonstrated kidney transplant improves cognitive outcomes the year after transplant [21]. However, frailty can adversely affect these outcomes and initiating dialysis for people with advanced cognitive impairment or dementia may not be indicated due to treatment compliance and poor prognosis. For these reasons decisions regarding treatment preferences at end-stage disease, including dialysis mode or conservative care, should be made as early as possible allowing for alignment with patient wishes [21].

28.5 Encephalopathy and Delirium

Definition and Clinical Importance: Encephalopathy refers to diffuse alteration of brain function or structure, which manifests clinically as an altered level of consciousness. Aside from renal impairment and the associated accumulation of toxins, other factors that have been implicated in the development of encephalopathy in CKD patients include thiamine deficiency, hypertension, fluid and electrolyte disturbances, drug toxicity, dialysis, and transplant rejection [28]. Features of uremic encephalopathy are broad and it may be of insidious onset and present as a complex of non-specific symptoms related to altered mental functioning and/or motor disturbances, ranging from sensorial clouding to delirium and coma. Early features can include fatigue, apathy, irritability, and

impaired concentration, while later features are more severe including confusion, disorientation, delirium, hallucinations, coma, and seizures [29]. Motor disturbances can accompany alterations in mental status and include tremor, fasciculations, asterixis, and seizures, which may be generalised or focal [29]. Prompt recognition and diagnosis are important as encephalopathies may be reversible with treatment [29]. The rate of decline in kidney function seems to have an effect as symptoms are more pronounced and progress more rapidly in acute kidney disease [29].

Diagnosis: Laboratory blood tests should include a complete blood count, electrolyte panel, glucose, urea, creatinine, liver enzymes, and ammonia [29]. If the patient is febrile, a lumbar puncture may be necessary to investigate the possibility of meningitis or encephalitis [29]. All patients should undergo cerebral imaging with CT or MRI to exclude a space-occupying lesion, haemorrhage, or ischaemic stroke [9, 29]. Electroencephalography (EEG) should be undertaken in all patients and may demonstrate a generalised slowing of the normal background with excess delta and theta waves. Triphasic sharp waves on EEG are considered a specific feature of metabolic encephalopathy (Fig. 28.4).

Management: The management of encephalopathy is focussed on identification and treatment of the underlying cause. In all patients with CKD, the first step in treatment of uremic encephalopathy is to correct any underlying metabolic disturbance. Symptoms are usually alleviated by dialysis treatment in patients with severe kidney failure, although mental status changes may take 1–2 days to improve [29]. Rapid shifts in electrolyte concentrations, particularly sodium, may exacerbate symptoms and should be avoided. Anticonvulsants should not be prescribed prophylactically but in those patients who have developed seizures, treatment with anticonvulsants is required. Preferred medications in this setting include phenytoin, sodium valproate, and carbamazepine where no dose adjustment is needed [30]. Many other anticonvulsants require dose reductions due to renal metabolism including levetiracetam, topiramate, and lamotrigine.

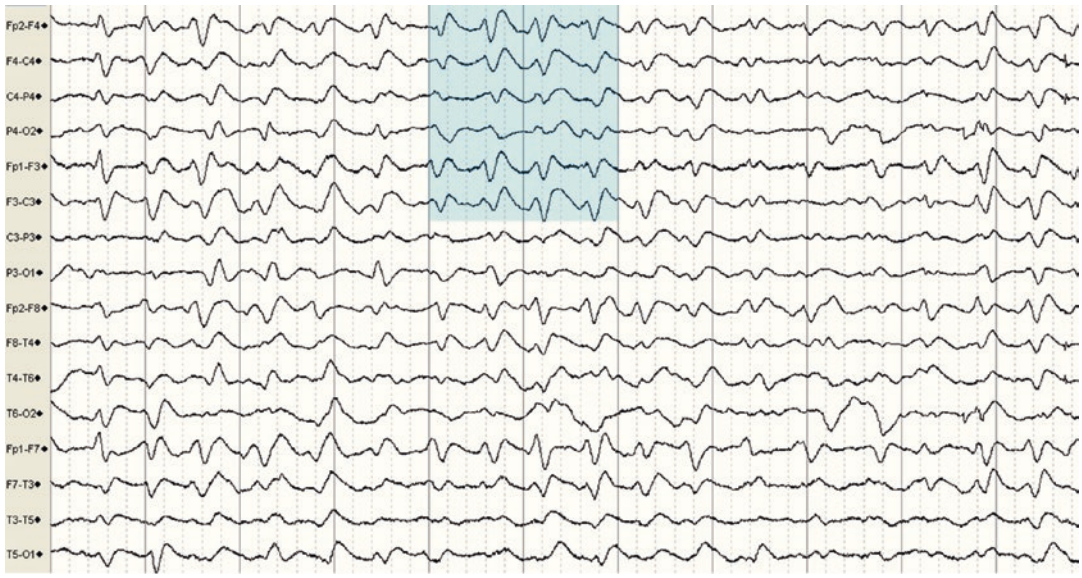

Fig. 28.4 Electroencephalograph for a chronic kidney disease patient who presented with drowsiness and confusion. Findings demonstrate a generalised slowing of the normal background with an excess of delta and theta waves, and abnormal triphasic waves (blue highlighted section), consistent with uremic encephalopathy

Before You Finish: Practice Pearls for the Clinician

- Peripheral neuropathy manifests in a majority of stage 3–4 CKD and almost all stage 5 CKD patients. It is likely to be present at earlier stages and with greater severity in patients with diabetic-CKD. Painful symptoms may respond to treatment with gabapentin, while dietary potassium restriction, glycaemic control, and exercise strategies may be beneficial.
- Proximal weakness and exercise intolerance caused by uremic myopathy may respond to exercise programs, adequate nutritional intake, and treatment with erythropoietin.
- For CKD patients with carpal tunnel syndrome, local corticosteroid injections may provide benefit.
- Patients with autonomic neuropathy may respond to sildenafil for impotence.
- Cognitive dysfunction and dementia are underrecognised and can be assessed using the mini-mental state examination or Montreal cognitive exam and should be differentiated from encephalopathy which presents with motor alterations including tremor and asterixis.

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29 Drug Prescription in Chronic Kidney Disease

Didem Turgut

Before You Start: Facts You Need to Remember

- Every patient is unique and needs an individualized approach. Thus, every patient has his/her own side-effect profile with medications.
- If you do not have to prescribe a drug, you do not have to. Be conservative.
- Prefer to decrease medication pill count which helps to increase adherence and decrease drug–drug interactions.
- Kidney function tests must be reevaluated regularly to avoid medication problems related to chronic comorbid diseases.
- Primary care physicians, caregivers, and patients themselves should be careful about clinical changes that would result in new coming side effects.

29.1 Difficulties Related to Drug Prescription in CKD

Safe medication use in CKD is a complex process (Fig. 29.1). Patient and drug metabolism related differences make this complexity progress. There are two key factors influencing drug prescription in patients with CKD, multimorbidity and development and treatment of CKD-related complications. Determination of kidney function and changes in pharmacodynamics and pharmacokinetics of drugs as kidney function declines are other factors of this complexity.

29.1.1 Multimorbidity in CKD

Multimorbidity, the co-occurrence of two or more chronic diseases, is a condition that affects up to 95% of patients with CKD [1]. According to a study of Lifeline group patients (n = 2742) multimorbidity was present in 83.3% of the CKD patients [2]. The most common comorbidities are diabetes, hypertension, cardiovascular diseases, cerebrovascular diseases, painful conditions, anemia, dementia, and thyroid disorders [1]. Even hospitalization rates in CKD patients are 2–3 times higher in those with multimorbidity [3].

Multimorbidity patterns across the CKD stages are also important. Hawthorne et al. published in their study that the two most prevalent comorbidities across all stages were hypertension (55%) and musculoskeletal disorders (40%). For stages 1–2, the most prevalent comorbidity was lung conditions (33.9%). For stages 3–5 the third most prevalent comorbidity was heart problems (35.1%, 40.3%, and 26.1%, respectively) [4].

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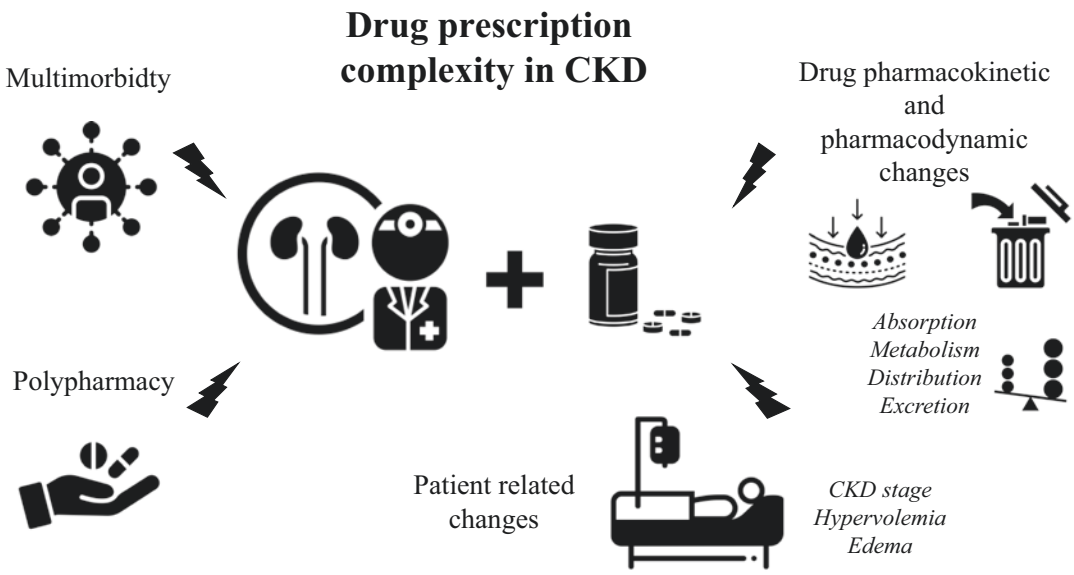

Fig. 29.1 Drug prescription complexity in Chronic Kidney Disease

Multimorbidity in CKD increases complexity with treatment medication regimens and self-management strategies. Multiple healthcare professionals are involved with these accompanying comorbidities resulting in medication accumulation and adverse medication events in CKD patients. As a result, to prevent polypharmacy shared decision-making and patient-centered approaches are necessary for this patient population [4, 5].

29.1.2 Polypharmacy and CKD

Polypharmacy is defined as taking five or more medications regularly and can increase the risk of drug and drug interactions, high medication doses, complex medication regimens, medication costs, medication non-adherence, and lower quality of life [6]. In the German CKD study, it was published that the prevalence of polypharmacy was almost 80%, ranging from 62% in patients with CKD Stage 1–86% in those with CKD Stage 3b with a mean of eight drugs (0–27) [7]. Polypharmacy is also associated with adverse outcomes which were documented in the Fukushima CKD Cohort Study. In the study, the use of more than five medications was associated with a high risk of kidney failure, cardiovascular events, and all-cause mortality in nondialysis-dependent CKD patients [8].

The most frequently prescribed medications are antihypertensives and lipid-lowering medications which are followed by diuretics, platelet aggregation inhibitors, and urate-lowering therapy [9]. According to an Australian study, 35% of CKD patients have been prescribed at least one potentially inappropriate medication [10].

29.1.3 Screening, Monitoring, and Managing CKD

Chronic kidney disease which is defined as decreased glomerular filtration rate (GFR) is generally associated with inappropriately adjusted drug doses. In CKD patients, according to the severity of the disease drug concentrations can increase ending with adverse drug reactions or unnecessary decreases in dosage may result in undertreatment. Even nonessential changes to an alternate drug with a lower efficacy are not rare.

In CKD patients not only decreased GFR affects, but proteinuria, hypoalbuminemia, or

hypervolemia also affects medication pharmacokinetics [11]. Hypervolemia most likely affects hydrophilic drugs rather than lipophilic drugs [12].

In patients with kidney diseases, the dosing of medications must be adjusted regarding actual GFR. In the past Cockcroft–Gault equation, creatinine clearance, and modification of Diet in Renal Diseases (MDRD) formula were used by physicians for GFR assessment [13]. Recently, CKD-EPI (named after the Chronic Kidney Disease Epidemiology Collaborative) formula is used for this purpose [14]. But there is not any consensus as to which method better estimate proper GFR values. The Cockroft–Gault equation is still most often used for estimating GFR in pharmacokinetic studies and for drug dosage adjustment, although some studies have shown the MDRD Study equations to be more accurate for estimating GFR [15, 16].

29.2 Changes in Pharmacokinetics of Drugs in CKD

Pharmacokinetics examines how the drug is absorbed, distributed, metabolized, and excreted by the body. The concentration-time profile of a drug reflects the net effects of these pharmacokinetic processes after drug administration. In general, high drug exposures increase the risk of adverse drug reactions, and low drug exposures are ineffective [13]. In CKD, both have negative effects on patient outcomes including treatment failures or amplified toxic side effects, especially with narrow therapeutic index drugs [12].

In general, during the development phase of drugs, dosing regimens are determined by normal or mildly affected kidney function. This results in limited pharmacokinetic data on drugs in patients with advanced kidney diseases. Limited data guide manufacturers to declare drug contraindications in patients with eGFR<30 mL/min/1.73 m^2 in the post-marketing phase [13, 17]. As a result, this patient group has been deprived of important drug options.

The dosing principles of a drug consist of the initial dose, maintenance dose, and dose frequency. Beyond this, in CKD patients therapeutic drug monitoring (TDM) should be performed for a good safety profile [12]. TDM is also associated with clinical targets related to a prescribed drug. For antidiabetics monitoring plasma glucose levels, for antibiotics targeting minimum inhibitory concentrations with infection control, for immunosuppressives targeting the drug blood trough levels determined by clinical trials are some examples.

In patients with CKD, the initial dose or loading dose does not differ regarding achieving a target first-dose serum concentration. Because rather than changes in drug clearance, a long half-time of the drug is more important to determine the target drug concentration [18]. Conversely, a high initial dose might be necessary in case of expanded volume of distribution (Vd) in nephrotic syndrome or changes in binding patterns of drugs to plasma proteins in hypoalbuminemia [19]. For drugs with highly lipophilic properties, the actual body weight should replace the ideal body weight [20].

In contrast to the initial dose, the maintenance dose depends on clearance and affects dose frequency. In general, rather than decreasing the frequency, a dose reduction is preferred according to the toxicity profile of the drug in CKD patients [21]. Dosing reduction may provide for more constant drug levels but increases the risk of toxicity from higher plasma trough concentrations [20]. Some antibiotics are the exception to this rule where high peak serum concentrations are beneficial [12].

For medication with a narrow therapeutic index, TDM can be beneficial despite dosage adjustments according to estimated GFR. TDM generally helps clinicians to minimize toxicities. But toxicity and adverse drug reaction may occur despite appropriate plasma drug concentration. For example, despite proper plasma concentration levels, concomitant administration of vancomycin and an aminoglycoside can increase the risk for nephrotoxicity of both agents [18, 22].

The knowledge about the properties of drugs, pharmacokinetic principles, and patient-specific conditions results in a rational approach to prescribing drugs. Here are sample examples of drugs that have special considerations to be used for patients with kidney diseases and changes in their pharmacokinetics.

29.2.1 Effects of Kidney Diseases on the Absorption Process

In clinical studies absorption of a drug is generally assessed by measuring the time at which the maximum plasma concentration occurs (Tmax). Absolute bioavailability (F) is assessed by comparing the area under the plasma drug concentration-time curve (AUC) following the oral and intravascular route [22, 23]. But these parameters are disregarded in patients with kidney problems. And the extent of absorption from the gastrointestinal tract is also not studied in detail in these patients. Tmax changes may be prolonged because of reduced gastric emptying or decreased intestinal absorption. Associated comorbidities have combined effects on various aspects of drug absorption in this way. Gastroparesis, uremia-induced vomiting, and edematous gastrointestinal tract all decrease oral bioavailability. For example, for similar diuretic effects, increased dose adjustment is necessary if gut edema is prominent in congestive heart failure or cirrhosis [24]. Gastroparesis might be important for some drugs such as short-acting sulfonylureas [25].

Concomitant administration of medications in kidney diseases can alter the absorption in several ways too. Phosphate binders and histamine 2-receptor antagonists can change gastric pH, altering medication absorption [26]. The best examples are furosemide, ketoconazole, and ferrous sulfate which are best absorbed in an acidic environment [27]. On the contrary, the administration of magnesium hydroxide and sodium bicarbonate can enhance the absorption of some weakly acidic molecules (e.g., ibuprofen, glipizide, glyburide, tolbutamide) by increasing their water solubility. Also, the ingestion of cation-containing antacids (e.g., calcium, magnesium), aluminum hydroxide, sodium polystyrene sulfonate, and iron may reduce drug absorption because of chelation with other medications. Fluoroquinolones and tetracyclines are antibiotics that are highly susceptible to chelate formation in patients with CKD [21, 23, 24].

29.2.2 Effects of Kidney Diseases on the Distribution Process

In CKD patients, alterations in the protein and tissue binding are associated with problems regarding drug distribution. The plasma binding of basic drugs appears to be generally unaffected but the ones that are acidic, such as penicillins, cephalosporins, phenytoin, furosemide, and salicylates, are most severely affected by reduced protein binding [23, 25]. Hypoalbuminemia with altered protein binding leads to increased levels of free concentrations of drugs. Conversely, alkaline drugs such as propranolol, morphine, oxazepam, and vancomycin bind primarily to non-albumin plasma proteins, whose plasma concentrations are often elevated in renal dysfunction. For this reason, plasma concentrations of alkaline drugs in CKD patients may be reduced [21–23].

The Vd of several drugs is significantly increased in patients with severe renal dysfunction [14, 21, 25]. An increased Vd may be the result of fluid overload, decreased protein binding, or altered tissue binding. The Vd of a few drugs, such as digoxin, pindolol, and ethambutol, is decreased probably due to a decrease in their tissue binding. This reduction in Vd results in increased drug serum concentrations if the loading dose is not reduced especially for digoxin [14, 28]. Increased total-body water, such as edema or ascites, is expected to increase the Vd in CKD patients. Especially hydrophilic drugs like pravastatin, fluvastatin, morphine, codeine, and vancomycin are affected by this change in Vd resulting in reduced serum concentration [22–29].

29.2.3 Effects of Kidney Diseases on the Drug Metabolism Process

There are Phase I and II drug metabolism processes that are affected in CKD. Slowed phase I and II metabolic reactions result in increased serum drug concentrations [26]. In general, few drugs are eliminated almost entirely unchanged by the kidneys. In many studies, it was documented that even drugs that are mostly or completely eliminated from the body by non-renal mechanisms may accumulate in patients with renal dysfunction if their dosage regimen is not adjusted [30]. Acetylation (e.g., dapsone, hydralazine, isoniazid, procainamide), glucuronidation (e.g., acetaminophen, morphine, lorazepam, oxazepam, naproxen), sulfation (e.g., acetaminophen, minoxidil, dopamine, albuterol), and methylation (e.g., dobutamine, dopamine, 6-mercaptopurine) are all slowed in patients with CKD [26, 31]. Hepatic cytochrome 450 (CYP) activity is also changed in renal function problems. For example, the plasma S/R warfarin ratio was increased by approximately 50% in ESRD patients compared to healthy controls, indicating that CYP2C9 activity in these patients was reduced more than the activity of the other enzymes contributing to the metabolism of warfarin [32].

29.2.4 Effects of Kidney Diseases on the Excretion Process

Renal excretion of medications is dependent on glomerular filtration rate, renal tubular secretion, and reabsorption. In CKD, medication elimination by glomerular filtration is decreased, resulting in a prolonged free drug elimination half-life [33]. The secretion of drugs, eliminated by the active transport system, into the proximal convoluted tubules is also reduced in CKD [34]. Some drugs eliminated in this way are ampicillin, furosemide penicillin G, phenylbutazone, probenecid, salicylic acid, cimetidine, dopamine, neostigmine, procainamide, and trimethoprim [33, 34].

In the elimination process, biologically active or toxic metabolites of parent drugs may accumulate in patients with CKD. For example, the active metabolite of midazolam, alpha-hydroxymidazolam; the active metabolite of allopurinol, oxypurinol, or morphine-3-glucuronide and morphine-6-glucuronide which are an active metabolite of morphine can accumulate in CKD patients [34, 35].

29.3 Changes in Pharmacodynamics of Drugs in CKD

Pharmacodynamics is interested in the biochemical and physiologic effects of a drug and its organ-specific mechanism of action, including effects on the cellular level. In CKD, the response to a given drug may change even though the drug's pharmacokinetics are not dramatically altered.

There are two different mechanisms in drug pharmacodynamics. The reversible and irreversible effects. The reversible effects are receptor-mediated, saturable, and observed with both increasing and decreasing concentrations. The irreversible effects are direct and proportional to rising concentrations. The reversible effects generally describe the individual drug response [36, 37]. For example, in the elderly, augmented drug response often has been explained by an impaired kidney function. But because of reversible pharmacodynamic effects, increased sensitivity and a higher drug potency at the receptor level increase drug response in the elderly [38].

In pharmacodynamics, the same concentration results in beneficial and adverse effects. Conventional drugs with a beneficial effect will also have adverse effects. The adverse drug reaction can even be used for pharmacodynamic monitoring of the therapeutic effect. As an example, mild myelosuppression with anemia, neutropenia, lymphocytopenia, and thrombocytopenia might indicate a sufficiently high dose of anticancer, anti-infective, or immunosuppressive drugs [36].

Here are sample examples of drugs that have changes in their pharmacodynamics. For reversible effect changes, an increased sensitivity has been reported for midazolam, nifedipine, morphine, phenytoin, and warfarin, where dose reduction might be necessary. But more resistance has been observed for albuterol and metoprolol which require a higher dose or a change to an alternative drug [36, 38]. For furosemide and canagliflozin, although T1/2 rises in CKD patients, a higher-than-normal dose with higher intratubular concentrations is needed. And the dose should not be reduced, but instead, be increased to obtain drug effect in the altered kidney functions. This observation related to furosemide and canagliflozin is a result of pharmacodynamic changes in kidney problems [39, 40].

Another pharmacodynamically based regimen is a time-dependent action in which drugs should be administered by continuous infusion to increase efficacy but decrease toxicity. Vancomycin, meropenem, and piperacillin are some of these drugs whose steady-state serum concentration is necessary for their target drug concentration [36, 41].

The insight into the pharmacodynamics might also affect dosing practice for direct-acting oral anticoagulants apixaban and rivaroxaban in kidney diseases. The antithrombotic efficacy and the bleeding risk were not different for apixaban and rivaroxaban even in CKD [42]. But in kidney failure, the T1/2 of apixaban rises to 17 h, whereas the rivaroxaban T1/2 increases to only 10 h. Instead of dosing 2.5 mg every 12 h, the pharmacodynamic dose adjustment of apixaban for kidney failure would suggest 5 mg once a day as per the daily dosage of rivaroxaban [43].

In contrast to the reversible effects, irreversible pharmacodynamic effects rarely have been published in the literature. Some drug examples for irreversible effects are ibrutinib, cisplatin, clopidogrel, and pantoprazole [36].

29.4 Concluding Remarks

Altered kidney functions affect more than just the renal clearance of drugs and/or active drug metabolites. Even when the dosage adjustments recommended for patients with CKD are carefully followed, adverse drug reactions remain common. Safe drug prescribing for patients with CKD can be complex, but with the application of a following algorithmic approach, the difficulties can be minimized [23, 25, 26, 44]. Additionally, clinicians should also be aware of what clinical guidelines say for drug dosing considering patients with kidney problems. A Clinical Update from Kidney Disease, Improving Global Outcomes (KDIGO) is summarized in Table 29.1 [45].

Table 29.1 Stepwise approach to adjust drug dosage regimens for patients with CKD and AKI

Step 1	Clinical history	Assess demographic information, past medical history including history of renal disease, and current clinical and laboratory information, including DNA polymorphisms to ascertain drug therapy needs
Step 2	Relevant GFR estimation	Use most appropriate tool to assess eGFR or CLcr for the patient based on age, body size, ethnicity, and concomitant disease states
Step 3	Current medications	Identify drugs for which individualization of the treatment regimen will be necessary
Step 4	Personalized treatment regimen	Calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's volume status and eGFR or CLcr
Step 5	Monitor	Monitor parameters of drug response and toxicity; monitor drug levels if available/applicable
Step 6	Revise regimen	Adjust regimen based on drug response or change in patient status (including renal function) as warranted

Adapted from [45]

Before You Finish: Practice Pearls for the Clinicians

- Assess the degree of kidney function severity and GFR, be sure of the stage according to universal methods, and determine a clinical action plan according to stages.
- Take the medical history, examine the patient, and specify the comorbidities the patient has.
- Review the medication list. Check the complete medication list including all prescriptions, over-the-counter and dietary supplements (including herbal, nonherbal, and vitamin supplements). Collect history of drug allergies/sensitivities, adjustment, or discontinuation of medication due to impaired kidney function or toxicity.
- Plan the medication list. Ensure that all drugs patients use are still required and that new medications have specific indications. Evaluate for potential drug interactions.
- Choose less nephrotoxic medications. Review the indication for the agent to determine whether the potential for harm outweighs the evidence for efficacy. For example, RAAS blockers, which can lead to hyperkalemia and AKI, should undergo harm versus benefit evaluation, especially in patients where the benefits of treatment targets are unknown or equivocal. Also, consider patient preferences.
- Calculate/adjust the dose based on the patient's GFR, drug characteristics, and literature recommendations.
- When in doubt, appropriate information for dosing guidelines should be sought in recently published monographs or texts. Decision-support platforms such as Micromedex and Lexicomp offer easily accessible monographs. The Natural Medicine Comprehensive Database is also a useful resource to consider the safety of herbals, dietary supplements, vitamins, and other nutraceuticals in CKD.
- Loading dose is important, not avoid. For maintenance doses, the most common recommendations are often to reduce the drug dose rather than expand the dosing interval.
- Monitor the treatment you have started. Document the signs of efficacy, toxicity, and change in symptoms of the patient. Monitor drug levels if monitoring is available to guide further therapy.
- Reassess the patient to evaluate drug effectiveness and the need for ongoing therapy.
- Follow recommended online sources.
  - FDA: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling, 2020 Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - KDIGO Drug Prescribing in Kidney Disease: Initiative for Improved Dosing. Available from: https://kdigo.org/wp-content/uploads/2017/02/201005_Grabe_Stevens.pdf
  - European Medicines Agency. Evaluation of medicines for human use. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf
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30 Pregnancy and Chronic Kidney Disease

Sarah Winfield and John M. Davison

Before You Start: Facts you Need to Know

- CKD stages 1 and 2 affect up to 3% of women of childbearing age and CKD stages 3–5 affect about 1 in 150 women.
- Over 95% of the women with CKD becoming pregnant will be CKD stages 1 and 2.
- CKD stages 3–5 complicate about 1 in 750 pregnancies.
- The prevalence of CKD in pregnancy is predicted to rise in the future due to increasing maternal age and obesity.
- Fertility declines with CKD progression over time, but women with CKD can still become pregnant so appropriate contraception is important.
- All women with CKD (even those with 'mild' CKD stages 1–2) are at increased risk of pregnancy complications and adverse maternal and foetal outcomes which are related to the severity of prepregnancy kidney dysfunction, increasing further with hypertension and proteinuria and in systemic diseases, such as diabetes and SLE.
- Risk of accelerated decline and irreversible loss of kidney function during pregnancy or immediately afterwards are higher with more severe degrees of kidney dysfunction and with poorly controlled hypertension.
- Progressive hypertension with proteinuria and/or renal deterioration in late pregnancy may be difficult to distinguish from pre-eclampsia, but the advent of placental growth factor (PlGF) testing has helped to address this clinical dilemma.
- The historically dismal maternal and foetal outcomes are improving with advances in obstetric, nephrological, and neonatal care and a more streamlined approach to multidisciplinary working, aided by the implementation of maternal medicine networks to 'join up' care for these women.

The provision of care for women with chronic kidney disease (CKD) contemplating pregnancy or who are already pregnant must involve clinicians working in a multidisciplinary team (MDT) in a tertiary centre [1, 2]. They must have up-to-date knowledge of the changes in kidney that occur in normal pregnancy and the potential adverse effects of kidney impairment, an awareness of risks and complications with CKD, experience of modern antenatal and foetal surveillance, and an ability to handle delivery care and after-

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wards. This chapter is based on some of the currently available literature and evidence-based guidelines, recently reported case series and personal experience [2–10]. We would also direct the reader to look at the excellent 'Clinical Practice Guideline on Pregnancy and Renal Disease' written by Kate Wiles et al. [11], which encompasses in detail all aspects (including contraception) of caring for women with renal disease. Also please have a look at the NICE Guidance for the Management of Hypertension in Pregnancy [12] which contains useful information for clinicians managing any women with hypertension in pregnancy. The care of women on dialysis or with a kidney transplant will not be dealt with in this chapter, but we acknowledge that there is growing expertise and confidence in the use of dialysis in pregnancy, leading to successful pregnancy outcomes in these women [13].

30.1 Prepregnancy Assessment and Counselling

The basic components of prepregnancy assessment and counselling should be establishment of baseline parameters, analysis of risks as well as provision of health education and advice, plus any interventions that might be considered helpful (Boxes 30.1 and 30.2). A woman (and her partner) will consider important questions such as 'should I get pregnant?' 'will my pregnancy be alright?' 'will I have a live, healthy baby?' and 'will I be alright after my pregnancy?' So the MDT must ensure that all the relevant evidence-based information is shared with the woman and her family. Even if some of the answers are going to be difficult to hear, a woman may choose to go ahead and try for a pregnancy (or continue with the pregnancy) in an effort to re-establish a normal life in the face of chronic illness [7–10]. A woman's autonomy and agency over the choices that she makes about her body and her health must be respected at all times, even if she wishes to proceed with a pregnancy that confers significant risk of morbidity and even mortality. It is the role of the MDT carrying-out the counselling to give the woman and her partner the correct evidence-based information in a way that is clear and non-judgemental and allows time and space for her to make important decisions [14] and for the team and the woman to 'co-produce' a plan for approaching pregnancy and also during pregnancy. It has been our usual practice to allocate an hour for a prepregnancy appointment, support the discussion with signposting to written resources, and send the woman (and her GP) a written letter with the contents of the discussion clearly written for reference.

Box 30.1 Organisation of Care in CKD

- Before pregnancy, all women of childbearing age with CKD should be made aware of its implications for their reproductive health and careers.
- Women need advice about input on contraception, modification of remedial risk factors, and optimisation of and/or alterations to medication for their CKD and any associated comorbidities (such as hypertension, diabetes, or SLE) in addition to explanations about the risks and rates of pregnancy complications, adverse maternal and foetal outcomes, and possible impacts on long-term renal prognosis.
- The MDT must work in partnership with these women to tailor personalised prepregnancy, antenatal, delivery, and postnatal care, in a centre with all the necessary facilities for dealing with high-risk patients and their babies.
- This 'active preparation for pregnancy' should involve the woman's partner if they have one or if they chose to be present at the appointment.
- Some women may not seek advice until they are already pregnant.
- Undiagnosed CKD may be suspected/diagnosed for the first-time during pregnancy when a complication or an adverse event occurs.

Box 30.2 Prepregnancy CKD Assessment criteria

- Cause of CKD (±systemic disease such as SLE or diabetes).
- Stage of CKD (eGFR).
- Presence or absence of significant proteinuria (urine PCR >30/≥300 mg/24 h).
- Normotension or 'well-controlled hypertension' with diastolic BP ≤80 mmHg.
- Past obstetric history.
- Genetic counselling may be required for familial CKD.
- Assessment of diet, BMI, nicotine, and alcohol intake.
- Consider counselling for CKD 1 and 2 if the woman wishes to have it.

A planned pregnancy is one that is desired before conception, occurs when contraception is discontinued in order to get pregnant and where the woman and the team looking after her aims to achieve optimal health beforehand.

30.2 Normal Pregnancy

The renal tract undergoes marked anatomical, haemodynamic, tubular, and endocrine changes as part of the systemic upheaval of maternal adaptation to pregnancy. The kidneys enlarge because both vascular volume and interstitial space increase but there is no accelerated renal growth nor morphological alterations akin to compensatory renal hypertrophy. The calyces, renal pelvis, and ureters dilate markedly, invariably more prominent on the right side, seen in 90% of women, mimicking outflow obstruction. The relevant functional changes are listed in Box 30.3.

Box 30.3 Normal Pregnancy and Renal Physiology

- Normal cardiovascular function and healthy renal system, with optimal adaptation to increasing demands of pregnancy, are prerequisites for successful obstetric outcome.
- Glomerular filtration rate (GFR) increases to 50% above prepregnancy values, primarily due to increased renal blood flow (RBF) rather than a rise in intraglomerular pressure, so there is unlikely to be hyperfiltration sclerosis.
- Serum creatinine (S_{cr}) in the first, second, and third trimesters averages 60, 54, and 64 μmol/L (0.66, 0.59, and 0.70 mg/dL), respectively, with measured creatinine clearances (C_{cr}) of 151, 154, and 129 mL/min, respectively, with return to S_{cr} baseline (70 μmol/L; 0.75 mg/dL) by 3 months postpartum. As well as gestational age-specific values, some units now use ethnicity-specific normal ranges as, for example, nonpregnant Afro-Caribbean women have higher S_{cr} levels than Caucasians.
- Serum urea (S_{urea}) averages 3 mmol/L (7 mg/dL) throughout pregnancy, a fall from the nonpregnant value of 5 mmol/L (12 mg/dL).
- Values of S_{cr} of 80 μmol/L (0.9 mg/dL) and S_{urea} of 6 mmol/L (14 mg/dL), which are acceptable in the nonpregnant state, are 'suspect' in pregnancy.
- 24-h urinary total protein excretion (TPE) increases throughout the trimesters in normal pregnancy and up to 300 mg per 24 h can be regarded as normal.
- Serum albumin (S_{alb}) decreases progressively from the mean of 38 g/L at 12 weeks gestation to 32 g/L by 36 weeks. Corresponding cholesterol levels are 4.5 mmol/L and 6.6 mmol/L, respectively. Occasionally, S_{alb} may

decrease by up to 10 g/L and with bigger increments than usual in serum cholesterol, plus oedema, usually in late pregnancy; nephrotic syndrome may be simulated. Source: Data from Refs. [2, 7, 10, 15–18].

30.3 CKD and the Prospects for Pregnancy

A woman may lose up to 50% of her kidney function and still maintain S_{cr} below 125 μmol/L (1.4 mg/dL), because of hyperfiltration by the remaining nephrons; however, if kidney function is more severely compromised, then further small decreases in GFR will cause S_{cr} to increase markedly. In women with CKD, whilst the pathology may be both biochemically and clinically silent, the internal milieu may already be disrupted. Most individuals remain symptom-free until GFR declines to less than 25% of normal, and many serum constituents are frequently normal until a late stage of disease. However, degrees of functional impairment that do not appear to disrupt homeostasis in nonpregnant individuals can jeopardise pregnancy (Box 30.4).

Box 30.4 CKD and Physiological Adaptation to Pregnancy

- Women with CKD have impaired ability to make physiological adaptations during pregnancy.
- Pregnancy GFR increments may be blunted, even absent, especially in CKD stages 3–5, with the likelihood of further GFR decline as pregnancy progresses.
- Failure of S_{cr} to decrease in the first trimester is suggestive of future complications.
- CKD may be associated with inability to boost renal hormones, leading to normochromic normocytic anaemia, reduced plasma volume expansion, and vitamin D deficiency.
- In CKD, significant proteinuria (total protein excretion >300 mg per 24 h) correlates with a protein concentration of 30 mg/dL in a 'spot' urine sample, and the use of 'spot' protein/creatinine ratio, with 30 mg/μmol (0.3 mg/mg) or more being significant has aided more rapid and convenient analysis of TPE than collecting a 24 hour urine specimen in a big container.
- Increased TPE up to 3 g/24 h can occur in CKD patients; an exaggeration of the physiological increase in healthy women and even the cessation of renoprotection from antiproteinuric drugs alone rarely indicate functional deterioration.
- Early in pregnancy BP can decrease and in CKD may mask mild hypertension that has been present but undiagnosed before pregnancy. Source: Data from Refs. [2, 7, 9, 15–19].

The traditional approach [7], with CKD defined as *mild*, *moderate,* and *severe*, based on S_{cr} has been replaced by a system based on the current CKD classification that is part of the US National Kidney Foundation (NKF) K/DOQI clinical practice guidelines, endorsed by the UK National Service Framework for Renal Services, and now widely adopted. Estimated GFR (eGFR) is estimated from the Modification of Diet in Renal Disease (MDRD) formula and its refinement CKD-EPI formula. Prepregnancy eGFR has a better sensitivity in detecting subclinical renal dysfunction and its influence on pregnancy outcome (if not CKD progression) as compared to S_{cr} alone [5, 9, 10]. In our clinical work we accept that S_{cr} values <125, >125 and > 180 μmol/L (<1.4, >1.4 and > 2.0 mg/dL)—*mild*, *moderate,* and *severe* impairment—respectively, correspond approximately to CKD stages 1, 2 and 3A, 3B, and 4 and 5, respectively.

30.4 Pregnancy in Women with CKD

Assessment of the CKD patient presents two basic and often conflicting issues: foetal prognosis (the effect of CKD on pregnancy) and the maternal prognosis, both during pregnancy and in the long term [11, 15]. Across the spectrum of CKD, there is a stepwise increase in the likelihood of complications and adverse outcomes such as hypertension, preeclampsia, deteriorating maternal renal function (often persistent), proteinuria, anaemia, urinary infections, foetal growth restriction, and foetal loss [20]. Aside from these obvious unfavourable outcomes, there are increases in 'surrogate' outcomes too (compared to normal pregnancy) including preterm delivery, caesarean section, and the need for neonatal intensive care unit access, clearly evident between CKD stages 1 and 2, underlining the importance of even minor decreases in kidney function [6, 10, 21] (Box 30.5 and Table 30.1).

Estimates are based on Refs. [4–10, 17, 22, 23] and from 62 women/93 pregnancies which attained at least 24 weeks gestation (Davison, unpublished data from 1993–2006).

Aim is to provide 'at a glance' information to facilitate counselling and management, whilst not belittling much more detailed coverage and analyses (with their own inherent weaknesses too) in those publications utilised.

All estimates expressed as a percentage.

FGR foetal growth restriction, S_{cr} serum creatinine, *PE* preeclampsia, *RF* renal function, *PP* postpartum, *ESRF* end-stage renal failure, *eGFR* estimated glomerular filtration rate (mL/min/1.73 m^2).

Box 30.5 Influences on Maternal and Foetal Outcomes in CKD

- Level of prepregnancy kidney impairment: CKD stage (eGFR).
- Satisfactory prepregnancy BP: Spontaneous or therapeutically achieved normotension and its optimal control throughout pregnancy. Relative risk of foetal death is 10 times higher when prepregnancy mean arterial pressure (MAP) ≥105 mmHg, compared with normotension. Absence of hypertension, almost regardless of kidney impairment, predicts best outcomes.
- Degree of proteinuria.
- Cause of CKD and the presence of a systemic disease/comorbidities.
- In addition, CKD itself has independent and significant effects on foetal outcome.
- Adverse past obstetric history. Source: Data from Refs. [3, 7, 8, 15, 18, 19].

CKD Stages 1 and 2 Normotensive women with intact or only mildly decreased but stable kidney function generally do very well, with more than 97% live births, about 75% of which are appropriate for gestational age. There is an increased incidence of superimposed preeclampsia or late-pregnancy hypertension as well as

Table 30.1 Prepregnancy CKD stage and estimates of obstetric complications/outcomes and renal prognosis

							Loss of > 25% RF		
CKD stage	Prepregnancy eGFR	S_{cr} (μmol/L)	FGR	Preterm delivery	PE	Perinatal death	During pregnancy	6 months PP	ESRF 1–2 year PP
Normal 1	≥90	<110	14	28	13	2	2	0	0
Mild 2	60–89 (<90)		30	35	40				
Mod 3	30–59 (<60)	>110	40	65	55	5	35	15	2
Severe 4	15–29 (<30)	>180	65	90	60	8	65	50	30
Estab RF5	<15 (but not on dialysis)	>250	>80	95	>70	15	90	60	45

increased proteinuria exceeding the nephrotic range (3 g per 24 h) in 50% of women in the second half of pregnancy. Pregnancy does not appear to adversely affect the course of the CKD [6, 7].

There are exceptions as certain types of CKD appear more sensitive to pregnancy, including lupus nephropathy [19, 24] and perhaps membranoproliferative glomerulonephritis. In addition, women with scleroderma and periarteritis nodosa do poorly (especially when there is marked kidney involvement and associated hypertension) and thus should be counselled to avoid pregnancy. Furthermore, there is some disagreement about whether pregnancy adversely influences the natural history of IgA nephropathy, focal segmental glomerulosclerosis, and reflux nephropathy [7]. It seems likely that prognosis with these renal lesions is actually similar to that of women with mild impairment in general, provided prepregnancy function is preserved and high blood pressure absent.

CKD Stages 3 and 4 Prognoses are poor but live births still approach 90%. Preeclampsia, foetal growth restriction, and/or preterm delivery occur in well over 50%. Many women experience renal functional loss more rapidly than would be expected from the natural course of their CKD, and poorly controlled hypertension is a harbinger of poor outcome. Best overall outcomes occur when prepregnancy eGFR is 40–60 mL/min and TPE ≤1 g/24 h. Poor outcomes are associated with eGFR <40 mL/min and TPE > 1 g/24 h, this combination resulting in worse outcomes than either feature alone [4]. Recent data [25] taken from a retrospective cohort study in 2021 of 178 pregnancies in 159 women (including 43 with renal transplants) with CKD 3–5 after 20 weeks gestation supports this. In this group, 79% of women had chronic hypertension. The live birth rate was 98% but 56% of babies were born before 37 weeks gestation. Chronic hypertension was the strongest predictor of delivery before 34 weeks gestation, with an incidence of 32% (31/96) in women with confirmed hypertension, compared with 0% (0/25) in normotensive women. Also, a gestational fall in serum creatinine of <10% of prepregnancy concentrations doubled the risk of delivery before 34 weeks for women with chronic hypertension from 20% [95% CI 9–36%] to 40% [95% CI 26–56%]. Data in this paper also highlights the increased risk of foetal growth restriction in this group of women, with birthweights below the tenth centile (odds ratio 2.57, 95% CI 1.20–5.53) where there was a urinary protein–creatinine ratio > 100 mg/mmol prior to pregnancy or before 20 weeks gestation. Furthermore, this work demonstrated that pregnancy-associated decline in renal function was greater in women with chronic hypertension and in women with a gestational fall in serum creatinine of <10% of prepregnancy concentrations. In this situation, the effect of pregnancy is thought to be the equivalent to 1.7, 2.1, and 4.9 of prepregnancy renal disease in CKD stages 3a, 3b, and 4–5, respectively, thus advancing the need for dialysis or transplantation by 2.5 years.

CKD Stage 5 (*But Not on Dialysis*) Without renal replacement therapy, the outlook for a pregnancy in a woman with CKD stage 5 is markedly curtailed. Preeclampsia/hypertension is common (>70%) as is significant proteinuria (60%), as well as deterioration in remaining kidney function, which is at times, rapid, substantial, and irreversible. Although infant survival rates are good (>80%), rates of preterm delivery (95%) and foetal growth restriction (FGR) (>80%) underscore the very high potential for obstetric complications in these women. As always, the importance of a MDT approach cannot be overstated, but in this particular situation of CKD 5, counselling about planning for or continuing with a pregnancy requires expert input from a team who is familiar with the process of dialysis because it is likely that the woman may need to commence this during the pregnancy. This is covered in more detail in another chapter of this book. Many women with CKD are amenorrhoeic and it is therefore difficult to decipher the exact timings of their menstrual cycle. This does not mean, however, that they cannot conceive, and so appropriate contraception should be commenced if pregnancy is not desired at this time. An important conversation for the woman with the MDT is around the ‘optimum’ time to try to conceive with the remaining renal function that they have, and risking further irreversible deterioration that

tips them into requiring dialysis earlier than they would have if they were not pregnant. Also, some women may wish to explore the option of transplant before they conceive, but this relies on other important factors such as donor availability, maternal age, etc. Fertility teams may need to become involved, and it is our experience that they are usually keen for the woman to have pre-pregnancy counselling before the commencement of fertility treatment. The wish to have a baby is personal and emotive even without renal disease, so it can be helpful for the MDT to involve a psychology healthcare professional to support the woman as she makes some potentially very difficult decisions.

30.5 Antenatal Strategy and Decision-Making

These patients must be seen as early as possible [1, 2, 26]. Thereafter assessments should be at 2–4 week intervals until 32 weeks' gestation and then every 1–2 weeks, depending on the clinical circumstances. In most cases, the basic principle is to manage the associated clinical features rather than the type of CKD.

1. Assessment of kidney function by S_{cr} or timed C_{cr} and by protein excretion as a spot urine protein/creatinine ratio. ***The use of eGFR from MDRD or CKD-EPI formulae is not valid in pregnancy, as actual GFR is underestimated*** [5]. If eGFR is used, it might erroneously signal to the clinician an exaggerated deterioration in kidney function and might prompt unnecessary delivery. ***Cystatin C as a GFR marker is of no use because there is placental production of Cystatin C, especially prominent in the third trimester***.
2. Careful blood pressure monitoring for early detection of hypertension (and assessment of its severity) and preeclampsia. Many units offer 'remote' BP monitoring via companies such as Hampton, and these help women to avoid travelling in and out of hospital for blood pressure monitoring, particularly when control is good. In kidney patients, it must be clear that the 'alert parameters' should be set at aiming for a blood pressure of less than 130/80 mmHg; otherwise, maternity teams may set parameters higher (as for non-renal patients) at 140–150/90–100 mmHg as for women without CKD.
3. Early detection and treatment of anaemia, usually by oral/intravenous iron therapy. Some recommend use of recombinant human erythropoietin if haematocrit is 20% or less, but caution is needed as hypertension can be caused or aggravated. Blood transfusion may need to be considered, particularly if delivery is imminent and postpartum haemorrhage is a risk.
4. From 12 weeks gestation, prophylactic aspirin 150 m once a day is advisable to reduce the risk of preeclampsia [27], if there are no contraindications to this (allergy, severe asthma, etc.). Thromboprophylaxis will be required when proteinuria exceeds 3 g/24 h or $S_{alb} < 25$ g/L, the dose of low molecular weight heparin depending on the level of kidney impairment [19, 23, 28].
5. Early detection of covert bacteriuria or confirmation of urinary tract infection (UTI) through monthly mid-stream urine samples and prompt treatment; if there are recurrent UTIs, then antibiotic prophylaxis should be given throughout pregnancy (e.g., Cephalexin 500 mg orally at night) until delivery.
6. Biophysical/ultrasound surveillance of foetal size, growth, development, and well-being is advisable, with timing of the scans and decision-making depending on the evolving clinical situation. Doppler studies can be used to assess placental function as well as helping to predict potential complications such as pre-eclampsia and foetal distress. Not all women, however, with abnormal uterine artery Dopplers will develop complications, and such tests must not be used in isolation.

The clinical 'watchpoints' associated with specific types of CKD are summarised in Table 30.2.

The following guidelines apply to all CKD patients:

Table 30.2 CKD and pregnancy

CKD	Clinical watchpoints
Chronic glomerulonephritis and focal glomerular sclerosis (FGS)	Can be high blood pressure late in pregnancy but usually no adverse effect if renal function is preserved and hypertension absent before pregnancy. Some disagree, believing coagulation changes in pregnancy exacerbate disease, especially IgA nephropathy, membranoproliferative glomerulonephritis, and FGS
IgA nephropathy	Some cite risks of sudden escalating or uncontrolled hypertension and renal deterioration. Most note good outcome when kidney function is preserved
Chronic pyelonephritis (infectious tubulointerstitial disease)	Bacteriuria in pregnancy and may lead to exacerbation
Reflux nephropathy	Some have emphasised risks of sudden escalating hypertension and worsening of kidney function. Consensus now is that results are satisfactory when pre-pregnancy function is only mildly affected and hypertension is absent. Vigilance for urinary tract infections is necessary. Screening of baby as soon as possible after birth, if not already detected in utero
Urolithiasis	Ureteral dilatation and stasis do not seem to affect natural history, but infections can be more frequent. Stents have been successfully placed and sonographically controlled ureterostomy has been performed during gestation
Systemic lupus erythematosus (SLE)	See Boxes 30.6 and 30.7
Diabetic nephropathy	No adverse effect on the renal lesion. Increased frequency of infections, oedema, or preeclampsia. Advanced nephropathy can be a problem
Human immunodeficiency virus with associated nephropathy (HIVAN)	Renal component can be nephrotic syndrome or severe impairment. Scanty literature. Should be considered when nephrotic proteinuria occurs suddenly, especially in immunocompromised patients
Adult PCKD	This autosomal dominant disorder is the Most common single-gene genetic disease of humans with an incidence of 1 in 400–1000. May request DNA probe screening of foetus. Functional impairment and hypertension are usually minimal in childbearing years. Most do not have clinical manifestation until fourth or fifth decade; only 17% diagnosed by age of 25. Patients do well if renal impairment is minimal. One in four has late-pregnancy hypertension
Periarteritis nodosa scleroderma	Foetal prognosis is poor. Maternal death can occur. Therapeutic abortion should be considered if disease onset during pregnancy shows rapid overall deterioration. Reactivation of quiescent scleroderma can occur during pregnancy and after delivery
Previous urologic surgery	Depending on original reason for surgery, there may be other malformations of the urogenital tract. Urinary tract infection is common during pregnancy and renal function may undergo reversible decrease. No significant obstructive problem, but caesarean section might be necessary for abnormal presentation or to avoid disruption of the continence mechanism if artificial sphincters or neo urethras are present
After nephrectomy, solitary and pelvic kidneys	Pregnancy is well tolerated. Might be associated with other malformations of the urogenital tract. Dystocia rarely occurs with a pelvic kidney

Source: Modified from Davison and Lindheimer [7]

30.5.1 Kidney Function

If there is significant deterioration at any stage of pregnancy, then think in terms of 'prerenal, renal, or post-renal' and of reversible causes such as UTI, diarrhoea, over-strict water and salt restriction, subtle dehydration or electrolyte imbalance (occasionally precipitated by inadvertent diuretic

therapy), temporary renal tract obstruction, or nephrotoxic drugs. Near term, as in normal pregnancy, a decrease in function of 15–20%, which affects S_{cr} minimally, is permissible. Failure to detect a reversible cause of a significant decrement is grounds to end the pregnancy by elective delivery. Do not allow acute kidney injury (AKI) to accelerate to such an extent that not even terminating the pregnancy will reverse the decline [2, 29]. When proteinuria occurs and persists, but blood pressure is normal and renal function preserved, pregnancy can be allowed to continue under closer scrutiny. Thus, increased proteinuria in isolation is not used to time delivery.

30.5.2 Temporary Dialysis

This may be judged necessary during pregnancy especially when S_{urea} is much in excess of 20 mmol/L (48 mg/dL), when intrauterine foetal death is more likely [2]. Refractory hyperkalaemia, severe metabolic acidosis, pulmonary oedema responding poorly to diuretics, and danger of volume overload with heart failure may also prompt consideration of dialysis.

It is essential to watch for dialysis-induced uterine contractions (resulting in preterm labour and delivery), and tocolytic agents can be used with care if indicated. Dialysis-induced hypotension must be avoided too, and also remember that, in the supine position, the patient's enlarged uterus may reduce venous return and aggravate the situation. Even when volume fluctuations are minimised, however, umbilical artery Doppler velocimetry still indicates that haemodialysis temporarily causes considerable foetal haemodynamic alterations.

Dialysis may increase the chance of successful outcome by 'buying time' for foetal maturation, but it does not arrest the inexorable decline in kidney function, ultimately to end-stage renal failure. As stated in Sect. 30.4, this is one of the risks associated with pregnancy with CKD that needs to be discussed with the woman when in the planning of or early stages of pregnancy.

30.5.3 Blood Pressure

The conventional dividing line for obstetric hypertension is 140/90 mmHg and, in patients with CKD, the aim should be to keep it between 120/70 and 140/90 [17, 19, 21, 23, 30–32]. Inappropriately low blood pressure is associated with foetal growth restriction (FGR) and high blood pressure with renovascular damage, so a balance is needed. Most of the specific risks of hypertension appear to be related to superimposed preeclampsia in women with CKD but the diagnosis cannot be made with certainty on clinical grounds alone as hypertension and proteinuria may be manifestations of the underlying CKD. Also, chronic hypertension alone has an increased preeclampsia risk fourfold that of normotensive pregnant women. Treatment of mild hypertension (diastolic blood pressure less than 95 mmHg in the second trimester or less than 100 mmHg in the third) is not necessary during normal pregnancy, but many treat women with CKD more aggressively, with a view that this preserves kidney function [7].

For women with hypertension during pregnancy, but without CKD, the CHIPS trial [33] supports targeting a diastolic blood pressure of 80–85 mmHg (vs 100–105 mmHg) using labetalol and in this study there was no increase in reported adverse maternal events. Severe maternal hypertension (>160/100 mmHg) had a lower incidence in women who were treated to the lower blood pressure target, but this did not reduce the impact on maternal morbidity [34]. For nonpregnant patients with CKD, progression of potential renal dysfunction is reduced with tight blood pressure control, but international guidelines have not yet agreed on a target for pregnancy and there is no published evidence to support the benefit of BP control before conception to improve pregnancy outcomes [35]. So we currently use the information that we have, plus clinical experience and intuition, on which to base recommendations regarding blood pressure control in women with CKD, working on the principle that we aim to 'preserve' renal function

and minimise the progression of CKD. We then tailor the rest of a woman's care around preventing adverse maternal and foetal events through surveillance and by providing a robust MDT approach, as well as supporting her to have a good pregnancy experience.

Medications such as methyldopa, calcium channel blockers, labetalol, and hydralazine are safe in pregnancy [27, 36]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers *should not be prescribed during* pregnancy. When patients are taking either of these before pregnancy, however, because of the significant renoprotection effect, there is a view emerging that changing to a safer drug or drugs can wait until the patient becomes pregnant.

30.5.4 Role of Kidney Biopsy in Pregnancy

Experience with kidney biopsy in pregnancy is limited, mainly because clinical circumstances rarely justify the risk of the possible complications, which are much higher in pregnancy than postpartum, 7 and 1%, respectively, the latter akin to the rate in nonpregnant subjects [26]. Thus, kidney biopsy is usually deferred until after delivery, provided hypertension is well-controlled and coagulation indices are normal.

Whilst pregnancy is considered by most to be a relative contraindication, there are a few generally agreed indications such as when severe nephrotic syndrome develops in early pregnancy or when the suspicion is of a rapidly progressive glomerular disease, for example, SLE in the second trimester, severe enough to warrant specific treatment [21].

30.5.5 Timing of Delivery

Decisions need to be individualised and involve the MDT [1], taking into account gestational age, current foetal and maternal well-being and prognosis as well as the risks of neonatal consequences of early delivery against the risks of complications of continuing the pregnancy [17, 37]. Indeed, if complications do arise, the judicious moment for intervention will inevitably take into account foetal status and a decision about the use of maternal corticosteroids for foetal lung maturation plus magnesium sulfate for neonatal neuroprotection [38]. In the absence of maternal and/or foetal deterioration, delivery should be at or near term (>37 weeks gestation). Planned preterm delivery may be necessary if there are signs of foetal compromise (e.g. persistent reduction in foetal movements, abnormal findings on foetal ultrasound scan, etc.), if kidney function deteriorates substantially, if uncontrollable hypertension supervenes or eclampsia occurs [17, 29, 37]. Obstetric considerations should be the main determinant for delivery by caesarean section. There is certainly an increased risk of emergency caesarean section in labour, spontaneous or induced, for either maternal or foetal complications.

During labour, kidney function and BP must be assessed frequently as well as undertaking continuous electronic monitoring of the foetus. Strict fluid balance must be maintained. If appropriate, prophylaxis with magnesium sulfate to prevent eclampsia must be considered, with careful maternal monitoring in a high dependency setting. During active management of the third stage of labour, use oxytocin not syntometrine. Where there is a prerenal insult such as haemorrhage, HELLP, or acute fatty liver of pregnancy (AFLP), on top of worsening CKD and/or preeclampsia, which can further acutely threaten maternal kidney function, nephrotoxic drugs must be avoided and the maternal circulation restored with careful fluid management as such patients are prone to fluid overload [17, 28, 37, 39].

30.6 Postpartum Care

Immediately after delivery, there is potential for instability in BP control and fluid balance as well as further deterioration in maternal kidney function, so close surveillance is still needed [1, 17, 28, 37, 39]. Be vigilant in avoiding NSAIDs for post-delivery analgesia because in many units

these are routinely prescribed, with patient self-administration.

Decisions will be needed about changing back to pre-pregnancy medication(s), especially renoprotective drugs, if required, but this may be delayed if mother wishes to breastfeed, dependent on any contraindications [27, 36]. With nephrotic syndrome, prophylactic heparin should be continued for 6 weeks after delivery [15].

If required, renal ultrasound should be arranged for the baby. Remember to arrange a postnatal review appointment with the MDT, both to reassess the patient and to debrief her and her partner about their pregnancy experience (which may have been complicated and worrying), their obstetric and renal future as well as contraception [2].

30.7 Systemic Lupus Erythematosus (SLE)

SLE is worthy of special mention because, even in a multidisciplinary setting, the physician and the obstetrician should have experience with SLE and awareness of the extensive literature [2, 19, 21, 22]. SLE may be present with or without other connective tissue diseases (the overlap syndrome) and the complex clinical problems are due to its profound immunological disturbances, its multi-organ involvement and the complicated immunology of pregnancy itself. Pre-pregnancy assessment and the clinical 'watchpoints' for pregnancy management and afterwards are outlined in Boxes 30.6 and 30.7.

Box 30.6 Pre-Pregnancy SLE Assessment and Counselling

- Prediction of good outcome is related to disease activity and remission, as well as optimal and stable medication(s) in preceding 6 months. Degree of renal impairment, level of hypertension, if any, and low complement levels are also important.
- As well as lupus nephritis, the presence of other comorbidities, such as antiphospholipid syndrome (APS), must be considered.
- Pulmonary hypertension is an absolute contraindication to pregnancy.
- Thromboprophylaxis must be carefully reviewed if considering a past history of thrombosis, nephrotic syndrome, and/or preeclampsia.
- Past obstetric history has also to be considered for any other adverse features.
- SLE increases the risk of spontaneous miscarriage, which can be as high as 30%.
- Four out of five pregnancies will be successful when SLE is in complete remission, even if originally there were severe histopathological changes on biopsy and heavy proteinuria.
- Maternal death rate is 20-fold higher than the normal population. Source: Data from Refs. [2, 7, 19, 21, 22].

Box 30.7 Pregnancy in SLE Patients

- Complications are common: Extrarenal flare (25%), renal flare (most commonly after delivery) (10%), FGR (at least 30%), preterm delivery (50%), and preeclampsia (at least 10%).
- In pregnancy up to 20% of patients have GFR decrements, progressive in 8%.
- Preeclampsia occurs earlier and more frequently in women with lupus nephritis, even compared to women with similar impairment due to a different CKD.
- Presence of lupus anticoagulant strongly associated with development of preeclampsia.
- Lupus nephritis classes III and IV are more likely to be associated with preeclampsia than classes II and V.
- In a known SLE patient, preeclampsia may be difficult to distinguish from a

renal 'flare' (even postpartum), but decreasing complement levels, urinary sediment analysis and increasing anti-dsDNA levels may be helpful as well as evidence of increased lupus disease activity in other organs.

- The most reliable arbiter for distinguishing preeclampsia from lupus nephritis is kidney biopsy, but it is rarely undertaken in pregnancy. It may be considered appropriate in the second trimester, if it is felt that the result will tailor/alter management, in relation to 'buying time'.
- SLE has a predilection for the childbearing age group, and if SLE nephropathy becomes manifest for the first time in pregnancy, it may be mistaken for preeclampsia.
- Extrarenal 'flares' occur predominantly in the second half of pregnancy, with renal 'flares' more common in puerperium, a time of increased vigilance as SLE medication(s) (if any) may need adjusting as well as those for ongoing management of hypertension and for thrombosis, in line with breastfeeding considerations. Source: Data from Refs. [2, 7, 19, 21, 22, 27].

30.7.1 SLE and the Foetus

As well as miscarriage and FGR, SLE confers other big risks on the foetus [21]. Congenital heart block (CHB) is associated with maternal anti-Ro and anti-La autoantibodies and occurs in up to 4% of the foetuses in these women, with a 15% recurrence risk in subsequent pregnancies. It develops between 18 and 20 weeks gestation, so if suspected (from a fixed foetal heart rate of 80 bpm), then foetal echocardiography is essential. Sometimes, hydrops fetalis may develop in utero, occasionally severe, and even those babies born unscathed, half will need pacing in the first year of their lives. Neonatal lupus rash, usually on the scalp and face, and classically akin to adult subcutaneous SLE lesions, can occur soon after delivery and up to 6 months thereafter. These very rarely coexist with CHB and may take several months to subside.

30.8 Suspicion and/or Diagnosis of De Novo CKD During Pregnancy

For some women, pregnancy may be their first major contact with health-care services and represents a valuable opportunity to detect chronic medical conditions, including CKD. If this possibility is raised, it is essential to try and establish a diagnosis as well as a course of management that will be helpful to both mother and foetus [7]. When a patient presents with hypertension, proteinuria, and/or abnormal kidney function, it is difficult to distinguish parenchymal CKD from preeclampsia [16–18, 23]. A previous history of kidney disorders, abnormal urine analysis, a family history of CKD, or a history of systemic illness known to involve the kidneys is obviously very helpful, but even so CKD and preeclampsia may coexist. In 10–20% of patients where preeclampsia is severe, of early onset and especially with heavy proteinuria, this may in fact be the first clinical presentation, indeed unmasking rather than development, of asymptomatic/undiagnosed CKD from pre-pregnancy, more so if the woman is multiparous [17, 18, 23].

Proteinuria alone, in the absence of urinary infection, can be an indication of kidney dysfunction. If TPE is consistently ≥500 mg/24 h, then renal impairment will be present in about half, 40% will go on to develop hypertension, 25% will have low birth weight babies, and 50% will deliver preterm. Some of these women may have been labelled preeclamptic in previous pregnancies, but remember that undetected CKD is very likely [7, 17, 40].

In women suspected of having CKD, their assessment and subsequent blood testing are sim-

ilar to those of nonpregnant patients but the definitive diagnosis has to wait until after delivery [18, 40]. If their kidney function and blood pressure remain stable, then pregnancy care should continue with MDT surveillance. Nephrology follow-up after delivery is essential for continued assessment and perhaps final diagnosis, with the aim of reducing progressive deterioration and concurrent escalation of cardiovascular and metabolic risks. Intervention with lifestyle changes and then timely pharmacological intervention with the first indication of sequelae is particularly important if there was preeclampsia, as it is a marker for remote cardiovascular, cerebrovascular, metabolic, and renal problems [31, 32, 40].

30.9 Loss of Kidney Function in Pregnancy and Afterwards in Women with CKD

Pregnancy should not cause or otherwise affect the rate of progression beyond what might be expected in the nonpregnant state, provided that before the pregnancy, kidney impairment was minimal and hypertension absent or very well controlled (Box 30.8). During pregnancy of course, there is a hypercoagulable state, with an augmented coagulation cascade and decreased fibrinolytic activity which even if only slightly augmented in CKD patients could mediate insidious AKI with thrombotic glomerular injury. Prolonged periods of protein trafficking are nephrotoxic too, with induction of proinflammatory and inflammatory cytokines causing glomerular injury along with tubulointerstitial damage. In the long-term prognosis, however, an important factor could be the sclerotic effect that prolonged, gestational renal vasodilation might have in the residual (intact) glomeruli of the kidneys of these women, especially if contributed to by an increased intraglomerular pressure. The situation may be worse in a single diseased kidney, where more sclerosis has usually occurred within the few (intact) glomeruli. Although the evidence in healthy women and those with mild kidney disease argues against hyperfiltration-induced damage in pregnancy, or any increase in intraglomerular pressure, there is little doubt that in some women with moderate, and certainly severe dysfunction, unpredicted, accelerated, and irreversible renal decline does occur in pregnancy and/or afterwards [2, 6, 7, 10, 17].

Box 30.8 Worsening CKD during Pregnancy and Afterwards

- Rate of CKD progression and gradual erosion of kidney function usually relates to the level of BP control, degree of proteinuria, underlying CKD, and previous rate of GFR decline.
- In pregnancy there may be accelerated and irreversible decline greater than that predicted based on the previous course.
- Renal insufficiency and hypertension, especially where poorly controlled, are the major risk factors for permanent exacerbations of underlying CKD.
- Risk of decline is highest when renal insufficiency is greatest.
- Cause of CKD, other than lupus nephritis, is probably not a major determinant of worsening CKD if factored for preexisting renal insufficiency and hypertension.
- With preeclampsia, kidney function often declines further, mimicking CKD deterioration.
- Sequential S_{cr} measurements showing escalating concentrations may be evidence of preeclampsia in the absence of any other renal diagnoses.
- Addition of a prerenal insult may further reduce kidney function, such as antepartum haemorrhage (APH) and/or postpartum haemorrhage (PPH). Regular use of NSAIDs can acutely and additionally threaten maternal kidney function, as can HELLP, preeclampsia, HUS, acute fatty liver of pregnancy (AFLP), or thrombotic microangiopathies. Source: Data from Refs. [2, 4–7, 9, 10, 15, 16, 21, 25, 28–30, 36]

30.10 Preeclampsia: Diagnosis, Significance, and Prognosis (Boxes 30.9 and 30.10)

Preeclampsia remains a major cause of maternal and perinatal morbidity and mortality and occurs in around 6% of all pregnancies. Interestingly, it is the commonest cause of glomerular disease worldwide. The diagnosis of preeclampsia, with the ability for appropriate intervention is based on traditional but often unreliable and nonspecific criteria of hypertension and proteinuria [12, 13, 27, 37, 41]. Evidence of involvement of one or more other organs with liver function abnormalities, thrombocytopenia, DIC, and/or patient-reported symptomatology may help to establish the diagnosis. In addition, marked rises in S_{cr} (without any other explanation), ever-increasing BP and/or escalating anti-hypertensive requirements may imply superimposed preeclampsia. Nevertheless, preeclampsia cannot be diagnosed clinically with certainty in women with CKD [2, 16–18, 23].

Superimposed preeclampsia affects one-third of women with CKD, and by elucidating the pathophysiology of preeclampsia and identifying some of the many underlying factors, measurement of 'biomarkers' may be used as an aid in predicting preeclampsia in 'at-risk' women, like those with CKD, and/or in diagnosing preeclampsia when the diagnosis is suspected but not certain. Ideally, it might be possible to distinguish between preeclampsia and the progressive hypertension, proteinuria, and renal deterioration of AKI in CKD patients. With the advent of 'pre-symptomatic' biomarker use, we have an exciting opportunity to prevent or modify risk and then tailor maternal surveillance and treatment accordingly [31, 33, 34, 40].

Box 30.9 Preeclampsia and CKD

- During pregnancy in CKD patients, hypertension worsens or develops in 30%, proteinuria increases in over 50% and decline in kidney function can often occur.
- If preeclampsia develops in CKD patients, then maternal kidney function often deteriorates further.
- In CKD, hypertension and proteinuria are not necessarily due to preeclampsia, as exacerbation of CKD can mimic preeclampsia and/or the two may coexist.
- The uncertainty of clinical diagnosis leads to difficulty in differentiating preeclampsia from not only exacerbation of CKD but also HUS, AFLP, and thrombotic microangiopathies.
- Risk of developing preeclampsia in CKD is higher with more severe degrees of renal impairment (from 10% up to 80%), higher still in the presence of hypertension.
- Preeclampsia is the most common cause of nephrotic syndrome in pregnancy, but it may also be secondary to underlying CKD, or both.
- Clinically useful circulating 'biomarkers' for preeclampsia have been identified and evaluated to assist not only with diagnosis but also with 'pre-symptomatic' prediction of risk and/or complications with the potential for therapeutic intervention(s). Source: Data from Refs. [2–4, 6, 8, 9, 16–18, 23, 24, 29, 30, 36, 38, 40, 42].

Box 30.10 Prognosis after Preeclampsia

- No longer assume that preeclampsia is a condition 'cured' by delivery.
- Although renal changes in general are believed to resolve completely after delivery ('delivery cures preeclampsia'), there is evidence that preeclampsia may leave permanent renal impairment or add further to the deficit of already damaged kidneys.
- Damage may be direct or indirect via hypertension and/or widespread endothelial dysfunction.

- After preeclampsia there is a three- to eight- fold increased risk of cardiovascular disease (including ischaemic heart disease, hypertension, and stroke) as well as obesity, dyslipidaemia, and end-stage renal disease.
- Preeclampsia and cardiovascular disease share risk factors such as hypertension, obesity, diabetes, and hypercholesterolaemia, so preeclampsia is certainly a marker for cardiovascular risk.
- Not yet definitely known whether preeclampsia per se adds to the risk; if so, then preeclampsia would be an independent risk factor and not just a marker.
- These remote risks are greatest in those who also had preterm births, FGR, and/or recurrent preeclampsia, all frequently seen in CKD women anyway.
- Preeclampsia will add to the already unfavourable cardiovascular and metabolic profile of CKD patients, as CKD patients already carry risk factors.
- Offspring of preeclamptic mothers are more likely to have a higher BP from childhood and a stroke in later life.
- There is a need to elucidate the underlying biological factors that underpin the association between preeclampsia and disease later in life. Source: Data from Refs. [2, 7, 8, 17, 22–24, 31, 32, 40].

In preeclampsia the balance between proangiogenic and antiangiogenic factors is altered [17, 18, 35, 40], and this affects placental function. This imbalance is due to disturbances in the vascular development of the placenta with underperfusion and ischaemia such that the hypoxic trophoblast secretes a wide range of antiangiogenic factors into the maternal circulation. These include placental growth factor (PlGF) as well as soluble fms-like tyrosine kinase-1 (sFlt-1) (a soluble decoy receptor for vascular endothelial growth factor (VEGF)) and soluble endoglin (sEng), both of which block VEGF-mediated signalling, which is important for normal endothelial function. Thus, there is widespread endothelial disruption, microangiopathy and a disturbed inflammatory response, potentially creating a favourable setting for autoimmunity, and the glomerulus is afflicted as part of all this, with disruption of podocyte and endothelial symbiosis. Podocyturia as well as markers of endothelial injury, such as von Willebrand factor, fibronectin, and osteopontin, are yet to be proven clinically useful [13, 17, 22, 36].

Pathogenic agonistic autoantibodies, although not specific, are highly prevalent in preeclampsia, one of which (AT $_1$-AA) can activate the major angiotensin II type 1 receptor (AT $_1$R) [13, 17, 43]. There then can follow hypertension, hypercoagulation, and glomerular dysfunction as well as FGR, secondary to AT $_1$-AA-induced placental damage and ischaemia and yet a further increase in sFlt-1 and sEng. Antibody titres correlate with the severity of disease and thus may be useful as a pre-symptomatic biomarker and their blockage and/or removal may potentially be a treatment option [35]. As sFlt-1 and PlGF reflect underlying placental and endothelial pathophysiology, their measurement is useful [38], and in 2021 Wiles et al. [42] looked at the biomarkers PlGF, sFlt-1, Hyaluronan, and VCAM in 232 pregnancies of 212 women with CKD to evaluate this. One-third of these women developed superimposed preeclampsia and, from 21 to 37 weeks gestation, PlGF levels were reduced in this group. This team found that plasma PlGF levels of <150 pg/ml had the highest sensitivity (79% (95% CI: 58–91%)) and the highest negative predictive value (97% (95% CI 93–99%)) for the prediction of delivery with superimposed preeclampsia within 14 days. They found that measuring Hyaluronan and VCAM levels in these women yielded less reliable predictive information regarding preeclampsia risk. Interestingly, they found that biomarker predictive performance was affected by the stage of CKD: low plasma PLGF, high hyaluronan, and high VCAM concentrations were much better at predicting superimposed preeclampsia in CKD 1–2 com-

pared to CKD 3–5. A ratio of PlGF:sFlt-1 of >38 in serum did not usefully predict the need to deliver in women with CKD.

In many obstetric units, PlGF measurement is becoming an increasingly utilised tool in the prediction of suspected preeclampsia, but it is important that a clinically useful predictive model also includes taking a good maternal history, looking at demographic and social factors, standard biochemical investigations, and ultrasound biophysical assessment in order to achieve useful stratification of risk [26, 36, 37, 39].

There is little doubt that women diagnosed with preeclampsia have a substantially increased risk of cardiovascular disease, cerebrovascular disease, end-stage renal disease, and metabolic problems in later life and this risk may also be associated with conditions that coexist with preeclampsia, including CKD [27, 29, 36, 37]. Lifestyle interventions after preeclampsia may decrease the cardiovascular risks, but information is now needed about the interplay between genetic, proteomic, and environmental factors so as to understand the clinical implications [36].

Before You Finish: Practice Pearls for the Clinician

- Pre-pregnancy assessment and counselling is a crucial approach for management of women with CKD, providing the ideal opportunity to establish baselines, to achieve optimal use of medication(s) and health education, and to discuss all aspects of pregnancy, including the woman's wishes and expectations. 'Co-produce' a plan with the woman, respecting her choices and autonomy.
- Once a CKD patient, always a CKD patient, and important determinants are pre-pregnancy renal status (CKD stage), the absence or presence of hypertension (and its management) as well as robust foetal surveillance, timely delivery, and appropriate neonatal care in the right place for mother and baby.
- All women with CKD are at increased risk of pregnancy complications with overall at least a two- to fourfold higher risk of adverse foetal outcome, even those with CKD stage 1.
- Absence of severe hypertension or renal dysfunction pre-pregnancy is favourable for pregnancy and renal prognosis. If dysfunction is severe, there is still a fair chance that pregnancy will succeed, but risks are much greater, including AKI and its aftermath.
- Type of renal disease probably does not influence outcome but the collagen disorders, IgA and reflux nephropathies and certainly SLE need special consideration.
- Proteinuria is common during pregnancy (up to 3 g/24 h) but we are still learning about the longer-term implications of the increased protein trafficking within the kidney.
- Severe hypertension is a much greater adverse feature than low but stable kidney function. 'Controlling a sign' does not modify the basic pathophysiology underlying clinical deterioration. Preeclampsia cannot be diagnosed clinically with certainty, but the advent of biomarkers may help in making surveillance plans for women with CKD and superimposed preeclampsia.
- Rapidly deteriorating kidney function, however, even without hypertension, can be ominous.
- Postnatal ongoing renal follow-up and debriefing are very important, as this gives the MDT an opportunity to listen to the woman's experience of her pregnancy, act on concerns but also celebrate and acknowledge good teamwork.

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Surgery and Chronic Kidney Disease

31

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Before You Start: Facts you Need to Know CKD is an independent risk factor for perioperative morbidity and mortality in both noncardiac and cardiac surgeries, with increased incidence of AKI, stroke, infection, and cardiovascular complications, as well as prolonged hospital stay.

- Comorbidities and complications of CKD must be screened for and optimized prior to surgery.
- Cardiopulmonary "fitness" is a key indicator of perioperative risk in major surgery.
- Drug handling is altered in CKD, and perioperative care should include careful dosing of medications according to kidney function.
- Safe perioperative care requires careful attention to hemodynamics and fluid balance and postoperative step-down or ICU care for high-risk patients.
- Prevention of AKI is essential in patients with CKD undergoing surgery and application of biomarkers and nephroprotective care bundles in high-risk patients effectively reduces the postoperative incidence and severity of AKI.

31.1 Setting the Context for Surgery in the Patient with CKD

31.1.1 Prevalence of CKD

In the general adult population, the incidence of CKD is approximately 13% of which 50% are older than 70 years. Most of the CKD patients suffer from mild to moderate CKD stages, whereas CKD stage 4 and 5 are seldom [1]. Due to the higher prevalence of diabetes, hypertension, hyperlipidemia, and the aging population, the incidence of CKD is constantly increasing. CKD itself is a multisystem disorder that considerably affects the function of other organs. Given the long-term sequelae of CKD (including the risk of becoming chronic dialysis dependent), it poses a tremendous burden on healthcare systems (e.g., dialysis or kidney transplantation just to mention some of them). Still, CKD is an often underdiagnosed disease with an estimated 50% of elderly patients meeting CKD criteria but without an official diagnosis of CKD [1].

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31.1.2 Impact of CKD on Perioperative Outcomes

CKD is an independent risk factor for perioperative morbidity and mortality, and this finding is consistent across a range of surgical specialties including cardiac surgery, vascular surgery, abdominal surgery, and orthopedics [2–5]. Perioperative risk in patients with CKD depends on several factors, including type of surgery, duration of surgery, whether intraoperative complications occur and whether the surgery needs to be performed in an emergency setting [6]. Several factors play a role, not the least of which is the recognition that CKD is a multisystem disease to which comorbidities such as hypertension, heart failure, ischemic heart disease, pulmonary hypertension, diabetes, metabolic syndrome, and peripheral vascular disease. These comorbidities are not only considerably more prevalent in the CKD population but also have a higher mortality rate in CKD patients [7, 8].

The degree of kidney dysfunction and the treatment quality prior to surgery influence CKD patient outcomes. Patients with ESKD are at especially high risk for postoperative complications and mortality. As such, patients with ESKD had almost three-fold increased mortality rates after open abdominal aortic surgery, compared to patients without ESKD (16.1% vs 4.8%) and this effect was also present in endovascular abdominal aortic surgery (10.3% vs. <1%) [9–11]. Due to ESKD-based dysregulations of the coagulation system, the immune system, electrolytes, and acid–base homeostasis, patients with ESKD are especially susceptible for such intra- and postoperative complications [12].

The chronically impaired kidneys are more vulnerable to insult and interference in the perioperative period. The contributions of tissue damage, renal hypoperfusion, drug toxicity, contrast nephrotoxicity, fluid overload, mechanical ventilation, and others lead to a higher risk of perioperative AKI in patients with CKD. If AKI occurs, it is often more severe than in patients without CKD and CKD patients are less likely than patients with previously normal kidney function to regain independence from dialysis after an episode of AKI [13].

31.2 Preoperative Considerations and Evaluation

31.2.1 Preoperative Evaluation in Patients with CKD

Given that CKD is often underdiagnosed due to its asymptomatic course, special attention should be paid to CKD screening preoperatively. The identification of these patients is based on risk factors (age, obesity, smoking), widespread diseases (diabetes, hypertension, or peripheral vascular diseases), and laboratory tests (serum creatinine, blood urea nitrogen, glomerular filtration rate). Table 31.1 summarizes recommendations of CKD screening triggers.

Improving screening rates for CKD in the general population is necessary to move from a treatment only approach to a preventative approach to tackle the global crisis of CKD [15]. This should include a physical examination and measurement of serum creatinine. GFR should be estimated using the CKD-EPI formula, but this must be interpreted with caution in patients with very low muscle mass, e.g. due to motor neuron disease, or paralysis. This is especially complicated in patients with low dietary intake of proteins, which is common in elderly patients. This leads to a regular overestimation of GFR in these patients. Cystatin C may be a more competent biomarker of kidney function in this cohort of patients as it is less influenced by muscle mass or dietary intake of protein and Cystatin C can also be used for the CKD-EPI formula to estimate GFR [16]. In a cross-sectional study, Inker and colleagues compared serum creatinine and serum

Table 31.1 Recommendations of indications for preoperative CKD screening [14]

Clinical factors	Sociodemographic factors
Diabetes	Elderly (age > 60 years)
Hypertension	Active smokers or history of smoking
Cardiovascular diseases	Low income/education
Obesity	African-American race
Systemic infections or autoimmune disease	Male gender
Family history of kidney disease	
History of AKI	

Cystatin C for the diagnosis of CKD [17]. Interestingly, the combination of both parameters performed better than any of the markers alone.

Additionally, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the diagnosis of CKD recommend the evaluation of albuminuria to screen for CKD, and degree of albuminuria informs CKD staging [18]. In descending order, it is recommended to use urinary albumin-to-creatinine ratio, urinary protein-to-creatinine ratio, or reagent strip urinalysis.

Furthermore, serum electrolytes (including magnesium, calcium, and phosphorus), blood glucose, blood urea nitrogen, complete blood count, coagulation tests, and albumin should be measured to allow for baseline references and adequate planning of preoperative optimization and intraoperative management. In patients with CKD and GFR <60 mL/min/1.73m^2, serum concentrations of BNP/NT-proBNP and troponin must be interpreted with caution because these measurements are distorted.

If CKD is diagnosed preoperatively, this should be documented in the (electronic) health record and all involved specialties be informed about this novel diagnosis. If radiological diagnostic workup using radiocontrast agents is required prior to surgery in patients at high risk for AKI, *KDIGO* [19] recommends the following precautions:

- Avoidance of high osmolar agents (1B);
- Use of lowest possible radiocontrast dose (not graded);
- Withdrawal of potentially nephrotoxic agents before and after the procedure (1C);
- Adequate hydration before, during, and after the procedure (1A);
- Measurement of GFR 48–96 hours after the procedure (1C).

Type of surgery and anesthesia must be reevaluated at this point and if possible, less invasive methods are preferable. This is true for both type of surgery and anesthesia. Changing surgical method, for example, to off-pump bypass or performing surgery under local or regional anesthesia may avoid kidney damage due to hemodynamic effects of general anesthesia or inflammatory stress due to extensive surgical injury or due to heart–lung machine. This has been demonstrated to reduce adverse effects in high-risk patients. For example, in vascular surgeries of the aorta, endovascular techniques reduced the rates of postoperative kidney complications and mortality as compared to open surgery [20, 21]. The same effect on kidney complications could be observed in general surgery, if robotic surgery was performed as compared to open surgery [22].

31.2.2 Preoperative Optimization of Blood Pressure and Heart Failure Therapy

Arterial pressure control and blockade of the renin–angiotensin system (RAAS) are considered vital in slowing progression of CKD. KDIGO recommends a target systolic blood pressure under 120 mmHg based on standardized office blood pressure measurement [23]. It is worth remembering that drugs such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blocking drugs (ARBs), and loop diuretics are often omitted on the day of surgery to minimize hemodynamic instability under anesthesia, and reintroduction may be delayed in the postoperative period in cases of major upper gastrointestinal or cardiac surgery. If control is suboptimal, hypertension and pulmonary congestion may become a problem postoperatively. Patients should also be screened for postural hypotension and for diastolic hypotension which is an underappreciated risk factor for adverse cardiovascular outcomes [24, 25].

31.2.3 Preoperative Optimization of Blood Glucose Control

Where elevations in glycosylated hemoglobin suggest suboptimal glucose control, an endocrinology consultation may be indicated. Perioperative stress and vasopressor medication

contribute to hyperglycemia and increased insulin requirements. Perioperative hyperglycemia contributes to increased risk of infection. Hospitals often have protocols for discontinuation of oral antidiabetics prior to surgery. Of note is that CKD patients are at higher risk of fasting hypoglycemia if the timing of discontinuation is not appropriate.

31.2.4 Preoperative Optimization of Phosphate and Parathyroid Hormone

Patients with more advanced CKD may already be treated with phosphate binders and vitamin D analogs. The effectiveness of these regimens should be reviewed preoperatively. Some patients with CKD may have undergone parathyroidectomy and are at risk of "hungry-bone syndrome" with hypocalcemia issues. Calcium and phosphate levels should be carefully monitored around the time of surgery when oral therapy may be withheld because of fasting or delayed return of gastrointestinal function.

31.2.5 Preoperative Optimization of Fluid and Electrolyte Status

Depending on the extent of surgery and anesthesia, increased insensible water losses, bleeding, and loss of voluntary control of fluid intake play an important role. Patients with higher stages of CKD are at risk of hyperkalemia, hyperchloremia, and dysnatremia in the perioperative period, and this risk is amplified by surgical tissue trauma, catabolism, fluid shifts, and changes in GFR and urine concentrating ability. 0.9% physiological saline solution may cause hyperchloremic acidosis and renal vasoconstriction when infused in larger amounts. In view of the aforementioned electrolyte disturbances and attributable risk of developing AKI, balanced crystalloids should be favored. In patients at risk of fluid overload (e.g. heart failure), fluid accumulation must be minimized according to edema and weight while also limiting the incidence of overt dehydration, which can lead to profound hypotension under anesthesia. Electrolyte stability, even if not a problem preoperatively, can become a significant problem following surgery. In advanced CKD, loss of potassium through the gastrointestinal tract can become an important part of regulation and this may be diminished or lost when the integrity of the gastrointestinal tract is compromised. Other perioperative contributors to altered potassium handling, such as insulin administration, acidemia, beta-receptor-active drugs should be anticipated and electrolytes regularly monitored.

31.2.6 Preoperative Optimization of Nutritional Status

Given the impact of hypoalbuminemia on drug carriage and edema formation, significant malnutrition in patients with CKD must be addressed prior to elective surgery. In patients with CKD and heart failure, poor gut perfusion can have an additive effect on nutritional status, whereas edema maintains weight despite altered body composition. Performing a nutritional assessment may be a worthwhile preoperative consult. In severe cases, supplemental nutrition solutions may be needed to optimize nutritional status before surgery.

31.2.7 Preoperative Management of Anemia

In general, anemia secondary to CKD only develops with severe CKD. In the absence of treatment, hemoglobin concentrations may fall to below 80 g/L (8.0 g/dL) with hematocrit in the 25–27% range. This level of anemia has a number of deleterious effects, not least of which is a decline in oxygen delivery and aerobic capacity. Preoperative anemia is associated with adverse postoperative outcomes in patients with CKD, especially if undergoing cardiac surgery [26–28]. This effect can be amplified by disorders such as ischemic heart disease and heart failure and has a serious

effect on quality of life. Replacement therapy with erythropoiesis-stimulating agents (ESAs) and iron is used with a goal hemoglobin level of 110–120 g/L (11.0–12.0 g/dL) and a hematocrit of 33–36% [29]. This is an acceptable level for the vast majority of patients and operative interventions. ESAs are not an option for acutely increasing hemoglobin levels or responding to perioperative blood loss, and blood transfusion should be cautiously indicated, being aware of possible complications such as fluid overload, transfusion reactions, and hyperkalemia. There is no evidence that supports aggressive preoperative transfusion strategies. Thus, preoperative blood transfusions should be withheld unless patients present with very low hemoglobin levels. Optimal hemoglobin levels to aim for in patients with CKD prior to surgery remain controversial in patients with advanced CKD and potential for later kidney transplantation, red blood cell blood transfusions should be avoided whenever possible in order to avoid the risk of allosensitization and if required should only receive hepatitis E negative blood transfusions [30].

31.2.8 Reducing Bleeding Risk

Chronic exposure to uremic toxins in advanced CKD has significant effects on bleeding time through alterations in platelet function (both activation and aggregation) and von Willebrand factor (vWF) levels (reducing platelet adhesion). This effect is not linearly related to GFR, urea, or creatinine levels and should be considered as a potential problem in CKD 3–5 patients. This risk is amplified by the use of antiplatelet drugs, for example, aspirin and clopidogrel. Aspirin is often continued perioperatively in patients without CKD, and a decision to do the same in the CKD patient requires a careful risk/benefit analysis. In addition to abnormalities of platelet function, anemia has effects on blood rheology and reduces physiological platelet margination to the periphery of blood vessels (where they can do most good in clot formation). In cases where perioperative bleeding risk is high, consideration should be given to increasing the hematocrit prior to surgery if this is significantly below the conventional goal of 33%. There are also a number of pharmacological options for improving bleeding time in uremic patients (see Table 31.2) in preparation for surgery, although controversial and mostly based on low-quality evidence. Several studies have investigated the efficacy of Desmopressin or octreotide to reduce bleeding complications after surgery or interventions, but have reported conflicting results [31–43].

The preoperative period is also an appropriate time to consider the impact of agents used as prophylaxis against deep venous thrombosis on bleeding. This is particularly the case for low-

Table 31.2 Pharmacological options for improving bleeding time in uremic patients

Drug	Dose	Comments
Desmopressin (DDAVP)	0.3–0.4 μg/kg iv	Effect peaks at 1–4 h post-dose and lasts 4–12 h. Be aware of tachyphylaxis if repeated dosing
Conjugated estrogens	Different dose regimens exist	Effect starts after 6 h and peaks at day 5–7, lasting 14–21 days
Cryoprecipitate	10 bags American red Cross prepared over 30 min	Onset 1 h, lasts 4–12 h
rhEPO	40–150 U/kg iv three times weekly aiming for hematocrit > 30%	Effect fully expressed after 4 weeks
Octreotide	100 μg s.c. twice daily	Adjuvant therapy for consideration in gastrointestinal bleeding Plasma half-life time of up to 100 minutes
Tranexamic acid (TXA)	Loading bolus at start of surgery: 15 mg/kg iv GFR-adjusted dose as bolus or continuous infusion thereafter during surgery	Reports of TXA (neuro-) toxicity in CKD and kidney transplant recipients. Dose adjustment may be required in patients with CKD. In patients on dialysis, TXA should only be reserved for life-threatening circumstances

Source: Adapted by permission from Macmillan Publishers Ltd.: Hedges et al. [44]

molecular-weight heparins which (1) are not easily reversed and (2) have the potential to accumulate in CKD patients. It may be appropriate to measure anti-Xa activity as a means of optimizing dosage and minimizing bleeding risk.

31.2.9 Preoperative Management of Medications

Preoperative decisions to continue or discontinue medications must be made on an individual basis and a careful risk–benefit assessment. Current recommendations of preoperative continuation or cessation suggest a general approach to the following medications (Table 31.3):

ACEi or ARBs should be discontinued if possible to avoid intraoperative hypotension. Management of anticoagulatory and antiplatelet medication, as well as diuretics should be individually decided on medical history and type of planned surgical procedure [14].

31.2.10 Prehabilitation

This refers to a preventive preoperative aerobic exercise program aimed at improving functional and aerobic capacity. In deconditioned patients, as little as 3–4 exercise sessions prior to surgery can have moderate effects on aerobic capacity. However, it has not been shown so far to improve perioperative outcomes in patients with CKD. Also, implementation of such prehabilitation programs may be difficult if surgery is required within a short period of time.

Table 31.3 Perioperative management of drugs

Continue	Discontinue
Beta-blockers	Alpha$_2$-agonists
Calcium-channel blockers	Non-statin hypolipemic agents
Digoxin	Theophylline
Statins	
H_2 blockers and proton pump inhibitors	
Inhaled beta-agonists	
Glucocorticoids	

31.2.11 Preemptive Dialysis for Patients with ESKD

For patients with ESKD, preoperative dialysis may be required and beneficial to improve preoperative fluid and electrolyte status as well as acid–base homeostasis. For patients on chronic hemodialysis, it is recommended to perform dialysis on the day before surgery, if possible. Dry weight should be achieved prior to surgery. Dialysis immediately before surgery should be avoided as fluid shifts and persistent anticoagulation from dialysis may interfere with the surgical procedure. If severe volume overload, especially with pulmonary edema, or hyperkalemia, especially with ECG changes, occur, indication for urgent dialysis prior to surgery should be considered. If dialysis is required shortly before surgery, it is preferable to avoid heparin, if possible, to minimize bleeding risk. Instead, regional citrate anticoagulation may be used in continuous veno-venous hemo(dia)filtration, or in patients treated with intermittent hemodialysis, heparin doses may be reduced by saline flushes during hemodialysis and ensuring adequate waiting time (at least 3 h) between end of hemodialysis and start of surgery.

31.3 Intraoperative Care for Patients with CKD

31.3.1 The CKD Patient in the Operating Room (OR)

31.3.1.1 Monitoring

More advanced ECG monitoring with 5-lead systems capable of ST-segment analysis is valuable, considering the increased cardiovascular risk in patients with CKD. Placement of an arterial line will allow continuous blood pressure monitoring during anesthesia facilitating early detection of hypotension and thus early initiation of stabilizing measures as well as monitoring of electrolyte and acid–base status. Given the significant association between hypotension and AKI, this is a main priority.

31.3.1.2 Vascular Access

Gaining vascular access in general is often an elaborate procedure in patients with CKD. This may be due to edema, damage after frequent prior insertion of catheters, or thrombosis.

Special attention and careful consideration of risk–benefit balance need to be paid when planning vascular access in patients with CKD undergoing surgery. Some patients may require establishment of an arteriovenous fistula (AV-fistula) as a shunt for hemodialysis. Intravascular access in this arm should be strictly avoided unless absolutely necessary to preserve vessels for later establishment of such a fistula. Intravascular cannulation endangers later establishment of an AV-fistula due to direct trauma of puncture site or due to subsequent inflammatory or fibrotic changes and increases risk of thrombosis [45–47]. Several vessels are of special importance for possible later dialysis access. This includes anterior forearm veins, cubital veins, and basilica veins for establishment of an AV-fistula, as well as subclavian and brachiocephalic veins if central venous access or right atrial catheter becomes necessary. Thus, intravenous catheters should preferably be placed in the dorsal hand veins and cannula size should be as small as possible to reduce vascular trauma. Usually, the non-dominant arm is used for AV-fistula and the dominant arm should thus be preferably used for intravenous and arterial lines in CKD patients undergoing surgery.

For patients undergoing major surgery, insertion of a central venous catheter may be carefully considered to facilitate monitoring and administration of inotropes or vasopressors, depending on the type of surgery planned. Subclavian vein access has a higher risk of venous stenosis and pneumothorax as compared to the internal jugular approach and should therefore not be the first choice. As an alternative, a tunneled internal jugular vein catheter may be a feasible option to preserve veins if dialysis access becomes necessary at a later time point. Before the first cannulation, healthcare providers should ask ESKD patients whether a "shunt arm" exists and if so, this arm should be marked as such. If an AV-fistula is present, this should clearly be communicated with the anesthetic and surgical team and this arm must be carefully packed and cushioned in to avoid any strain due to patient positioning during surgery. If non-AV-fistula dialysis access exists, such as a right intra-atrial catheter or a central venous (high flow) catheter exists, this hemodialysis catheter must not be used to take blood samples or apply drugs as frequent use increases risks of infection and thrombosis. Finally, arteriosclerosis is commonly present in patients with CKD and should be anticipated before arterial cannulation. Ultrasound may be used to identify and navigate to the adequate site for cannulation and rule out excessive arteriosclerosis. Generally, we recommend use of ultrasound-guided techniques for both intravenous and intra-arterial cannulation in patients with CKD in order to minimize risk of miscannulation and repeated puncture of blood vessels with subsequent complications.

31.3.2 Anesthesia in Patients with CKD

Patients with CKD are particularly prone to over- or under-dosing of drugs. This is caused by alterations to some of the major pharmacological determinants of drug handling. When providing anesthesia to patients with CKD, significantly altered physiology needs to be considered. Changes in volume of distribution, protein binding capacities, drug metabolism, and drug excretion are common and unpredictable. Therefore, special attention to drug dosing must be paid when performing anesthesia in patients with CKD. In all phases of pharmacokinetics, considerable changes may be observed (Table 31.4):

Table 31.4 General pharmacological considerations in patients with CKD

L—Liberation	–
A—Absorption	Possible delayed gastric emptying
D—Distribution	Volume of distribution increased or decreased due to changes in total body water before/after dialysis, edema, protein levels (particularly albumin)
M—Metabolization	Decreased metabolism, particularly CYP3A4, leading to increased bioavailability
E—Excretion	Longer half-life time for medications with renal elimination

31.3.2.1 Intravenous Anesthetic Agents

The effects of intravenous anesthetic agents are terminated not by elimination of the drug from the body but by redistribution of drug out of the brain into other tissues. All commonly used anesthetic agents (propofol, thiopental, ketamine, midazolam) may be used in CKD patients. However, thorough care must be taken of their hemodynamic effects. CKD is no contraindication, but drug choice should be determined by preexisting comorbidities. For induction of general anesthesia with propofol, similar dosing can be used as in non-CKD patients because pharmacokinetics is not considerably altered. However, the vasodilatatory and negative inotropic properties of propofol must be considered. When using propofol as an induction agent, it should be reminded that propofol diminishes the nephroprotective effects of remote ischemic preconditioning (see below), compared to volatile anesthetics [48, 49]. In patients with CKD, maintenance of anesthesia with TIVA (total intravenous anesthesia) is a practical method given its controllability. Intravenous induction agents may also be safely used for monitored anesthesia care or sedation, while benzodiazepines and opioids should be used restrictively, because of potential accumulation.

31.3.2.2 Inhalational Anesthetics

The volatile anesthetic gases are widely used for the maintenance of general anesthesia and also for the gaseous induction of anesthesia in the pediatric population. The most commonly used agents are sevoflurane, isoflurane, and desflurane. Despite metabolism of sevoflurane to release potentially nephrotoxic inorganic fluoride ions, renal toxicity is not observed in humans. Sevoflurane has been reported safe for use even in patients on dialysis [50–53]. ,Sevoflurane also reacts with some carbon dioxide absorbents during low-flow anesthesia to release a substance called compound A. Although nephrotoxic in rats, extrapolation to humans suggests a nephrotoxic threshold of 150–200 ppm, a level that is not reached even at extremely low gas flows for prolonged periods, for example, after 5 h at 0.25 l/h, the level of compound A peaks at less than 20 ppm. All commonly used inhalational anesthetic gases can therefore be considered safe in all stages of CKD.

31.3.2.3 Neuromuscular Blocking Agents (NMBAs)

In CKD, degradation or drug elimination of neuromuscular blocking agents (NMBAs) may be prolonged. Therefore, neuromuscular function monitoring is recommended. Long-acting NMBAs, or those with significant renal excretion such as rocuronium, should be avoided or used with caution in patients with CKD.

31.3.3 Non-depolarizing NMBAs

1. Atracurium and cis-Atracurium: Atracurium and its stereoisomer cis-atracurium both undergo a spontaneous degradation process at body temperature (“Hofmann elimination”). This process is independent of kidney and hepatic functions. Both drugs are often used in CKD patients for this reason. However, their use in rapid sequence inductions may be limited due to their longer onset time compared to others.
2. Rocuronium and Vecuronium: The aminosteroid NMBAs rocuronium and vecuronium both undergo significant renal excretion of approximately 30–40%. Their duration of action is thus prolonged in patients with severe kidney disease. Yet, rocuronium may still be used in patients with CKD as required, due to its rapid onset of action and availability of a reversal agent. CKD patients should be monitored appropriately for neuromuscular blockade if rocuronium was used.
3. Pancuronium: Pancuronium is a long-acting non-depolarizing muscle relaxant. It has a reduced clearance and prolonged half-life in CKD. It also has an active metabolite which is half as potent as pancuronium itself. For this reason, it should only be used (and then with caution) if other agents are not suitable.

31.3.4 Depolarizing NMBAs

1. Succinylcholine: Special caution must be applied when using succinylcholine (suxamethonium) in patients with CKD. This has several reasons: First, plasma cholinesterase levels are reduced in CKD. This can prolong the action of the depolarizing muscle relaxant suxamethonium (and also the non-depolarizing muscle relaxant mivacurium). Second, suxamethonium leads to muscle contractions of the small fibers, known as fasciculations. Potassium is released from muscle cells and puts the patient at risk of hyperkalemia, which already is a common problem in CKD. Following application of succinylcholine in RSI dose (3xfold ED95), transient increases in potassium levels of approximately 0.5–1 mEq/L must be expected. However, succinylcholine can be considered safe to use in CKD if the preoperative potassium levels are below 5.5 mEq/L and no acute ECG changes are present. This also applies to patients on dialysis. If potassium levels are 5.5 mEq/L or higher, or if acute ECG changes are present, we would advise against the use of succinylcholine unless absolutely necessary. Rocuronium may be a more appropriate induction agent for RSI in this circumstance (see above).

31.3.4.1 Reversal Agents for NMBAs

Reversal of non-depolarizing NMBAs may be performed using neostigmine. However, clearance of neostigmine is slightly reduced and half-life prolonged in CKD. Neostigmine is usually administered alongside atropine or glycopyrrolate to balance out its parasympathomimetic effects (bradycardia and AV block). Atropine is shorter acting and may wear off before the neostigmine in CKD. Glycopyrrolate is a better choice. A preferable alternative over aforementioned combinations is the cyclodextrin drug called sugammadex. It reverses the effects of aminosteroid muscle relaxants like rocuronium (and to a lesser degree pancuronium and vecuronium) by selectively binding the NMBA. A key feature is its rapid onset of action and that it can be used at deep level of block where traditional acetylcholinesterase inhibitors would be ineffective. The sugammadex-NMBA complex is normally excreted unchanged by the kidneys. Although clearance of this complex is reduced, this is without clinical effect, and the standard dose of sugammadex is adequate in patients with kidney disease.

31.3.4.2 Analgesics

Opioids are the mainstay of analgesic therapy in the intra- and postoperative period in patients with CKD. Other analgesic agents, such as ketamine may be considered as alternatives or in combination as well. Opioids must be carefully dosed and titrated in patients with CKD and prolonged half-life time in CKD patients must be considered. Remifentanil, fentanyl, or sufentanil are usually not or only minimally affected by CKD. Thus, they can be used intraoperatively [54–56]. Given its hepatic metabolism and short redistribution phase, fentanyl is easy to use in patients with CKD and can even be used in patients with ESKD. Alternatively, remifentanil may be the opioid of choice in patients undergoing surgery due to its rapid breakdown by nonspecific plasma esterases. This mechanism is not altered in patients with CKD and therefore, remifentanil does not accumulate. Its controllability and short duration of action makes it a useful drug for patients with CKD during surgery.

Generally, pain control in the direct perioperative period (e.g. in the recovery area) must be performed with special precautions. However, this caution should not result in under-treatment of pain. Unfortunately, this is too often the case [57]. Acetaminophen (paracetamol) is safe to use in CKD patients in the perioperative period at the standard dose and frequency. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for analgesia in the perioperative period is not recommended given the adverse effects likely outweigh the benefits. They are potentially nephrotoxic, which can produce an acute drop in GFR and may also precipitate acute interstitial nephritis in a patient population already at high risk for AKI. NSAIDs are also associated with an increased risk of cardiovascular complications,

gastrointestinal bleeding, edema, hypernatremia, and hyperkalemia.

Opioid analgesics are not directly nephrotoxic. However, they may trigger urinary retention and have an antidiuretic effect. Although they are a mainstay of postoperative analgesia after moderate and major surgery, caution is required as many opioids, or their active metabolites, are excreted by the kidneys. The five key principles of pain control are especially relevant in patients with CKD or ESKD [58]:

1. By mouth: Prefer oral prescription to avoid vascular puncture in CKD patients.
2. By the clock: Prefer regular administration, consider eventually prolonged effect in CKD patients.
3. By the ladder: Carefully titrate opioids to effect in CKD patients.
4. For the individual: Consider special requirements after surgery, including type of surgical injury (e.g. neuropathic pain after amputation).
5. Attention to detail: Closely monitor kidney function during opioid use; adapt drug dose if acute decline in kidney function.

When using opioids in patients with CKD, altered pharmacokinetics must be accounted for in comparison to patients without CKD. Morphine, for example, has the active metabolite morphine-6-glucuronide (M6G), and in advanced kidney failure, the half-life of M6G may be prolonged from 2 to as much as 27 h. Fentanyl and alfentanil are relatively safe to use in kidney failure although the required dose may be reduced (they have no active metabolites). Buprenorphine is a potent pain medication for patients with CKD and does not require dose adjustment due to its relatively safe profile. Another advantage of buprenorphine is that it is not washed-out during dialysis. Other opioids that may be especially considered in patients with CKD are fentanyl and hydromorphone (requires dose adjustment). Advantageously, hydromorphone does not undergo phase 1 metabolism. This avoids complications of unpredictable toxicity and drug–drug interactions seen with the CYP2D6- and CYP34A-metabolized opioids. More than 80% of 55 patients with cancer and kidney failure who experienced adverse effects, primarily with morphine, improved after a switch to hydromorphone [59]. Drugs such as oxycodone, codeine, tramadol, and meperidine are best avoided or significantly dose adjusted in patients with CKD 4–5 and if used in earlier stages of CKD require dose adjustment and caution. Long-acting opioids should be avoided in CKD patients, if possible.

31.3.4.3 Regional and Neuraxial Anesthesia as an Option in CKD

Local or regional anesthesia with or without monitored anesthesia care (MAC) offers the opportunity to avoid the increased risks of general anesthesia in patients with CKD. If surgery can be performed in local, regional, or neuraxial anesthesia and if this is in line with patient preferences, it should be preferred over general anesthesia.

The most feared complications of neuraxial (spinal and epidural) analgesia are bleeding and infection resulting in neurological complications. These concerns are justified given the impact of uremic toxins on platelet and leukocyte function. Clearly, if clinicians have reasons to suspect significant coagulation dysfunction, this technique is not suitable. Nevertheless, CKD per se is not a contraindication. Upper limb nerve blocks have been used to provide anesthesia for the formation of arteriovenous fistulae in CKD stage 5 patients, and peripheral neural blockade is safe in CKD provided standard contraindications are absent. Data even suggest higher patency rates of AV-fistulas after regional anesthesia compared to local anesthesia [60]. However, in CKD and ESKD patients, it should be noted that block onset may be delayed, and duration reduced in the setting of low bicarbonate levels and reduced protein binding capacities [61]. With the increasing emphasis on enhanced recovery techniques (minimizing opioid usage, optimizing postoperative mobility, and return of gastrointestinal function), alternative techniques for analgesia in abdominal surgery are popular. These include transversus abdominis plane (TAP) block and

rectus sheath block. Both techniques are appropriate in CKD patients in the absence of overt coagulopathy. With all regional anesthesia techniques, suitability should be assessed on an individual basis considering the anticipated benefits and the risks. Drugs such as clopidogrel should be stopped 7 days prior to major neuraxial blocks, and low-molecular-weight heparin should not be administered within the 12 h preceding the block. Prior to application of regional or neuraxial anesthesia techniques, platelet counts and coagulation testing should be carried out and this must be repeated before removal of regional anesthesia catheters, especially if the patient received heparin. This area is well covered in guidelines from the American Society of Regional Anesthesia.

31.3.4.4 Hemodynamic and Fluid Status Optimization

Hemodynamic management is of high importance. Even short periods of intraoperative hypotension are associated with marked increases in rates of postoperative AKI and myocardial injury [62–64]. Both duration and severity of intraoperative hypotension determine renal injury.

There are two main approaches to advanced hemodynamic management. They share the goal of optimizing oxygen delivery through optimizing preload and hence stroke volume and cardiac output.

31.3.4.5 Hemodynamic Management Using Static Parameters

The first approach is the use of additional "traditional" static measures including central venous pressure (CVP) monitoring via central venous catheter (CVC) or pulmonary artery wedge pressure (PAWP) monitoring via a Swan-Ganz right heart catheter for preload estimation. There are significant limitations in using CVP and PAWP to assess intravascular volume status. The correlation between these measures and response to a fluid challenge is poor. In the absence of cardiac output or stroke volume monitoring, this approach also emphasizes fluid administration and blood pressure control at the expense of optimizing flow, that is, perfusion. The use of predominantly vasopressor agents to reverse hypotension in these patients (e.g. phenylephrine) will sustain blood pressure but diminish forward flow and tissue perfusion, as well as increasing left ventricular afterload. A falsely reassuring picture of adequate mean arterial pressure may be obtained. Cardiac output monitoring helps to maintain a more balanced hemodynamic approach, but if used it should be commenced prior to anesthesia to set a baseline level. Finally, invasive methods of monitoring cardiac output must be carefully weighed against the increased risks of these methods in patients with CKD (see section "vascular access").

31.3.4.6 Hemodynamic Management Using Dynamic Parameters

The second approach is a more formal "goal-directed" dynamic approach aimed at optimizing stroke volume with fluid boluses before adding inotropic or vasopressor support and also keeping an adequate perfusion pressure target (generally maintaining systolic BP within 25–30% of baseline and keeping mean arterial pressure above 70 mmHg in normotensive patients and 75–80 mmHg in patients with hypertension). At the extremes of this approach, prespecified cardiac index targets may be chased. This can be done using a pulmonary artery catheter, but increasingly this has given way to techniques such as esophageal Doppler that make use of a CVC and arterial catheter. These methods are based around thermodilution or indicator dilution-based calibration of stroke volume followed by continuous monitoring based on the shape of the pulse waveform. Complex automated algorithms within proprietary monitors provide information on stroke volume variation (SVV) or pulse pressure variation (PPV). These parameters can be used to assess volume status and need for fluids. Techniques such as transpulmonary thermodilution are also able to describe the amount of lung edema (extravascular lung water) and intrathoracic blood volume. Goal-directed approaches often result in more positive fluid balances since these techniques are based on the premise of giving fluid until the heart no longer responds with an increase in stroke volume. This is a controversial area, and it could be

rationally argued that this approach by definition aims to touch the hem of cardiac failure. Finally, machine learning based tools for the prediction of intraoperative hypotension provide opportunity to detect hemodynamic deterioration early on or even before it clinically occurs and initiate preventative measures. Such innovative treatment approaches could considerably improve the intraoperative hemodynamic management and are currently under clinical investigation [65–67].

31.3.4.7 Low Cardiac Output in Patients with CKD

Low cardiac output has been associated with increased risk for postoperative AKI [68]. Hence, inotropic support should be considered in an early stage, especially in patients with ventricular dysfunction. Drug choices include conventional agents such as dobutamine and epinephrine, accepting that these agents can significantly increase myocardial oxygen demand and cardiac afterload or cause cardiac arrhythmias. Alternative agents such as phosphodiesterase inhibitors (e.g. milrinone) may be more appropriate alternatives in the cardiac surgical setting. However, while increasing cardiac output, they may also result in a drop in arterial pressure through reduction in systemic vascular resistance. An interesting choice is the calcium-sensitizing inotrope levosimendan. This agent improves contractility and produces an increase in cardiac output without significantly increasing myocardial oxygen demand. It has not yet achieved widespread use but has been used successfully in both cardiac and noncardiac settings.

31.3.4.8 Transesophageal Echocardiography (TEE)

TEE should be considered in the cardiac surgical setting and in very high-risk patients undergoing major noncardiac surgery. TEE allows for direct visualization and quantification of the cardiac response to fluid, inotropes, and mechanical ventilation. As invasive cardiac output monitoring might not always be appropriate in CKD patients (see section "vascular access"), TTE can be used to monitor cardiac output and prevent low cardiac output states. Usage is restricted by the availability of equipment and trained personnel, particularly in the noncardiac surgical setting. However, the availability of single-use probes and dedicated lower-cost equipment, specifically designed for perioperative and ICU usage, will increase the uptake of this technique.

31.3.4.9 Fluid Choices

Besides fluid volume, one should also strongly consider the type of fluid to give preoperatively. In patients with CKD who are at risk for AKI, application of chloride-rich solutions may lead to hyperchloremic acidosis and is associated with a significant increase in metabolic acidosis and AKI rates [69]. Many anesthesiologists use solutions such as Ringer's lactate which contains less sodium and chloride than 0.9% saline and has lactate which is converted to bicarbonate by the liver. These solutions are less likely to induce hyperchloremia and hypernatremia, but they do contain potassium, and this requires close monitoring if used in significant volumes. Moreover, use of Hydroxyethyl starch (HES) solutions must also carefully balance against potentially harmful effects on the kidneys. While the evidence on perioperative use of HES solutions is still conflicting, high-quality data from the ICU setting suggest a considerable nephrotoxic effect [70–72]. HES solutions should thus be avoided in patients with CKD if possible. Although there is no data demonstrating superiority as a resuscitative fluid, the use of human albumin in the perioperative period may be justified in patients with significant hypoalbuminemia (<25 g/L) to assist with drug carriage and to maintain colloid pressure.

31.3.4.10 Perioperative Renal Protection

The chronically impaired kidney is especially vulnerable to additional insult and may never get back to where it started if AKI occurs. Pharmacological approaches for kidney protection have not shown beneficial effects. Consequently, the most important aspect of kidney protection is to do the basics well:

- Avoid hypovolemia or hypervolemia.
- Maintain adequate perfusion pressure and flow.
- Avoid nephrotoxic agents, if possible.
- Avoid hyperglycemia.
- Avoid sepsis.
- Aggressively manage postoperative complications.
- Avoid intra-abdominal hypertension.

It is critical to avoid getting into the spiral of repeated fluid challenges and aggressive fluid administration for oliguria or hypotension that does not respond more than transiently to fluid. *Fluid overload is nephrotoxic*. It leads to diminished filtration pressure through increased venous pressures, it raises the prospect of intra-abdominal hypertension which reduces renal perfusion, and it leads to renal interstitial edema. As an encapsulated organ, parenchymal swelling leads to renal hypoperfusion and hypofiltration. A knee-jerk response of giving yet more fluid will make matters worse, and in this scenario fluid removal may improve renal injury and function.

31.4 Postoperative Care

31.4.1 Early Detection of CKD Patients at High Risk for AKI

Early postoperative identification of patients at high risk of AKI is of high importance to start nephroprotective measures as early as possible. Recent developments in the fields of biomarker research and artificial intelligence offer new tools for the identification of patients at risk for AKI or to detect early deterioration before clinical deterioration or worsening of renal function becomes apparent.

Biomarkers of tubular dysfunction or injury, such as urinary neutrophil-gelatinase-associated lipocain (NGAL) reflect tubular dysfunction and have been investigated in patients with CKD [73, 74]. In a study of patients with CKD, NGAL was inversely correlated with eGFR and correlated with degree of interstitial fibrosis and tubular damage [75]. Similarly, urinary kidney injury molecule 1 (KIM-1) serves as an AKI prediction biomarker due to its significant upregulation in ischemic or nephrotoxic AKI [76]. However, the most established biomarker of tubular injury is the combination of the cell-cycle arrest biomarkers urinary tissue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) as [TIMP2]*[IGFBP7]. This biomarker reflects tubular epithelial cells' response to stress or damage by initiation of G_1 cell-cycle arrest. Elevated urinary [TIMP2]*[IGFBP7] has been demonstrated to predict AKI with high sensitivity and specificity and is also usable in patients with CKD [77]. Since their discovery, several RCTs demonstrated that the implementation of a biomarker-guided implementation of a nephroprotective care bundle (see below) significantly improves outcomes and prevents both incidence and severity of AKI [78–80]. When available, the implementation of strategies of routine measurement of such AKI biomarkers should be considered in patients with CKD after major surgery.

31.4.2 Postoperative Prevention of AKI in Patients at High Risk

For patients at high-risk for AKI (e.g. CKD and biomarker-positive), the KDIGO recommends the implementation of a standardized care bundle. This care bundle comprises regular monitoring of kidney function, hemodynamic optimization, and consideration of advanced hemodynamic monitoring, as well as avoidance of hyperglycemia, nephrotoxic drugs, and radiocontrast agents, if possible. Several RCTs have demonstrated the efficacy of the biomarker-guided implementation of this care bundle in high-risk patients [78–80]. Hemodynamic optimization should be considered a priority and the avoidance of hypotension and low cardiac output are likely the most effective measures of the care bundle [68].

Fluid management: Fluid balance should be closely monitored and where possible, neutral balance should be aimed for in the perioperative

period by 48 h after surgery [81, 82]. Fluid overload should be strenuously avoided, and this may require the earlier use of vasopressor agents [83]. Maintenance intravenous fluids, if administered, should be given in low volumes depending on urine output and insensible loss, for example, modern enhanced recovery programs tend to use a restrictive maintenance regimen of 0.5 mL/kg/h assuming normal urine output. Bolus doses of balanced crystalloid can be used to maintain stability or deal with acute losses when blood transfusions are not required. There is no clear utility to monitoring central venous pressure or PAWP as these bear little relation to fluid responsiveness. However, CVP is still a commonly used measure and may be more useful as a warning of venous congestion which may also impact the development of AKI. Venous congestion must especially be avoided in patients with CKD as this is associated with increased AKI rates postoperatively, especially in patients with chronic heart failure (cardiorenal syndrome) and/or following cardiac surgery [84, 85]. Increasingly, intra-abdominal hypertension (IAH) is recognized as an important contributor to renal stress, as IAH increases renal venous pressure and decreases renal blood flow and hence GFR [86]. Overall, the term "*congestive nephropathy*" was recently introduced to describe the several negative effects that are caused by renal tissue edema or venous congestion [87].

Drug dosing: As discussed earlier in this chapter, special attention must be paid in regard to drug dosing. This is especially important in the postoperative phase, considering changes in fluid status, acid/base balance, or acute kidney dysfunctions that may occur postoperatively. In patients with postoperative sepsis or fluid overload, application of a higher loading dose may be required, particularly for hydrophilic drugs and when rapid onset of effect is desired, such as antibiotics [88]. To achieve more stable steady states of drug doses, frequent but lower dose application of drugs is often preferable, compared to rare, but high-dose applications in patients with CKD. If available, therapeutic drug monitoring should be used to assess drug dosages, especially for potentially nephrotoxic drugs, such as vancomycin.

In the setting of postoperative AKI, drug dosing becomes even more complicated due to the highly dynamic changes in kidney dysfunction and possible fluid overload. If AKI occurs based on sepsis, excessive fluid loading therapy, capillary leakage, and edema significantly increase drug distribution volume [89, 90]. Simultaneously, acutely (and chronically) impaired kidney function decreases renal drug clearance and maintenance doses should be reduced accordingly for drugs with renal excretion.

Cardiovascular goals: Blood pressure should be maintained within 25% of baseline values, and blood pressure should be measured continuously or periodically. ECG monitoring should be continued in high-risk patients for at least the first 72 h. Besides fluid balance, physical assessment of fluid status and peripheral perfusion should be performed regularly. Passive leg raising test and peripheral capillary refill time are especially useful tools in this regard. Furthermore, low cardiac output states must be avoided. If in doubt, non-invasive assessment of cardiac output, for example, using TTE or non-invasive cardiometers should be applied. In patients at high risk or in shock (e.g. vasoplegic or septic shock postoperatively), establishment of invasive cardiac output measurement by transpulmonary thermodilution or Swan-Ganz catheter may be useful; however, this must be weighed against the risk of this invasivity and vascular damage in CKD patients (s. section "vascular access"). Low cardiac output is a known risk factor for postoperative AKI and cardiac dysfunction is a common finding in CKD patients, especially postoperatively. Cardiac index (cardiac output/body surface area) should be maintained at acceptable levels and be at least 2.5 L/min/m^2 in high-risk patients. Recent evidence suggests that maintaining higher cardiac index is negatively associated with AKI incidence, especially for more severe stages of AKI [68] (Table 31.5).

Laboratory testing: Arterial blood gases, complete blood count, blood urea nitrogen, creatinine, and electrolytes should be followed to maintain an adequate pH and hematocrit and to

Table 31.5 Recommendations for perioperative targets and goals in patients with CKD

Target	Goal
Achieve euvolemia, avoid complications of fluid therapy	Passive leg raising test Capillary refill time Hemodynamic monitoring Ultrasound of vena cava Avoid using chloride-rich solutions if possible
Maintain adequate hemodynamics and renal perfusion pressure	Hemodynamic monitoring (especially TTE, TEE, or transpulmonary thermodilution) MAP reduction max 25% of preoperative MAP >65 mmHg (higher goals in chronic hypertension) Cardiac index >2.5 mL/min/m^2 if high-risk Intra-abdominal pressure < 15 mmHg
Monitor kidney function	Daily measurement of serum creatinine Measurement of urinary output Frequent assessment of electrolytes and blood-gas-analysis perioperatively
Identify renal stress or deterioration early	Measure biomarkers postoperatively (e.g. [TIMP-2]*[IGFBP7])
Avoid hyperglycemia	Blood glucose target 110–149 mg/dL (6.1–8.3 mmol/l)
Avoid nephrotoxic agents	Avoid colloids and chloride-rich solutions Discontinue or avoid nephrotoxic drugs if possible (e.g. NSAIDs) perioperatively Consider alternatives to radiocontrast

enable correction of dysnatremia and dyskalemia. pH should be maintained above 7.3, considering the potential for mild respiratory acidosis from the effects of pain or analgesics.

Analgesia: A multimodal analgesic regimen is recommended, including the use of local anesthesia (nerve blocks or infiltration techniques), acetaminophen, and judicious opioid for severe pain that is limiting mobilization and return of function.

Nutrition: This should be recommenced as soon as possible after surgery, ideally via the gut as opposed to parenteral nutrition. Even small volumes of enteral feeding have a trophic effect on gut mucosa and help maintain gut-associated lymphoid tissue. However, in critically ill patients, nutritional intake should begin slowly and carefully. Excessive hyperglycemia should be avoided. Currently, tight glycemic control (goal: 110–150 mg/dL) is recommended in high-risk patients in the ICU. However, this recommendation builds on a single-center study and conflicting evidence exists [91–93].

Medications: Patients should recommence their normal ischemic, antihypertensive, and heart failure medications as soon as their hemodynamic status, kidney function, and fluid losses are suitable for this. This is often done as a staged reintroduction of drug classes.

Before You Finish: Practice Pearls for the Clinician

- Identify and stage patients with CKD presenting for surgery and assess their comorbidities. Preoperative assessment of kidney function and risk assessment are pivotal in patients with CKD.
- Look for areas where general medical status can be optimized prior to surgery.
- Consider all CKD patients to be at increased risk of cardiovascular complications, drug dosing complications, and AKI in the perioperative period.
- Vascular access is difficult in patients with CKD and must be restricted to the minimum required in order to preserve vessels for eventual later dialysis access.
- Biomarkers such as [TIMP-2]*[IGFBP7] identify patients with tubular injury and high risk for AKI before functional impairment of kidney function and clinical deterioration occurs. This early identification can guide nephroprotective therapies.
- Use advanced hemodynamic monitoring intraoperatively and in the ICU setting for high-risk cases.
- Avoid even short periods of hypotension and low cardiac output to prevent AKI.
- Avoid the temptation to repeatedly give intravenous fluids for hypotension if this is not effective—fluid overload is (nephron)toxic!

Intravenous fluids should be titrated to effect with hemodynamic monitoring.

- Avoid the use of nephrotoxic drugs and radiocontrast agents where possible, and use opioids with caution.
- There is no magic bullet for renal protection—careful attention to the basics of oxygenation, hydration, and perfusion is the key. Implementation of nephroprotective care bundles in high-risk patients improves outcomes and prevents AKI.

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Chronic Kidney Disease in the Elderly

32

Agnes Shin Man Choy, Kai Ming Chow, and Philip Kam Tao Li

Before You Start: Facts you Need to Know

- The prevalence of chronic kidney disease increases with the population age.
- Age-related decline in many physiologic systems results in susceptibility to sudden health status changes triggered by minor stressor events, including the increased risk of acute kidney injury and the propensity to developing chronic kidney disease.
- Chronic kidney disease in elderly is associated with increased risk of end-stage kidney disease and all-cause mortality.
- Frailty in elderlies with chronic kidney disease poses additional challenge for management.

Kidney supportive care should be an adjunct to the management of patients with chronic kidney disease at all stages of their illness. The proportion of palliative care usually increases with time until when the end-of-life approaches. It is best provided in collaboration between nephrology team and palliative care team.

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Around 850 million people are currently suffering from different types of kidney disorder, while one in ten adults worldwide has CKD [1]. CKD, defined as evidence of structural or functional kidney impairment for 3 or more months, is generally progressive and irreversible, affecting multiple metabolic pathways [2]. It is associated with increased risk of mortality, cardiovascular events, hospitalisation, and progression to kidney failure requiring kidney replacement therapy (KRT) [3, 4]. The prevalence of CKD increases with age, and according to a study, 47% in people older than 70 years, mostly because of reduced GFR will develop CKD [5]. For elderly, CKD is associated with increased risk of all-cause mortality and end-stage kidney disease compared with younger individuals [6].

The elderly is notable for their diminishing physiologic reserves available to meet challenges to homeostasis. This concept is known as homeostenosis, referring to the increased vulnerability to disease from maturity to senescence. Frailty is a state when physiologic reserves are maximally invoked just to maintain homeostasis and any challenges or minor stressor events will cross some threshold and thus susceptibility to sudden health status changes [7]. The concept of frailty provides a good explanation for the frequent observation that age older than 65 is a risk factor for nonrecovery from acute kidney injury and even progression to severe chronic kidney disease.

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It is important to take precaution and keep in mind the kidney changes with ageing. Based on available evidence, our practice is to consider the changes in terms of anatomic and functional changes (Box 32.1). A series of pathologic studies have documented a reduced number of functioning glomeruli and an increased number of sclerotic glomeruli with age. One of the important studies, based on the core-needle kidney biopsy of over 1000 healthy adult living kidney donors [8], provided a unique opportunity to evaluate the kidney histology findings in relation to age. The prevalence of nephrosclerosis, as defined by the presence of two or more different histology abnormalities (global glomerulosclerosis, tubular atrophy, interstitial fibrosis, arteriosclerosis) increased linearly with age. The prevalence was reported at 55% among patients aged 60–69 years and up to 75% among those older than 70 years. Such abnormalities, however, occur in only 3% of donors 18–29 years old [8]. **The average age-related decline in glomerular filtration rate has been reported as 6 mL/min/1.73 m^2 with each age decade**. However, there was a lack of association between the age-related decline in glomerular filtration rate and nephrosclerosis.

Box 32.1 The Ageing Kidney: Anatomic and Functional Changes

Anatomic changes:

- Decrease in kidney size, with thickness of kidney parenchyma.
- Increase in kidney fat and fibrosis.
- Increase in number of sclerotic glomeruli.

Functional changes:

- Decrease in kidney blood flow.
- Decrease in glomerular filtration rate (linear relationship with age).
- Decrease in maximal urine concentrating and diluting capacity (explaining the higher rate of nocturia and predisposition to dehydration, respectively).
- Decrease in functional reserve (explaining the increased risk of acute kidney injury).
- Impaired recovery after kidney insults.
- Increased dependence on renal prostaglandins to maintain intra-renal perfusion.
- Increased susceptibility to nephrotoxicity related to medications or intravenous contrast.
- Decrease in plasma renin activity and plasma aldosterone level.

32.1 Management of CKD in Elderly

Patients with CKD are at an increased risk for premature death and cardiovascular diseases. Cognitive impairment, depression, fatigue, and reduced physical function are also common in patients with CKD. These burdensome symptoms can disrupt the daily living and impair the quality of life of patients and their family members [1, 9, 10]. The management of CKD can be challenging because patients' symptoms and prognoses are highly variable and follow uncertain trajectories [11]. These are especially important when formulating management plan for elderly with CKD. Consequently, there is increasing recognition of the need to identify and address patient priorities, values, and goals.

General management of chronic kidney disease in the elderly is similar to that for younger patients: careful assessment of the stage of disease, elimination of factors for acute deterioration, evaluation of any complication or comorbidity, and monitoring of kidney disease. At the same time, geriatric issues such as frailty, quality of life, life expectancy, end of life issues, pharmacokinetics and pharmacodynamics of drugs should be addressed when managing CKD in elderly. The goal of CKD management is to halt or retard disease progression. Acute kidney injury could be precipitated by medications like nonsteroidal anti-inflammatory drug (NSAID),

nephrotoxic antibiotics, radio-contrast exposure, combinations of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) [12]. Hence these groups of drugs should be avoided. Also, optimization of blood pressure control and glycaemic control is always of paramount importance in slowing down the progression of CKD. Nevertheless, primary prevention should remain a priority. Prevention of CKD progression can be attempted by lifestyle and diet modifications such as a plant-dominant low protein diet and by effective pharmacotherapy, including the use of sodium glucose transport protein 2 (SGLT2) inhibitors [13]. Despite the known high cardiovascular risk in individuals with CKD, recent subgroup analysis of the ASPirin in Reducing Events in the Elderly (ASPREE) trial suggested that aspirin as primary prevention did not improve outcomes in older people with CKD but experienced elevated bleeding risk [14–17].

Due to the ageing population worldwide, there are increasing numbers of elderly patients reaching end-stage kidney disease. Though age itself should not be a barrier to kidney replacement therapy, however, increasing age commonly coincides with increasing frailty and comorbidities. The survival advantage is lost for patients initiating dialysis at an older age [18–21]. Dialysis in elderlies should be contemplated when GFR falls below 20 ml/min/1.73 m^2 as time needs to be spent discussing with patients and their carers about the wish for dialysis or palliative care. And if they opt for dialysis, what modality of kidney replacement therapy the patient and the carer would agree upon.

32.2 Emerging Role of Conservative Management of CKD in Elderly

Patients who reach advanced stages of CKD often face decisions about whether or not to initiate treatment with maintenance dialysis, and if so, when. Although dialysis is commonly regarded as a life-prolonging therapy for patients with advanced CKD, the potential benefits of dialysis can be outweighed by the potential burdens and complications of treatment, especially at older ages. Specifically, elderly patients on peritoneal dialysis may be too sick to perform the exchanges. They may no longer be able to live independently, may become malnourished and have increased risk of peritonitis. Similarly, elderly patients on haemodialysis often have enormous problems with vascular access, requiring frequent and unpleasant temporary catheters, becoming more dependent for daily care, and require transport to and from dialysis centres. In the past two decades, there was growing evidence to suggest that patients with advanced age or comorbidities experience high mortality rates and high symptom burdens on dialysis. Patients who start dialysis at age 75 have on average 1-year and 3-year adjusted survival of 63% and 33%, respectively. In addition, some observational studies showed that there is no survival benefit to start dialysis for patients older than 80 years of age as compared with active medical management [18–21].

Patients with advanced CKD often experience a high frequency of physical and psychological symptoms, though the frequency and intensity of symptoms vary significantly from one individual to another. Symptoms of CKD may be directly related to uraemia or complications of CKD, or they can be caused by underlying comorbidities. In general, the approach to symptoms management should involve the evaluation for causes, reversible factors, and the level of distress or dysfunction caused by symptoms. Intervention can be either pharmacological or non-pharmacological, while the limitation of therapy should be acknowledged [10]. Patients sometimes may underreport symptoms unless being asked explicitly, and there are robust data that regular assessments with validated tools can reduce symptom burden over time. Table 1 listed out the possible options for assessment tools [22]. Common symptoms encountered by patients with CKD include fatigue, skin pruritus, nausea and vomiting, oedema, dyspnoea, muscles cramping, sleep disturbance, pain, and depression [9, 10, 23, 24]. These symptoms can

Table 1 Symptom and function assessment tools

Edmonton symptom assessment system revised kidney (ESAS-r: Kidney) (https://www.albertahealthservices.ca/frm-20351.pdf)
Integrated palliative care outcome scale kidney (IPOS-kidney) (https://pos-pal.org/maix/ipos-kidney-in-english.php)
Karnofsky performance status (KPS) score (http://www.npcrc.org/files/news/karnofsky_performance_scale.pdf)
Eastern cooperative oncology group (ECOG) (https://ecog-acrin.org/resources/ecog-performance-status

be prolonged and adversely affecting patients' quality of life, and hence timely effective management of them is crucial.

CKD and its associated symptoms and treatment, including dialysis, can disrupt daily living and impair the quality of life of patients and their family members. Eventually, this can impact treatment satisfaction and outcomes. Hence, there is increasing recognition of the need to identify and address patient priorities, values, and goals [25].

Life participation, defined as the ability to do meaningful activities of life including, but not limited to, work, study, family responsibilities, travel, sport, social, and recreational activities, was established as a critically important outcome across all treatment stages of CKD [25, 26]. Patients want to live well, maintain their role and social functioning, and have a sense of control over their health and well-being. Life participation places the life priorities and values of those affected by CKD and their families at the centre of decision making [27]. Different from the medical model where chronic disease is traditionally focused on pathology, problems, and failures, patient empowerment allows them to gain greater control over decisions of actions affecting their health [27].

As mentioned before, the survival advantage is lost for patients initiating dialysis at an older age [28]. Hence, kidney supportive care becomes a blooming subspecialty in the field of nephrology. It involves the application of palliative medicine principles and practices to patients with CKD regardless of the underlying causes and dialysis modality. The main goal of kidney supportive care is to alleviate patients' suffering throughout the trajectory of illness via the treatment of symptoms, empathic communication, and support for psychosocial distress.

Kidney supportive care includes, but not limited to, end-of-life care. It should be an adjunct to the management of patients at all stages of their illness. Supportive care should be available at the time of diagnosis, for pre-terminal symptoms control, for symptomatic relief and psychological support, as well as in the end of life. It involves numerous areas of focus that are applicable to patients across the illness spectrum of advanced CKD. Apart from managing patient's physical symptoms, physicians also need to explore patient's awareness on their disease prognosis. Physicians also need to pay extra attention to the non-physical dimensions of patient's suffering and to elicit their preferences on managing advanced CKD without dialysis. Alternatively, this can be called maximum conservative management or conservative care. Kidney supportive care should include primary palliative care provided by nephrology team, as well as co-management with the palliative care team, especially for those patients with complex distress. Collaboration between nephrology team and the palliative care team can offer an additional layer of support to patients and families. The team may include physicians, nurses, social workers, chaplains, and dietitians [22].

The proportion of palliative care usually increases with time until when the end-of-life approaches, it becomes the whole core of care for the patient and family, prioritising quality of life and allowing the loosening of futile restrictions such as tight diabetic control. While the rate of CKD progression can be highly variable depending on factors such as comorbidities, it is important that the integration of palliative care begins

early and continues to be revisited throughout the course of the disease. As a result, kidney supportive care is best provided in collaboration between the nephrology team and palliative care team.

The decision about whether to start dialysis and which modality to choose should be a joint decision between the patients and their families or carers. The role of renal physicians is to provide adequate information on disease prognosis, benefits, and risks of treatment options available and to facilitate the patients to express their values and preferences for treatment. Nephrology team should also encourage the family to listen to the patient's concerns and to elicit the views from family members in order to resolve the disagreement and to work towards a consensus for an agreed care plan. If a patient with advanced CKD decided not for dialysis and opted for conservative management, the aims of care include managing fluid balance, anaemia, bone health and blood pressure as well as managing symptoms so as to maximise the quality of life of patients [27].

There is no standard definition of conservative management in the previous published literature until more recently, a consensus conference has proposed a detailed, specific definition for conservative care in end-stage kidney disease (ESKD), suggesting adoption of the term "comprehensive conservative care" to reflect the full extent of conservative management [29]. Comprehensive conservative care included interventions to delay progression of kidney disease and to minimise risk of adverse events or complications, shared decision making, active symptom management, detailed communication including advance care planning (ACP), psychological support, social and family support, and cultural and spiritual domains of care. It does not include dialysis [29].

32.3 Facilitating Advance Care Planning

Advance care planning is an essential component of quality palliative care that is likely to improve the lives and deaths of patients with ESKD. It is a process of reflection and discussion between patients, families, and health care providers to clarify patients' values, treatment preferences and goals of care for use in the event that the individual loses his or her capacity for medical decision making. It allows patients to prepare for death, strengthen relationships with loved ones, achieve a sense of control, and relieve burdens placed on others [30, 31]. Table 2 shows the suggested scope of ACP discussion. There are no standards of care regarding when to initiate or how to conduct ACP discussion. It is important to recognise that ACP is an evolving process and is not bound at one point in time. Patients often need time to reflect on information and how it has an impact on their life. Determining how ACP will benefit any patients from their perspectives and fostering patients' empowerment are critical to effective facilitated ACP and will guide the initial ACP process. Information giving is a fundamental component of facilitated ACP and should be started early in course of the illness. Information needs to focus on the individuals and how their illness and treatment will affect daily life and what they value most. Not uncommonly, patients may modify their preference for life sustaining therapy on their expected functional and cognitive ability. Appropriate time to review ACP includes at the time of change in health, during acute illness, and in out-patient setting after discharge from hospital [32, 33].

Table 2 Suggested scope of ACP discussion

Disease	Anticipated progression and prognosis
Treatment	Treatment options available, benefits, and risks
Patient's preferences and vales	Expectation from treatments Ceiling of treatment/ treatment limit Preference for personal care Personal goals to accomplish
Family members	Family values and concerns
Others	Arrangement after death, e.g. funeral process

32.4 Conclusions

With the increasing elderly population with kidney failure, although dialysis is commonly regarded as a life-prolonging therapy for patients with advanced CKD, however, the potential benefits of dialysis reduced notably for older people with major comorbidities and poor functional status. Quality of life, symptoms, and hospital free survival may be at least as important to consider and be actively managed. Hence, kidney supportive care is of growing importance worldwide. It should be an adjunct to the management of patients at all stages of illness, including at the time of diagnosis, for pre-terminal symptoms control, for symptomatic relief and psychological support, as well as in the end of life. Collaboration between nephrology team and the palliative care team can offer an additional layer of support to patients and families. The decision about whether to start dialysis and which modality to choose should always be a shared decision making between the patients and their families or carers. There is increasing recognition about the need to identify and address patient priorities, values, and goals when deciding on the plan of kidney replacement therapy. Life participation places the life priorities and values of those affected by CKD and their families at the centre of decision making. The main aim of it is to reduce patient's suffering through symptoms management, communication, and support for psychosocial distress. End-of-life care and discussion of advanced care planning should be facilitated as an integral part of kidney supportive care.

Before You Finish: Practice Pearls for the Clinician

- The potential benefits of dialysis reduced notably for older people with major comorbidities and poor functional status.
- Conservative management could be a reasonable alternative to dialysis for elderly patients with chronic kidney disease and multiple comorbidities.
- Shared decision making between patients and their families is always recommended to come to a joint decision on kidney replacement therapy.
- Collaboration with palliative care team could offer better holistic care for patients with end stage kidney disease who opted not for dialysis.
- There is growing interest in efforts to enhance advance care planning for patients with advanced kidney disease.

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Chronic Kidney Disease and Cancer

33

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Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) is highly prevalent in cancer patients.
- Cancer prevalence is higher in the CKD population, for a number of tumors but especially cancers of the urogenital tract.
- Cancer screening in the CKD population is key, but appropriate screening tools and protocols remain to be defined.
- Measuring the actual glomerular filtration rate (GFR) of a patient (isotopic methods) is the gold standard method but cannot be routinely performed.
- Estimating the GFR by calculations from serum creatinine can be performed and the most recent CKD-EPI formula should be utilized in determining dose adjustments for chemotherapeutic agents.
- Nephrotoxic drugs should be avoided, whenever possible, in patients presenting with preexisting renal impairment.
- The role of both underlying cancer and anticancer therapies in leading to CKD is important to recognize as the preservation of GFR is likely to improve outcomes.

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33.1 Introduction

The overall incidence of cancer is rising throughout the world. In addition, as populations age and the prevalence of conditions such as diabetes and hypertension increases, the prevalence of chronic kidney disease (CKD) is also increasing. Very few studies have looked at the incidence and prevalence of CKD among cancer patients. One study evaluated the causes of CKD in patients who had a diagnosis of cancer in their childhood. Over 700 childhood cancer survivors were followed and their kidney function was assessed longitudinally [1]. The factors that were major predictors of loss of glomerular filtration rate (GFR) later in life after experiencing treatment for childhood cancers were: nephrectomy, abdominal radiation, high dose ifosfamide exposure, and high dose cisplatin exposure. CKD following cancer can be a result of numerous etiologies, several of which may be acute but have lasting deleterious effects to lower GFR and lead to progressive loss of nephrons. These include: acute tubular necrosis (ATN) (either due to nephrotoxins or in the setting of ischemia (sepsis)), tumor infiltration of the renal parenchyma, and/or vascular, tubular, interstitial, or glomerular toxicities of chemotherapy agents. The toxicities from chemotherapy are the most common causes of CKD in cancer patients. In addition, since many of these patients are living longer, they are not immune from developing CKD asso-

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ciated with common causes such as hypertension and diabetes mellitus.

What is striking is that CKD, especially end-stage kidney disease (ESKD), has a significant impact on cancer therapy and outcomes. The CANcer and DialYsis (CANDY) study [2], which retrospectively evaluated treatment patterns and clinical outcomes in patients undergoing chronic dialysis who subsequently developed cancer, showed that chemotherapy was omitted or prematurely stopped in many cases or was often not adequately prescribed, and survival was poor in this cohort of patients. This study highlights the challenges oncologists face when treating patients with cancer on chronic dialysis. Unfortunately, no such study exists for CKD patients. While one French study demonstrated that few patients in their centers required dose adjustments for chemotherapy agents due to a prior diagnosis of CKD [3], another analysis of patients from Belgium did note that the prevalence of patients with cancer and estimated GFR < 90 ml/min per 1.73 m^2 was 64% [4]. These are important findings suggesting that GFR needs to be carefully assessed in patients with cancer. Furthermore, for many chemotherapeutic protocols, dose adjustments for suboptimal GFR are poorly defined and not evidence-based.

The risk of cancer in CKD patients is higher than the general population for certain tumor types such as renal cell carcinoma [5, 6]. Wong et al. analyzed a cohort of over 3000 patients over a mean of 10 years. They found that men, and stage 3 or higher CKD had an increased risk of cancer. The risk increased with GFRs starting at 55 ml/min per 1.73 m^2 and with an increase in risk of 29% for every 10 ml/min decrement [5]. The major cancers involved were primarily of urinary origin and lung cancers. Weng et al. [7] published the largest study to date analyzing the cancer-specific mortality in CKD. In this study, CKD was significantly associated with liver cancer, kidney cancer, and urinary tract cancers. In kidney and urological cancers, the lower the GFR, the higher the mortality risk from kidney and urological cancers. In addition, CKD appears to be a risk factor for poorer outcomes with cancer. While not clear, an underlying pro-inflammatory state, altered host immunity, and nutritional status might be major contributors to this association. Furthermore, alterations in potentially curative therapeutic regimens may occur in the setting in CKD which may limit efficacy.

33.2 Assessment of GFR in Cancer Patients

Chemotherapeutic agents used to treat cancer generally have narrow therapeutic indices along with potentially serious adverse toxicities. Accurate dosing is required to ensure optimal outcomes and to avoid toxicity. For those drugs excreted through the kidney, a precise understanding of kidney function is needed to ensure achievement of therapeutic levels and avoidance of these toxicities. Unfortunately, many drugs used for the treatment of cancer lack data on appropriate dosing when kidney function is impaired. This is not acceptable as it places the large number of patients with chronic kidney disease at risk for both toxicities and suboptimal outcomes.

In general, two pathways are involved in the excretion of drugs and their metabolites by the kidney: glomerular filtration and tubular secretion. Glomerular filtration is relevant for smaller, non-protein bound substances. Tubular secretion is a more common pathway for protein-bound compounds. In addition, tubular reabsorption of a drug can also occur which can raise the concentration of the drug. In most cases, the best measure of kidney function is the glomerular filtration rate (GFR) which has generally been accepted as a measure of functioning kidney mass [8]. Measures to directly and indirectly measure GFR have been well validated and there is extensive experience with their operational characteristics which makes their use ideal in design of clinical trials, determination of appropriate dosing guidelines for various levels of kidney function, and for the care of patients with cancer. In addition, a critical and often underappreciated issue is that he United States Food and Drug Administration

(FDA) has recommended that pharmacokinetic studies in kidney impairment models be conducted for medications which are not eliminated by the kidney, recognizing the fact that non-kidney clearance mechanisms can be altered in patients with impaired kidney function [9].

While many methodologies exist to measure GFR, many are not practical in daily clinical use [10]. Serum markers (such as creatinine and cystatin C) have been developed to be used in GFR estimating equations, while in some circumstances, more precise determination of GFR is needed and then urinary clearance of an ideal filtration marker can be utilized (typically through radionuclides and radiocontrast agents where clearance can be determined as the amount of indicator injected divided by the integrated area of plasma concentration curve over time) [11, 12]. Substances such as ^{125}I-iothalamate and ^{51}Cr-ethylenediaminetetra-acetic acid (EDTA) (detected by plasma levels) or 99m-Tc mercaptoacetyltriglycine (MAG3) and 99m-Tcdiethyl triamine penta-acetic acid (99mTc-DTPA) (detected by gamma counter) can be used for direct GFR measurement [11, 12]. More typical and more practical is estimation of GFR through various regression equations that may include: creatinine clearance estimation, estimated GFR measurements, or cancer-specific equations that aim to take into consideration patient-specific factors impacting kidney function measurement. While the National Comprehensive Cancer Network (NCCN) and the International Society of Geriatric Oncology (SIOG) recommend an assessment of kidney function before the administration chemotherapeutic drugs, even in patients with "normal" kidney function, there are no collective guidelines declaring which method of estimating kidney function is preferred in patients with cancer [13].

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed to improve shortcomings of prior equations and is most commonly used in current clinical practice [14]. This equation utilizes serum creatinine values as well as age, gender, and race to calculate an estimated GFR [14]. There are also forms of the CKD-EPI equation that incorporate serum cystatin C to better refine GFR estimation [15]. Data suggests that 3.6% of US adults would be classified as having CKD solely on the basis of a creatinine-based GFR estimate of 45–59 ml per minute per 1.73 m^2 [16]. A strategy of measuring cystatin C when the creatinine-based estimate is in this range and then re-estimating GFR with the use of both these markers could correctly reclassify a substantial proportion of such patients as not having chronic kidney disease and not being at high risk [15, 17]. The CKD-EPI equation is currently recommended by the National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) and the Kidney Disease Improving Global Outcomes guideline groups [18]. A point of recent controversy is that the CKD-EPI equation incorporates race (black vs. non-black) as a variable and the appropriateness of this has been questioned as race is a social and not a biological construct [19]. Thus, it may be appropriate to avoid race correction in the estimation of GFR but more study is needed [20]. Over the past several years, several publications have shown superior performance of the CKD–EPI equation in the cancer patient population over other methodologies [13].

A major caveat with the use of the CKD-EPI equation is that cancer patients who are ill may be in a non-steady-state condition where estimating equations are less likely to be accurate. These changes in GFR over time were demonstrated in a large retrospective evaluation of patients with solid tumors without CKD. Patients had an average decline in GFR of 7 mL/min/1.73 m^2 after 2 years of diagnosis or a CKD stage decline from stage 2 to 3 or 4 [21]. In another study, the risk of acute kidney injury was 17.5% and 27% in the first and fifth year of cancer diagnosis, respectively, demonstrating that GFR is changing in a substantial number of cancer patients [22]. In these circumstances, the use of GFR estimating equations may give false values. This issue highlights the need for direct, real-time measurements of GFR at the point-of-care. This ability would allow for adjustment of drug dosing based upon accurate assessment of measured GFR. There are now two methodologies in development that allow for direct quanti-

tative GFR measurement that may simplify acquisition of this critical data. One technique uses a novel 5-kilodalton fluorescein carboxymethylated dextran (rapidly filtered by the kidney) and the other uses a transdermal sensor to measure the removal of a fluorescent tracer from the blood [23–25]. Both of these methods would allow for a new paradigm of care where patients might be expected to get measured GFR levels just prior to drug dosing. The measured GFR would be used to adjust the dose of chemotherapy to ensure maximal efficacy and minimal toxicity. In addition, these techniques could be used during drug development to develop more precise dosing guidelines.

33.3 Etiologies of CKD in Cancer Patients

There are numerous unique etiologies of CKD in patients with underlying cancer. The most common include CKD due to chemotherapeutic agents, glomerular disorders, renal cell cancer, paraprotein-induced kidney disease and associated with stem cell transplantation.

33.3.1 Chemotherapy and Targeted Therapy Induced CKD

Many chemotherapeutic agents are associated with nephrotoxicity. Risk factors that can increase nephrotoxicity include patient age, preexisting CKD, exposure to other nephrotoxins (such as aminoglycoside antibiotics and iodinated contrast agents), and volume depletion. Most commonly, chemotherapy agents lead to electrolyte disorders or AKI, but there is significant risk of CKD from some agents. Table 33.1 lists some of the more common renal toxicities of chemotherapy agents [26].

Cisplatin is a potent tubular toxin, associated with many tubulopathies [27, 28]. These changes are mild and transient in most patients and sustained elevations in serum creatinine are less common. In one study of 54 patients followed for more than 3 months, only one developed late onset azotemia [29]. Although long-term follow-up studies indicate that kidney function either remains stable or improves over time, some patients may have a significant reduction in creatinine clearance despite normal serum creatinine levels [30].

Table 33.1 Chemotherapy, targeted therapy, and immunotherapy associated kidney dysfunction

Compartment of the kidney	Toxicity	Chemotherapy agent
Glomerular	Membranoproliferative glomerulonephritis	Gemcitabine, sirolimus
	Minimal change disease	Interferon alpha, beta, and gamma, pamidronate, doxorubicin (adriamycin), daunorubicin (daunomycin), sirolimus, nivolumab
	Focal segmental glomerulosclerosis	Sirolimus, temsirolimus, everolimus, doxorubicin (adriamycin), daunorubicin (daunomycin)
	Collapsing glomerulopathy	Interferon alpha, beta, and gamma, pamidronate, gefitinib, sirolimus, doxorubicin (adriamycin), daunorubicin (daunomycin), clofarabine
	Membranous nephropathy	Sirolimus
	Lupus like nephritis	Ipilimumab
	IgA nephropathy	Sirolimus
Vascular	Thrombotic microangiopathy	Anti-angiogenic agents (bevacizumab and tyrosine kinase inhibitors), gemcitabine, cisplatin, mitomycin and interferons, pembrolizumab, and nivolumab
Tubular/interstitial	Acute tubular necrosis	Platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed, clofarabine, arsenic trioxide
	Acute interstitial nephritis	Sorafenib, sunitinib (but can be any chemotherapy)
		Checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab)
	Crystal nephropathy	Methotrexate

Alkylating agents such as ifosfamide, cyclophosphamide, and melphalan are used for many cancer treatments. Of these, ifosfamide is most often associated with nephrotoxicity [31]. Moderate to severe renal injury occurs when doses are above 100 g/m^2. In addition, ifosfamide may lead to long-term reductions in GFR. Farry et al. published long-term follow-up of adult patients at a single center that received ifosfamide and they found that there was a 15 ml/min decrease in GFR in the first year of treatment and then 22 ml/min in the next 4 years after treatment [32].

Nitrosoureas have been noted to cause CKD. Semustine, carmustine, and lomustine are lipid soluble alkylating agents used in treatment of brain tumors [33, 34]. All three of these agents produce dose-related nephrotoxicity which can progress to CKD. In one study of over 150 patients treated with semustine and/or carmustine, all patients who received more than ten doses developed CKD [34]. Typically in these cases the urinary sediment is bland with not much proteinuria. In many patients, the serum creatinine may not rise till months after treatment. Biopsy findings show extensive glomerular and interstitial fibrosis and tubular atrophy [33].

Targeted therapies have recently evolved as promising agents for treatment of various cancers. Tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors are some examples of such therapies. Tyrosine kinase inhibitors are classically associated with thrombotic microangiopathy (TMA). One case series reported that over time there is a chronic interstitial insult that leads to CKD in patients receiving these drugs [35]. Both sunitinib and sorafenib have been associated with acute interstitial damage and ultimately in chronic interstitial damage [35]. In addition, alectinib, a second generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor, has been reported to be rarely associated with progressive CKD [36].

Many antiangiogenic agents and tyrosine kinase inhibitors lead to renal limited or systemic TMA and/or hypertension [37, 38]. Renal limited TMA may go undiagnosed and requires a high degree of clinical suspicion for confirmation by kidney biopsy. However, if diagnosed early, the syndrome can be reversible in some cases with cessation of the offending agent. Unfortunately, development of CKD is not unusual in patients with this syndrome [39].

In addition, all glomerular toxicities of chemotherapy agents can be potential causes of CKD if the insult is ongoing and long-term. Thus, for all agents with any potential nephrotoxicity, monitoring of GFR and urine studies should be mandatory. Early diagnosis and rapid cessation of offending medications is critical to limit renal fibrosis and the eventual development of CKD.

Newer immunotherapy includes checkpoints inhibitors such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed death 1 (PD-1) [40]. These agents have revolutionized the treatment of malignancies by engaging the patient's own immune system against the tumor rather than targeting the cancer directly. Drugs of this class include: ipilimumab, pembrolizumab, and nivolumab. These drugs have been associated with acute kidney injury that is generally immune-mediated and consistent with acute interstitial nephritis [41]. The onset of kidney injury seen with PD-1 inhibitors is usually late (3–10 months) compared to CTLA-4 antagonists related renal injury, which happens earlier (2–3 months) [41]. Glomerular diseases such as minimal change disease, membranous nephropathy, TMA, and lupus like nephritis also have been rarely reported with these agents. PD-1 as opposed to CTLA-4 inhibitors has been associated with kidney rejection in transplantation [41]. Steroids appear to be effective in treating the immune-related adverse effects noted with these agents [41]. Whether these drugs are associated with CKD is not yet clear but vigilance in monitoring GFR over time is warranted.

33.3.2 Paraneoplastic Glomerular Disease and CKD

Various kinds of cancers have been associated with glomerular diseases which can lead to progressive CKD. The pathophysiology underlying

this association in most cases is not clear. Both solid and hematological malignancies can produce abnormal tumor cell products which could lead to paraneoplastic glomerular disease. Table 33.2 summarizes the major solid and hematologic malignancies that have been associated with glomerular diseases.

Table 33.2 Solid and hematologic malignancies associated with different glomerular diseases

Malignancy	Glomerular diseases reported
Lung cancer[a]	MN, MCD, MPGN, IgAN, FSGS, CGN, TMA
Colon cancer	MN, MCD, CGN
Stomach cancer	MN
Pancreas cancer	MN, MCD, IgAN
Bladder cancer	MCD
Renal cell cancer	AAA, CGN, IgAN, MCD,FSGS, MPGN
Prostate cancer	MN, CGN
Breast cancer	MN, FSGS, MPGN,TMA
Esophageal cancer	MPGN, FSGS
Gastric cancer	MPGN, CGN, TMA
Head and neck cancer	MN, IgAN
Ovarian cancer	MN,MCD
Cervical cancer	MN
Endometrial cancer	MN
Melanoma	MN, MPGN
Skin cancers (basal, squamous cell)	MN
Hodgkin's disease	MCD, MN, MPGN, IgAN, FSGS,CGN, AAA,Anti GBM
Non-Hodgkin's disease	MN, MCD, MPGN, IgAN, FSGS
Chronic lymphocytic leukemia	MN, MCD, MPGN, FSGS, CGN
Acute myelogenous leukemia	MN, FSGS
Chronic myelogenous leukemia	MN, MCD, MPGN
Monoclonal gammopathy of unclear significance	MPGN
T cell leukemia	FSGS

MN membranous nephropathy, *MCD* minimal change disease, *MPGN* membranoproliferative glomerular nephritis, *FSGS* focal segmental global sclerosis, *CGN* crescentic glomerulonephritis, *IgAN* IgA nephropathy, *TMA* thrombotic microangiopathy, *AAA* AA amyloidosis, *GBM* glomerular basement membrane

[a]Includes small cell, nonsmall cell, squamous cell, and bronchogenic cancers

Membranous nephropathy (MN) is the most commonly reported glomerular disease in patients with solid tumors [42, 43]. The prevalence of malignancy in 240 patients with biopsy proven MN was around 10% [44]. Interestingly, only half of these patients had cancer-related symptoms at the time of their biopsy. Most were diagnosed with cancer within a year of being diagnosed with MN [44]. The finding of nephrotic-range proteinuria in a patient with cancer or the development of proteinuria within a few months of diagnosis of cancer should raise strong suspicion of glomerular disease, especially MN.

Delineating primary from secondary/cancer-associated MN has been a great challenge for nephrologists and pathologists. Various studies have evaluated different parameters which could help make this differentiation. These parameters could be clinical or historical clues, serological markers, or histopathological findings on the kidney biopsy.

Podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R) autoantibodies were first identified by Beck et al. in 2009 [45]. It was postulated that these circulating antibodies were mainly found in patients with primary MN. A study analyzed 10 patients with solid tumors and MN and three out of these 10 patients had both elevated levels of anti-PLAR2R antibodies and moderate glomerular IgG4 deposition on kidney biopsy; findings suggestive of an underlying primary MN in these patients with solid tumors [46]. These three patients had persistence or relapse of proteinuria despite tumor resection, further supporting the notion that these were indeed patients with primary MN. Hoxha et al. showed enhanced staining of PLA2R in glomeruli of patients with primary MN compared with normal staining in tumor-associated MN [47]. Ohani et al. showed increased glomerular deposition of both IgG1 and IgG2 subtypes in patients with cancer-associated MN as compared with primary MN [48]. While the presence of circulating anti-PLA2R antibodies or enhanced glomerular PLAR2R staining or the predominance of IgG4 in the glomeruli of patients with MN suggests primary MN even in the presence of

cancer, caution is warranted in excluding malignancy solely on the basis of anti-PLA2R antibodies. A recent study by Radice and colleagues analyzed 252 consecutive MN patients and found that 7 patients with cancer were anti-PLA2R positive [49]. Thus, anti-PLA2R positivity in a patient with MN should not be considered sufficient to abstain from seeking a secondary cause, especially in patients with risk factors for neoplasia.

Minimal change disease (MCD) has been associated with hematologic malignancies such as Hodgkin lymphoma, non-Hodgkin lymphoma, and other leukemias. Of all the lymphoid malignancies, MCD is classically associated with Hodgkin lymphoma, occurring in about 1% of Hodgkin's patients. In one case series, the diagnosis of MCD preceded the diagnosis of lymphoma by several months; 71% of patients with Hodgkin lymphoma and MCD had systemic symptoms (i.e. fever, weight loss, and night sweats), and 90% had positive laboratory parameters suggesting an inflammatory syndrome (as assessed by C-reactive protein level, sedimentation rate, and fibrinogen level) [50]. MCD-associated nephrotic syndrome usually relapses simultaneously with the hematologic malignancy and remains highly responsive to specific treatment for the malignancy. MCD can occur at the time of relapse even if it was initially absent, emphasizing the need to evaluate proteinuria during the follow-up of patients with Hodgkin lymphoma.

There is also an association of increased cancer risk in patients with glomerulonephritis (GN). In a recent Danish study in 5594 patients with glomerulonephritis, 911 cancers were diagnosed [51]. Of these, 35% were prevalent at the time of kidney biopsy. Increased cancer rates were seen for: minimal change, focal segmental glomerulosclerosis, mesangioproliferative, membranous, membranoproliferative, ANCA-associated vasculitis, and lupus nephritis. Increased cancer rates were seen for lung, prostate, renal, non-Hodgkin lymphoma, myeloma, leukemia, and skin. The increased incidence was mainly limited to −1 to 1 year after biopsy, but skin cancer showed an increased risk over time. The diagnosis with the highest risk for cancer was membranoproliferative GN.

33.3.3 CKD Associated with Hematopoietic Stem Cell Transplantation (HSCT)

CKD is now an increasingly important complication following HSCT. Hingorani et al. found that CKD was identified in 23% of recipients surviving at least 3 months after HSCT [52]. Acute kidney injury and graft versus host disease (GVHD) were noted as risk factors for the development of CKD. Another study found that the average fall in GFR in patients that develop CKD is 24.5 ml/min/1.73 m^2 over 24 months [53]. Approximately 16.6% patients who underwent HSCT developed CKD (454). Most of these patients were treated with non-myeloablative protocols. The growth in non-myeloablative protocols may actually increase the risk of CKD as older patients with more comorbidities become candidates for this procedure. Calcineurin inhibitors (CNIs), which are used for prophylaxis and treatment of graft versus host disease (GVHD), have been associated with the development of nephrotoxicity and may contribute to the development of CKD. Hypertension (HTN) and TMA are two comorbidities linked to the development of CKD [54–56].

Myeloablative allogeneic HSCT protocols can lead to low grade TMA that over time leads to CKD. This has also been termed bone marrow transplant nephropathy or radiation nephropathy and resembles thrombotic microangiopathies [54]. Clinically, non-nephrotic proteinuria, worsening hypertension, and renal dysfunction are adequate to diagnose TMA in most of these patients. Hypertension is usually the first sign of beginnings of renal limited TMA in many of these cases.

Glomerular disease can be a cause of CKD following HSCT. In HSCT patients with nephrotic-range proteinuria, the renal biopsy findings may include MN, MCD, and FSGS [57]. However, MN accounts for a majority of the cases of HSCT associated glomerular diseases,

while MCD accounts for most of the remaining cases [57]. The etiology and pathogenesis of nephrotic syndrome after allogeneic HSCT were elucidated by Luo et al. [58]. They compared 257 patients with nephrotic syndrome after allogeneic HSCT with non-nephrotic syndrome patients. They concluded that there was association of occurrence of chronic GVHD in patients with nephrotic syndrome after allogeneic HSCT.

33.3.4 CKD Associated with Renal Cell Carcinoma

In the USA, it is estimated that there will be over 64,000 incident cases and 13,700 cancer-related deaths from renal cell carcinoma (RCC) per year [59]. Given the age and comorbid conditions in this patient population, it is not surprising that 25% of patients with RCC have CKD [60]. In fact, approximately 10% of tumor nephrectomy specimens demonstrate features of diabetic nephropathy, 2–9% may have focal segmental glomerulosclerosis, and another 20% show hypertensive nephrosclerosis [61]. In the past, radical nephrectomy was considered the treatment of choice for isolated RCC or solitary renal masses (SRM). However, there is increasing awareness that radical nephrectomy is associated with a higher risk of CKD. Therefore, there has been a shift to partial nephrectomy as the treatment of choice for RCC [62–64]. Huang et al. reported the probability of being free from a GFR less than 60 ml/min/1.73 m^2 5 years after the procedure was 67% and 23% for partial and complete nephrectomy, respectively, with no difference in oncologic outcome [65]. Furthermore, the lower risk of CKD following partial nephrectomy has translated to improved overall survival for patients with localized RCC [65–67]. In a pooled analysis of 41,010 patients, partial nephrectomy was associated with a 61% risk reduction in developing CKD, and 19% risk reduction for all-cause mortality [68]. The American Urological Association released a position statement in 2009 that partial nephrectomy (nephron-sparing surgery) is preferred for T1 tumors (less than 7 cm in size) as the oncologic outcomes are equivalent to radical nephrectomy and the preservation of kidney function is beneficial for long-term outcomes [69]. Most recently, the American Society of Clinical Oncology (ASCO) published guidelines on the management of small renal masses (incidentally image-detected, contrast-enhancing renal tumors ≤4 cm in diameter) that further highlights the recommendation for "nephron-sparing surgeries" such as partial nephrectomy over radical surgical approaches [70]. This guideline recommends that radical nephrectomy should only be considered for patients with anatomically complex small renal masses for whom partial nephrectomy might result in unacceptable morbidity.

A recent study also highlights that "surgically induced CKD" such as that occurring after nephrectomy is more stable than CKD due to medical causes such as diabetes [71]. This is especially true if the postoperative GFR is >45 ml/min/m^2. However, all patients undergoing either partial or radical nephrectomy should have close nephrology follow-up with close attention to treatment of risk factors for CKD progression.

33.3.5 CKD Associated with Paraproteins and Plasma Cell Disorders

Plasma cell disorders encompass a spectrum of diseases that include multiple myeloma, immunoglobulin (Ig)-mediated amyloidosis, plasmacytomas, and the premalignant condition of monoclonal gammopathy of undetermined significance (MGUS). Kidney involvement in these disorders is common and abnormal GFR is seen in up to half of myeloma patients at the time of presentation [72, 73]. Abnormal kidney function in patients with multiple myeloma significantly contributes to excessive mortality and can limit clinical outcomes associated with both systemic therapies and stem cell transplantation (SCT) [73]. Three distinct syndromes account for the vast majority of Ig-mediated kidney disease: (1) cast nephropathy, in which proteinaceous deposits consisting of filtered monoclonal Igs in combination with other urinary proteins (such as

Tamm-Horsfall protein) obstruct the renal tubules as well as elicit an accompanying tubulointerstitial nephritis that typically results in AKI; (2) monoclonal Ig deposition disease (MIDD), characterized by the deposition of monoclonal proteins in the glomerulus and tubular basement membranes leading to local tissue injury; and (3) AL amyloidosis, where monoclonal light chains with specific physiochemical properties form β-pleated sheet structures that deposit in the glomeruli and lead to local tissue injury.

Given the wide spectrum of kidney disease associated with plasma cell disorders, kidney biopsy is recommended when any of these etiologies is suspected. Suspicion should be based upon clinical findings such as fatigue, weight loss, bone pain, and orthostatic hypotension or the presence of autonomic neuropathy coupled with laboratory abnormalities such as anemia, hypercalcemia, proteinuria, Fanconi Syndrome, and a low anion gap (due to the presence of an excess of cationic light chain proteins). Urine dipstick analyses typically do not detect light chains, but tests of total urine protein are abnormal. Thus, a negative urine dipstick test for albumin and the simultaneous detection of significant urine total protein is highly suggestive of light chain proteinuria and requires further testing. Of note, both MIDD and AL amyloidosis typically present with nephrotic-range proteinuria and albuminuria indicative of global glomerular damage.

33.4 Consequences of CKD in Cancer Patients

In the IRMA-2 study, the potential impact of CKD on survival of cancer patients has been assessed on a 2-year follow-up of the patients. The results showed that patients with a GFR lower than 60 mL/min/1.73 m^2 at time of inclusion in the study had a lower survival rate as compared to patients with a GFR greater than or equal to 60 mL/min/1.73 m^2 [74]. In fact, multivariate analysis showed that patients with a GFR lower than 60 mL/min/1.73 m^2 had a mean survival of 16.4 months as compared to 25.0 months for patients with a GFR greater than or equal to 60 mL/min/1.73 m^2 among the whole cohort of patients, whatever the type of tumor and the stage of the cancer disease ($N = 4267$). Considering the 2382 patients who had a nonmetastatic disease, the impact of CKD on survival was still significant with survivals of 21.0 vs. 25.0 months for patients with a GFR lower than or greater than or equal to 60 mL/min/1.73 m^2, respectively. Hazard ratios [95% confidence interval] were 1.27 [1.12–1.44].

In Japan [75] and Korea [76], there also was a significantly reduced survival rate in patients with CKD. In the Korean study, the authors demonstrated that CKD was an independent predictor of cancer-specific mortality, with hazard ratios for death of 1.12 ($p = 0.04$) and 1.75 ($p < 0.001$) for patients with a GFR within 30 and 60 mL/min/1.73 m^2 and below 30 mL/min/1.73 m^2, respectively.

The reasons for the reduced survival of cancer patients with CKD are not fully understood but likely include several factors: (1) comorbid conditions such as diabetes, hypertension, and cardiovascular disease that are independently associated with higher mortality, (2) restricted access to clinical trials due to arbitrary exclusion criteria focus on low GFR, (3) errors in dosing of chemotherapeutic medications (either over- or under-dosing) due to lack of dosing guidelines in CKD patients, and (4) interruptions in therapy due to changes in GFR that may require cessation of medications cleared by the kidney. Clearly, more research is needed to understand this mortality link.

33.5 Risk of Cancer in CKD Patients

Just as cancer and its related therapies may lead to CKD, there is an increased risk of cancer in patients with CKD. There are a number of putative factors which may account for the increased cancer risk in CKD patients, such as defects in immunological functions secondary to uremic state, carcinogenic uremic toxins (nitrosodimethylamine), impaired antioxidant defenses, vitamin

D deficiency, use of erythropoiesis-stimulating agents, cumulative immunosuppression, and risk of acquired cystic kidney disease [77, 78]. More research is needed to clearly understand the links. Wong et al. [79] demonstrated that, over a cohort of 3654 participants, men, but not women, with at least stage 3 CKD had a significantly increased risk for cancer (test of interaction for gender $p = 0.004$). The increased risk of cancer began at a GFR of 55 mL/min/1.73 m^2, and the risk of cancer (mostly lung and urinary tract) was increased by 29% for each 10-ml decline in eGFR (MDRD formula). A Danish registry study conducted over 16 years (1993–2008) reported on the incidence and prevalence of cancer in 823 patients with autosomal dominant polycystic kidney disease (ADPKD) and end-stage kidney disease (ESKD). The authors analyze the data over two 8-year periods of time: 1993–2000 and 2001–2008. The incidence of cancer per year of risk did not change significantly: 3.1% (95% CI 1.8–5.4) in 1993–2000 vs. 2.6% (95% CI 2.1–3.3) in 2001–2008 ($p = 0.4$). However, the average percentage in cancer prevalence gradually increased, from 10.4% (95% CI 8.1–13.3) in 1993–2000 to 14.0% (95% CI 12.8–15.4) in 2001–2008, resulting in a rise of 35% ($p = 0.0002$). Considering yearly prevalences, it almost doubled, from around 8.5 in 1993 to 15 in 2008 [16]. The primary causes of death among the 431 patients who died over the whole period changed when ranked according to the death rates/1000 years on renal replacement therapy. Death rates for cancer and infections did not significantly change between the two periods, while deaths from cardiovascular and cerebrovascular diseases significantly decreased, by 1.5 and 3.6, respectively. This made cancer the third cause of death during the second period (2001–2008). The most frequent cancers in this population were basal cell carcinoma, squamous cell carcinoma of the skin, breast cancer, cancer of cervix uteri, melanoma, and cancers of the colon, respiratory tract, bladder, prostate, and kidney, by descending order of frequency.

The interpretation of usual tumor markers screening tests in ESKD patients is complex due to a high incidence of false-positive results. This highlights the need for clinicians to rely on standard cancer screening recommendations for the population with CKD along with clinical judgment regarding the benefit of screening in a population with a potentially limited longevity [80]. For instance, tumor markers such as cancer antigen 125 (CA 125), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), or neuron-specific enolase (NSE) are glycoproteins with a relatively moderate-to-high molecular weight. They are not effectively removed by renal replacement therapies such as hemodialysis or peritoneal dialysis, and they thus may accumulate and be falsely elevated [80]. Stool occult blood testing is also altered by the high incidence of mucosal bleeding and gastric and colonic angiodysplasia in patients on dialysis, and the rate of false-positive is also high.

33.6 Dosing of Chemotherapeutic Medications in CKD

In patients with reduced GFR, the pharmacokinetics of drugs is often modified. Not only the urinary route of elimination is impaired but also the other phases of the pharmacokinetics may be altered by the presence of CKD and uremic retention solutes. These modifications may require dosage adjustments of anticancer medications in patients with CKD and cancer. Most often, these consist of a reduction of the administered dose in order to reduce accumulation, overdosage, and dose-dependent side effects. However, the dose must be at a certain threshold to maintain efficacy. Most often in patients whose GFR is greater than 60 mL/min, there is no need for dose adjustment and the usual dosage can be and should be used. Reducing the dose in these patients will lead to a loss in efficacy. In patients whose GFR is lower than 60, approximately 50% of anticancer drugs require dosage reductions and clinicians should work closely with experienced oncology-trained pharmacists to determine the correct dose.

33.7 Conclusion

In cancer patients, estimating renal function with an appropriate and validated method is mandatory in order to diagnose kidney disease and ensure proper dosage of medications. Understanding the various etiologies of CKD unique to the patient with cancer is also critical to ensure proper diagnosis and therapy. Prevention of a fall in GFR should be a clear goal for all cancer patients since progressive CKD resulting either from the cancer or its treatment leads to a shortened lifespan and negates some of the amazing gains seen with modern advances in cancer treatment.

Before You Finish: Practice Pearls for the Clinician

- A GFR estimate must be calculated in all cancer patients to screen for kidney disease.
- Throughout the course of a patient's cancer treatment, GFR should be periodically assessed and a nephrologist should be involved in the care of patients with eGFR <60 ml/min.
- CKD patients are at a higher risk for a number of cancers. Usual screening protocols may need to be modified in CKD patients since there is a higher frequency of false-positive for several tumor markers.
- A GFR estimate lower than 60.
  - Is an independent risk factor for reduced survival.
  - requires drug dose adjustments for many agents to limit the risk of overdose and toxicity.
- Even drugs with a major non-urinary elimination route may require dose reductions in case of reduced GFR.

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Chronic Kidney Disease in the Intensive Care Unit

34

Rachel Jeong, Pedro Fidalgo, and Sean M. Bagshaw

Before You Start: Facts You Need to Know

- CKD patients have a high prevalence of comorbid disease compared to non-CKD patients; however, CKD patients have reasonable short-term outcomes following ICU admission compared to non-CKD patients.
- The most common diagnoses contributing to ICU admission in CKD patients are sepsis and septic shock and decompensated cardiovascular disease.
- AKI is a common complication of critical illness, most often precipitated by sepsis, and remains a strong negative modifier of short- and long-term survival.
- CKD is an important and independent non-modifiable risk factor for the development of AKI and long-term accelerated loss of kidney function among CKD survivor of critical illness.
- While numerous factors influence the decision to start renal replacement therapy, the most common initial modality prescribed after ICU admission worldwide remains continuous renal replacement therapy, particularly for hemodynamically unstable patients.

34.1 Introduction

The worldwide prevalence and incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are increasing substantially, largely attributable to an aging population coupled with large increases in the rates of hypertension, type 2 diabetes mellitus, and obesity.

CKD patients are characterized by a higher burden of comorbid illness, including coronary artery disease, heart failure, diabetes mellitus, hypertension, and cerebrovascular disease, and generally have higher health services utilization, including rates of hospitalization, when compared to non-CKD critically ill patients. Moreover, patients with CKD, particularly those with ESKD, have a several-fold higher risk of developing critical illness. These features, along with rising prevalence rates and the availability of long-term renal replacement therapy (RRT), have increased the proportion of patients with CKD requiring ICU support. This will likely present challenges for clinicians working in resource-limited settings regarding decision-making for ICU support for CKD patients.

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34.1.1 Epidemiology of CKD and ESKD in ICU

There is limited data available on the prevalence of CKD among all critically ill patients supported in ICU settings, and most studies have focused on the subset of dialysis-dependent patients with ESKD [1]. Available data would suggest the proportion of patients admitted to ICU with ESKD ranges between 1 and 9%. The reported variability in ESKD admissions across studies is likely accounted for by regional differences in practice patterns and policy, availability of ICU resources, patient case-mix, and study design. ESKD patients have consistently been shown to have an estimated fourfold higher annual likelihood of admission to ICU when compared with the non-ESKD general population.

ESKD patients admitted to ICU have several notable differences in baseline characteristics when compared with non-ESKD patients [2, 3]. ESKD patients are generally younger, have more comorbid disease, more likely medical (i.e., non-operative admissions), and have higher illness severity scores compared with non-ESKD patients. However, these observations may be susceptible to selection bias. Available epidemiologic surveys of ESKD patients admitted to ICU are limited by not accounting for those patients referred and refused ICU admission.

34.1.2 Precipitants for Critical Illness in CKD and ESKD

The most common precipitants of critical illness prompting ICU admission among ESKD patients are sepsis/septic shock and decompensated cardiovascular disease including cardiogenic shock, myocardial ischemia/infarction, arrhythmic complications, and pulmonary edema. Cardiac arrest, malignant arrhythmias, and myocardial infarction account for over 40% of deaths, and sepsis is the second most common cause of death in CKD and ESKD patients. Cardiac arrest and cardiopulmonary resuscitation (CPR) are more common events occurring among ESKD patients compared with non-ESKD prior to ICU admission. This may relate to several factors including: a higher prevalence of comorbid cardiovascular disease (such as left ventricular hypertrophy and atherosclerosis) and diminished cardiopulmonary reserve, a higher incidence of primarily arrhythmic complications, and the factors related to dialysis (such as rapid fluid/electrolyte shifts, inaccurate dry weight prescription, or excessive interdialytic weight gain).

34.1.3 Outcomes for CKD and ESKD in ICU

Surprisingly, the early mortality for critically ill ESKD patients is lower than for those with acute kidney injury (AKI) or CKD, suggesting that the prognosis is driven largely by acute illness severity rather than baseline comorbidities. Patients with ESKD admitted to the ICU are often younger, have lower severity of illness, and less comorbidities. However, ESKD patients have consistently higher short-term mortality rates (9–44%) when compared to non-AKI critically ill patients and an age and sex-matched general population. The wide variation in reported rates is likely attributed to differences in study design, sample size, and selection bias. Factors that have been shown to be associated with ICU mortality in ESKD patients are older age, higher illness severity score (i.e., APACHE II or SAPS II), burden of non-renal organ dysfunction/failure, medical or non-surgical admission type, and provision and duration of life-sustaining technologies (i.e., mechanical ventilation, vasopressor therapy).

Studies reporting long-term survival among ESKD patients show a trend for an increased mortality rate within the first 6-months after ICU discharge, with a relatively stable but increased risk for mortality thereafter. At 2 years after ICU admission, survival is generally poor. Observational studies estimate only 1/3 of ESKD patients admitted to ICU were still alive. Although long-term mortality in ESKD patients is several times higher when compared to the general population, the presence of ESKD does not appear to independently predict long-term mortality, suggesting short-term prognosis is more related to

the acute illness severity rather than CKD and dialysis dependence.

It has been increasingly recognized that CKD influences the risk of developing AKI, and that AKI per se contributes to CKD progression and incidence of ESKD. The incidence of AKI treated with RRT among critically ill patients is increasing, and resultant loss of glomerular filtration rate (GFR) prompting dialysis dependence after hospital discharge occurs in approximately 25% of patients [4]. The most important risk factor for incident ESKD and dialysis dependence among survivors of critical illness is prior CKD. This would suggest continued surveillance of kidney function among survivors of critical illness is vital.

Data on changes to functional status and health-related quality of life (HRQL) for ESKD patients surviving an episode of critical illness are currently lacking. However, in non-ESKD critically ill patients surviving critical illness, in particular for those with severe AKI receiving acute RRT, long-term reductions in HRQL and impaired functional status are common. These data coupled with the reduced HRQL for ESKD patients imply this may be a significant issue for survivors of critical illness.

CKD patients, particularly those with ESKD, consume more health resources in association with admission to ICU compared with non-CKD patients. These patients have longer durations of ICU stay, longer duration of hospitalization, and higher rates of short-term rehospitalization. Moreover, these patients often remain chronically ill following ICU discharge due to issues related to cardiovascular comorbidity, malnutrition, and deconditioning. These likely reflect frailty, diminished cognitive and physiological reserve, and increased vulnerability to further adverse events.

34.1.4 Prognostic Scoring for CKD and ESKD in ICU

ICU prognostication using ICU-specific illness severity or organ failure scores (i.e., APACHE II, SAPS III, SOFA) can be challenging among patients with CKD/ESKD. Most scoring systems have not been specifically validated for CKD/ESKD patients and their performance routinely overestimates the risk of death [1]. However, a small single-center study of CKD patients in the ICU showed significantly higher APACHE II, SAPS III, and SOFA scores in non-survivors compared to survivors, suggesting good diagnostic utility [5]. Larger scale studies are needed to assess whether or not the perceived lack of benefit of ICU support for CKD/ESKD patients is warranted.

34.2 ICU Support of the Patient with Chronic Kidney Disease

The pathological changes accompanying CKD, although frequently not clinically evident until later stages of kidney disease, can present unique challenges for CKD patients presenting with critical illness. Details of some of the unique challenges in the acute management of CKD patients in the ICU are detailed in Table 34.1.

There is a paucity of data with respect to the specificity of the management of CKD patients in the ICU especially in the early stages of the disease. CKD patients should receive the same standard of care as the general population while accounting for some of the unique challenges that patients with CKD/ESKD may pose to ICU management.

34.2.1 Hemodynamic Monitoring and Mechanical Ventilation Support

The general principles for support and management of critically ill patient in the ICU focus on advanced hemodynamic and physiologic monitoring and multi-modal organ support to guide restoration of tissue perfusion and oxygen delivery (Table 34.2).

Most patients have intravascular placement of arterial catheter for continuous blood pressure monitoring, due to either the presence of hemodynamic instability and to monitor resuscitation

Table 34.1 Selected challenges to the ICU management of critically ill patients with CKD and ESKD

Parameter	Issue	Consequence
Comorbid disease	High prevalence of DM, hypertension, CVD, frequent exclusion from RCT of ICU-specific interventions	Increased susceptibility to poor wound healing, compromised perfusion to vital organs/organ dysfunction, low quality evidence-base for many aspects of management
Volume homeostasis	Reduced GFR and relative oliguria	Fluid accumulation, diuretic resistance, susceptibility to fluid overload complications
Dry weight evaluation	Unmeasured fluid losses and muscle wasting	Inaccurate estimation for determined fluid removal targets for RRT
Electrolyte homeostasis	Reduced GFR, reduced capacity to excrete free water and K^+, $PO4^3$, Mg^+, and other electrolytes	Increased susceptibility to hyponatremia, hyperkalemia, acidosis, and other electrolyte abnormalities
Hemostasis	Alternations in vWF complex; platelet activation/aggregation; and NO metabolism	Increased susceptibility to bleeding
Anemia	Relative EPO deficiency and resistance, functional iron deficiency, reduced RBC lifespan, anemia of chronic disease	Increased incidence of anemia, greater susceptibility to transfusion
Immunology/ inflammatory response	Impaired T-cell activity, deficient antibody production, altered opsonization/phagocytosis, chronic increased production of inflammatory cytokines/mediators	Increased susceptibility to infection, blunted response to infection
Antimicrobial therapy	Altered pharmacokinetics (reduced clearance, altered Vd, altered protein binding, extracorporeal clearance), multiple prior antimicrobial exposures	Increased prevalence/susceptibility to ARO, increased susceptibility to treatment failure/ toxicity
Vascular access	Vascular calcification, PD catheter or CVC present, multiple prior central venous catheters	Difficulty obtaining arterial and venous access, susceptibility to catheter-related infection, risk of vessel stenosis

DM diabetes mellitus, *CVD* cardiovascular disease, *GFR* glomerular filtration rate, *NO* nitric oxide, *Vd* volume of distribution, *ARO* antimicrobial resistant organisms, *RCT* randomized controlled trial, *ICU* intensive care unit, *PD* peritoneal dialysis, *CVC* central venous catheter, *vWF* Von Willebrand factor, *RBC* red blood cells, *NO* nitric oxide

(i.e., fluid therapy or titration of vasoactive therapy) or to facilitate frequent blood sampling. Arterial catheters display systolic, diastolic, and mean arterial pressure readings along with a continuous waveform. Analysis of the pressure waveform may provide useful information regarding a patient's clinical status. Variability on pulse contours is related to the elasticity, amplification, and distortion of smaller peripheral arterioles. CKD patients with significant peripheral vascular disease and/or arteriolar calcification may have reduced vessel elasticity (i.e., arterial stiffness) and exacerbated amplification that results in relative increases in systolic pressure and low diastolic pressure with rapid diastolic run off (i.e., widened pulse pressure). ESKD patients with a fistula or graft will have accelerated diastolic run off and as such, a lower diastolic and mean arterial pressure. In addition, given the prevalence of comorbid conditions in CKD such as cardiac valvular disease, ventricular hypertrophy (LVH), or pulmonary hypertension, arterial catheters may have misleading instantaneous accuracy, though likely have preserved trending [6].

Additional static hemodynamic measures, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), have focused on providing an estimate of left ventricular preload to guide fluid resuscitation. The challenge with these static pressure-derived measures is their lack of predict ability to determine whether a patient will positively response to a fluid challenge (i.e., show improvement in cardiac output and performance associated with a fluid bolus). These measures are confounded by alterations in ventricular wall compliance (i.e., LVH in ESKD). Both CVP and PAOP lack

Table 34.2 Methods for monitoring and support of organ failure in critically ill patients

Organ system	Monitoring	Support
Circulatory	Indwelling arterial catheter, central venous catheter, pulmonary artery catheter, respiratory variation in pulse pressure or stroke volume (LiDCO, PiCCO, FloTrac/Vigileo), echocardiography, impedance cardiography, cardiac-specific troponin, b-type natriuretic peptide	Fluid therapy, vasoactive therapy (inotropes, vasopressors), pacemaker, indwelling mechanical support (intra-aortic balloon pump, Impella, ventricular assist device), extracorporeal support (veno-arterial extracorporeal membrane oxygenation)
Respiratory	Pulse oximetry, arterial blood gas, end-tidal CO2, flow-volume loops on mechanical ventilator, chest radiography	Non-invasive mechanical ventilation (nasal, mask, helmet CPAP, or BIPAP), conventional mechanical ventilator, oscillator, extracorporeal support (veno-venous extracorporeal membrane oxygenation)
Renal	Routine blood/urine biochemistry, urine microscopy, urine output, fluid balance, novel urine or plasma kidney damage-specific biomarkers (NGAL, KIM-1, IL-18, L-FABP, NAG), renal ultrasound, renal Doppler resistive index	Renal replacement therapy (CRRT, SLED, IRRT)
Gastrointestinal	Feeding tolerance, diarrhea, routine blood biochemistry, abdominal radiography	Enteric nutrition, parenteral nutrition, glycemic control, micronutrient supplementation
Liver	Routine blood biochemistry (liver enzymes, lactate, glucose, ammonia)	Molecular adsorbent circulation system
Hematologic/ inflammatory	Clinical examination, complete blood count/ smear, C-reactive protein, procalcitonin	Blood transfusion, early/broad-spectrum antimicrobials, extracorporeal blood purification
Neurologic	Neurologic examination, CSF examination, brain radiology (CT, MRI, angiography), EEG, brain damage-specific biomarkers (neuron-specific enolase, S100β, myelin basic protein), invasive ICP monitoring, cerebral microdialysis	Sedation, antiepileptic therapy, intracranial hypertension management, intraventricular drain

CO_2 carbon dioxide, *CPAP* continuous positive airway pressure, *BiPAP* bilevel positive airway pressure, *NGAL* neutrophil associated lipocalin, *KIM-1* kidney injury molecule-1, *IL-18* interleukin-18, *FABP* fatty acid binding protein, *MARS* molecular adsorbent circulation system, *NAG* N-acetyl-β-D-glucosaminidase, *CRRT* continuous renal replacement therapy, *SLED* sustained low-efficient dialysis, *IRRT* intermittent renal replacement therapy, *ICP* intracranial pressure

precision in individual patients and should not be used in isolation to guide resuscitation. This may contribute to excessive and inappropriate fluid prescription. The central venous oxygenation ($ScVO_2$) is generally accepted surrogate for the mixed venous oxygen saturation (S_vO2) and reflects the adequacy of global cardiac output and oxygen delivery. It is important to note that the $ScVO_2$ may be high when measured via central venous catheters in ESKD patients with established AVFs due to the presence of an admixture of arterial and venous blood, making the interpretation and utility of such results challenging [7].

Functional dynamic metrics that utilize the observed variability in left ventricular filling across the respiratory cycle, measured as the variation in pulse pressure (PPV) or stroke volume (SVV), have been shown to better predict fluid responsiveness in mechanically ventilated critically ill patients [8] (Box 34.1). The premise is that variations in systolic blood pressure and stroke volume are greater in hypovolemic states due to the increase in collapsibility of the vena cava, increased transmural effect on the right atrium, and the relationship between stroke volume and preload being on the steep portion of the Frank-Starling curve. Large variation in SVV or PPV (>12%) indicates fluid administration will translate into increased cardiac output. There are important limitations to the use of PPV/SVV and

these measures are susceptible to errors in states where patients are not adapted to controlled mechanical ventilation (i.e., breathing spontaneously, variable tidal volume [Vt]) or are not in sinus rhythm (i.e., atrial fibrillation). Variation in the inferior vena cava diameter during respiration, as seen by echocardiography is an additional functional dynamic measure of fluid responsiveness. In spontaneously breathing patients, only passive leg raising (PLR) has been shown to reliably predict fluid responsiveness. PLR involves transient elevation of the lower extremities above the heart of a recumbent patient, mimicking the effect of a modest fluid bolus on the central circulation.

Mechanical ventilation is a core life-sustaining technology that largely defined the modern practice of critical care. Most critically ill patients require mechanical ventilation, whether for lung-specific indications (i.e., acute respiratory distress syndrome), systemic indications (i.e., shock), or post-operative support. A summary of the most common modes of mechanical ventilation provided in the context of critical illness is shown in Table 34.3. Epidemiologic data have shown an increased utilization of mechanical ventilation for critically ill patients in recent years. These patients are generally burdened with a high prevalence of comorbid disease, particularly CKD, representing up to one quarter of all mechanically ventilated patients.

Kidney disease, both acute and chronic, can present unique challenges with respect to respiratory physiology, lung–kidney interaction, and mechanical ventilation support [9]. First, CKD/ESKD patients often have high prevalence of comorbid respiratory illness such as restrictive or obstructive defects, pleural disease, pulmonary calcification, sleep-related breathing disorders, or dialysis-associated hypoxemia. Patients receiving PD have chronically elevated intra-abdominal pressure and diminished functional residual capacity. These factors predispose to limited pulmonary reserve. Second, CKD/ESKD

Table 34.3 Common modes of invasive mechanical ventilation in the ICU

Mode	Description	Advantages	Disadvantages
VCV	Machine delivered, patient triggered, flow targeted, frequency equal to minimum set rate, present Vd (volume limited)	Ensures the delivery of a minimum Vt and total minute ventilation	May be uncomfortable if high inspiratory flow needed by patient, may predispose to dynamic hyperinflation (auto-PEEP), may predispose to VILI
PCV	Machine delivered, patient triggered, pressure targeted, frequency equal to minimum set rate, breath terminated by present Ti (pressure limited)	Pressure limited, control of plateau/mean airway pressure, better patient comfort	Vt variable, does not ensure delivery of minimum ventilation
PSV	Patient triggered and pressure targeted Vt, breath terminated by present inspiratory flow rate, patient determined Vt, Ti, and frequency	Better patient–ventilator synchrony, augments patients' breather, better patient comfort, used commonly to wean	Vt, Ti, frequency variable; does not ensure delivery of minimum ventilation; unsuitable for patients with impaired respiratory drive
SIMV	Machine delivered synchronized breaths at present Vt, flow or pressure targeted, preset minimum rate, patient can breath spontaneously with PSV between machine delivered breaths	Ensures the delivery of a minimum Vt and total ventilation, allows some spontaneous breathing	May be uncomfortable, may increase work of breathing, may prolong weaning
CPAP	Machine set PEEP, patient triggered, patient determined Vt, Ti, and frequency	Augments spontaneous breathing, reduced inspiratory work, patient comfort, used commonly to wean	Vt, Ti, frequency variable; does not ensure delivery of minimum ventilation; may increase work of breathing

VCV volume-controlled ventilation, *PCV* pressure-controlled ventilation, *PSV* pressure support ventilation, *SIMV* synchronized intermittent mandatory ventilation, *Vt* tidal volume, *PEEP* positive end expiratory pressure, *VILI* ventilator-induced lung injury, *Ti* inspiratory time

patients often have diminished cardiac reserve, and all have compromised capacity to excrete solute and water. Acute cardiac events and/or fluid accumulation (i.e., non-compliance with diet, inaccurate dry weight prescription, missed dialysis) can predispose to acute cardio-renal syndrome and pulmonary edema. Third, the development of acute injury to the kidney can induce a systemic inflammatory response with distant pathophysiologic effects in the lung (i.e., alterations in alveolar permeability and aquaporin expression). Fourth, the positive pressure applied during mechanical ventilation acts to increase intrathoracic, intrapleural, and intra-abdominal pressures both during inspiration and for the duration of the respiratory cycle (i.e., PEEP) with the aim to improve and maintain adequate gas exchange. This can stimulate an array of hemodynamic, neural, and hormonal responses that can negatively impact kidney perfusion and further inhibit excretory function. This is observed as immediate and reversible declines in urine output and fluid retention, contributing to worsening fluid accumulation. Finally, mechanical ventilation may provoke ventilator-induced lung injury (VILI) leading to an exacerbating cascade of systemic inflammation that may have distant injurious effects on the kidney [9]. Data have also shown the development of AKI may delay weaning from mechanical ventilation [10]. This is likely multi-factorial and related to greater difficulties with volume and acid–base homeostasis in AKI. By extension, CKD/ESKD patients are similarly likely to encounter prolonged weaning from mechanical ventilation.

The most severe form of respiratory failure is acute respiratory distress syndrome (ARDS), defined as rapid onset (1 week) respiratory symptoms and hypoxemia associated with bilateral opacities resulting in respiratory failure not fully explained by cardiac failure or fluid overload. The incidence of milder forms of ARDS is 78.9/100,000 person-years, while more severe ARDS occurs at a rate of 58.7/100,000 person-years. The most common predisposing factor is pulmonary and non-pulmonary sepsis. The mortality remains significant, in the range of 35–40% and long-term morbidity among survivors remains severely burdensome. The development of AKI or worsening kidney function in the setting of ARDS is common, occurring in excess of 44%, and has an important modifying impact on increasing mortality risk (60–80%) [10, 11]. It is believed part of the attributable mortality in ARDS has related to the developing of secondary harm associated with the mechanical ventilator (i.e., VILI). Accordingly, a number of "lung protective" strategies for improving outcome in ARDS have been evaluated (Table 34.4). The advent of open-lung low-tidal volume ventilation to prevent alveolar over-distension, cyclic col-

Table 34.4 Ventilation and other supportive therapies in ARDS

Strategy	Description	Comment
Lung protective ventilation	Target tidal volume 6 ml/kg ideal body weight, set positive end expiratory pressure (PEEP) to avoid alveolar collapse, maintain plateau pressure <30 cm H_2O, may precipitate permissive hypercapnea	The "low-tidal" volume and "open" lung ventilatory strategy is aimed at minimizing iatrogenic injury from mechanical ventilation (i.e., ventilator-induced lung injury [VILI]). VILI is induced by volutrauma, barotrauma, atelectrauma, and biotrauma. Level I evidence have shown utilizing lung protective ventilation has shown reductions in mortality, durations of ventilation, and durations in ICU
Recruitment maneuvers (RM)	The rationale for utilizing RM in ARDS is to improve alveolar recruitment and gas exchange. RM are generally a series of continuously applied (20–40 s) high levels of PEEP (30–40 cm H20)	RM can improve oxygenation in suitable ARDS candidates with recruitment alveolar segments, however, can be associated with hemodynamic instability. No level I evidence

(continued)

Table 34.4 (continued)

Strategy	Description	Comment
Neuromuscular blockade (NMB)	Early short-term use of continuous NMB (<48 h) in severe ARDS may improve gas exchange and reduce VILI	Level I evidence found lower 28-day and hospital mortality associated with a strategy of early short-term continuous infusion of NMB in severe ARDS and no increase in the rate of ICU-acquired weakness
Daily sedation interruption	A strategy of daily interruption or minimal sedation has been advocated to reduce duration of ventilation, duration of ICU stay, and the incidence of delirium	These patients did not necessarily have ARDS. Level I evidence did not show evidence of reduced duration of ventilation or delirium associated with daily sedation interruption among ventilated patients receiving a sedation protocol
Conservative versus liberal fluid therapy strategy	The rationale for a conservative fluid management strategy is based on the premise of minimizing non-essential fluid and active removal of excess fluid once physiologic stability was achieved	Level I evidence found that a conservative fluid strategy, compared with a liberal fluid strategy, resulted in a non-significant reduction in mortality, and significant shorter durations of mechanical ventilation, ICU stay, and trends for lower utilization of RRT. These findings were similar for the subgroup with AKI
Prone positioning	ARDS is often a heterogeneous syndrome with worse air space consolidation in basal (dependent) lung segments. The rationale for prone positioning is to improve V/Q matching and reduce VILI by having patients in prone position for 12–16 h/day	Prior trials have found prone positioning improves oxygenation, and recent level I evidence found a strategy of early prone positioning was associated with improved survival at 28 and 90 days. Prone positioning should be protocolized
Inhaled vasodilators (iNO; prostacyclin)	The rationale for inhaled vasodilators, by reducing PVR and improving V/Q matching in ARDS, can improve oxygenation	Meta-analyses of small, randomized trials have found no improvement in mortality with inhaled vasodilators for ARDS, however, was associated with transient improvements in oxygenation and increased risk of AKI. Inhaled vasodilators are a reasonable salvage therapy for refractory hypoxemia
Extracorporeal membrane oxygenation (ECMO)	Candidates should have potentially reversible respiratory failure, severe hypoxemia (Murray score >3.0), ideally veno-venous circuit via dual-lumen catheter, early referral to experienced centers	ECMO has generally been reserved as salvage therapy for adult patients; however, level I evidence from randomized trials and observational data during the pH1N1 pandemic found reasonable survival
Ineffective or harmful interventions	High-frequency oscillatory ventilation, surfactant, anti-oxidants/glutamine supplementation, statins, N-acetylcysteine, ibuprofen, ketoconazole	Numerous high-quality randomized trials in adults have no clear evidence of benefit for these therapies

AKI acute kidney injury, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *HFOV* high frequency oscillatory ventilation, *iNO* inhaled nitric oxide, *NMB* = neuromuscular blockade, *PVR* pulmonary vascular resistance, *RM* recruitment maneuvers, *VILI* ventilator-induced lung injury

lapse, and barotrauma may be associated with iatrogenic alveolar hypoventilation and hypercarbic respiratory acidosis. This may be poorly tolerated in patients with AKI or CKD/ESKD with loss of kidney compensation and inability to buffer the accumulated CO_2. Higher PEEP can also have significant hemodynamic effects by exacerbation venous congestion in the kidneys, alter the renin–angiotensin–aldosterone axis, and alter kidney perfusion pressure. These patients may require earlier initiation of RRT to manage severe acidemia and excessive fluid accumulation.

34.2.2 Fluid, Electrolyte, and Acid-Base Management

Patients with CKD/ESKD are more susceptible to fluid and metabolic complications due to impaired fluid, electrolyte, and acid–base homeostasis.

Fluid therapy is perhaps the most common intervention received by critically ill patients. The key concept for dosing fluid therapy in critically ill patients is to actively address ongoing losses coupled with constant reassessment of need for further hemodynamic support. While the optimal endpoints for fluid therapy during resuscitation remain controversial, increasing evidence suggest resuscitation needs to be individualized and that the integration of functional hemodynamics measures to guide fluid responsiveness is superior to static measures of volume status.

Fluid therapy also represents a central cornerstone for the prevention and/or the management of AKI, through maintenance of renal blood flow, glomerular filtration, and renal oxygen delivery. However, there is no evidence that fluid therapy will reverse AKI once established. Reduced urine output is common and often precedes overt AKI, however, lacks specificity. Oliguria in the absence of clear hypovolemia or fluid responsiveness is not necessarily an indication for a fluid challenge. The distinction is important. In the context of hypovolemia and/or reduced arterial filling, fluid therapy would appear appropriate. However, there is no evidence to support a fluid challenge in the resuscitated patient with oliguric AKI. While such a fluid challenge may be intended to promote diuresis, dilute tubular toxins, and attenuate tubular obstruction from casts, there is no data to suggest it attenuates the severity of AKI or improves clinical outcome. Instead, unnecessary fluid therapy and accumulation is associated with increased risk for morbidity, including worsened AKI, delayed kidney recovery, and mortality [12]. Fluid accumulation can contribute to increased renal venous pressure and may reduce renal perfusion pressure, particularly if compounded by arterial hypotension and intra-abdominal hypertension. Kidney edema, due to increased interstitial and tubular pressures, can exacerbate declines in glomerular filtration pressure and propagate AKI. Fluid accumulation can also mask the presence and severity of AKI by increasing the total body water and by hemodilution of creatinine. Diuretic therapy should be reserved for mitigating fluid accumulation and overload in responsive patients rather than for preventing AKI or promoting recovery of kidney function. In patients whose fluid balance cannot be managed adequately with conservative fluid administration or diuretic therapy, RRT should be considered. In addition, the routine practice of providing "maintenance" of unmeasured fluid deficits such as "third space losses" for most critically ill patients is questionable, particularly for those with CKD/ESKD, and often contributes unnecessary fluid accumulation.

In addition, the types of fluid administrated are increasingly recognized as having dose-dependent qualitative toxic effects. Colloids are commonly used for acute resuscitation in critically ill patients. Synthetic colloids, such as hydroxyethyl starch (HES) have appeal for resuscitation fluids based on the premise they attenuate the inflammatory response, mitigate endothelial barrier dysfunction, improve microcirculatory flow, and contribute to more rapid hemodynamic stabilization; however, accumulated data have now suggest use of these fluids in critical illness is associated with dose-dependent hazard for severe AKI requiring RRT, bleeding complications, and death [13] (Box 34.2). In addition, these solutions are prohibitively more expensive when compared with crystalloids. Albumin is routinely used for resuscitation in liver failure patients with spontaneous bacterial peritonitis for prevention of hepatorenal syndrome and limited clinical data suggest albumin may improve outcome in severe sepsis.

Resuscitation with high chloride concentration solutions (i.e., 0.9% saline—strong ion difference: 0 mEq/L) can directly contribute to iatrogenic hyperchloremic metabolic acidosis. The physiologic stress with large volume resuscitation of chloride rich solutions may be less tolerated in CKD patients. Preferential use of balanced solutions with a lower "chloride load" is thought

to be beneficial by more closely mimicking the chloride content and strong ion difference of plasma. Randomized trials comparing resuscitation with saline (0.9%) to balanced crystalloid solutions (i.e., Ringer's lactate, plasma-lyte) have shown variable results; however, the preponderance of evidence suggests there may be benefit with preferential use of balanced solutions [14–18]. Importantly, individualization of resuscitation fluid type, volume, and duration is needed (i.e., avoiding iatrogenic hyperchloremic metabolic acidosis in CKD patients) (Box 34.3).

There is uncertain benefit for supplemental intravenous bicarbonate therapy for treatment of metabolic acidosis. Bicarbonate is commonly used in critical illness when confronted by severe metabolic acidosis (i.e., pH <7.15); however, its use is guided by limited clinical evidence. Bicarbonate supplementation intended to treat loss of bicarbonate from the buffer pool (i.e., renal tubular acidosis) would appear logical; however, its use to treat acidosis due to elevated lactate has been less certain. Bicarbonate administration (1–2 mEq/kg) can transiently increase serum pH and serum [bicarbonate], however, may precipitate untoward adverse effects including worsening intracellular acidosis, iatrogenic metabolic alkalosis, extracellular accumulation of CO_2, hypernatremia, and hypocalcemia. The 2021 Surviving Sepsis Guidelines do not recommend use of bicarbonate in patients with septic shock and lactic acidosis to improve hemodynamics or reduce vasopressor requirements. However, they do suggest the use of bicarbonate therapy in severe metabolic acidemia (pH ≤7.2) and AKI (KDIGO stage 2 or 3) as a weak recommendation based on low quality evidence. When bicarbonate is administered, consideration should be given for a slower infusion, allowing for adequate CO_2 removal, and correction of hypocalcemia, along with reversal of the underlying contributing factor for the acidosis.

34.2.3 Nutritional Support

Malnutrition is an important contributor to increased morbidity and mortality in critical illness. Both the presence of kidney dysfunction and critical illness are risk factors for malnutrition, and the presence of both concurrently can be even more detrimental. AKI and CKD/ESKD can alter the metabolism of macronutrients, with protein catabolism (i.e., protein energy wasting) being a hallmark feature. In addition to fluid, electrolyte, and acid–base derangements, kidney dysfunction can also induce a pro-inflammatory state, increase oxidative stress, and increase insulin resistance. Similarly, critical illness is a physiologic state characterized by widespread systemic inflammation, metabolic derangement, and catabolism. Therefore, critically ill patients, particularly those with pre-existing CKD/ESKD and malnutrition, may be unable to adequately absorb or utilize nutrients. This may be further compounded by increased clearance of nutrients and the effects of heat loss on energy expenditure during RRT.

The goal of nutritional support in critical illness is to provide sufficient nutrition to maintain homeostatic and metabolic needs without precipitating complications. Importantly, determination of the optimal caloric intake for critically ill patients ideally should involve the interdisciplinary contributions of a dietician. Dieticians can assist with ensuring optimal nutritional prescription for critically ill patients with AKI or CKD/ESKD as their course and therapies evolve (i.e., resolving organ dysfunction, recovering kidney function, transition from continuous to intermittent RRT). Early nutritional support in critical illness will not be significantly modified by the presence of CKD; however, in patients with advanced CKD or ESKD not supported with RRT, specialized enteric formulas are available that are more caloric dense (2 kcal/mL), lower in selected electrolytes (i.e., K^+, $PO4^-$, Mg^+), and fluid restricted. The intent of these specialized formulations is to provide adequate nutritional support while mitigating the development of metabolic complications or unnecessary fluid accumulation in patients with reduced GFR.

The preferred method for delivery of nutritional support is enteric nutrition (EN). This should be started early after ICU admission, within 48 h. The rationale for prioritizing EN is

based on the premise that it will preserve gut mucosal integrity and microbiome, reduce bacterial and endotoxin translocation, and reduce the risk of gastrointestinal bleeding. If there remains intolerance to EN, failure to meet nutritional targets with EN, or there are other medical or surgical reasons to avoid EN, current evidence suggests starting total parenteral nutrition (TPN) within 3–7 days.

The optimal energy intake in critically ill patients is controversial. In general, the optimal calorie amount is between 70 and 100% of measured energy expenditure. It is accepted that one should avoid under- or overfeeding as both can be detrimental. In the early phases of critical illness where there is a higher endogenous energy production, full feeding may cause overfeeding, which may be associated with adverse outcomes such as prolonged ventilatory support and increased mortality. On the contrary, underfeeding can cause severe calorie debt, depletion of energy stores, and increase risk of infectious complications. Despite concerns for overfeeding, underfeeding is highly prevalent [19]. Indirect calorimetry is the gold standard to assess energy expenditure and caloric needs and can be used to guide nutritional therapy. For patients receiving RRT, indirect calorimetry should be performed at least 2 h after an intermittent dialysis session, as CO_2 is removed during dialysis and the expired VCO_2 may not be accurate [20].

The optimal amount of protein supplementation in AKI and CKD is unclear. Current practice guidelines recommend avoiding protein restriction in critically ill patients as an attempt to prevent or delay initiation of RRT. Patients receiving RRT require a higher protein intake (intermittent RRT: 1.3–1.5 g/kg/day, continuous RRT: 1.5–1.7 g/kg/day) due to increased dialytic clearance of amino acids. Patients receiving RRT also require special attention to trace elements (i.e., selenium, zinc, and copper) and water-soluble vitamins (i.e., vitamin C, folate, and thiamine). There is insufficient data to suggest the use of high-dose parenteral glutamine in critically ill patients with AKI, CKD, or ESKD.

Critically ill patients with CKD may have baseline susceptibilities (e.g., diabetes mellitus) associated with enteric feeding intolerance from gut dysmotility (i.e., medications, electrolyte disorders, comorbid disease) and suboptimal absorption (i.e., gut wall edema). Measures to improve the success of enteric nutritional support include use of prokinetics agents (i.e., erythromycin, dose-adjusted metoclopramide), advancement of small bowel feeding tubes, elevation of the head of the bed (~30–45°) and not using specified gastric residual thresholds that often result in suboptimal delivery of targeted feeds [21].

The acute stress of critical illness coupled with nutritional support can often precipitate stress-induced hyperglycemia. The avoidance of significant hyperglycemia, hypoglycemia, and variation in glycemic control is associated with improved outcomes. However, tight glycemic control (TGC) with intensive insulin therapy (IIT) (BG 4.4–6.0 mmol/L) may be associated with increased risk for hypoglycemia and worse outcome. Accordingly, current practice guidelines recommend a more pragmatic and less intensive strategy targeting glycemic control between 6.1 and 10.0 mmol/L (Box 34.4).

34.2.4 Sepsis

Sepsis is a leading cause of death in patients with CKD and ESKD and commonly a precipitant of critical illness. CKD patients may be more susceptible to development of infectious complications and sepsis for multiple reasons, including:

- indwelling central venous catheters (CVC), AVFs, and arterio-venous grafts for hemodialysis;
- peritoneal dialysis (PD) catheters;
- acquired immunodeficiency related to primary etiology of kidney disease;
- immune dysregulation related to retention of uremic toxins (i.e., defective host responses in phagocytic cells, lymphocytes, and antigen processing; dysbiosis of gut microflora);
- systemic inflammation related to altered gut permeability and bacterial/endotoxin translocation during dialysis.

This risk if further modified by additional factors such as comorbid disease (i.e., peripheral vascular disease and diabetes mellitus; smoking) and frequent interaction with health care services (i.e., colonization with antimicrobial resistant organisms [MRSA, VRE] and frequent exposure to antimicrobials).

Indwelling access catheters are a significant source of bloodstream infections and sepsis in CKD/ESKD patients. They are directly related to the duration of usage, most commonly caused by gram-positive organisms (*Staphylococcus aureus*, coagulase negative staphylococcus) and associated with higher risk of morbidity and mortality. The risk is two- to threefold higher for non-tunneled (most commonly inserted in the ICU) compared with tunneled catheters. For ESKD patients receiving dialysis via tunneled catheters, the risk of bloodstream infection, infection-related hospitalization, and infection-related death is further two to threefold higher than for those receiving hemodialysis via arteriovenous fistulas or grafts. Important morbidity from temporary catheters arises from the risk of development of metastatic foci of infection from highly virulent bacteria such as staphylococcus aureus, including endocarditis, septic arthritis, osteoarthritis, and epidural abscess. PD peritonitis also carries a risk of major morbidity and mortality and high rates of technique failure after admission to the ICU.

The most common sources of non-dialysis related infections among CKD/ESKD patients are:

- upper and lower respiratory tract infections (i.e., community and/or hospital-acquired);
- genitourinary infections (i.e., pyocystis, pyelonephritis, peri-nephric infection);
- cellulitis/osteomyelitis;
- gastrointestinal infections (i.e., *Clostridium difficile*, cholangitis, hepatitis, gastroenteritis, diverticulitis, cholangitis);
- central nervous systems infections (i.e., mucormycosis);
- other infections: HIV, tuberculosis.

Pneumonia is a common contributor to morbidity and mortality in CKD/ESKD patients. The risk of developing pneumonia is 3–5 times higher among CKD/ESKD patients compared with matched population with normal kidney function and is associated with a higher likelihood of ICU admission and 4–6 times the total duration of hospitalization.

The prevalence of asymptomatic pyuria among CKD/ESKD patients with residual urine production is common (30–40%) but of undetermined significance and the diagnosis of genitourinary infection mandates the presence of a positive culture result. Indeed, genitourinary infections may be the most common source of nosocomial infection occurring in hospitalized CKD/ESKD patients due primarily to urinary catheterization. These sources of infection may predispose to bloodstream infection in susceptible CKD/ESKD patients and necessitate ICU referral for resuscitation and hemodynamic support. In anuric ESKD patients, urinary catheterization except for diagnostic indications should be avoided.

Cellulitis is a common precipitant of infection in CKD/ESKD patients often predisposed by poor peripheral circulation (i.e., diabetes mellitus, peripheral vascular disease) coupled with extravascular peripheral edema or infection introduced through repeated puncture of the native vascular access. By extension, suboptimal treated cellulitis may result in osteomyelitis of adjacent bony structures. Severe cellulitis may present with bloodstream infection in susceptible CKD/ESKD patients and prompt ICU admission.

The incidence of common gastrointestinal infections in CKD/ESKD patients is similar to the general population; however, their physiologic reserve to withstand these infections may be severely blunted and further predispose to added morbidity. The exceptions include susceptibility to infectious hepatitis (hepatitis B and C virus), peritonitis among patients receiving peritoneal dialysis, and Clostridium difficile colitis due to frequent antimicrobial exposure and interaction with health services.

Sepsis is defined as life-threatening organ dysfunction, identified by an acute change in Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of ≥2 points due to infection, caused by a dysregulated host response to infection [22]. Septic shock is a subset of sepsis associated with significantly increased hospital mortality, where despite volume resuscitation, vasopressors are required to maintain a mean arterial pressure ≥65 mmHg and the serum lactate is >2 mmol/L. The diagnostic criteria for sepsis and septic shock are shown in Box 34.5. It is important to recognize that many of these criteria may be modified due to CKD/ESKD and its treatment alone (i.e., dialysis-induced endotoxemia or hypotension) or due to concomitant comorbid disease (i.e., reduced cardiac reserve due to cardio-renal syndrome, autonomic dysfunction due to diabetes mellitus), drug therapy (i.e., β-blockers, coumadin), or not being applicable (i.e., serum creatinine elevation or oliguria in anuric ESKD).

The general principles and initial management of sepsis in CKD/ESKD patients are similar to the acute resuscitation of patients with suspected sepsis and AKI without kidney disease (Box 34.6). Early "bundled" resuscitation coupled with prompt broad-spectrum antimicrobial therapy and source control should be established in accordance with clinical practice guidelines [23]. If there is suspicion the source of sepsis is a vascular access catheter, this should be promptly removed once further central venous access has been confirmed. Special attention should be taken in ESKD patients with difficult vascular access prior to removing an infected tunneled dialysis catheter; in those with no alternate central venous access, a guidewire-exchange of the existing tunneled dialysis catheter to a temporary catheter by interventional radiology may be required to preserve their "lifeline."

34.2.5 Acute Kidney Injury

Acute kidney injury (AKI) is a common complication encountered in hospitalized patients, occurring in more than half of critically ill patients [24]. Recently, the KDIGO Consensus Conference in 2020 published an expansion and harmonization of the definition of acute and chronic kidney diseases, while the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury includes the staging of AKI [25, 26] (Table 34.5; Box 34.7). These criteria do not currently integrate evolving novel diagnostic bio-

Table 34.5 KDIGO diagnostic criteria and severity staging for acute and chronic kidney disease

	AKI	AKD	CKD
Duration	≤7 days	≤3 months	>3 months
Functional criteria	• Increase in SCr 1.5× baseline within 7 days Or • Increase in SCr by 26.5 μmol/L within 2 days Or • Oliguria (urine volume <0.5 mL/kg/h) for ≥6 h	• AKI Or • Increase in SCr 1.5× baseline Or • eGFR <60 mL/min/1.73 m^2 Or • Decrease in GFR by ≥35%	• GFR <60 mL/min/1.73 m^2
And/or		And/or	And/or
Structural criteria	Not defined	Marker of kidney damage (e.g., albuminuria)	Marker of kidney damage (e.g., albuminuria)

(continued)

Table 34.5 (continued)

AKI staging	Serum creatinine	Urine output
Stage 1	Increase of 1.5–1.9 times baseline or ≥26.5 μmol/L	<0.5 mL/kg/h × 6–12 h
Stage 2	Increase of 2.0–2.9 times baseline	<0.5 mL/kg/h × ≥12 h
Stage 3	Increase of ≥3.0 times baseline or ≥ 353.6 μmol/L; or start of RRT	<0.3 mL/kg/h × ≥24 h; or anuria ≥12 h

AKD acute kidney disease, *AKI* acute kidney injury, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *SCr* serum creatinine

Source: Lameire NH, Levin A, Kellum JA, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516-526. [25]

Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO 2012 Clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012; 2: 1–141. [26]

markers specific for kidney damage (i.e., cystatin C, NGAL, KIM-1, IL-18, L-FABP, urinary TIMP-2*IGFBP7, urinary CCL14). Yet, these biomarkers show promise to improve the capacity for early diagnosis, prognostication, and informed decision-making in AKI by helping to better discriminate of etiology of loss of kidney function (i.e., AKI vs. CKD), the underlying pathophysiologic mechanisms contributing to AKI, risk of worsening AKI and need for RRT, and long-term risk of CKD.

Development of AKI portends a worse prognosis in critically ill patients and predicts adverse outcomes, such as the receipt of RRT, prolonged ICU and hospital stay, and increased mortality risk [27]. The severity of AKI is associated with gradient increases in the risk of death, and death occurs in over half of critically ill patients with AKI treated with RRT [28, 29]. Importantly, for CKD patients developing acute on chronic kidney injury, the risk of accelerated progression to ESKD is increased several folds.

AKI is a syndrome with variable pathophysiology and contributing factors. The risk factors for development of AKI are often multidimensional and are related to synergy between pre-morbid susceptibility (i.e., older age, CKD, diabetes mellitus, hypertension, liver disease) and factors contributing to critical illness (i.e., sepsis, shock states, diagnostic procedures involving contrast media, major surgery) [24, 30]. The diagnostic evaluation of AKI should integrate routine biochemistry, urinalysis, and imaging where indicated to rule out immediately reversible etiologies (i.e., post-obstructive) or those requiring specialized interventions (i.e., vasculitis).

An understanding of the pathophysiology of AKI is important to provide appropriate management for these patients. Our current understanding of the pathophysiologic mechanisms contributing to AKI remains incomplete; however, contrary to the conventional view, recent data argue against ischemia-reperfusion as the predominant pathophysiologic mechanism contributing to AKI. The causal role of alternations in renal blood flow, neurohormonal responses, microcirculation and endothelial function, immune cell infiltration and activation, immune-mediated toxic injury, apoptosis, and inflammatory mediator-induced organ crosstalk are only beginning to be better understood.

The general strategies for prevention and management of AKI are similar for those with and without CKD [31] (Table 34.6). Specific interventions for prevention and treatment of established AKI are few and most have focused on preventing development of contrast-induced AKI in susceptible patients such as those with CKD. Several specific examples of mitigating risk of developing AKI or its complications are outlined in Table 34.7 [26, 31].

Table 34.6 Summary of strategies for initial resuscitation of critically ill patients with CKD/ESKD and for the prevention and management AKI

Intervention	Comment
Restore/optimize arterial filling[a]	Responsiveness to a fluid challenge should be assessed using functional hemodynamic monitoring. Isotonic or balanced crystalloid solutions should be used for acute resuscitation, with preference for balanced crystalloids for large volume resuscitation. Synthetic colloids (i.e., hydroxyethyl starch) and hyper-oncotic solutions should be avoided for fluid resuscitation in those at risk for AKI
Restore/optimize cardiac output[a]	The addition of inotropic therapy should be considered for patients with absolute or relative low cardiac output states
Restore/optimize mean arterial pressure[a]	The addition of vasopressor therapy, in conjunction with fluid therapy, should be considered in patients with persistent hypotension despite adequate volume administration
Restore/optimize oxygen carrying capacity	The consideration for blood transfusion should be given for ICU patients with AKI or CKD patients with severe anemia and evidence of tissue hypoperfusion and hypoxia. No evidence to support increasing the dose of erythropoietin stimulating agents during acute illness and possible risk of harm (increased risk of thrombosis)
Remove/avoid all non-essential nephrotoxins or perform appropriate therapeutic monitoring/ dose-adjustment when necessary	Avoid aminoglycosides unless there is no suitable alternative, utilize azole or echinocandin antifungals, or lipid formulations of amphotericin if there is no suitable alterative to treat systemic fungal infection
Consider context-specific interventions based on current clinical practice guidelines	For contrast-media exposure, hepatorenal syndrome, rhabdomyolysis, sepsis, vasculitis
Monitor for/avoid excess fluid accumulation	AKI and CKD are associated with greater risk for fluid accumulation. Monitor daily fluid intake/output and daily/cumulative fluid balance, recognizing there is some "ebb and flow" to fluid balance in critical illness
Monitor for/avoid complications of overt kidney failure	Monitor AKI and CKD patients for serious complications such as hyperkalemia, acidemia, fluid overload, drug toxicities, and appropriately plan for RRT
Maintain glycemic control	Glycemic control has been associated with reduced incidence of AKI and lower utilization of RRT. The balance of evidence now recommends maintaining glycemic control with a target blood glucose (BG) 6.1–10.0 mmol/L (110–149 mg/dL), rather than using intensive insulin therapy (IIT) to maintain tight glycemic control (BG 4.4–6.0 mmol/L) due to the increased risk of hypoglycemia

[a] There should be early use of invasive/functional hemodynamic monitoring (i.e., arterial catheter, central venous pressure, echocardiography, pulmonary artery catheter, or methods to measure stroke volume or pulse pressure variation)

Table 34.7 Selected examples of acute physiology and interventions with the potential for negative effects on kidney function

Intervention	Example	Action
Altered systemic hemodynamics		
Reduced arterial filling	Diuretics	Discontinue
Negative inotropic therapy	B-blockers	Discontinue
Anti-hypertensive therapy	CCB	Discontinue
Altered renal hemodynamics		
Afferent arteriolar vasoconstrictors	NSAIDs	Discontinue
Efferent arteriolar vasodilators	ACEi/ARB[a]	Discontinue

(continued)

Table 34.7 (continued)

Intervention	Example	Action
Altered renal venous pressure		
Elevated intra-abdominal pressure	Excess fluid accumulation	Avoid
Nephrotoxins		
Antibiotics	Aminoglycosides, vancomycin, colistin, Sulfamethoxazole, foscarnet	Discontinue, monitor, or dose-adjust
Antifungals	Amphotericin	Discontinue, monitor, or dose-adjust
Antivirals	Acyclovir, HAART	Discontinue, monitor, or dose-adjust
Immunosuppression	Tacrolimus, cyclosporine	Discontinue, monitor, or dose-adjust
Fluid therapy	Dextrans, hydroxyethyl starch	Avoid
Diagnostic imaging	Radio-contrast media	Avoid
Cytotoxic chemotherapy	Cisplatin, methotrexate	Discontinue, monitor, or dose-adjust

CCB calcium channel blockers, *NSAID* non-steroidal anti-inflammatory drugs, *ACE* angiotensin enzyme converting, *ARB* angiotensin receptor blocker, *HAART* highly active anti-retroviral therapy, *IAP* intra-abdominal pressure
[a] ACEi and ARB lead to reduction in glomerular blood flow, which has beneficial effects for kidney survival in chronic kidney disease patients but may lead to worsening kidney function in patients with AKI

34.2.6 Renal Replacement Therapy

Renal replacement therapy (RRT) is a vital, life-sustaining, and organ support technology applied in approximately 10–15% of all critically ill patients with AKI, and the use of RRT is increasing over time [30].

However, RRT also increases the complexity and health resource use for critically ill patients and recent data have suggested its utilization may be associated with higher risk of death and dialysis dependence among survivors. These data highlight the existing uncertainty regarding many aspects of the decision to initiate and the process of delivery of RRT to critically ill patients.

Current guidelines recommend the utilization of an uncuffed, non-tunneled dialysis catheter for acute RRT in the ICU (Box 34.7). The position of these acute catheters should avoid insertion in the subclavian vessels when feasible to mitigate the risk of long-term complications such as stenosis/thrombosis. Existing tunneled dialysis catheters may be used if already in situ; however, use of fistulas or grafts in acute critical care settings, particularly for CRRT, should be avoided.

The optimal time to start RRT in critically ill patients with AKI and/or CKD has historically been controversial [32]. There is general consensus that RRT should be urgently initiated in the presence of medically refractory complications related to AKI, such as severe electrolyte abnormalities (i.e., hyperkalemia), acid–base disturbances (i.e., acidemia), and fluid overload (i.e., pulmonary edema) [26] (Table 34.8). Early initiation of RRT in the absence of these urgent indications was hypothesized to improve outcomes by avoiding and mitigating severe complications attributed to AKI complications, particularly in critical illness. The large international STARRT-AKI trial randomized 3019 critically ill patients with severe AKI to strategies of accelerated (early) and standard (delayed) RRT and found no survival difference between RRT initiation strategies [33]. However, there was greater risk of adverse events and dialysis dependence at 90 days among survivors in the accelerated-strategy group. Moreover, a significant proportion of patients in the standard-strategy group did not receive RRT. These findings are supported by recent systematic reviews [34, 35]. While early or

Table 34.8 Indications for starting RRT in ICU

Indication	Comment
Renal replacement therapy	
Life-threatening indications	These indications have not been evaluated in trials
Hyperkalemia	Evidence of refractory elevated potassium, rapidly rising or cardiac toxicity. RRT is effective for temporarily reducing serum potassium
Acidemia	Evidence of refractory acidemia and inability to adequately compensate (pH <7.15). RRT can rapidly mitigate metabolic acidosis; however, correction requires targeted treatment of the precipitating disease
Pulmonary edema	Evidence of fluid overload contributing to worsening hypoxemia, contributing to the need for ventilatory support or prevention of weaning from ventilatory support. RRT can effectively reduce extravascular lung water in diuretic-resistance states
Uremic complications	Pericarditis, bleeding, encephalopathy. In modern ICU practice, withholding RRT until uremic complications arise would be uncommon
Non-emergent indications	
Azotemic control	Conventional criteria evaluate blood accumulation of urea and creatinine; however, numerous additional metabolites/uremic toxins can also accumulate. Blood concentrations of these metabolites may be confounded by added factors such as nutritional status, catabolism, and volume status
Fluid overload/ accumulation	Fluid overload/accumulation that is refractory to diuretics can be an important determinant for starting RRT
Acid-base/electrolyte abnormalities	Additional factors such as metabolic acidosis, marked electrolyte abnormalities (sodium, magnesium) can be potentially treated with RRT; however, no standardized criteria exist
Renal support	These indications in critical illness may occur separately from patients with either life-threatening complications of AKI or advanced AKI, rather can be viewed as a platform for organ support to prevent complications and facilitate treatment
Volume homeostasis	Fluid accumulation is worse in AKI and is associated with worse outcome. RRT may represent part of a strategy to mitigate excessive fluid accumulation
Nutritional support	RRT can better enable the delivery of full nutritional support (i.e., enteral or parenteral) without the concern for excessive fluid accumulation
Acid-base/electrolyte homeostasis	RRT may represent part of a strategy to enable "permissive hypercapnia" in ICU patients with severe ARDS and AKI/CKD or mitigate adverse effects from anticipated electrolyte disorders (i.e., tumor lysis syndrome)
Immunomodulation	RRT may represent a strategy for modulating and restoring immune function in sepsis and associated with severe inflammatory states. Studies are ongoing
Drug delivery	RRT can better enable the delivery of essential drugs (i.e., antimicrobials) without the concern for excessive fluid accumulation

ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *RRT* renal replacement therapy

pre-emptive initiation of RRT does not improve mortality, the safety of more prolonged delay in RRT initiation in the absence of urgent indications or for persistent AKI is unknown. The recent AKIKI-2 trial randomized 278 patients to a delayed or more-delayed strategy to RRT initiation and found the number of days-alive and RRT-free days (primary outcome) was not different between the strategy [36]. However, a pre-specified adjusted analysis found that the more-delayed strategy was associated with higher mortality, implying that the prolonged effects of persistent AKI (i.e., azotemia, medication toxicity), even in the absence of urgent indications, may contribute to excess mortality.

The choice of ideal RRT modality for critically ill patients has long been debated. A recent systematic review did not show a clear survival advantage nor difference in dialysis dependence for one modality, continuous RRT (CRRT), slow-low efficiency dialysis (SLED), or intermittent RRT (IRRT), over another in critically ill patients

Table 34.9 Description of the characteristics and comparisons of RRT modalities used to treat critically ill patients

Characteristics	CRRT	SLED/EDD	IRRT
Duration (h)	20–24 h/day	8–12 h/day	3–6 h/day
Blood flow rate	100–250 mL/h	200–300 mL/h	400–500 mL/h
Dose intensity	20–25 ml/kg/h	Kt/V 1.2–1.4	Kt/V 1.2–1.4
Comparison			
Risk of hemodynamic instability	↓↓	↑/↓	↑↑
Azotemic control	↑↑	↑/↓	↓↓
Electrolyte homeostasis	↑↑	↑/↓	↓↓
Volume control	↑↑	↑/↓	↓↓
Risk of bleeding	↑↑	↑/↓	↓↓
Patient mobilization	↓↓	↑	↑↑
Immunomodulation	↑↑	↓	↓↓
Cost (per day)	↑↑	↑/↓	↓↓
Special circumstances[a]	Most suitable	Not recommended	Not recommended

CRRT continuous renal replacement therapy, *SLED/EDD* slow-low efficiency dialysis/extended daily dialysis
[a] Shock states; severe hyponatremia; elevated intracranial pressure (i.e., traumatic brain injury; fulminant hepatic failure)

with AKI [37] (Table 34.9). Ideally, the modality chosen should suit the patient's acute physiology and therapeutic objectives while avoiding treatment-related complications. CRRT is the preferred modality in hemodynamically unstable patients, and those with acute brain injury or fulminant hepatic failure who are at risk for intracranial hypertension and cerebral edema [26]. CRRT has also been shown superior for maintaining fluid homeostasis and mitigating fluid overload. These data suggest that CRRT may be the preferred initial modality for critically ill patients with AKI.

The optimal mode of CRRT to improve outcome remains uncertain. The purported advantages to hemofiltration (CVVH) compared with hemodialysis (CVVHD) are the improved convective clearance of middle molecular weight solutes such as inflammatory and toxic mediators. Recent data have suggested equivalent outcomes in terms of survival and recovery of kidney function; however, CVVH may be associated with short filter lifespan and higher treatment costs compared with CVVHD [38, 39].

The optimal time to transition from CRRT to either SLED or IRRT is currently unknown; however, pragmatically will coincide with physiologic stabilization and following weaning from vasoactive support.

The utilization of peritoneal dialysis (PD) in critical illness may be a feasible and safe option for the treatment of AKI. A systematic review, which included three studies of critically ill patients, found that there is probably little or no difference in survival, kidney function recovery, and infectious complications with PD compared to extracorporeal therapy for treating AKI [40]. The International Society of Peritoneal Dialysis (ISPD) guidelines recommend that PD be considered for the treatment of AKI as a grade 1B recommendation [41]. However, in critically ill, catabolic patients, there may be insufficient solute clearance and inadequate fluid removal with PD. Therefore, the choice of modality of RRT should be individualized to the patient, as well as local practices and infrastructure.

Determination of the optimal dose intensity for small solute clearance for critically ill patients with AKI has long been a clinical priority. Early randomized trials clearly favored a more intensive strategy; however, later high-quality data derived from large randomized trials failed to show a benefit with this approach. Two multi-center randomized trials, the Department of Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network (ATN) Study and the Randomized Evaluation of Normal vs Augmented Level (RENAL) Replacement Therapy Study found no incremental benefit in critically ill patients with AKI from a more intensive (high-dose) RRT compared with a less

intensive RRT strategy [42, 43]. The more intensive strategy did not decrease mortality, accelerate recovery of kidney function, or alter the rate of non-renal organ failure. Importantly, these findings do not imply that the dose of RRT is not important, but rather, the evidence would suggest there is no need to exceed a CRRT dose of 20–25 mL/kg/h effluent flow rate or IHD three times per week with delivered Kt/V_{urea} 1.2–1.4 per treatment for small solute clearance. Higher net ultrafiltration rates (greater than 1.75 mL/kg/h) compared with lower rates (less than 1.01 mL/kg/h) appear to be associated with higher mortality in secondary analyses of clinical trials and retrospective studies [44, 45]; however, confirmatory data in the form of prospective trials are currently lacking.

In general, RRT should be discontinued when it is no longer indicated due either to sufficient residual or recovering kidney function or a change in the overall goals of care of the patient. The best predictor for successful weaning from RRT for critically ill patients is the volume of spontaneous urine production in 24 h. Those capable of producing ≥450–500 mL urine per day have a higher likelihood of short-term recovery and dialysis independence. There is no evidence to suggest improved or accelerated recovery and dialysis independence with early forced diuresis with furosemide.

34.2.7 Pharmacotherapy

Drug pharmacokinetics in critical illness and AKI are significantly modified due to alterations in drug bioavailability, reduced protein binding, increased volume of distribution, altered biotransformation, and reduced intrinsic clearance and elimination. Appropriate drug dosing is further complicated by a number of factors, including baseline comorbid disease of patients (i.e., CKD), need for multiple drugs that potentially interact with vital functions, lower thresholds for toxicity, evolving illness severity and organ dysfunction (i.e., changes in GFR) and superimposed extracorporeal drug removal (Table 34.10).

In general, there are several pragmatic steps to help guide drug dosing in critically ill patients with AKI and in those receiving RRT [46]. First, the literature should be reviewed for existing data on drug dose guidance for a specific drug [47]. Second, for drugs with primary renal elimination, a bedside estimate of baseline GFR and a dynamic assessment of total creatinine clearance, if applicable, should be undertaken, assuming there is no significant secretion or reabsorption. Consideration should be given to patients receiving RRT who have recovering or residual renal function. The prescription of RRT should be taken into consideration, including mode of RRT (con-

Table 34.10 Summary of factors affecting drug elimination in critically ill patients receiving RRT

Factor	Comment
Drug characteristics	Molecular weight, charge, and non-renal elimination can impact clearance
Drug availability	
Vd	Increased in critical illness and AKI, generally requires larger loading dose, and reduces drug availability for EC clearance
PB	Only unbound fraction available, reduced in critical illness and AKI, reduces drug availability for EC clearance
Plasma	Only drug within intravascular compartment available for EC clearance
Extracorporeal therapy	
Dose intensity	Higher dose intensity, such as prescription of HVHF, will increase EC clearance; clearance impacted if large discrepancy between prescribed and delivered dose
BFR	Higher blood flow rate will deliver more drug to filter, only important at either very low or high blood flow or large discrepancy between prescribed and delivered dose
Mode (convection vs dialysis)	EC clearance dependent on total effluent flow rate and/or dialysate flow rate
Replacement fluid	Pre-filter replacement fluid administration will result in hemodilution and lower EC clearance
Filter membrane	Sieving/diffusion coefficient important, whereas surface area has limited impact on EC clearance
Organ recovery	Residual or recovery kidney function can greatly increase overall clearance during extracorporeal therapy

tinuous vs. intermittent; convective vs. dialytic clearance), characteristics of the filter membrane (i.e., flux and surface area), and dose of RRT. Third, particularly for drugs with a narrow therapeutic index and risk of toxicity, therapeutic drug monitoring, when possible, should be undertaken (i.e., phenytoin, vancomycin, aminoglycosides). Fourth, several drug classes may be administered based on their observed clinical response, such as with sedatives, analgesics, or vasoactive medications. However, selected drugs have potentially toxic metabolites that can accumulate in patients with reduced kidney function. As examples, the elimination of α1-hydroxymidazolam (main metabolite of midazolam) and glucuronide metabolites of morphine are principally eliminated by the kidneys and thus may accumulate in AKI/CKD. Finally, given the complexity, there is a recognized need for a dedicated ICU pharmacist among the inter-disciplinary ICU team, particularly for patients with CKD or AKI.

34.3 Conclusions

The prevalence of CKD and ESKD is increasing. These patients are burdened by high comorbid disease, are more likely to interact with critical care services, and have worse short-term and long-term outcomes compared with non-CKD patients. Short-term mortality is predominantly driven by acuity of illness rather than CKD status per se and CKD status should likely not preclude critical care support. The pathophysiologic changes associated with CKD/ESKD and development of superimposed AKI can present unique challenges for clinicians in the ICU management of these patients.

Before You Finish: Practice Pearls for the Clinician

- CKD and ESKD status alone should not exclude consideration for admission in the ICU.
- Prognostic score results should be carefully considered since they routinely overestimate mortality in ESKD patients.
- The principles of management of sepsis should be applied to CKD, fluid accumulation and overload being an obvious caveat.
- Fluid therapy should be considered a drug therapy and dosed accordingly.
- After an AKI episode, kidney function should be monitored for the development of CKD.
- Consider initiation of RRT ahead of absolute indications in critically ill patients. CRRT is the preferred option for the hemodynamically unstable patient.
- Avoid nephrotoxic drugs for patients with CKD and/or at risk for AKI.
- Adjust drug regimens to renal function, except for the loading dose of antibiotics.

Box 34.1 Definitions of Functional Hemodynamic Metrics

Pulse pressure variation (PPV): Defined as the maximum pulse pressure minus the minimum pulse pressure, divided by the average of these two pressures over a mechanically delivered breath. PPV is based on the premise of pulsus paradoxus, the changes in arterial pressure during inspiration and expiration. PPV is not a true measure of preload or volume status, but an indicator of the position of the Frank-Starling relationship curve between stroke volume and preload to predict fluid responsiveness.

$$\mathrm{PPV}(\%) = \left(\mathrm{PP}_{\max} - \mathrm{PP}_{\min} / \left[\left(\mathrm{PP}_{\max} + \mathrm{PP}_{\min}\right)/2\right]\right) \times 100$$

Stroke volume variation (SVV): Defined as the percentage of change between the maximum and minimum stroked volume over a certain interval. Similar to PPV, SVV is not a true measure of volume status or preload but rather an assessment of response to fluid resuscitation.

$$\mathrm{SVV} = \left(\mathrm{SV\ maximum} - \mathrm{SV\ minimum}\right) / \left[\left(\mathrm{SV\ maximum} + \mathrm{SV\ minimum}\right)/2\right]$$

Box 34.2 What the Guidelines Recommend for Fluid Resuscitation in Critically Ill Patients

- Do not use HES in patients with severe sepsis or at risk of AKI
- Gelatin should not be used in patients at risk for AKI
- Do not use HES or gelatin in organ donors
- Do not use synthetic colloids in patients with head injury or intracranial bleeding
- Albumin may be used for resuscitation in severe sepsis
- Do not use albumin in patients with head injury
- Hyper-oncotic solutions should not be used for fluid resuscitation
- New colloid should be introduced into clinical practice only after patient safety parameters are established

Source: Reproduced with permission from Springer Science and Business media: Reinhart K, Perner A, Sprung CL, et al. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med.* Mar 2012;38(3):368-383 [24]

Box 34.3 Definition and Calculation of the Strong ion Difference

The strong ion difference is the difference between the sums of concentrations of the strong cations and strong anions dissolved in plasma. In normal plasma with preserved serum protein content, the SID is approximately 40 mEq/L.

Strong ion difference (SID): $[Na^+] + [K^+] + [Ca^+] + [Mg^+] - [Cl^-]$—[other strong anions]

Solution	$[Cl^-]$ (mEq/L)	SID (mEq/L)
Plasma	95–105	40
0.9% saline	154	0
Plasma-Lyte	98	50

Chloride is the predominant strong anion capable of modifying serum pH. Increases in serum chloride concentration (0.9% saline administration) will reduce SID and contribute to metabolic acidosis with normal anion gap.

Accumulation of organic acids (i.e., lactate, ketoacids) will increase other strong anions and induce metabolic acidosis by lowering SID with a normal serum chloride concentration and elevated anion gap.

Box 34.4 What the Guidelines Recommend for Nutritional Support in Critically Ill Patients

- Initiate nutritional support via the enteral over parenteral route
- Initiate early enteral nutrition (EN) (within 48 h)
- If there is intolerance, or inability to meet caloric needs or contraindications with EN, parenteral nutrition (PN) should be started after 3–7 days
- In critically ill patients, initial caloric and protein targets should be 20–30 kcal/kg/day and 1.0–1.3 g/kg/day adapted to catabolism levels and individual needs. Patients on RRT should receive higher protein intake (intermittent RRT: 1.3–1.5 g/kg/day; continuous RRT: 1.5–1.7 g/kg/day)
- Protein restriction is not recommended during the early catabolic phases of critical illness for patients with AKI, CKD, or ESKD. Additional protein supplementation is needed for patients receiving RRT

- Glycemic control with insulin is recommended for target blood glucose between 6.1 and 10.0 mmol/L. Hyperglycemia, hypoglycemia, and wide variations in blood glucose should be avoided
- Do not use glutamine supplementation in patients with severe sepsis or multiorgan dysfunction
- Indications for PN in AKI/CKD are similar to non-AKI/CKD patients
- Inter-disciplinary consultation with critical care dietician is recommended

Source: Adapted from Fiaccadori E, Sabatino A, Barazzoni R, et al. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. *Clin Nutr*. 2021;40(4):1644-1668 [20]

Box 34.5 Diagnostic Criteria for Sepsis and Septic Shock

Sepsis:
Defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, where organ dysfunction is identified by an acute change in total SOFA score ≥2 points

Septic shock:
Defined as a subset of sepsis, where despite adequate volume resuscitation:

1. Vasopressors required to maintain MAP ≥65 mmHg

And

2. Serum lactate >2 mmol/L

SOFA Variables:
PaO_2/FiO_2 ratio
Glasgow Coma Scale score
Vasopressor requirement: type and dose rate of infusion
Serum creatinine or urine output
Bilirubin
Platelet count

MAP mean arterial pressure, *SOFA* sequential [sepsis-related] organ failure assessment
Source: Reproduced from: Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10 [22]

Box 34.6 What do the Guidelines Say you Should do? Surviving Sepsis Campaign Guideline: Hour-1 Bundle

Hour 1

- Measure serum lactate (remeasure if initial lactate >2 mmol/L)
- Obtain blood cultures prior to administration of antimicrobials
- Administer broad-spectrum antimicrobials (see Antimicrobial therapy and source control)
- Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
- Administer vasopressors if hypotensive during or after fluid resuscitation to maintain MAP ≥65 mmHg

Source: Reproduced from: Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10 [22]

Antimicrobial therapy and source control

- Aim to administer broad-spectrum "effective" intravenous antimicrobial therapy within the first 1 h of recognition of sepsis. Each 1 h delay in administration of appropriate antimicrobials during the first 6 h is associated with an 8% decrease in survival
- In patients with sepsis/septic shock and high risk of MRSA, empiric MRSA coverage is recommended
- In patients with sepsis/septic shock and high risk for multidrug resistant organisms, two antimicrobials with gram-negative coverage are suggested
- In patients with sepsis/septic shock and high risk of fungal infection, empiric antifungal therapy is suggested
- Evaluation for a specific anatomical diagnosis of infection should be undertaken for consideration for emergent (within 6–12 h) source control measures (i.e., surgical for septic arthritis, catheter removal for bloodstream infection, chest thoracostomy tube insertion for empyema). Delay to source control when present is also associated with significant decrease in survival

MAP mean arterial pressure
Source: Reproduced from: Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10 [22]

Box 34.7 Relevant Clinical Practice Guidelines

1. ***CHRONIC KIDNEY DISEASE*:** Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Working Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* Suppl. 2013; 3(1): 1-163. [48] Available at: https://kdigo.org/guidelines/ckd-evaluation-and-management/
2. ***ACUTE KIDNEY INJURY*:** Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int*. Suppl. 2012; 2: 1–141. [26]. Available at: https://kdigo.org/guidelines/acute-kidney-injury/
3. ***SEPSIS*:** Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med.* 2021; 49(11):e1063-e1143. [49] Available at: https://www.sccm.org/SurvivingSepsisCampaign/Home
4. ***FLUID THERAPY:*** Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS; European Society of Intensive Care Medicine. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med*. 2012 Mar;38(3): 368-83. [50]
5. ***NUTRITIONAL SUPPORT*:** Critical Care Nutrition - Canadian Clinical Practice Guidelines. [51] Available at: https://www.criticalcarenutrition.com/resources/cpgs/past-guidelines/2015

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35 Chronic Kidney Disease Management Programs and Patient Education

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Before You Start: Facts You Need to Know

- Chronic kidney disease (CKD) prevalence is increasing with one in ten adults affected worldwide. Due to the asymptomatic nature of the early disease, many individuals are unaware of their disease and present late for care.
- Beyond the increased morbidity and mortality for those with CKD, there are financial, social, and societal impacts related to the diagnosis.
- Multidisciplinary team approaches including involvement by community health workers, pharmacists, nursing, primary care providers, healthcare institutions, and payers are necessary to change the progression of kidney disease.
- Patient engagement is developed through education programs, self-management strategies, and peer support. This engagement is essential for successful long-term management.

35.1 Chronic Kidney Disease Management Programs

With the increasing prevalence of CKD worldwide and the implications in terms of financial burden on healthcare systems for care and the increased cardiovascular morbidity and mortality, the need for early identification and management is important. Beyond the health effects, there are the additional impacts on the ability to work, remain in school, or change in family roles when needing to start renal replacement therapy that make kidney disease a potentially life-changing event. These other changes necessitate that management strategies extend beyond diagnosis, slowing progression of kidney disease, and treatment of complications of kidney disease. The healthcare burden and financial burden have led to development of CKD management programs. Disease management refers to multiple approaches to identify patients with health conditions and encourage adherence to treatment plans with the goals of reducing healthcare costs [1, 2]. Such programs have been used successfully with other health conditions such as diabetes and congestive heart failure. There has not been as much ease in implementation of CKD management programs.

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35.2 Barriers to Development of CKD Management Programs

Understanding the unique challenges of CKD are key prior to building a management program. The asymptomatic nature of kidney disease and the unfamiliarity with how the kidneys work contribute to the late diagnosis and presentation to care for many patients [3, 4]. For many individuals the extent of knowledge of kidney disease is that some people have received a kidney transplant and some are on dialysis. This is in combination with primary care providers not prioritizing CKD due to the number of competing health issues to be addressed during visits, the challenges in providing the education and counseling to patients, absence of the appropriate testing for diagnosis of kidney disease, and the lack of an established co-management strategy with nephrologists. Compounding these issues are the gaps in assessment of at-risk populations. Social determinants of health such as access to care, access to healthy food choices, ability to get to appointments, and lack of support symptoms result in less opportunities for medical care and less opportunity for early diagnosis. These factors are often not addressed or accommodated during program development. Addressing the needs of a CKD population would require significant resources: financial, personnel, engagement of community programs, and healthcare institutions. Additionally, the nature of CKD being progressive and potentially requiring several years of management, it is harder to see benefits in terms of healthcare costs and changes in morbidity and mortality. The arguments advocating for healthcare institutions and payers to commit to the costs of CKD management programs are made difficult by the lack of immediate results or cost savings.

35.3 Can CKD Programs Be Successful and Improve Outcomes?

Gauging outcomes start with defining the goals of CKD management programs. The overall goals include identifying those at risk, early diagnosis, delay of progression of kidney disease, management of complications, reduced hospitalizations, and overall cost savings. There are many variations in programs depending on if it is a practice-based program, a healthcare plan, or a public health initiative. This coupled with the need for long-term follow-up or large numbers of individuals studies has limited the amount of data on the benefit of CKD programs. One area that lends itself to analysis is the impact of CKD programs on the amount of money spent on care, rates of hospitalization, rate of pursuing home dialysis, and rates of transplantation. Lower rates of "crash starts" of dialysis (those without previous preparation), reduced number of days in the hospital when starting dialysis, and decreased expenditures when starting dialysis have been demonstrated with use of multidisciplinary clinics for those with advanced CKD [5]. There has also been success for healthcare programs to incorporate CKD programs that involved primary care providers through treatment guidelines/protocols and engaged nurse case managers who serve to guide those patients identified with CKD through education, reinforcing treatment plans and self-management strategies [6]. With this multidisciplinary approach, there were reductions in hospitalization and significant cost savings in annual cost of care across all the stages of CKD in a population of 7420 patients. Savings of $276.80 for those patients with stage G3 and $480.79 for stage G5 CKD can add up to significant healthcare costs per year and the initial cost of implementing the program, the primary care provider education, and the maintenance of a team of nurse clinical managers. More impactful is that the interventions involved low cost strategies of education to primary care providers and nurses that could be duplicated at other locations and were achievable with voluntary participation by primary care providers.

35.4 Development of a CKD Management Program

Considering the barriers in CKD care and what strategies have been successful, a framework of a CKD management program can be defined. A meaningful CKD program will require a multi-

Table 35.1 Elements of a successful CKD management program

Component	Details
Provider education (primary care)	– Co-management strategies
	– Education on screening and diagnosis of CKD
	– Information on when to refer
Provider education (nephrology)	– Co-management strategies
	– Education on counseling regarding early CKD diagnosis/management
	– Education on counseling regarding renal replacement therapy
	– Guideline/protocols for CKD management
Insurers/payer/healthcare administration	– Commitment of resources for CKD screening
	– Commitment of resources for CKD management
Multidisciplinary team	– Addressing risk factors and management of CKD
Patient	– Understanding of kidney disease
	– Incorporation of self-management behaviors
	– Active role in healthcare decisions

CKD chronic kidney disease

disciplinary team (MDT) and have features to address the roles by the different team members (Table 35.1). The structure of a CKD management program will target the goals of timely identification of those with CKD, patient education, patient engagement, slowing progression of kidney disease, renal replacement therapy planning, and provider education.

The patient is the central member of the CKD management team. Without initiatives to provide patient education in a useful manner and encouragement of self-management behaviors, other aspects of programming will not be meaningful. Primary care providers, nephrologists, nursing, pharmacist, community health care workers, public health advocates, healthcare administrators and insurers all have roles in CKD management.

The lack of awareness of being at risk for CKD and late identification of those with CKD are two obstacles to providing meaningful care. One component of CKD management programs will incorporate protocols for screening of high-risk populations and utilization of electronic medical records to risk stratify individuals. Provider education on patients to screen, developing protocols for timely referral to nephrology, laboratory testing for different stages of CKD, and establishing co-management framework for nephrology and primary care providers to work together is an important step in CKD management programs. Use of community health workers, public health campaigns, and nursing managers will help reinforce education efforts and potentially reach those that do not have routine access to care.

Protocol/guidelines are necessary for CKD management programs. These allow for primary care providers to readily adopt management in their routine practice without an excess burden of time. Protocols to standardize frequency of labs, frequency of visits, and timing of nephrology referral will allow for ability to study the impact of interventions and ensure quality standards for care of this patient population. Primary care provider education will supply the tools necessary to counsel and manage patients with early CKD. A structured co-management plan between primary care providers and nephrologists will avoid duplication of work, will allow healthcare providers to know their responsibilities and optimize their areas of expertise. Nephrologists would take lead on management of the risk factors of progression of kidney disease, diagnostic workup of proteinuria, acute kidney injury, and glomerular disease, and management of those with advanced CKD (stage G4 and up). Nephrology practices would utilize workflows for patient education topics dependent on level of kidney function, renal replacement counseling and preparation, management of complications of CKD including anemia, bone mineral metabolism, and electrolyte changes, and best practices for immunizations, nutrition, and cardiovascular risk factor manage-

ment. An approach with delineation of responsibilities will allay concerns of patients regarding continuity of care and how the different team members play a role in their care.

CKD management programs will seek input from dieticians, pharmacists, social workers, and case managers. The dietary challenges of having CKD can be overwhelming in an effort to reconcile the different restrictions for different comorbidities. Pharmacist input can help address the medication changes and potential safety events with the potential risk of accelerating CKD progression. The potential for depression, disability, interruption in work or schooling need to be acknowledged. The diagnosis of kidney disease or the development of end-stage kidney disease are life-changing events. Case managers and social workers can help with screening for depression or difficulty coping and help identify resources for patients.

35.5 Health Literacy Within Chronic Kidney Disease

Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" [7]. It requires a complex group of reading, listening, analytical, decision-making skills, and the ability to apply these skills to health situations [8]. Health literacy has a direct impact on vulnerable groups such as the elderly, racial or ethnic minority group, polymedicated patients, immigrants, low socioeconomic status, and the chronically ill [9]. It is very likely that patients with CKD or end-stage kidney disease will fall within one of these vulnerable groups.

A low level of health literacy can lead to a lack of understanding of information about treatments, poor knowledge about chronicity, late detection of diseases, medication errors, misuse of healthcare services, and higher rate of morbidity and hospital admissions [9–12]. For moderate to severe CKD (considered CKD stage G3 or higher), the prevalence of poor health literacy ranges from 5% to 60% [9]. In advanced CKD (considered CKD stage G4 or higher) prevalence of inadequate health literacy is estimated at 23% [10, 11]. Poor health literacy in CKD has been associated with higher reported cardiovascular disease, poor blood pressure control, poor self-management skills, missed dialysis sessions, more emergency department visits, more kidney disease-related hospitalizations, higher morbidity/mortality, and fewer transplant referrals [10, 13–16].

Many studies have shown that health literacy can be improved through educational interventions. Patient education involves increasing a patient's knowledge about a disease in order to change behavior. For CKD, there are opportunities for patient education at all stages from time of diagnosis with CKD to end-stage kidney disease. The largest effects of patient education have been observed on increases in CKD-specific knowledge. There was some evidence that programs may have a positive impact on health-related outcomes. It has been linked to higher rates of pre-dialysis nephrology care; better proteinuria and blood pressure control; higher rates of peritoneal dialysis, preemptive kidney transplant wait listing, and kidney transplantation; and increased time to commencement of renal replacement therapy [15, 17–22].

35.6 Patient Education in Chronic Kidney Disease

Most patient education that is provided, including learning about dialysis options, comes from their treating nephrologist during a 20–30 min routine clinic visit. In these situations, the education must fit alongside the rest of the visit requirements. The opportunity to ask questions is limited by time. Some nephrology practices offer dialysis educational sessions led by dialysis-experienced nurse educators and may include a tour of in-center dialysis facilities or home dialysis equipment. Patients might receive written handouts regarding education for CKD including different dialysis options. Some patients will seek advice from "expert" patients who are already receiving dialysis or a kidney transplant [23].

Recent studies show dissatisfaction with current practices for CKD and dialysis education. Individuals feel that education is provided too late, the information is too complex or hard to understand, or feel that choices are limited. There are reports of unequal and insufficient presentation of all available dialysis modalities and insufficient facilitated communication with "expert" patients [23–29].

35.7 Guidance on Patient Education in Chronic Kidney Disease

There is a wide variation in patient education interventions from the educators (i.e. nurse educator vs. multidisciplinary panel), structure (i.e. one-on-one, group, in-person, virtual, etc.), intensity (i.e. one class vs. multiple classes), and topics covered. Studies are also variable in these characteristics and in study design such as outcome measures, sample sizes, and relatively short follow-up [18]. These differences make it difficult to compare the efficacy in the educational interventions.

Best practices in chronic disease education are individually tailored, understandable for patients with low health literacy, and culturally competent [30]. For there to be benefit, patient education must be high in quality, which includes that it is sufficient and useful [31, 32]. Sufficient patient education means that an adequate degree of essential knowledge is delivered to support patients' empowerment [22, 33]. Useful patient education refers to education that patients need for their use and can implement in their lives and care [22, 34]. Overall, we see that patient education in CKD is desirable when it supports self-management of day-to-day aspects of a patient's health [35].

There are several guideline organizations within CKD that address patient education on CKD. In general, they all recommend educating patients with CKD and their family/caregiver using an MDT. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease recommends focusing on dietary counseling, education and counseling about different renal replacement therapy modalities, transplant options, vascular access surgery, and ethical, psychological, and social care [36]. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Hemodialysis Adequacy: 2015 Update recommends beginning education with CKD patients with stage G4 or higher focusing on kidney failure and options for its treatment [37]. The National Institute for Health and Care Excellence (NICE) guidelines recommends shared decision-making over the course of CKD offering education on CKD and information tailored to the severity and cause of CKD, the associated complications, and the risk of progression [38, 39]. There are no specifics on how to offer patient education. Table 35.2 offers suggestions to developing patient education on CKD.

35.7.1 Multidisciplinary Team

At a minimum, there should be a nephrologist and CKD nurse. Optimally, there should be additional members involved in education with expertise in different areas to comprise an MDT. Usually the MDT consists of a healthcare provider, certified nurse specialist, social worker, and dietician. Some literature will include a physical therapist, mental health professional, and "expert" patient as well [44]. Physical therapist can help with daily functioning and improve quality of life. The mental health professional can help with coping and stress with living with a chronic illness. The "expert" patient can provide peer-to-peer support and add to aspects of daily life while dealing with CKD. It is helpful for the MDT to have a close relationship with the patient to reduce the stress of encounters [40, 41, 45].

35.7.2 Structure

A lot of thought should be focused on the structure of the patient education on CKD. There are different formats to providing information. If we

Table 35.2 Approach to developing patient education on CKD [30, 36–43]

Core aspect	Details
Target audience	Patients with CKD and family/caregivers
Educators	Involvement of a multidisciplinary team
	• Healthcare provider: Physician, NP, PA
	• Certified nurse specialist
	• Social worker
	• Dietician
	Optional members: Physical therapist, mental health professional, "expert" patient
Structure	Determine format:
	• One-on-one
	• Group class
	• Written material
	• Technology-based (websites, videos, webinars, etc.)
Content/ topics	Examples of suggested topics:
	• General information on CKD
	• Treatment options for CKD
	• CKD complications and management
	• Managing the effects of CKD on daily life
	– Diet and exercise
	– Self-monitoring of blood glucose and blood pressure
	– Avoidance of nephrotoxins
	– Adherence to complex medication regimens
	• Ways for delaying CKD progression
	• Renal replacement therapy (including hemodialysis (in-center/home), peritoneal dialysis, kidney transplant, and conservative management) and necessary preparation
	• Coping with CKD and resources available
	• Nutrition and CKD
Community Resources	Written material
	"Expert" patient
	Incorporate models (example: dialysis equipment, vascular access model, food portions diagram, etc.)
	Tour of dialysis facility

CKD chronic kidney disease, *NP* nurse practitioner, *PA* physician assistant

focus on in-person education, then we need to consider whether it should be one-on-one sessions vs. group classes. One-on-one might be appropriate if the individual patient lacks sufficient knowledge [41]. Group classes have advantages of providing peer support. Group classes provide a more efficient use of resources in that you can reach more people at once if done effectively.

At least one session of patient education on CKD should be provided as part of CKD management. Optimally, the number of sessions should be driven by the number needed to reach an informed and balanced decision [41]. The number of sessions will also vary by the mode of education such as in-person vs. technology-based. For example, it may be easier for someone to watch six videos on an e-learning website than to attend six in-person sessions.

35.7.3 Topics Covered

At a minimum, topics should include general of CKD, CKD treatment of associated conditions, renal replacement therapies including transplantation and conservative management, how to delay the progression of disease, and additional manage CKD (such as diet). Topics can be expanded to cover coping with CKD, blood pres-

sure control, medication compliance, advance directives, etc. The topics that can be cover are not limited to these areas [41]. The specific needs of your CKD patient population can further tailor the program.

35.7.4 Resources

Written materials are helpful for some patients. They provide a reference that can be reviewed multiple times and at the pace of the patients learning. Materials should be written at about a seventh to ninth grade reading level [46]. Ideally, written education is best understood when written at a reading level that is 3–5 grades lower than their last grade of school completed [47]. In this technological age, there are many high-quality multimedia resources available such as websites, blogs, videos, webinars, etc. that can aid in educating patients on CKD. Having a list of suggested online resources will guarantee the accuracy and quality of information provided to patients [41, 48].

In the long-term the ability to visit a dialysis unit or see models of home dialysis equipment help to relieve anxiety. There are some reports that in the short term if might create anxiety as well. An "expert" patient can help provide support, understanding, and insight into living with CKD that healthcare professionals might not be able to provide. There is some bias toward their own experience by the "expert" patient that will need to be taken into account [41].

35.7.5 Learning Style/Teaching Method

The literature supports that patients want a wider range of teaching methods and particularly active learning methods [49–51]. Along the lines with the principles of adult learning theory, patients want more time spent on helping apply information to their own lives [52]. As people age, they move from a dependent learning toward self-directing learning. This would imply that adult patients are more apt to seek out information like finding classes or from online resources. As individuals mature they move from using information for future application to immediate use in their daily life [53]. As the population ages, there should be accommodations for visual impairment, decreased attention span and short-term memory, and slower processing of new information [54].

35.7.6 Timing of Education

Education regarding CKD is usually undertaken in the pre-dialysis period and thus called "pre-dialysis education," but there is more than dialysis options that should be covered. Additionally "pre-dialysis education" might need to be extended beyond the pre-dialysis period. Examples of patients that might benefit from this are those that are highly distressed in the pre-dialysis period or become open to other treatments only once they have started treatment [52].

A good example of patient education that extends beyond dialysis is transitional care units (TCU). TCUs (also sometimes called transitional start units) designed to provide a more gentle start to dialysis therapy with more frequent dialysis, increased provider interaction, acknowledgment of emotional and mental needs particular to new patients and their families, and an in-depth patient-centered education curriculum [55]. TCUs are usually utilized for patients that have not received much pre-dialysis care. They provide detailed patient-centered education on all modalities of renal replacement therapy including kidney transplantation. Initially started as a platform to bridge the gap between an unplanned, acute, or new start with the hope to transition more patients to home therapies [56]. TCUs have been proven to improve mortality and other quality parameters such as permanent vascular access [55–59]. Table 35.3 is an example of how a 4-week TCU is organized with regard to education.

Table 35.3 Example of 4-week TCU education [55, 56]

Week 1: Introduction to TCU and MDT; Get to know the patient
Week 2: In-depth discussion of in-center hemodialysis, home hemodialysis, peritoneal dialysis, kidney transplant, and conservative care; Discuss vascular access
Week 3: Continue education; Facilitate interaction with other patients on home dialysis modalities; Possible use of home hemodialysis equipment; Confirm desired dialysis modality; Initiate referral for creation of access (as applicable)
Week 4: Transition to appropriate dialysis setting; Confirm access plan and appointments (as applicable); Confirm transplant evaluation appointments; If conservative management, then arrange palliative care or hospice referrals/consultations; Discuss advanced care planning

This education occurs while the patient is receiving hemodialysis. Education is provided by multidisciplinary team (healthcare provider, dialysis nurse educator, dietician, social worker). *TCU* transitional care unit, *MDT* multidisciplinary team

35.8 Use of Technology for Patient Education on Chronic Kidney Disease

There are various formats for providing education including individual meetings, group classes, written handouts, videos, etc. that provide useful information for patients. Technology has been used to enhance healthcare delivery for years. The Internet is now an essential source of health information: 80% of Internet users look online for health information and 25% of Internet users watch health-related videos [60]. In the USA, about 90% of adults own a mobile device and nearly 60% of them access the Internet with their phones [61]. Many patients make health decisions based on the information they find online. More than 50% of patients who use the Internet say they were influenced by online health information and tools when choosing healthcare providers, treatments, and services [48, 62].

The availability of Internet-based technology can increase the reach of telehealth education to the CKD population with limited mobility due to physical disability or frailty and to those patients who live in rural areas. Telehealth educational opportunities are also more flexible and adaptable to learner preferences. They can reach more learning styles; for example, by using both visual and auditory modalities of content delivery. Additionally, all of these educational opportunities occur outside the traditional office visit, which allow healthcare professionals the opportunity to reinforce key ideas and answer questions during an office visit [23, 30, 48, 63]. Examples of Internet-based education are listed in Table 35.4.

Table 35.4 Internet-based education examples[63]

• Tailored e-learning
• Comprehensive informational websites
• CKD patient advocacy websites
• Blogs
• Webinars
• Email listservs
• Social media

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In summary, it is important to understand that no matter how patient education is organized not all patients will benefit. You are more likely to benefit more patients by having a varied approach to education and teaching methods. Patient education on CKD should cover multiple topics, using different formats for educating, offering education at varying points within a CKD spectrum, applying principles to daily life for the patients, and using multiple members of the team for education.

Before You Finish: Practice Pearls for the Clinician

- CKD management programs should be designed to address the needs of the patient and not just limited to medical care.
- Patient education and encouragement of self-management is the core of successful CKD management.
- Unlike other diseases, the benefits of CKD management are seen after long-term management.
- CKD management programs require a multidisciplinary approach including nephrologists, primary care providers, social work, pharmacist, dieticians, nursing, health care administration, and payers.

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36 Conservative/Palliative Treatment and End-of-Life Care in Chronic Kidney Disease

Alvin H. Moss

Before You Start: Facts You Need to Know About End-of-Life Care

- Kidney supportive care should be offered to all patients with advanced CKD.
- Prognosis is an inherent issue in transitioning to end-of-life care, but there are few tools to predict outcomes in CKD patients who choose not to begin dialysis.
- Patient-centered advance care planning is an integral aspect of kidney supportive care and is based on determining a patient's goals for care.
- Nephrology clinicians need to initiate advance care planning discussions.
- Advance directives like identifying a healthcare surrogate or proxy decision-maker and medical orders like do-not-resuscitate preferences and Portable Orders for Life-Sustaining Treatment (POLST) should be determined for each patient.
- Symptom burden is high throughout CKD, including near the end of life, and systematic symptom assessment and management are therefore important aspects of supportive care for CKD patients.

36.1 Supportive or Palliative Care in CKD

The terminology in this chapter is key to understanding the nuances in the continuum of care for patients with kidney disease. In medical literature, supportive care is often used as a synonym for palliative care. In this chapter, the term "supportive care" is used because patients and healthcare professionals prefer it [1]. Supportive care refers to the care that the nephrology team provides, while palliative care refers to the care provided by specialists in palliative care. The word "palliative" has been defined as that which reduces violence associated with disease or a process of easing burdens associated with disease during the dying process that is not curative in nature. The World Health Organization defines palliative care as "An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spir-

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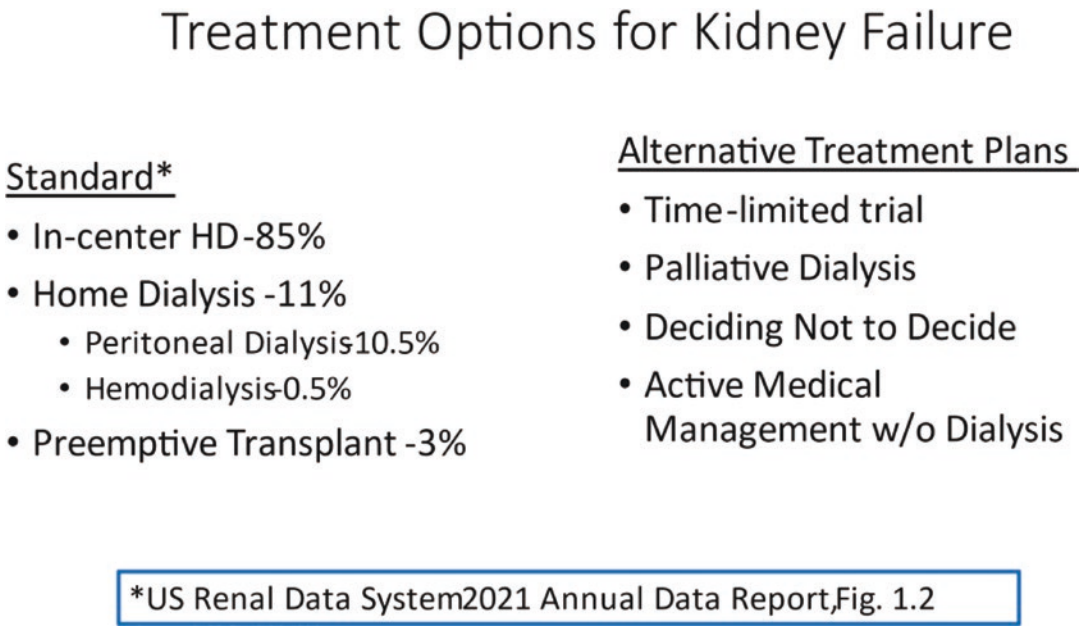
itual." Life-sustaining technology such as dialysis may provide palliation of some symptoms although the use of organ sustaining technology might be considered counter to the palliative approach. The term "active medical management without dialysis (AMMWD)" is increasingly used to describe a program of care that excludes kidney replacement therapy but encompasses management of biochemical abnormalities as well as symptoms accompanying CKD and, ultimately, the dying process. Importantly, AMMWD can be proactive and deliberate as directed by patient preferences and values and does not mean "no care." International interest in AMMWD continues to increase, particularly for those 75 years of age and over who constitute a large and the fastest growing proportion of dialysis patients in the USA and for whom the costs of care are formidable. In contrast to the 1980s–1990s and even early years of the last decade when the ability to provide life-prolonging care perhaps promoted a blind eye to the propriety of doing so, the concept that dialysis may not be the best option for every patient is growing in acceptance.

Providing informed consent requires an individualized approach and the presentation of clear expectations. In patients with CKD, the option of dialysis is ideally posed before symptoms develop, and there is need for active intervention to delay death. A patient's decision to pursue or forgo dialysis will likely be influenced by clinical information provided about prognosis, the dying process, and the quality of life on dialysis. Sharing one's expectations about the anticipated clinical course for a patient poised to die from complications of kidney failure may be helpful to patients as they contemplate their wishes informed by evidence-based information provided to them by their physicians.

Because older patients and those with poor functional status may not live long enough to need dialysis [1–3], it is reasonable to consider prognosis when deciding whether or not to proceed with dialysis. Tools for predicting outcomes in patients with advanced CKD are available [4] and useful to help patients and families decide on the best course of action. Poor functional status and the presence of frailty suggest shorter survival among older dialysis patients as do older age, poor nutritional status, comorbid conditions (especially dementia, peripheral vascular disease, and ischemic heart disease), and answering "no" to the surprise question ("Would you be surprised if this patient died within the next 6 months?") [5, 6].

Such clinical hallmarks of a poor prognosis are important factors to consider when contemplating dialysis as well as when discussing goals of care. The burdens associated with dialysis are multifaceted (social, financial, medical, and logistic), and some patients may not be willing to accept such burdens, instead favoring quality over quantity of additional life. Thus, identifying patients likely to benefit from AMMWD before starting dialysis may save them the traumas accompanying kidney replacement therapy. There are also other alternative treatment options to beginning standard in-center or home dialysis [Table 36.1]. Renal professional societies have recommended that a shared decision-making conversation in which patients are informed of all treatment options for kidney failure with their attendant benefits and burdens should precede a choice [3]. For those choosing to proceed with dialysis, repeated evaluation and ongoing conversations about quality of life and the burdens of dialysis should accompany changes in clinical, physiologic, emotional, and social functioning as such changes may prompt a patient, their family, or their nephrologist to consider withdrawal of dialysis.

Table 36.1 Options for kidney failure treatment to fully inform patients



36.2 End-of-Life Care in CKD

Although care at the end of life is an integral aspect of total care of an individual with CKD, we know even less about end-of-life (EOL) care in CKD than we do about EOL care in those on dialysis. There are few studies of illness trajectory in CKD patients who choose not to begin dialysis, and, thus, there is little information about dying and EOL care in this population. The most comprehensive study to date was reported from the large Kidney Supportive Care program at St. George Hospital in New South Wales, Australia [7]. They found that patients who chose not to undergo dialysis compared to those who did were older (84 vs. 74 years), more often had 3 or greater comorbidities (43% vs. 25%), lived a shorter median period of time (14 months vs. 53 months), had fewer hospital days per year (9 vs. 20), and a better symptom score (2.2 points lower).

An understanding of the tradeoffs including prognosis inherent in starting dialysis or not is key to engaging in advance care planning, an essential component of EOL (Fig. 36.1). In CKD patients choosing not to begin dialysis, principles of decision-making will rely on prognosis, including expected survival and quality of life with and without dialysis. Small studies of elderly patients with CKD who choose AMMWD show a shortened survival compared with patients beginning dialysis [8–12], Table 36.2. In these studies, as in dialysis patients, comorbidity portends a poor prognosis as do age and poor functional status. The typical illness trajectory of patients with solid organ disease (e.g., congestive heart failure or chronic obstructive pulmonary disease) is characterized by a progressive downward slope with intermittent acute episodes or sentinel events from which the patient never returns to his or her baseline status (Fig. 36.2). It is assumed that dialysis patients also follow this pattern of illness with sentinel events represented by hospitalizations, e.g., with a myocardial infarction, limb amputation, or episode of access-associated bacteremia. There is only one study of illness trajectory in CKD [13]. A small number of elderly CKD patients managed with AMMWD demon-

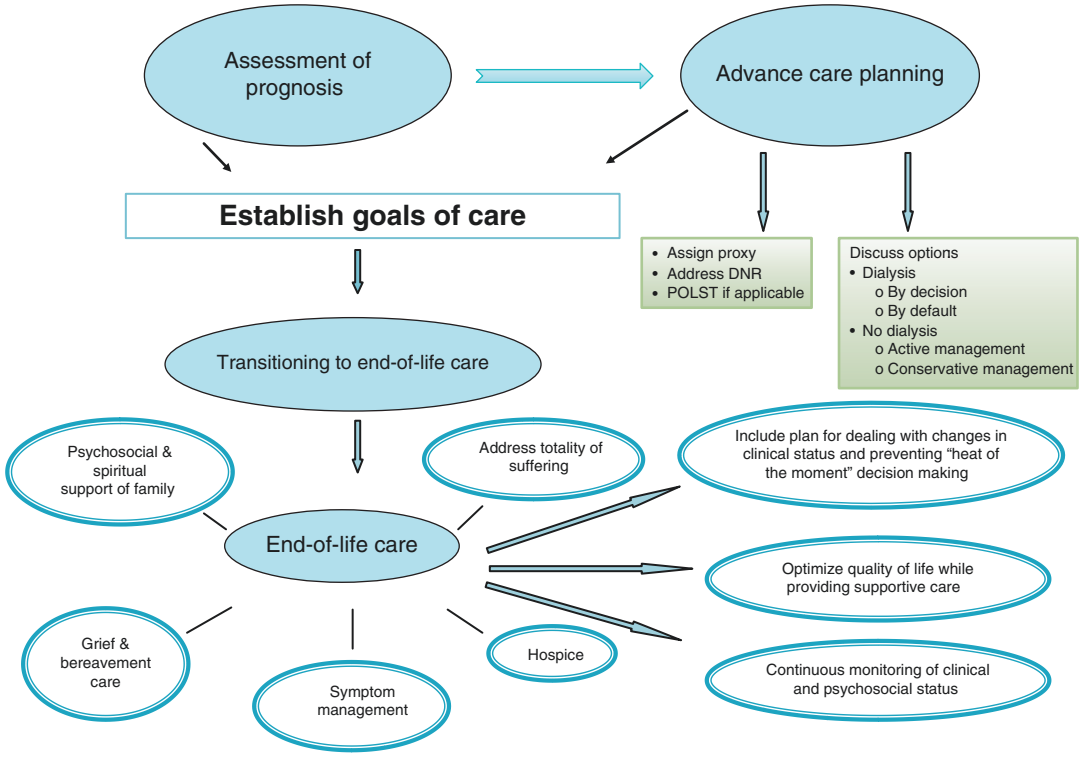


Fig. 36.1 Palliative care in CKD includes advance care planning as well as end-of-life care. This figure depicts an algorithm for palliative care in CKD. *DNR* do not resuscitate, *POLST* portable orders for life-sustaining treatment

Table 36.2 Survival in elderly patients with and without dialysis

	N		Survival			
Author	Dialysis	Conservative	Dialysis	Conservative	Age	Est GFR
Carson [8]	173	20	37.8 months	13.9 months	≥70	11[a]
Brunori [9][b]	56	56	84% 1 year	87% 1 year	>70	5–7[c]
Murtaugh [10]	52	77	84% 1 year	68% 1 year	>75	<15[a]
Joly [11]	107	37	74% 1 year	29% 1 year	≥80	<10[d]
DaSilva-Gane [12]	124	30	1317 days	913 days[e]	33–84	10–17[a]

[a] Modification of Diet in Renal Disease (MDRD) formula
[b] Diet intervention
[c] Mean of creatinine clearance and urea clearance in a 24-h urine collection
[d] Cockcroft-Gault formula
[e] Comorbidity was the primary factor

strated a fairly well-preserved functional status until shortly before death when an abrupt fall in functional status heralded a rather quick death (Fig. 36.2). Knowing the usual illness trajectory serves multiple purposes including functioning as a guide for addressing and reviewing advance care planning and goals of care, planning for future events and interventions, and completing tasks required before death. Illness trajectories are intimately entwined with illness prognosis and an understanding of each in CKD will facilitate identification of appropriate individuals for decision-making and assist in the transition to EOL care. Additional study of prognostic factors and illness trajectory in CKD is needed.

Transitioning to EOL care requires an honest assessment of prognosis, establishment of goals of care through advance care planning, and edu-

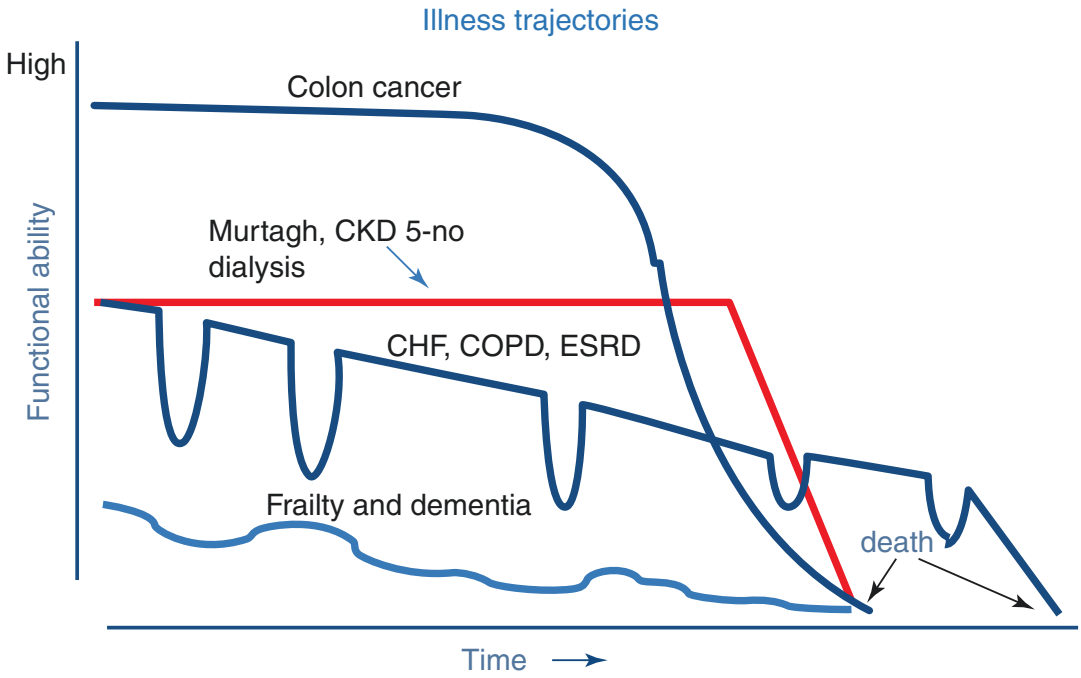


Fig. 36.2 Illness trajectories of various chronic diseases; *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *ESRD* end-stage renal disease. (Reprinted from Holley [14] with permission from the American Society of Nephrology)

cating the patient and family about options for EOL care (Fig. 36.1). As with all other patient populations, ethical and cross-cultural issues will affect decision-making and EOL care in CKD patients. This is most evident during the advance care planning process where a patient and family's values will influence and direct goals of care. Useful questions for addressing values and stimulating discussion during advance care planning are shown in Box 36.1.

Box 36.1 Useful Questions for End-of-Life and Advance Care Planning Discussions

- *Addressing patient goals*
  - Given the severity of your illness and that your time is short, what is most important for you to achieve?
  - What is most important to you in your treatment? What treatments do you want and what do you want to avoid?
  - What are your biggest fears?
  - What are your most important hopes?
  - Is it more important to you to live as long as possible, despite some increased suffering, or to live with less suffering for a shorter time?
- *Addressing patient values*
  - What makes life most worth living for you?
  - Are there any circumstances under which you would not find life worth living?
  - What do you consider your quality of life to be like now?
  - Have you seen or been with someone who had a particularly good (or difficult) death?
  - If you choose to start dialysis, under what circumstances, if any, would you want to stop dialysis?

36.3 Establishing and Achieving Goals of End-of-Life Care

Assessment of a patient's wishes for EOL care is an important part of comprehensive care irrespective of whether or not a patient chooses to begin dialysis. Many choose to forgo dialysis in order to avoid prolongation of the dying process and in an attempt to assure that their desires about treatment remain under their control. Patients and families have taught us that they use advance care planning for a variety of things, to achieve a sense of control, to have treatment choices followed, to relieve burdens on family, to strengthen relationships with loved ones, to avoid inappropriate prolongation of dying, and to be at peace with God [15, 16].

Pertinent issues to address include whether the patient wishes to die at home, in hospital, or elsewhere and specifics about what symptoms are and are not acceptable. Patients who choose to forgo or even withdraw from dialysis may be offered the option of reconsidering, an act which may be emotionally helpful to some patients who fear that the dying process will be too unbearable.

Aims of AMMWD include control of symptoms such as itching, restlessness, dyspnea, confusion, and pain, as well as emotional and spiritual support. Studies have shown that patients choosing AMMWD do not have more symptoms at the end of life than those who have been treated with dialysis [7, 17]. Patients with kidney failure should be prepared for symptoms arising as a result of kidney functional decline. The close follow-up and careful symptom management accomplished by the Kidney Supportive Care program in New South Wales show that patients treated with AMMWD need not have more symptoms than dialysis patients at the end of life [7].

Chronic pain has been reported in half of dialysis patients, 82% of whom have moderate-severe pain [18] (see also Chap. 22). Pain management for patients choosing to forgo dialysis requires attention to the reduced kidney clearance of many drugs. In addition, the myriad sources of pain in patients with kidney disease also require consideration. The propensity for side effects which may be exacerbated in patients with kidney failure prompted the development of specific recommendations for managing pain and other symptoms in patients on dialysis (Table 36.3). Pain management, irrespective of whether a patient chooses dialysis or the non-dialytic route, is a key component to the care of patients with advanced kidney failure. Plans for treatment should be made in anticipation of symptoms. Neuropathic pain is common and often poorly responsive to opioids, requiring addition of adjuvant medications like tricyclic antidepressants or anticonvulsants. An important part of AMMWD is recognizing evolving symptoms of respiratory distress which may in turn cause anxiety and a patient or family member to question their decision to forgo dialysis.

Table 36.3 Treatment of common EOL symptoms in CKD patients

Symptom	Treatment options
Pruritus	Antihistamines, skin lotion with menthol, dexamethasone, difelikefalin
Dyspnea	Relaxation exercises, diuretics, oxygen, morphine
Pain	Opioids ± adjuvants[a]
Dry mouth	Artificial saliva, swabs, good local care
Nausea, vomiting	Haloperidol at 50% normal dose, Compazine
Constipation	Senokot, stool softeners, lactulose, enemas prn—avoid phosphosoda, magnesium
Respiratory tract secretions	Hyoscyamine 0.125 mg po or SL, scopolamine patch

Source: Data from Davison [18], Douglas [21], Davison [22], and Fishbane [23]

Adjuvants for neuropathic pain (e.g., gabapentin, pregabalin) require dose adjustments and slow titration of dose; avoid >600 mg daily of gabapentin

[a] If needed for more than 1–2 days, use fentanyl; active kidney-excreted, short-acting hydromorphone metabolites may accumulate without dialysis and cause opioid-induced neurotoxicity. Do not use a fentanyl patch stronger than 12 μg in opioid naïve patients. Long-term morphine, meperidine, codeine, propoxyphene contraindicated because of the accumulation of kidney-excreted neurotoxic metabolites. Use with caution: oxycodone, tramadol (avoid sustained release form in CKD)—limited data in CKD. Whenever an opioid is prescribed, laxatives also need to be prescribed because of opioid-induced constipation

Preparing the patient for such events, both emotionally and with specific plans to ameliorate the symptoms, will help avoid patient and family anxiety. The Coalition for Supportive Care of Kidney Patients has developed an Active Medical Management without Dialysis Pathway to help clinicians, patients, and families anticipate mounting uremic symptoms at the end of life and to establish an action plan that avoids patients going to the emergency department and "crashing" into dialysis [19]. There is also a chapter in the textbook *Palliative Care in Nephrology* written by leaders of the Kidney Supportive Care program in New South Wales, Australia, explaining how to care for patients who choose AMMWD with information about validated clinical tools to assess symptoms and online symptom management resources [20]. A plan to address dyspnea, itching, control of pain, (Table 36.3) and a generalized discussion of what a family might expect is the key to a smooth and acceptable course of AMMWD.

Family members of patients choosing AMMWD or dialysis withdrawal may need emotional support in addition to guidance in recognizing changes in symptoms that might warrant adjustments in the management program. The logistics of providing care must be considered if families choose not to engage in hospice. Close monitoring of clinical and psychosocial as well as emotional parameters in addition to routine symptom assessment by the health-care providers focusing on new pain, worsening chronic pain, or the development of new uremic symptoms is integral to ongoing care. For CKD patients choosing to proceed with dialysis, establishing goals of care includes plans for dealing with symptoms and changes in clinical status. It is important to continually monitor the patient's response to dialysis, their comorbid conditions, functionality, and quality of life on dialysis. The option of withdrawal from dialysis should be incorporated into the overall plan of care as the patient's preferences may change or the patient's medical status may deteriorate.

Advance care planning is best initiated in the early as opposed to late stages of CKD when a plan for EOL care can be established and tailored to a patient's prognosis, values, and preferences (Fig. 36.1). AMMWD can be proactive, deliberate, and directed by individual patient preferences and values, and patients and families should be educated that AMMWD does not mean "no care." It is care toward a different goal. Presenting clear expectations, setting contingencies, and incorporating the opportunity for withdrawal for those who choose dialysis may facilitate decision-making in times when clinical events make objectivity difficult. Discussions of prognosis and advance care planning afford patients and families the opportunity to shape the direction of life at its end and, by doing so, provide solace, comfort, and hopefully peace.

36.4 Advance Care Planning

Advance care planning is an important component of palliative care and should be addressed with each CKD patient. The purpose of advance care planning is to establish the goals of care within a care plan consistent with a patient and family's values and preferences [14]. Advance care planning requires the patient's participation and thus his or her ability and interest in the process as well as some perceived benefit and the resources to participate. Completing written advance directives may be an aspect of advance care planning, but because circumstances change and most patients make decisions about desired interventions based on their health status, values, and quality of life (as opposed to the intervention being considered), completing a written advance directive is not the goal of advance care planning. However, some written directives are useful to guide decision-making when the patient has lost the capacity to participate, and their completion should be encouraged to all patients. These include designation of a surrogate decision-maker or health-care proxy and execution of a living will if consistent with the patient's wishes. Completion of medical orders to specify the treatment limitations the patient wants at the end of life such as a do-not-resuscitate (DNR) order if applicable, or portable orders for life-sustaining treatment (POLST) or the equivalent where avail-

able can be very helpful in medical emergencies (Box 36.2). The majority of states in the USA have adopted POLST, making them legal medical orders. Orders on the POLST generally include DNR status, preferences for hospitalization, medically administered nutrition and hydration through a feeding tube, intubation and ventilation, intensive unit care, and, in some cases, dialysis. Although discussing advance directives and medical orders and engaging in the process of advance care planning may be difficult, surveys of various patient groups indicate that patients and families overwhelmingly believe their physicians should raise these issues and initiate the discussions. Focusing on the day-to-day issues raised by medical care can often prevent the setting of goals and exacerbate hopelessness, fear, and uncertainty. Helping CKD patients see future possibilities consistent with their personal values can help maintain hope [24]. Thus, engaging in discussions of prognosis and advance care planning should not be viewed by nephrologists as an act that extinguishes hope for patients and their families. Advance care planning affords patients and their families the opportunity to direct and control their care (Fig. 36.1) and requires physician input.

Box 36.2 Web Resources for Advance Care Planning and End-of-Life Care

1. Coalition for Supportive Care of Kidney patients and website is: (www.kidney-supportivecare.org).
2. The Caring Connections website offers information about advance care planning and free downloads of state-specific, legal advance directives (http://www.caringinfo.org/stateaddownload).
3. The Portable Orders for Life-Sustaining Treatment form contains patients' end-of-life wishes in an easily identifiable, portable format with reviewable medical orders. The form honored throughout the health-care system is recognized as a preferred practice by the National Quality Forum in its A National Framework and Preferred Practices for Palliative Care and Hospice Care Quality (http://www.polst.org).
4. Hemodialysis mortality predictor (http://touchcalc.com/calculators/sq).
5. The UK website for end-of-life care (http://www.endoflifecareforadults.nhs.uk/assets/downloads/EndofLifeCareAKD.pdf).

Once the goals of care are established, plans for EOL care services can be determined. In dialysis patients, we know that EOL care should be discussed whenever conversations involve consideration of prognosis, treatments with low probabilities of success, patients' hopes and fears, and if the physician would not be surprised if the patient died within the next 6–12 months. It seems reasonable to extend this recommendation to those with advanced CKD. Interdisciplinary coordinated care provides opportunities for peaceful dying and "good deaths" by addressing all the domains of suffering (physical, psychological, spiritual, functional, and social) as well as managing symptoms occurring during the end of life (Fig. 36.1).

Figure 36.3 shows the symptoms reported on the Memorial Symptoms Assessment Scale-Short Form during the last 30 days of life in 49 patients with CKD stage 5 managed conservatively and followed prospectively [25]. There are few studies of symptoms experienced at the end of life in any population. Murtagh et al. [25] is the only report of end-of-life symptoms in CKD patients who chose not to begin dialysis. In her study, the mean number of symptoms reported was 16.65 ± 4.04 SD with a range of 6–24; the maximum number of symptoms reportable on the MSAS-SF is 32. Seven additional "renal symptoms" assessed in Murtagh's study included restless legs, muscle cramps, bone/joint pain, dry skin, muscle soreness, chest pain, and headaches [25]. The total number of symptoms possible was therefore 39, and adding these additional possible symptoms, the mean reported number of the 49 studied patients was 20.35 ± 5.20. Similar symp-

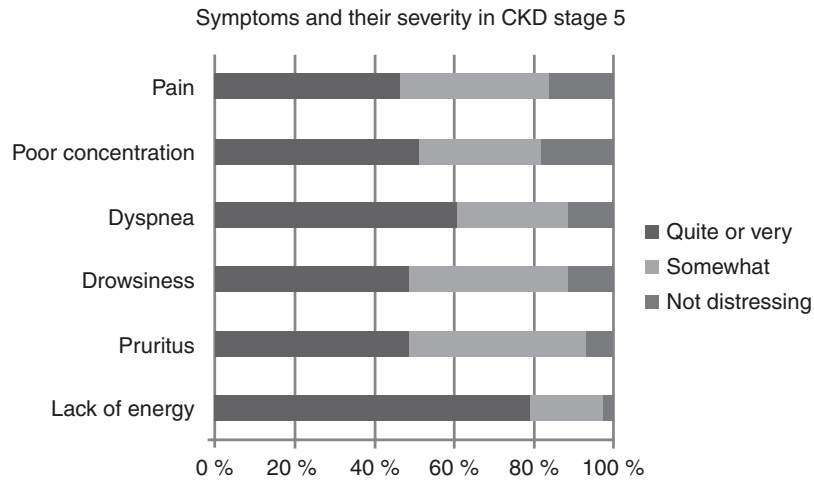


Fig. 36.3 Symptoms reported by CKD stage 5 patients undergoing conservative care. (Adapted from Murtagh et al. [25], Copyright 2010, with permission from Elsevier)

toms have been reported by patients with ESRD who discontinued dialysis with pain, fatigue, dyspnea, and anxiety commonly noted by surviving loved ones [26]. The little information available about symptoms experienced by patients at the end of life suggests that CKD patients have higher symptom distress than cancer patients, especially pruritus, drowsiness, and dyspnea. Constipation, edema, dry mouth, and fatigue were similar among the CKD patients and previous reports of cancer patients during EOL care. There is no information to determine the cause of these symptoms or whether they are due to underlying uremia or comorbid conditions. Clearly, symptoms near the end of life are common among CKD patients, and additional study is needed. End-of-life care for CKD patients forgoing dialysis should include routine symptom assessment with treatment focused on reported symptoms. Table 36.3 illustrates some treatments for commonly reported symptoms. Multidisciplinary care, including hospice and outpatient palliative medicine consultation and follow-up, should be encouraged for all patients in an attempt to alleviate distressing symptoms.

Coordination of EOL care for CKD patients may rest with the patient's primary care provider, nephrologist, or palliative medicine specialist, depending on the availability of services and the patient and family's desires. Hospice care is a Medicare benefit in the US health-care system and requires an anticipated survival of 6 months or less if the disease takes its normal course, stipulated by 2 physicians based on the usual course of the patient's underlying disease. The patient must elect hospice care which requires acknowledgement by the patient and family of the likelihood of death and the relinquishment of attempts at curative therapies. Hospice care includes nurses, aides, clergy, volunteers, and physicians (the nephrologist, the patient's own primary provider, the hospice medical director, and palliative medicine specialist if available) who work with the family to treat the patient's physical and psychological symptoms and to provide psychosocial and spiritual support to the patient and family. Most hospice care is performed in the home with the family and loved ones acting as the primary caregivers. Hospice care continues after the death of the patient through grief and bereavement care provided to the family and loved ones (Fig. 36.1). This continues for a year following the patient's death.

Although there are multiple guidelines for complications of CKD, there are no specific guidelines for EOL in CKD patients. The Renal Physicians Association clinical practice guideline, *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis* (Box 36.3), includes guidelines on establishing a shared decision-making relationship, informing patients about CKD, advance care planning, decisions to withhold or discontinue dialysis, resolving conflicts around dialysis decision-making,

providing effective palliative care, and communicating about prognosis, treatment options, and goals of care and is the one guideline focused on aspects of EOL care for CKD and dialysis patients. This guideline also incorporates clinical tools addressing depression and cognitive capacity assessment, functional status, prognosis assessment, and communication skills [2]. In 2013, the Kidney Disease Improving Global Outcomes organization convened an international conference to provide a roadmap and make recommendations to improve kidney supportive care including at the end of life [1]. The working group subsequently published a number of papers in a Moving Points in Nephrology issue of the *Clinical Journal of the American Society of Nephrology*, October 2016.

Box 36.3 Relevant Guidelines for EOL Care in CKD

1. Renal Physicians Association Clinical Practice Guideline. Shared decision-making in the appropriate initiation of and withdrawal from dialysis. 2nd ed. Rockville: Renal Physicians Association; 2010 [2].
2. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, et al. Guidelines for the management of chronic kidney disease. CMAJ. 2008;179:1154–62 [27].
3. Douglas C, Murtagh FEM, Chambers EJ, Howse M, Ellershaw J. Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Pall Med. 2009;23:103–10 [21].

Guidelines for comprehensive conservative kidney management for CKD patients are included in the Canadian Guideline for the management of CKD (Box 36.3) but are general (recommending shared decision-making and interdisciplinary care) and, due to lack of controlled trials in this aspect of nephrologic care, are opinions rather than evidence-based recommendations. General guidelines for EOL care are available in the UK (Box 36.3). Thus, EOL and AMMWD are now recognized as topics of importance to nephrologists and the kind of care they provide. However, there is much work still to be done to develop more comprehensive evidence-based guidelines for CKD EOL care, especially in the area of symptom management.

Although decisions about initiating dialysis are among the most important made by a patient with advanced CKD, until recently, there was little discussion of prognosis and the option of AMMWD. These discussions are difficult and require communication skills and an assessment of the patient's goals and values (Fig. 36.1). Such discussions naturally lead to advance care planning, an activity that should be initiated by nephrologists or other nephrology clinicians such as nurse practitioners alone or in conjunction with social workers for all patients and families facing advanced CKD. Resources for this aspect of clinical nephrology exist on the web (Box 36.2) and through clinical practice guidelines (Box 36.3) which will undoubtedly expand over the next several years. Figure 36.1 and the available guidelines (Boxes 36.3 and 36.4) focus on key components in EOL discussions which can be addressed whenever a clinician initiates a conversation about dialysis. Alternative treatment options [Table 36.1] are appropriate for some patients and deserve equal consideration by patients and families. It is only through clinician-initiated discussions that alternatives can be considered.

Box 36.4 What the Guidelines Says You Should Do: Key Components of End-of-Life Discussions

- Respect and assure the integrity of the informed consent process.
- Assure decision-making capacity and cognitive capacity for comprehension.

- Determine and agree on the patient's goals for both short- and long-term care.
- Recognize the importance of life experience and tailor the discussion accordingly.
- Engage the patient's family in the decision-making process.
- Distinguish informed consent for the option of dialysis from that associated with the dialysis procedure.
- Present estimate of kidney and overall prognosis with and without dialysis.
- Present anticipated changes in functional status with and without dialysis.
- Describe burdens of dialysis, including potential for both intra- and interdialytic distress.
- Explain risks of dialysis procedure, including those risks related to dialysis access.
- Make plans for dealing with symptoms that could occur should kidney failure progress faster than anticipated and/or faster than other comorbid conditions.
- Discuss desires for acute symptom management and goals to avoid heat of the moment decisions.
- Clarify that palliative care is available irrespective of their decision to pursue or forgo dialysis.
- Incorporate the option of withdrawal into practical plan and monitor patient's status accordingly.
- Consider hospice particularly for patients with additional terminal illness.

Source: RPA Clinical Practice Guideline [2].

Before You Finish: Practice Pearls of End-of-Life Care

- Initiate advance care planning early in the continuum of chronic kidney disease.
- Develop a plan for end-of-life care according to the patient's prognosis, values, and preferences and readdress these issues throughout the trajectory of CKD.
- For patients with advanced kidney disease progressing toward kidney failure, in a shared decision-making discussion present the risks and benefits of dialysis as well as those anticipated should the patient choose to forgo dialysis.
- Assure patients that AMMWD can be proactive, deliberate, and directed by individual patient preferences and values and does not mean "no care."
- On average patients who choose AMMWD may live over a year, have symptoms comparable to those who start dialysis, and spend fewer days in the hospital.
- Patients choosing AMMWD and those withdrawing from dialysis should be offered hospice care as interdisciplinary care can assist in the management of symptoms and end-of-life care for patients and families.

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37 How to Prepare a Chronic Kidney Disease Patient for Transplantation?

Rahmi Yılmaz

Before You Start: Facts You Need to Know

- Preparing a patient with CKD for transplantation involves careful evaluation for contraindications of transplantation and potential medical and surgical complications.
- A potential renal transplant recipient (RTR) should be evaluated for underlying cause of ESKD, comorbidities such as obesity and diabetes mellitus, malignancies, infectious diseases, gastroenterological problems, urologic disorders, hematologic disorders, and cardiovascular status.
- Evaluation of potential RTR should be initiated with a thorough medical, surgical, and psychosocial history and a detailed physical examination.
- Pretransplantation workup includes a number of serologic tests and radiologic and immunologic studies.
- HLA alloantibody profile of potential RTRs should be assessed to delineate the antigens regarded as unacceptable for transplant.
- Immunological evaluation should include the detection and characterization of clinically relevant antibodies.

37.1 Time for Referring to Transplant

Renal transplantation should be recommended to patients with irreversible advanced chronic kidney disease (CKD). The rate of progression in renal injury among patients with CKD is unpredictable because of underlying various renal diseases and superimposed acute kidney injury attacks. Therefore, for patients not requiring dialysis, time referring to a transplant program remains unclear. Patients with CKD stage 4 or a glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2 should be referred to a transplant program at least 6–12 months before dialysis initiation to allow identification/work-up of living donors and plan for possible pre-emptive transplantation [1, 2] (Box 37.1). Patients who are already on dialysis should also be referred to the transplant program after medical stability is achieved and kidney damage is thought to be irreversible. However, referral to a kidney transplant program does not imply immediate transplantation. Preemptive transplantation should be considered when the glomerular filtration rate falls below 10 mL/min. Beyond the glomerular filtration rate, optimal timing is related to the presence of symptoms and the preferences of living donors [2]. Renal transplantation may not be suitable for some patients with CKD. Guidelines do not recommend referring or recommend delaying kidney transplant evalua-

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tion in patients with the conditions in Boxes 37.2 and 37.3. Patients with a potential contraindication to transplantation should be individually discussed with a transplant center to determine candidacy. Several studies have reported improved patient and graft survival when patients receive their first transplant before the need for maintenance dialysis, although this is not the case for patients who are receiving a second transplant; among the latter, a period of dialysis prior to re-transplantation is associated with better patient survival [3].

Box 37.1 What the Guidelines Say You Should Do: Time for Referring to Transplant

- The timing of transplantation should maximize the use of the patient's own kidneys but avoid the morbidity and expense of access placement and dialysis treatments [1].
- Potential transplant recipients should be referred for evaluation by a transplant program once renal replacement therapy is expected to be required within the next 12 months [2].
- Preemptive transplantation should be considered when the glomerular filtration rate falls below 10 mL/min. Beyond the glomerular filtration rate, optimal timing is related to the presence of symptoms and the preferences of living donors [2].

Box 37.2 Guidelines Recommend Not Referring Patients for Kidney Alone Transplant Evaluation with the Following Conditions [2]

- Multiple myeloma, light chain deposition disease, or heavy chain deposition disease unless they have received a potentially curative treatment regimen and are in stable remission.
- AL amyloidosis with significant extra renal involvement.
- Decompensated cirrhosis (consider for combined liver-kidney transplant).
- Severe irreversible obstructive or restrictive lung disease.
- Severe uncorrectable and symptomatic cardiac disease that is deemed by a cardiologist to preclude transplantation.
- Progressive central neurodegenerative disease.
- Document the reason(s) for not referring patients for transplant evaluation.
- Inform patients about the reason(s) for not referring for transplant evaluation.

Box 37.3 Guidelines Recommend Delaying Transplant Evaluation in Patients with the Following Conditions Until Properly Managed [2]

- An unstable psychiatric disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk.
- Ongoing substance use disorder that affects decision-making or puts the candidate at an unacceptable level of post-transplant risk.
- Ongoing, health-compromising nonadherent behavior despite education and adherence-based counseling.
- Active infection (excluding hepatitis C virus infection) that is not properly treated.
- Active malignancy except for those with indolent and low-grade cancers such as prostate cancer (Gleason score ≤ 6), and incidentally detected renal tumors (≤ 1 cm in maximum diameter).
- Active symptomatic cardiac disease (e.g., angina, arrhythmia, heart failure, valvular heart disease) that has not been evaluated by a cardiologist.

- Active symptomatic peripheral arterial disease.
- Recent stroke or transient ischemic attack.
- Active symptomatic: peptic ulcer disease, diverticulitis, acute pancreatitis, gallstone/gallbladder disease, inflammatory bowel disease.
- Acute hepatitis.
- Severe hyperparathyroidism.

37.2 Evaluation of a Potential Renal Transplant Recipient

Evaluation of a potential renal transplant recipient (RTR) should be initiated with a thorough medical, surgical, and psychosocial history and a detailed physical examination. History of blood transfusion, pregnancies, and previous transplantation should be assessed for potential risks for sensitization. Previous cardiopulmonary diseases and abdominal operations should be carefully evaluated. In addition to history and physical examination, a number of routine laboratory tests are required. After this information is collected, possible contraindications for renal transplantation in each case should be reviewed.

37.3 Medical Evaluation of a Potential Renal Transplant Recipient

37.3.1 Age

Advanced age alone is not a contraindication for renal transplantation but age related co-morbidity is an important limiting factor [4]. Many elderly patients (over 65 years old) have been transplanted successfully and with an acceptable rate of long-term graft function. In recent years, life expectancy has increased in the world. Medical comorbidities, physical capacities, and mental health of elderly patients should be evaluated prior to transplantation, rather than an age-based exclusion. Frailty assessing, cancer screening, and cardiovascular evaluation remain critical in the risk analysis and decision to transplant older individuals [2, 5]. Global mortality in elderly patients on the waitlist is higher than among elderly RTRs. However, those patients have a greater risk of developing concomitant illnesses or neoplasms and limited life expectancy which reduces the potential benefit of transplantation. Therefore, life expectancy is a more important factor rather than identifying a specific age cut off. Estimated life expectancy of those patients should be longer than predictable wait time and enough to reveal the benefits of renal transplantation. A recommended criterion is that the patient would be expected to survive for at least 5 years after transplantation [1, 6].

37.3.2 Obesity

Obesity is related with increased post-transplant complications, delayed graft function, surgical wound infection, higher mortality (associated cardiovascular complications), and poorer graft survival. Although upper limit of BMI is controversial, no benefit was noted in patients with BMI greater than or equal to 40 kg/m^2 [7–9]. Therefore, weight reduction to BMI of 30 kg/m^2 or less should be recommended before the transplantation [8, 10]. In particular, obese patients with cardiovascular disease should not go through the transplantation before an adequate amount of weight loss has been reached. A recent guideline has suggested bariatric surgery for transplant candidacy with a BMI above 40 kg/m^2 [2]. Additionally robotic transplantation may be an alternative option for individuals with severe obesity in selected centers [11].

37.3.3 Diabetes Mellitus

Renal transplantation provides survival benefit in diabetic patients with ESRD as compared to those diabetics on waitlist. Pancreas transplantation provides glycemic control and improves microvascular or macrovascular complications

and quality of life of renal transplant recipients. Therefore, pancreas transplantation should be considered as an alternative to insulin therapy for ESRD patients with Type 1 diabetes who have undergone, or plan to undergo, renal transplantation [2]. Patients who have a living kidney donor should consider undergoing renal transplantation before considering subsequent, cadaveric, pancreas transplantation [1, 7]. As a complication of DM, neurogenic bladder is frequently seen in diabetic patients; therefore, a detailed urologic evaluation is recommended before transplant operation [12]. Screening for undiagnosed DM and impaired glucose tolerance may be performed by fasting blood glucose, glycated hemoglobin (HbA1c), or oral glucose tolerance test. Fasting blood glucose and HbA1c are insensitive tests for diagnosis of DM among end stage kidney disease (ESKD) patients [13]. Therefore a recent guideline suggests testing for abnormal glucose metabolism by oral glucose tolerance test in candidates who are not known to have diabetes [2] (Box 37.4).

Box 37.4 What the Guidelines Say You Should Do: Diabetes Mellitus [2]

- The candidates with type 1 or type 2 diabetes mellitus (DM) should be considered for kidney transplantation (1B).
- The candidates with ESKD and type 1 DM be considered for simultaneous pancreas-kidney transplantation in regions where this procedure is available.
- Testing for abnormal glucose metabolism should be performed by using oral glucose tolerance test in candidates who are not known to have diabetes.

37.3.4 Infections

The clinical preparation of a patient prior to transplantation should include exposure history, cultures for colonization, serologic tests, and administration of vaccines. Exposure to several microorganisms that may be activated by immunosuppressive agents after grafting and current latent infections and colonization should be investigated by a detailed history. Travel history for endemic infections (parasitosis, fungal infections, hepatitis viruses, mycobacterium, etc.), employment and hobbies including exposure to pets, soil, and toxins (psittacosis, endemic fungi, atypical mycobacteria), history of sexually transmitted diseases (especially HIV exposure), vaccinations and childhood illnesses, prior surgery such as splenectomy, porto-systemic shunting, or sinus surgery, exposure to mycobacterial infection, especially mycobacterium tuberculosis, BCG vaccination, and the results of previous tuberculin skin testing or interferon-gamma release assays and drug and alcohol use should be questioned in each patient [14]. Transplant candidate vaccination is to be checked for hepatitis A, hepatitis B, pneumococcus, diphtheria, tetanus, pertussis, polio, varicella, measles, mumps, rubella. Laboratory testing should be performed for past infectious exposures and active or latent infections. However, some tests should be applied to selected patients with high risk factors. Routine and special tests for potential recipients are presented in Box 37.5. Screening for cytomegalovirus (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), tuberculosis, Treponema pallidum, Epstein-Barr virus (EBV), human T Lymphotropic virus (HTLV), herpes simplex virus (HSV), toxoplasmosis, strongyloides, and varicella-zoster virus (VZV) is recommended for assessing the risk of post-transplant disorders and prophylactic strategies [7, 14]. Patients with HIV, hepatitis B and C should be evaluated by viral load testing. Testing for latent tuberculosis, tuberculin skin testing (TST) is recommended despite anergy is most common finding in those patients. Additionally, interferon-gamma release assays (IGRAs) may be useful in the detection of latent tuberculosis. X-ray chest films may also be helpful for determining the prior exposure to tuberculosis. Transplant candidates, who have a history of tuberculosis exposure or recent TST conversion or positive IGRA and who have no clinical or radiologic evidence of active disease should

receive anti-tuberculosis prophylaxis. If donor has a history of untreated tuberculosis, prophylaxis should be administered to recipients of transplants [2, 7, 14] (Box 37.6).

Box 37.5 The Recommended Laboratory Tests in Evaluation of a Potential Renal Transplant Recipient

Urinalysis, urine culture
Serologic examination
Hepatitis A, B, C, and D
Tuberculosis (tuberculin skin testing or interferon-gamma release assays)
HIV
Cytomegalovirus (CMV)
Epstein-Barr virus (EBV)
Herpes simplex virus (HSV)
Varicella-zoster virus (VZV)
Syphilis (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR])
Human T-lymphotropic virus (HTLV)-I and HTLV-II
Urine and feces ova examination for parasites (if serology is positive)

Box 37.6 What the Guidelines Say You Should Do: Infections

- All potential transplant recipients should be tested for prior exposure to viral infections [7].
- HIV per se is not a contraindication for kidney transplantation [6].
- Active tuberculosis (TB) treatment should be completed prior to kidney transplantation [2].
- Latent TB treatment should be started prior to or immediately following kidney transplantation in low TB prevalence areas [2].
- We suggest that all candidates with HCV infection be evaluated for severity of liver disease and presence of portal hypertension [2].
- We recommend that patients with HCV and compensated cirrhosis (without portal hypertension) undergo isolated kidney transplantation [2].
- We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation [2] and deferring HCV treatment until after transplantation.
- We recommend that all patients with HCV who are candidates for kidney transplantation be considered for direct-acting antiviral (DAA) therapy, either before or after transplantation [2].
- We recommend that patients from hepatitis D virus (HDV) endemic areas be screened with HDV serology if they are positive for HBsAg or anti-HBc (1A).
- We recommend that HBsAg positive and/or HBV DNA positive candidates undergo isolated kidney transplantation if they do not have decompensated cirrhosis and Living Donor Deceased donor HCV-infected candidates for a kidney transplantation.
- We recommend that anti-HBc antibody positive (HBsAg negative) patients not receive antiviral prophylaxis given that the risk of reactivation is low (1D).
- We suggest that anti-HBc antibody positive (HBsAg negative) patients have a plan in place for post-transplant monitoring of HBsAg and HBV DNA for a minimum of 1-year post-transplantation.

37.3.5 Pulmonary Evaluation

There is limited information about optimal pre-transplant evaluation of patients with pulmonary diseases. However, the evaluation should be similar to that for the general population who undergo other types of surgery. The guidelines suggest

that patients with home oxygen therapy requirement, uncontrolled asthma, and severe chronic obstructive pulmonary disease/pulmonary fibrosis/restrictive disease should not be candidates for transplantation [2, 15]. Predictive value of FEV1 <25%, PO_2 room air <60 mmHg with exercise desaturation SaO_2 < 90%, >4 lower respiratory tract infections in the last 12 months, and/or moderate disease with progression are the criteria for severity of pulmonary disease [15]. The pulmonary complications in patients who smoke have been reported to be increased over that of non-smoker patients. Thus, smoking cessation should be strongly recommended to patients before transplantation [16]. Chest CT is recommended for current or former heavy tobacco users (≥30 pack-years) [2].

37.3.6 Cardiovascular Diseases

Patients with ESKD have a high prevalence of cardiovascular disease. It is important to optimize the cardiovascular status of the transplant recipient before surgery because of high perioperative risk and post-transplant complications. The stress of surgery and anesthetic agents may stimulate various cardiac events. In addition, perioperative cardiac complications may cause delayed graft function. Interventions such as coronary angioplasty/stenting or coronary artery bypass surgery could also affect the allograft. Therefore, transplant recipients should be evaluated for cardiovascular risk and cardiac interventions prior to transplantation [2, 17]. A careful history and physical examination are recommended to recognize active cardiac diseases. In addition, a preoperative resting 12-lead ECG is recommended for potential renal transplantation recipients with or without known cardiovascular diseases. Noninvasive stress testing such as exercise testing or thallium perfusion scintigraphy/dobutamine echocardiography for patients with limited mobility should be considered in asymptomatic patients with multiple cardiovascular risk factors including diabetes mellitus, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia [18]. Echocardiography may be considered to identify valvular disease, cardiomyopathy, or systolic/diastolic dysfunction and pulmonary hypertension [18]. If initial evaluation reveals that transplant candidates have cardiac failure or exercise induced angina or hypotension or ischemia, those patients should be referred for further cardiological evaluation. Coronary angiography is recommended in patients with strong evidence of ischemic heart disease [17, 18]. However routine prophylactic coronary revascularization is not recommended in patients with stable CAD who have no symptoms and have no survival indication for revascularization [2, 18]. Transplant candidates should be carefully assessed for peripheral vascular disease which may lead to technical complications during transplant surgery. In addition to physical examination of pulse and evaluation of arterial murmurs, abdominal X-ray study is also recommended. A Doppler ultrasonographic study is indicated for patients with signs of arterial occlusion and vascular calcifications. Angiography may be considered in patients with severe peripheral vascular disease for vascular repair before transplantation [2, 12]. Cerebrovascular disease may also be an important cause of morbidity and mortality in patients after transplantation. If transplant candidates are presented with signs or symptoms or vascular calcifications in X-ray study, Doppler ultrasonographic evaluation of supra-aortic trunk is indicated to complete evaluation. Patients with a history of transient ischemic attack should be referred for further neurological evaluation. If carotid surgery is required, it should be applied before transplantation [2, 12] (Box 37.7).

Box 37.7 What the Guidelines Say You Should Do: Cardiovascular Evaluation

- Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions based on the presence of multiple CAD risk factors regardless of functional status [2, 18].
- Kidney transplantation candidates who have an LVEF less than 50%, evidence of ischemic left ventricular dilation, exercise induced hypotension, angina, or demonstrable ischemia in the distribution of multiple coronary arteries should be referred to a cardiologist for evaluation and long-term management [2, 18].
- Routine prophylactic coronary revascularization is not recommended in patients with stable CAD who have no symptoms and have no survival indication for revascularization [2, 18].

37.3.7 Malignancies

Active malignancy is an absolute contraindication to transplantation [16]. This contraindication is linked with short survival and/or progression or de novo development of malignancy by immunosuppressive therapy. For patients with a history of malignancy, close consultation with oncology is essential. Minimum disease-free waiting time is required for almost all cancers before transplantation. Waiting time depends on the type of tumor and changes between 1 and 5 years [2, 14, 19] (Table 37.1). For potential transplant recipients, screening is recommended for renal, colorectal, prostate, cervical, and breast cancer prior to transplantation [2, 14, 18] (Table 37.2) (Box 37.8).

Box 37.8 What the Guidelines Say You Should Do: Malignancies

- Current or active malignancy was absolutely contraindicated for waitlisting in adults and children because of "the risk of dissemination and fatal outcome" with exceptions made for small or superficial skin, prostate, or bladder cancers [4].
- Renal transplantation should only be considered in potential recipients with previous malignancy (excluding non-melanoma skin cancer) if there is no evidence of persistent cancer [7].
- Patients with current or previous cancer be discussed with an oncologist and considered on a case by case basis [2, 3].

Table 37.1 Waiting time for neoplastic diseases before transplantation [2, 18]

Neoplastic disease	Waiting time
Incidental renal cancer	No
Bladder cancer (non-invasive papilloma)	No
In situ cervical carcinoma	No/2 years
Basal cell tumor	No/2 years
Squamous cell carcinoma (skin)	No/2 years
Wilms tumor	2 years
Renal cancer if <5 cm	2 years
Breast carcinoma (stage 0–2)	2–5 years
Melanoma (in situ)	2–5 years
Bladder carcinoma (invasive)	2 years
Uterine body cancers	2 years
Testicular cancer	2 years
Thyroid cancer	2 years
Lymphoma	2–5 years
Colorectal carcinoma	
Duke A or B1	2–5 years
Duke C	2–5/>5 years
Duke D	2–5/contraindicated
Invasive cervical carcinoma	>5 years
Renal cell carcinoma if >5 cm	>5 years
Breast carcinoma (stage III–IV)	>5 years/ contraindicated
Melanoma invasive	>5 years
Multiple myeloma	Contraindicated

Table 37.2 Screening procedures for cancer before transplantation

Organ	Procedure
Renal	Native renal ultrasound to assess for acquired cystic disease or masses
Lung	Chest X-ray
Hematologic	Complete blood count
	Leukocyte formula
	Erythrocyte sedimentation rate
	Immunofixation electrophoresis (>60 years of age)

(continued)

Table 37.2 (continued)

Organ	Procedure
Colorectal	Abdominal ultrasonography
	Colonoscopy if >50 years of age
Prostate	PSA for male >50 years of age
Cervical	Pap smear
Breast	Mammogram for women >40 years of age or with family history of breast cancer

37.3.8 Urologic Disorders

Urinary tract pathologies are observed in up to 25% of all ESRD patients; therefore, all potential renal transplant recipients should be evaluated for the presence of urological disorders [20]. Congenital or acquired anomalies of urinary system should be treated before transplantation. Detailed clinical history and physical examination, microscopic urine sediment examination, and abdominal ultrasound are basic instruments of urological evaluation. Additional complementary urodynamic studies may be helpful to assess the recurrent urinary infections, micturition dynamics, and residual diuresis. Augmentation cystoplasty and urinary diversion procedures may be required in some patients with dysfunctional bladder. Similarly, prostate resection before transplantation may be necessary in some male transplant recipients with outflow tract obstruction due to prostate hypertrophy. Pretransplant native nephrectomy is not recommended for all patients with autosomal dominant polycystic kidney disease (ADPKD). Recurrent infection, bleeding and/or intractable pain, enormously enlarged kidneys may be indications for unilateral or bilateral nephrectomy [12, 20]. Symptomatic urinary tract infections should be treated prior to kidney transplantation. However, routine prophylactic nephrectomy was not recommended for recurrent pyelonephritis or cyst infections [2].

37.3.9 Etiology of Kidney Disease

Certain kidney diseases have a chance to recur in the post-transplantation period. Although the incidence of recurrence and graft loss are heterogeneous, the reported recurrence rate of kidney diseases after renal transplantation is presented in Table 37.3 [12, 14, 21]. Despite the high risk for some kidney diseases to recur, recurrence rarely causes early graft loss. Therefore, transplantation is generally not contraindicated; however, a waiting time period is recommended for diseases with a high recurrence risk. In patients with antiglomerular basement membrane disease, lupus nephritis, vasculitis, and thrombotic microangiopathy, transplantation is recommended after the disease becomes inactive for 6–12 months on minimum or no immunosuppression [3, 7].

Table 37.3 Recurrence and graft loss rate of primary renal disease following transplantation [12, 14, 21]

Disease	Recurrence %	Graft loss %
FSGS	20–40	20–50
IgA nephropathy	20–60	45–70
Membranous GN	10–30	10–50
MPGN Type I	20–65	15
MPGN Type II	50–100	30
Systemic lupus erythematosus	5–54	7
ANCA-associated vasculitis	9–36	7–30
AA amyloidosis	14	Frequent
Anti-GBM disease	Infrequent	Frequent
Cryoglobulinemia	50	Frequent
Fibrillary glomerulonephritis	43	Frequent
Hemolytic uremic syndrome	60	73
Henoch-Schonlein purpura	15–35	11–13

37.3.10 Gastrointestinal Disorders

The potential transplant recipients should be evaluated for gastrointestinal disorders prior to transplantation. Peptic ulcer disease may be aggravated after transplantation; therefore, candidates with peptic ulcer should be treated until the lesions disappeared by endoscopic examination before transplantation [2]. In addition, H2 receptor antagonists or proton pump inhibitors should be admitted to all candidates for prophylaxis in the post-transplant period [22]. Cholecystitis or diverticulitis may cause serious morbidity and mortality in immune suppressed patients [12, 14]. Therefore, transplant candidates should be evaluated by ultrasonography

and colonoscopy for the presence of cholelithiasis or diverticulosis. Kidney transplantation should be delayed until symptoms have resolved in candidates with active diverticulitis. However, the recent guideline does not recommend screening asymptomatic candidates for diverticulosis and performing prophylactic colectomy in patients with a history of diverticulitis or asymptomatic diverticulosis [2]. Similarly, screening and prophylactic cholecystectomy are not recommended for asymptomatic candidates for cholelithiasis [2].

37.3.11 Hematological Disorders

Hematological pretransplantation workup includes complete blood count, measurement of partial thromboplastin time and international normalized ratio (INR). Coagulation disorders may cause post-transplantation thrombosis, thereby graft loss. If transplant candidates have history of recurrent miscarriage, arterio-venous thrombosis, hemodialysis graft or fistula thrombosis, lupus, prior graft thrombosis, they should be screened for activated protein C resistance ratio or factor V Leiden mutation, antiphospholipid antibody, lupus anticoagulation, protein C or protein S deficiency, antithrombin III deficiency, and homocysteine levels. Hypercoagulability is not a contraindication for transplantation; however, anticoagulation therapy is recommended for patients in the perioperative period [2, 12, 14]. Candidates should not be excluded from consideration for kidney transplantation because of their need for anticoagulation, antiplatelet therapy, or a history of heparin-induced thrombocytopenia [2].

37.3.12 Psychiatric/Psychosocial Evaluation

Psychosocial state of transplant candidates should be evaluated by an experienced competent individual before transplantation [2]. Cognitive impairment, mental illness, nonadherence to therapy, and drug or alcohol abuse are potential problems that might adversely affect the outcome of transplantation. Cognitive impairment is not an absolute contraindication to kidney transplantation. Some individuals with irreversible cognitive impairment may be acceptable candidates for transplantation in the presence of a reliable primary support person who will take charge of administering immunosuppressive medications and monitor compliance with medical follow-up. Patient nonadherence to therapy is a contraindication to kidney transplantation. Kidney transplantation should be delayed until patients have demonstrated adherence to therapy for at least 6 months [15]. Alcohol and substance abuse can interfere with a patient's ability to adhere to therapy after renal transplantation. Patients with alcohol and/or substance abuse need to be adequately treated before transplantation. Transplantation should be delayed until the patient has demonstrated freedom from substance abuse for at least 6 months. Individuals with a significant mood or anxiety disorder, psychosis, substance abuse, or a severe personality disorder should be referred for psychiatric diagnoses, treatment, and follow-up to reduce barriers to transplantation. However, active affective disorders are contraindications to transplantation, depression in ESRD can be readily treated and case reports also demonstrate the successful transplantation in patients with major psychoses, if adequate support and supervision are provided [1, 2, 15].

37.3.13 Immunologic Evaluation

Pretransplant immunologic evaluation involves a number of immunologic tests before transplantation (Box 37.9). Beside the blood antigens (ABO), human leukocyte antigens (HLA) are the strongest transplantation antigens and can stimulate a primary immune response. Antibodies against HLA are found in patients who have been immunized by pregnancy, blood transfusion, or a prior HLA mismatched allograft. The presence of HLA antibodies is associated with antibody mediated rejection in the early period of transplantation called hyperacute rejection which causes early graft loss. Patients with HLA antibodies have increased risk of delayed graft function and rejection in the perioperative period. However, in recent years, patients were successfully transplanted with immunologically incompatible grafts (HLA-or ABO-incompatible) using various desensitization

protocols that reduce the preexisting antibody levels in transplant recipients. An increased degree of HLA antigen mismatching is associated with a greater risk of chronic graft loss and short graft survival, although not early rejection. Therefore, tests for blood and HLA typing and for antibodies to lymphocyte antigens are recommended to potential transplant recipients before transplantation [23–25]. Panel reactive antibody (PRA) defines the presence of HLA antibodies and sensitization against the potential donors. Complement dependent cytotoxicity (CDC) and the enzyme-linked immunoabsorption (ELISA), flow cytometry and luminex based assays can be used to determine the PRA. When a potential donor known for kidney transplantation, a test called crossmatch (XM) which evaluate for any evidence of preformed antibodies with specificity for potential donor is recommended for prevention of hyperacute or acute antibody mediated rejection. Different techniques included CDC with AHG or dithiothreitol (DTT) and flow cytometry and ELISA and luminex are available assays which differ in their degree of sensitivity. Recently, a highly sensitive screening technique as the single antigen bead assay has been introduced. This technique may provide virtual crossmatching and immunologic risk assessment for transplant recipients before transplantation. HLA antibody screening and donor specific antibody (DSA) determination should be regularly performed by PRA tests or single antigen bead assays especially in highly sensitized patients. CDC T and B cell AHG crossmatch are usually recommended for all allograft recipients in many centers. When CDC XM is positive, the process should be repeated with addition of DTT. CDC positive/DTT negative test should not prevent transplantation. The result of a CDC positive/DTT positive test is a contraindication to transplantation unless donor specific antibodies (DSAs) can be reduced with desensitization protocols. Flow cytometry can be used as a crossmatch test and is routinely performed in some centers; however, T and B cell flow crossmatch are recommended for highly sensitized potential recipients with a history of a positive PRA or with a previous transplant history in others. Despite in the setting of a positive flow crossmatch with negative CDC XM is associated with increased risk for acute antibody mediated rejection; it is not a contraindication to transplantation. Similarly, if DSA positivity is present in single antigen bead assay but the CDC XM is negative, this should be interpreted as an increased immunologic risk, however, it is not an absolute contraindication to transplantation especially after elimination of DSA by desensitization [23–25] (Box 37.10).

Box 37.9 Immunologic Tests Before Transplantation

- For patients on waiting list
  - Blood antigens (ABO) typing
  - Human leukocyte antigens (HLA) typing
  - HLA antibody detection
  - Panel reactive antibody (PRA)
  - Donor specific antibodies (DSA) determination by single antigen bead assays
- For patients with a potential donor known
  - Crossmatches by complement-dependent cytotoxicity (CDC), ELISA, flow cytometry, Luminex

Box 37.10 What the Guidelines Say You Should Do: Immunologic Evaluation

- High immunological risk is indicated when there are high titers circulating antibodies specific for mismatched donor HLA antigens present at the time of transplantation [25].
- A patient's HLA alloantibody profile must be assessed to delineate the antigens regarded as unacceptable for transplant [25].
- A pretransplant crossmatch should be performed for all patients unless a program exists for identifying those individuals who can confidently be defined as sensitized.

- Patients with no detectable HLA-specific antibodies can be transplanted on the basis of a negative virtual crossmatch (vXM) without waiting for a crossmatch test to be performed [25].
- Serum samples of patients on the waiting list must be sent to the histocompatibility laboratory no less than 3 months for routine antibody monitoring and also following transfusion of any blood products [25].
- ELISA technology is more sensitive than complement-dependent cytotoxicity (CDC), whereas Luminex bead technologies are more sensitive than both CDC and flow cytometry, enabling the detection of low levels of HLA-specific antibody [24].
- Candidates should be informed about their access to transplantation based on blood type and histocompatibility testing results [2].
- Candidates with antibodies should be referred to a larger deceased donor pool, kidney exchange programs, and/or desensitization [2].
- Antibody avoidance (e.g., kidney exchange programs or deceased donor acceptable mismatch allocation) should be considered before desensitization [2].

37.3.14 Follow-Up in the Waiting List

Transplant candidates on waitlist should be ready for transplantation at any time. Therefore, dialysis nephrologists and potential transplant recipients themselves must inform the transplant programs of major developments in the patient's health that could be relevant to their transplant candidacy. Standard health maintenance screening is required, together with the routine updating of serologic and other blood test results that may be relevant to the pre- and/or post-transplant management. Patients considered to be low risk on waitlist should be reevaluated at least every 2-years. Annual screening for CAD is required for patients accepted to be at high risk because of previously documented CAD, diabetes mellitus, advanced age, or obesity. Patients with obesity are frequently requested or required to lose weight in order to be listed on the waitlist or maintain their active status. Those patients should be also encouraged to engage in frequent physical activity [15]. Patients on waitlist may be sensitized by the development of antibodies against histocompatibility antigens as a result of blood transfusion, pregnancy, and prior failed transplants. A patient's HLA alloantibody profile must be assessed to delineate the antigens regarded as unacceptable. Therefore, pretransplant, samples should be obtained and tested at 3 monthly intervals and after known sensitizing events [25].

Relevant Guidelines

- American Society of Transplantation Guideline: The evaluation of renal transplantation candidates: clinical practice guidelines. Am J Transplant 2001; Supp1: 5–95. https://www.unitedhealthcareonline.com.
- BTS/RA Living Donor Kidney Transplantation Guidelines 2018 Guidelines for Living Donor Kidney Transplantation. www.bts.org.uk.
- Canadian Society of Transplantation Guideline: Consensus guidelines on eligibility for kidney transplantation. CMAJ 2005; 173: S1. https://www.cst-transplant.ca.
- KDIGO EXECUTIVE COMMITTEE, KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation Transplantation, April 2020, Volume 104, Number 4S. www.transplantjournal.com.
- UK Renal Association Guideline: Clinical practice guideline on the assess-

ment of the potential kidney transplant recipient. Nephron Clin Pract 2011; 118: c209. https://www.renal.org/guidelines.

- British Society for Histocompatibility & Immunogenetics and British Transplantation Society guideline: The detection and characterization of clinically relevant antibodies in allotransplantation. Int J Immunogenet. 2010 Dec;37(6):435–7. https://www.bts.org.uk.
- Deutsche Gesellschaft für Immungenetik (G.O., C.S., and N.L.), The European Federation for Immunogenetics (F.H.J.C. and S.V.F.), and the British Society for Histocompatibility and Immunogenetics Association (C.J.T.) Consensus Report: Consensus Guidelines on the Testing and Clinical Management Issues Associated With HLA and Non-HLA Antibodies in transplantation. Transplantation 2013; 95(1): 19–47. https://www.efiweb.eu.
- The European Renal Best Practice (ERBP) Guideline: Management of donor and recipient of kidney transplant in the peri-operative phase (including preparation and acceptance of living donors) Nephrol Dial Transplant (2013) 28: ii1–ii71. https://www.european-renal-best-practice.org.

Before You Finish: Practice Pearls for the Clinician

- Advanced age is not a contraindication to transplantation.
- Bariatric surgery should be recommended for transplant candidacy with a BMI above 40 kg/m^2 [2].
- Renal or combined kidney-pancreas transplantation provides significant survival advantage to diabetic patients.
- Routine prophylactic coronary revascularization is not recommended in patients with stable CAD who have no symptoms and have no survival indication for revascularization.
- Regardless of clinical or radiologic evidence of active tuberculosis; potential RTRs, who have a history of tuberculosis exposure or recent TST conversion or positive IGRA should receive anti-tuberculosis prophylaxis.
- Minimum disease-free waiting time is required for almost all cancers before transplantation.
- Pretransplant native nephrectomy is not recommended for all patients with autosomal dominant polycystic kidney disease (ADPKD).
- Despite the high risk for some kidney diseases to recur, recurrence rarely causes early graft loss.
- Hypercoagulability is not a contraindication for transplantation; however, anticoagulation therapy is recommended for patients in the perioperative period.
- The result of a CDC positive/DTT positive test is a contraindication to transplantation unless donor specific antibodies (DSAs) can be reduced with desensitization protocols.
- Antibody avoidance (e.g. kidney exchange programs or deceased donor acceptable mismatch allocation) should be considered before desensitization.

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How to Prepare a Chronic Kidney Disease Patient for Dialysis

38

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Before You Start: Facts You Need to Know

- Preparation for dialysis must be patient centered.
- The goals of preparation include an informed selection of dialysis modality, preemptive kidney transplantation, when possible, timely placement of appropriate dialysis access, timely initiation of dialysis, reduction of morbidity, and optimal survival.
- In patients who choose hemodialysis as kidney replacement therapy, dialysis access should be placed early whenever possible, to preclude the need for temporal venous catheters.
- The decision of when to start dialysis should be individualized based on symptoms and/or the appearance of complications yet should not be delayed until patient reaches a specific value of estimated eGFR or becomes too symptomatic.

38.1 The Importance of Preparation Before Dialysis Initiation

Careful planning before dialysis aims to prevent a diversity of medical and social problems associated with advanced end-stage kidney disease (ESKD). Patients with ESKD have exceedingly high morbidity and mortality rates, particularly in the first year after dialysis initiation, when annual mortality rate may exceed 25%. Currently, 20–60% of patients initiate dialysis in an unplanned manner [1]. All-cause mortality peaks in the second to third months on hemodialysis (HD) and then falls significantly and even more after the first year. For example, incident HD patients in 2009 had an all-cause mortality of 435 deaths per 1000 patient years at risk in month 2 and then fell to 206 at month 12; cardiovascular mortality peaked at 169 at month 2 and decreased to 78 at month 12.

Mortality due to infection peaks at months 2 and 3 with 40–43 per 1000 patient deaths [2]. In some reports nearly 35% of HD patients died within the first 90 days. A retrospective cohort study using data from the Dialysis Outcomes and Practice Patterns Study (DOPPS; 1996–2004) found a mortality risk highest during the first 120 days after HD initiation (27.5 deaths per 100 person-years) compared with risk from days 121 to 365 after initiation (21.9 deaths per 100 person-years; *p*: 0.002) [3]. All these studies sug-

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gest that inadequate predialysis nephrology care may be strongly associated with mortality, highlighting the potential benefits of a careful preparation plan before dialysis.

Some factors associated with an increased risk of mortality (Table 38.1) at dialysis initiation are not modifiable, including age >75 years, cancer history, lung disease, neurologic disease, HIV/AIDS, or psychiatric disorders, among others. There are also multiple differences between men and women with respect to preparation prior to the start of dialysis. In general, men initiate dialysis more frequently and have higher mortality rates compared to women; there is speculation that the protective effects of estrogens in women and/or the detrimental effects of testosterone, together with unhealthier lifestyles, might cause kidney function to decline faster in men than in women [4]. In addition to sex differences, ethnic disparities account for important disparities in access to predialysis care [5, 6]. Nevertheless, there are other patients' features associated with mortality, such as temporary access use at the beginning of HD, or serum albumin levels <3.5 g/dL that can be modifiable with clinical care [3]. An optimal preparation for dialysis allows proper patient education, modality selection, and creation of a permanent access.

Table 38.1 Adjusted hazard ratios (AHR) and 95% confidence interval between patients' characteristics and death <120 days after initiation of HD among incident HD patients (n = 4802), DOPPS 1996–2004

Variable	AHR, 95% CI
Age, per 10 years	
65–74	1.65, 1.22–2.22
≥75	2.49, 1.86–3.31
White race versus nonwhite	1.40, 1.07–1.80
Catheter versus AV fistula or AV graft	1.62, 1.05–2.51
Serum albumin <3.5 g/dL	1.57, 1.18–2.09
Serum phosphorus <3.5 mg/dL	1.47, 1.02–2.10
Comorbid conditions (yes versus no)	
Cancer, other than skin	1.41, 1.07–1.85
Congestive heart failure	1.71, 1.35–2.17
HIV/AIDS	2.85, 1.34–6.06
Lung disease	1.33, 1.04–1.69
Psychiatric disorders	1.35, 1.09–1.68
Nephrology pre-ESRD care (yes versus no)	0.65, 0.51–0.83

Source: Data from Bradbury et al. [3]

Adequate preparation for dialysis can improve survival. There is no study that has tested an intervention strategy focused in preparing patients before chronic dialysis; nevertheless, there is strong evidence that a targeted program of medical and teaching intervention at the beginning of HD results in improved morbidity and mortality during the first 90 days, and this improvement is sustained during the following 120 days [7]. A longer duration of predialysis nephrology care is associated with a graded survival benefit, especially when evidence-based KDOQI guidelines goals are accomplished [8]. Predialysis nephrology care is associated with a risk reduction of myocardial infarction, incident atrial fibrillation, congestive heart failure, and stroke of between 14% and 10%, once a subject starts dialysis [9–11]. According to KDIGO guidelines [12], patients with progressive chronic kidney disease (CKD) in whom the risk of kidney failure within 1 year is 10–20% or higher, as determined by validated risk prediction tools, should be managed in a multidisciplinary care setting. In counterpart, suboptimal peritoneal dialysis (PD) or HD initiation (defined as initiation as an inpatient and/or with a central venous catheter (CVC) in the case of HD) is associated with an increased mortality in the following 6 months [13].

In this chapter, we discuss the goals of an adequate preparation for dialysis and present a practical step-by-step approach to help bridge the gap in care and reduce the high mortality seen in the first few months after initiation.

38.2 Objectives of Adequate Preparation for Dialysis

See Box 38.1.

Box 38.1 The Goals of an Adequate Preparation for Dialysis

- Patients who choose to start dialysis should initiate the therapy in the presence of mild to moderate symptoms, avoiding severe symptoms requiring urgent dialysis.
- Ideally, patients must not require hospitalization for the management of untreated acute or chronic complications of uremia.
- Ideally, all dialysis initiation should be planned and nonurgent; "nonurgent start" being defined as dialysis initiation that may be more than 48 h after presentation [14].
- Patients must have a thorough understanding of the different treatment options (see Box 38.2. Quality standards for predialysis education).
- Ideally, patients should have a functioning permanent access for the dialysis therapy decided jointly between the patient and the nephrologist.
- ***Shared Decision Making*** is the preferred model for medical decision, including the appropriate initiation of and withdrawal from dialysis [15].

There are predialysis actions that are strongly associated with better outcomes: a specialized consultation 6 months before dialysis (***timely referral***), more than 10 visits to a nephrologist in the 3 years prior to starting dialysis (***high cumulative care***), and a higher frequency of consultations in the "critical period," i.e., the weeks prior to the start of dialysis (***consistent critical period care***) [16]. In some observational cohorts, rather than early referral, frequency of visits (>10) and continuous long-term care appear to be the most important factor to decrease adverse outcomes [17, 18]. *Timely referral*, *cumulative care,* and *consistency critical period care* should be the ideal goal of predialysis care programs.

Box 38.2 Quality Standards for Renal Replacement Therapy Option Education (RRTOE) [19]

- The RRTOE team consists of a nephrologist and a CKD nurse (at minimum), and ideally, a renal nutrition expert should also be part of the team.
- RRTOE should begin at least 12 months before the predicted start of dialysis for CKD stage 4 or 5; if this is not possible, upon referral for dialysis.
- Materials/resources recommended for RRTOE include (a) one-to-one meetings with staff at the dialysis unit, (b) written booklets appropriate to disease stage, level of education, and cultural background, (c) multimedia showing the dialysis modality in action, (d) patient decision aids, (e) tours of dialysis facilities, (f) online material, among others.

38.3 Selection of the Patient

The first step is to properly identify CKD patients who may progress in the near future to a more advanced stage and require renal replacement therapy. It is inappropriate to consider only one element such as an estimated glomerular filtration rate (eGFR) below a certain threshold for kidney replacement therapy preparation, as specific conditions vary among patients. For example, many elderly individuals with CKD are unlikely to exhibit significant progressive kidney function decline to require dialysis, or the likelihood of dying prior to initiating dialysis far exceeds the likelihood of starting dialysis therapy. In addition, patients with certain nephropathies, in particular tubulointerstitial, display a

slower progression pattern, which may justify an individualized delay in the preparation for dialysis.

No single characteristic can reliably identify which individuals and at what rate they will progress to ESKD. In Box 38.3, we focus on at least one additional evaluation tool, associated with a high probability of reaching ESKD, in addition to an isolated low eGFR, which could aid to identify those who would benefit from timely preparation for future dialysis. The slope of decline of the eGFR against time allows us to recognize those patients whose renal function is deteriorating at a rate that predicts they will require dialysis in the next 1–2 years and who therefore should be referred to the multidisciplinary team. Age alone should not be used as a barrier for referral and treatment; dialysis decision should be made on a composite assessment of the health and functional status of the individual. In every consultation with a patient likely to reach ESKD, the nephrologists must work in the process of information and therefore timely preparation for dialysis. Moreover, all patients with advanced CKD could benefit from education individually tailored to the patient's probability of need of future renal replacement treatment. Novel interventions are available to integrate advanced care planning into predialysis care, such as motivational interviewing-based coaching and nurse-led care model [20, 21]. It is advisable to take time to assess the perception of advanced kidney disease and provide as much information as possible to modify erroneous or inaccurate beliefs about dialysis, stronger negative perceptions of illness at the start of predialysis care are associated with unfavorable physical and mental health-related quality of life [22].

Box 38.3 Characteristics Associated with Progression to ESKD

- eGFR <30 mL/min/1.73 m^2 and young age, high blood pressure, underlying kidney disease (diabetes, APKD, primary glomerular disease), and development of CKD associated conditions (such as secondary hyperparathyroidism with increased serum phosphorus and/or anemia with low hemoglobin levels),
- Rapid decline in kidney function over time (slope of eGFR against time).
- Persistent albuminuria (albuminuria category 3 KDIGO [A3] = albumin excretion rate >300 mg/day or albumin/creatinine ratio >30 g/g).
- History of acute kidney injury with requirement of transient dialysis.
- Presence of other comorbidities such as neoplasms, cardiovascular, pulmonary, or hepatic diseases.

Source: Data from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [12].

38.4 Selection of Dialysis Modality

Preparation for dialysis should begin early enough in the course of CKD to allow time for patients to consider treatment options and, in the case a dialytic method is chosen, to establish a permanent functioning access for the dialysis modality of choice. Depending on multiple factors, including patients' personal will, style of life, age, presence of comorbidities, and availability of local dialysis facilities, among many other, patient's/physician's choice can include three options: non-dialytic maximum conservative management (Chap. 36), preemptive kidney transplantation (Chap. 37), and dialysis.

38.4.1 Hemodialysis Versus Peritoneal Dialysis

We summarize the general characteristics of the two major modalities of kidney replacement therapy: HD and PD in Table 38.2. The preferred choice of dialysis modality in patients with

Table 38.2 Hemodialysis and peritoneal dialysis

Modality of renal replacement therapy	Hemodialysis	Peritoneal dialysis
Technique	Blood is exposed to dialysate across a semipermeable membrane. Small solutes and electrolytes diffuse down a gradient due to concentration differences	The peritoneum is a semipermeable membrane and is exposed to high intraperitoneal osmotic or oncotic gradients (glucose or glucose polymers)
	Water can be driven through the membrane by hydrostatic force	Small solutes diffuse through small pores and macromolecules diffuse through large pores by convection
Dialysate characteristics	A solution containing predefined concentrations of electrolytes	A solution containing high glucose or glucose polymers and a predefined concentration of electrolytes
Patients' characteristics favored by method	1. Patients' desire of dialysis-free days	1. Infants or very young children
	2. Functional dialysis access	2. Difficult vascular access
	3. Possibility to attend a dialysis center	3. Desire to avoid attending a dialysis center
Advantages	Patients are free of any dialysis responsibilities between sessions	PD may be less expensive in many environments
		PD may allow patients more independence and freedom to travel and, in some instances, to work, in particular if an automated peritoneal modality is employed
Consider	Home HD, performed in some centers (nocturnal or short HD), has shown a relatively better survival as compared with in-center conventional HD	PD may be performed manually on a 24-h basis, called continuous peritoneal dialysis (CAPD) or with support or a device, in general at night, called automated peritoneal dialysis (APD)
		PD may not be the best option for patients who do not have social stability and family support, in particular if elderly

ESKD differs between countries, within countries between communities, and due to a multiplicity of other reasons: availability of the technologies, economic capabilities of the health system and in some instances of the individuals themselves, economic incentives to provide specific modes of treatment, the experience of the physicians in particular and in general of the dialysis center, the appropriate training of healthcare professionals to provide home dialysis therapies, and many others [23].

The available epidemiological evidence of survival studies is not strong enough to guide patients'/physicians' selection of a specific dialysis modality. In general, most previous studies described that the relative risk of death between the HD and PD appears to change over time after dialysis initiation. Observational data published in the last decades indicated that PD is associated with better survival during the first 1–2 years of renal replacement treatment, whereas HD is associated with better survival thereafter. Some explanations for this shift have been proposed. A reduced rate of loss of residual renal function in PD patients early in the treatment and a greater level of comorbidity among HD patients at initiation [24] seem to benefit early PD survival, whereas technique failure due to recurrent peritonitis and loss of ultrafiltration with an increase in peritoneal membrane transport [25] and less frequent monitoring of PD patients by their nephrologists might be factors becoming adversely relevant after the first few years on PD. Another potential explanation is that patients with little or

no predialysis nephrology care invariably started HD with a central venous catheter. In this case, the late and unplanned arrival to dialysis in the absence of predialysis nephrology care implies that patients may be in worse health conditions and of course, the use of a hemodialysis catheter instead of a well-planned permanent access may be strong factors that make the death risk of HD to appear higher, early in the course of renal replacement treatment.

At present, there is no consistent evidence of higher long-term death risk in PD patients in the USA. The adjusted survival of PD and HD is almost identical in recent studies [26]. Furthermore, the 10-year survival of patients who started treatment with any of the two therapies in 1999 was remarkably similar (HD and PD 12%) [2]. Conclusion from old studies suggests that these survival differences are not attributable to the dialysis therapy itself and no randomized studies for this purpose have ever been performed for obvious reasons and ethical implications. Instead, they either reflect biases arising from where geographically patients were treated with HD and PD or point opportunities for improvements in patient management.

In addition to general differences between treatment modalities, survival is also dependent on other patient-specific influential factors such as age, gender, race, body weight, and educational status. Understanding these subgroup differences and mortality trends is essential for optimizing patient outcomes. In Table 38.3 absolute and relative contraindications to HD and PD are listed. Most patients with ESKD are suitable for treatment with either PD or HD.

Patients selected to HD or PD must know and understand the following points:

1. *Preservation of veins and avoidance of unnecessary catheters*: Most patients undergoing HD may require several arteriovenous fistulae or grafts in both upper extremities if they are not subjected to early kidney transplantation. Patients selected for PD also must preserve their veins, considering the potential failure of the PD technique during the course of treatment. Cannulation of veins above the wrist in either upper extremity should be avoided in as much as possible [27]. Every effort should be made to limit phlebotomy and intravenous catheters to veins in the hand. Peripherally inserted central catheters (commonly known as PICC lines) must not be used because they can cause thrombosis of the upper arm veins precluding future vascular access in the entire ipsilateral upper extremity. PICC lines in patients with prior venous thrombosis and use of double-lumen 5-F or triple-lumen 6-F PICCs are risk factors for deep venous thrombosis. If the patient needs a temporary central venous access during surgery or hospitalization, internal jugular access must be the preferable site. Subclavian site for catheter placement should be considered as a last resort given the significant risk of subclavian vein stenosis, which may compromise the construction of a permanent access.
2. *Timely construction of a vascular access*: Sufficient time should be allocated for placement and maturation of a permanent dialysis access. Education about CKD, dialysis therapies, and dialysis access should be initiated in individuals with an eGFR 20–30 mL/min/1.73 m^2. Furthermore, vascular access

Table 38.3 Contraindications to PD or hemodialysis

	Peritoneal dialysis	Hemodialysis
Absolute	Peritoneal adhesions, fibrosis, or abdominal malignancy which precludes use of the peritoneal cavity	Impossibility to have an appropriate vascular access
	Non-correctable hernia, abdominal wall stoma, or diaphragmatic fluid leak	
Relative	Recent abdominal aortic graft	Coagulopathy
	Ventriculoperitoneal shunt	Difficult vascular access
	Body mass index ≥40 kg/m^2	Needle phobia
	Skin infection	
	Inflammatory bowel disease (e.g., Crohn's, ulcerative colitis)	

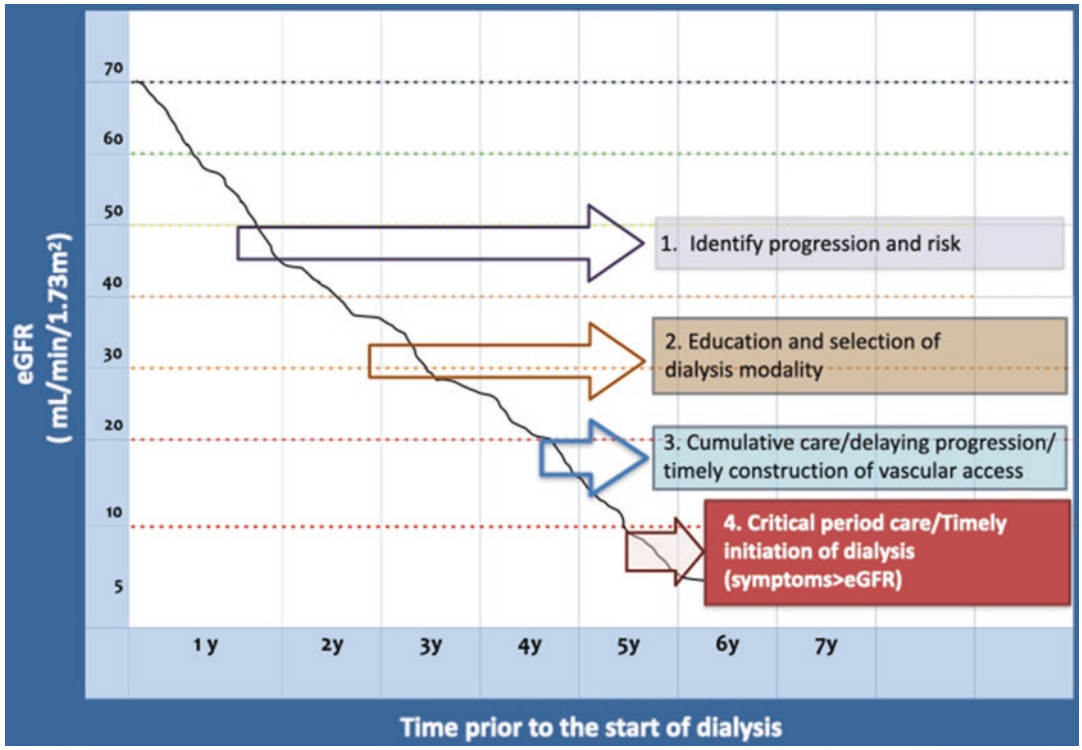

Fig. 38.1 Preparation for dialysis: The figure shows a hypothetical case progressing from CKD stage 3b to ESKD (stage 5) with a relentless and time-dependent decline in kidney function along 6 years of follow-up. In this hypothetical case, the identification of progression from stage 3b to 4 (*purple arrow*) should indicate the right time to start patient education and selection of dialysis modality, when eGFR is around 30–20 mL/min/1.73 m^2 (*brown arrow*). Once modality is selected, construction of a vascular access or placing of a peritoneal catheter must be done according to clinical criteria and institutional facilities, months (HD) or days to weeks (PD) before planned initiation of dialysis (*blue arrow*). The initiation of HD or PD must happen according to clinical judgment, not only by an isolated eGFR value (*red arrow*). Almost all patients should start dialysis when eGFR is below 7 mL/min/1.73 m^2. Some authors have suggested that the majority of patients do not show this progressive and predictable decline in kidney function, and this scheme must be adapted according to individualized clinical scenarios

should be placed in patients with an eGFR 15–20 mL/min/1.73 m^2, in whom progression to ESKD seems likely (Fig. 38.1).

38.4.1.1 Hemodialysis

The first permanent vascular access, either arteriovenous (AV) fistula or arteriovenous vascular (AV) graft, should be placed early enough to allow, if needed, the time to either revise the initial access or second access to be placed, mature, and be adequate for cannulation prior to initiation of dialysis. A justification not to place an AV fistula or an AV graft is the technical or mechanical impossibility to place them; in these cases, a cuffed catheter may be the appropriate vascular access. A second condition that may justify not to place an AV access in advance of HD initiation is if the patient has poor functional status and/or frailty that implies a very short life expectancy as well as cardiovascular comorbidities in advanced age patients that contraindicate the construction of a high flow permanent vascular access [28].

In Table 38.4 the advantages and disadvantages of vascular accesses, including AV fistulae, AV grafts, and cuffed catheters, are summarized. If the patient is going to be on HD, the first option must always be AV fistula and an AV graft as a second-line option. For new HD patients initiating with an AV fistula, median time to first cannulation varies greatly between countries: Japan

Table 38.4 Vascular access

Vascular access	Advantages	Disadvantages	Commentary
AV fistula	Can last many years	Early failure (failure to mature)	Preferred vascular access
	Lower frequency of stenosis, thrombosis, and infection, as compared to AV grafts	Longer time to first cannulation than AV graft	
AV graft	Lower risk of early failure than AV fistula	Requires more frequent intervention for maintaining patency	Useful in elderly patients with limited life expectancy
	Early cannulation		May be selected in patients with history of AV fistula failure to mature
Cuffed venous catheter	No "waiting time" after placement	Patients with catheters develop infections more often, have higher levels of inflammatory markers and higher mortality	Effective flow >350 mL per minute can rarely be obtained, which results in lower dialysis efficiency
	Can be used as a long-term vascular access for patients in whom an AV access cannot be created or with very short life expectancy	High rate of vascular stenosis and potential development of superior vena cava syndrome	Increased recirculation which lowers dialysis efficiency

Source: Data from Saggi et al. [29]

and Italy (25 and 27 days), Germany (42 days), Spain and France (80 and 86 days), and the UK and USA (96 and 98 days). These differences explain the variations in recommendations on the timing of fistula creation (Table 38.5). Cannulation of an AV fistula within the first 2–3 weeks of creation is associated with reduced long-term fistula survival. AV grafts ideally should be left to mature for at least 14–21 days before the first cannulation.

38.4.1.2 Peritoneal Dialysis

Peritoneal catheters may be categorized as acute (without subcutaneous cuff) or chronic (with subcutaneous cuff, commonly known as Tenckhoff catheter due to the fact that this model is the one most extensively used). A chronic catheter should be placed initially in all cases, as acute catheters are rigid and imply an increased risk of perforation, do not have cuffs to protect against bacterial migration from the skin site to the subcutaneous tract so incidence of peritonitis increases beyond 3 days of use, and need to be replaced in short periods of time. In addition, acute catheters commonly present early dysfunc-

Table 38.5 Timing of hemodialysis vascular access creation

Country	Organization	Timing
United states	National Kidney Foundation Kidney Disease Outcomes Quality Initiative	At least 6 months before the anticipated start of HD
Canada	Canadian Society of Nephrology	eGFR from 15 to 20 mL/min when the rate of eGFR decline is between 2 and 5 mL/min/year, but may be earlier if the rate of decline is >5 mL/min/year
United Kingdom	The Renal Association	At some point after an individual reaches eGFR <30 mL/min/1.73 m^2
Australia	National Health and Medical Research Council	The exact timing depends on patient-related factors
Japan	Japanese Society for Dialysis Therapy	Considered when eGFR <15 mL/min/1.73 m^2, AVF should be constructed at least 2–4 weeks before the initial puncture

Source: Data from Woo et al. [30]

tion and hernia formation. Acute catheters were extensively employed in the past, yet nowadays there is no justification for their use in clinical practice unless this is the only available option.

In patients who have been selected or chosen to perform PD, the optimal interval between chronic catheter placement and the start of PD is approximately 1–2 weeks (known as the break-in period), which allows sufficient time for the catheter track to heal and minimizes the chance of a leak when dialysate is instilled in the peritoneal cavity [31]. In PD, patient understanding of the technique is a major challenge and a predialysis teaching period of at least 45–90 days is recommended to reduce peritonitis rates and increase the success of the treatment [32]. During the break-in period, at least once per week and preferably up to 3 times per week, heparinized saline or 1.5% dialysate is infused into the abdomen and drained. When PD has to be started within a week of catheter placement or even immediately after placement, the abdomen is drained and left dry for part of each day, the volume of infusion may be reduced to half of its total usual volume, and patient activity is initially restricted when peritoneal fluid is preset in the abdominal cavity, to minimize intraperitoneal pressure increase and avoid potential leaks around the catheter tunnel.

While chronic PD catheters are typically implanted by surgical dissection in the operating room, effective and safe techniques for bedside placement or in an ambulatory surgical suite, utilizing guidewire and dilators or peritoneoscopy, also exist. It has often been argued that PD can be used for patients who are referred late, as in most patients, PD can be started within 24–96 h of placement of a PD catheter, as long as care is taken to instill low volumes of fluid with the patient lying supine. Implementation of a "PD first" program, as a policy or as a preferable system, has been argued by some as of benefit, yet this may depend on local resources and expertise and should also ideally depend on patient's participation on the decision process [26]. In some centers, the use of the embedded PD catheter technique is associated with low rates of surgical, mechanical, and infectious complications. In this technique, the free end of the catheter is embedded in a tunnel under the abdominal subcutaneous fat for a period of 4–6 weeks, before PD therapy initiation.

38.5 Timely Initiation of Dialysis

As stated above, among patients with advanced CKD (eGFR <15 mL/min/m^2), the most widely accepted indication for initiating dialysis is based on the appearance of uremic signs or symptoms, for example, volume overload, hyperkalemia or acidemia refractory to medical therapy, or significant protein-energy wasting syndrome. Weight loss due to hyporexia or poor caloric intake is probably one of the earliest signs indicating the need to initiate replacement therapy. In ESKD subjects who have not received dietary intervention, a spontaneous decrease in protein intake of 0.70 g/kg/day is observed when eGFR is between 10 and 25 mL/min/1.73 m^2, but when eGFR is below 10 mL/min/1.73 m^2, mean protein intake decreases to 0.54 g/kg/day [33]. The majority of patients will be symptomatic and will need to start dialysis with eGFR in the range 6–9 mL/min/1.73 m^2 [34].

In asymptomatic CKD patients, there is controversy about a prespecified eGFR target or eGFR decline rate at which dialysis should be initiated. One of the problems with the calculation of eGFR based on serum creatinine is that it may be quite inaccurate when kidney function is extremely reduced. Although a low serum creatinine concentration generally indicates a better GFR, a low creatinine concentration may also be caused by decreased muscle mass due to malnutrition or may be increased by overhydration. Furthermore, there is data that indicates that among patients with advanced CKD, serum creatinine is more dependent on muscle mass than kidney function itself. Cystatin C has demonstrated its usefulness in improving the estimation of eGFR in elderly patients or those with significant sarcopenia. Compared to creatinine-based eGFR, lower values of cystatin C based eGFR are associated with a higher risk of ESKD and mortality, yet it is not systematically employed in this scenario [35].

In the past, guidelines recommended that starting dialysis should be considered when a certain eGFR value was reached (≤10 mL/min/1.73 m^2 or even higher in diabetic patients) [36]. Observational evidence has shown that initiating dialysis at an eGFR <5 mL/min/1.73 m^2 increases the risk of mortality by 12% compared to initiating dialysis at an eGFR between 5 and 10 mL/min/1.73 m^2 [37], so many nephrologists suggest starting dialysis with eGFR ≤5 mL/min/1.73 m^2 even in asymptomatic patients. Some professionals do not calculate eGFR in ESKD patients and, in subjects with few symptoms, initiate dialysis when serum creatinine is >10 mg/dL or BUN >100 mg/dL, resembling the criteria used in AKI. Very late dialysis initiation (eGFR around 3 mL/min/1.73 m^2, especially in younger men with hypertension and an adequate residual urine volume) did not increase the risk of mortality compared to starting dialysis with higher renal function [38]. We consider that the decision to start dialysis should not be solely based upon the value of serum creatinine or eGFR and requires a careful individualized decision based in a complete individual evaluation of the patient, which may be highly variable, as described.

In the only trial that has consistently explored the outcome of advanced CKD patients in relation to the actual kidney function at which they initiated renal replacement treatment, the IDEAL trial [39], there was no difference in survival between patients randomly assigned to the intent-to-start-early group (a mean MDRD eGFR 9.0 mL/min) or the intent-to-defer group (a mean MDRD eGFR 7.2 mL/min). It was remarkable that 76% of patients randomized the intent-to-defer group developed uremic symptoms before creatinine clearance reached 7 mL/min. In addition, there was a high cross-over rate in both arms, resulting in a difference in time to dialysis initiation of 6 months between the groups. An important conclusion of the study is that waiting to initiate dialysis until signs of uremia appear do not necessarily jeopardize the patient and that starting renal replacement therapy on the basis of a predefined estimated eGFR value of less than 12 mL/min does not improve the outcome (Box 38.4). The uselessness of a specific eGFR value as the main determinant for dialysis initiation also applies in other subpopulations, such as patients with diabetes [40] or adults older than 60 years [41].

After the results of the IDEAL trial, which failed to demonstrate that initiating dialysis above 12 mL/min/1.73 m^2 could improve outcomes, there has been a trend to start dialysis at lower levels of kidney function using an approach centered on symptom assessment and patient-level goal ascertainment. For example, in the USA the percentage of incident ESKD patients who initiated dialysis with an eGFR >10 mL/min/m^2 decreased by 40% after the IDEAL trial [42]. Similarly, in Canada, early dialysis initiations decreased from 39% to 34% [43]. Although there are no ongoing clinical trials to address this area of uncertainty, in an observational study of a Swedish cohort, very early dialysis initiation (eGFR 15–16 mL/min/1.73 m^2) was associated with a minimally lower absolute risk (around 5%) of 5-year mortality compared with initiation of dialysis at eGFR 6–7 mL/min/1.73 m^2 [44]. Current guidelines do not support preemptive dialysis initiation, except 2011 European guideline included one exception (see Box 38.4).

In asymptomatic ESKD patients, the rate of eGFR decline may be another criterion for dialysis initiation. A rapidly declining eGFR (>4 mL/min/year), systolic blood pressure >140 mmHg, proteinuria >1 g/g, and serum albumin <3.5 g/dL could predict that those patients who will develop an accelerated decline in renal function may benefit from early initiation of dialysis [34, 45].

Should we discard the estimation of eGFR by formulas according to serum creatinine to start dialysis? In addition to traditional biochemical measurements, it is expected that in the coming years new tools will be validated to decide the initiation of dialysis, such as questionnaires focused on quality of life or non-traditional in-office evaluations, such as water overload assessed by ultrasound [46].

Box 38.4 What Guidelines Say You Should Do: Timing the Initiation of Dialysis

- The 2014 Canadian Society of Nephrology guideline recommends an "intent-to-defer" strategy, whereby patients with an eGFR G5 are closely monitored, with dialysis initiated when clinical indications appear or eGFR is ≤6 mL/min/m^2, whichever of these occur first [47].
- The 2011 European guideline states that subjects with CKD G5 should be considered to start dialysis when there is one or more uremic symptoms or when the kidney function is deteriorating more rapidly than 4 mL/min/year of eGFR and close supervision is unfeasible or uremic symptoms are difficult to detect [34].
- The 2015 KDOQI Clinical Practice Guideline suggests to initiate renal replacement treatment based primarily upon an assessment of signs and/or symptoms of uremia, evidence of protein-energy wasting, and if there is inability to safely manage metabolic abnormalities and/or volume overload with medical treatment. The work group elected not to recommend a specific eGFR target to initiate dialysis [48].
- The 2018 UK National Institute for Health and Care Excellence (NICE) recommendations suggested initiation of dialysis when there are uncontrollable uremic symptoms, biochemical abnormalities or fluid overload, or an eGFR of 5–7 mL/min/1.73 m^2 in asymptomatic patients [49].
- The 2019 KDIGO Controversies Conference states that dialysis should be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure, inability to control volume status or blood pressure, a progressive deterioration in nutritional status refractory to dietary intervention, or cognitive impairment. The current data do not support preemptive dialysis initiation [14].

38.6 Retarding Initiation of Dialysis

Patient preparation for dialysis treatment should begin about 4–12 months prior to the anticipated dialysis need if one takes in consideration 1–6 months of iterative CKD education for patients to accept potential need for dialysis and 3–6 months for placement and maturation of dialysis access [29] (Box 38.5). Of note, CKD progression rates can change over time, making it challenging to precisely anticipate the need for dialysis. Complications of advanced CKD such as fluid overload, anemia, hyperkalemia, and acidosis must be approached and treated according to what is written in other chapters of this book.

In certain patients with advanced CKD, the following strategies can defer dialysis initiation:

1. *Patient-centered multidisciplinary care:* Multidisciplinary care focused on comprehensive education about lifestyle, diet, over the counter medications with kidney toxicity, and other medical problems prevents worsening renal function. Although it may seem as an administrative overload, evidence supports that care by a coordinated team consisting of a nephrologist, a nutritionist, a nurse, and a pharmacist delays CKD progression, prevents AKI events, and improves several biochemical variables [50, 51]. In addition, there must be a change not only in patient education, but also in the curricula of nephrologists, focusing on the patient and not only on the disease. Psychosocial issues are of upmost importance in preparing for dialysis. For example, as expected, patients regard the proposal to start dialysis as bad news, which often shatters their life and environment and has important consequences for medical follow-up [52]. Teaching nephrologists through different strategies as role-play or simulation may be effective ways of learning how to deliver bad news with empathy and acquiring listening skills is also of major relevance and part of appropriate predialysis care [53].
2. *Prevent drug-induced nephrotoxicity*: Abrupt onset and even sometimes irreversible acute kidney injury that precipitates end-stage kid-

ney disease can occur with the use of nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, contrast dye, diuretics, or others, especially in patients with risk factors (age >60 years, CKD, volume depletion, heart failure, or sepsis). Selective cyclooxygenase-2 inhibitors have a similar adverse kidney effect in glomerular autoregulation to other NSAIDs. Acetaminophen can be associated with chronic interstitial nephropathy. CKD patients with chronic pain should use alternate agents for pain and avoid NSAIDs as much as possible [54]. Diuretics are some of the most observed newly initiated medications right before dialysis [38, 55]. Although increased doses of diuretics may be directly related to an accelerated progression of ESKD or simply represent a medical attempt to avoid water overload, the need to prescribe a high dose of diuretics predicts an increased risk of needing dialysis sooner.

3. *Stop inhibitors of the renin–angiotensin system only on an individualized basis*: In patients with proteinuria <1 g/g and eGFR <20 mL/min/1.73 m^2, stopping angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) may in some selected cases increase eGFR and postpone dialysis initiation for several months. In some patients, this maneuver may increase eGFR at the time of discontinuation of ACEi/ARB, especially in patients >65 years old or those whose kidney function was declining despite ACEi/ARB treatment. Nevertheless, in general, longer predialysis ACEi/ARB use is associated with lower risk of dialysis-requiring congestive heart failure [56] and postdialysis mortality [57]. In predialysis patients on ACEi/ARB, meticulous attention should be paid to prevent AKI episodes, avoid hypotension episodes, counseling about potassium intake and evaluate the use of novel potassium binders in certain cases. In case of hypotension or repeated episodes of AKI, it is reasonable to discontinue these drugs [58].
4. *Correction of metabolic acidosis*: Patients with serum bicarbonate 16–22 mmol/L on 2 consecutive measures and blood pressure (<150/90) must receive oral sodium bicarbonate tablets 600–1000 mg thrice daily and increase as necessary to achieve and maintain HCO_3 level ≥23 mmol/L. Absence of a deleterious effect on BP despite increased sodium intake has been observed suggesting that sodium salts other than sodium chloride have a negligible effect on BP [59].
5. *Diet*: The benefits of dietary protein restriction to approximately 0.6–0.8 g/kg per day on the progression of CKD in humans remain controversial, and there is a lack of controlled and randomized studies to support extensive protein restriction. In addition, the use of nutritional supplements with low amounts of protein, phosphorous, and potassium; ketoanalog-supplemented very-low-protein diets; or vegetarian diet might prove to be useful, yet there is a lack of scientific validated and controlled information supporting them. Dietary restrictions should be considered on an individual case-by-case basis. 2012 KDIGO guidelines suggest the use of a low, high-quality protein diet of 0.8 g/kg per day among select predialysis patients who are highly motivated to follow such a diet [12]. Patients who are on a protein-restricted diet should be closely monitored, preferably by a dietitian, with follow-up every 2–3 months for adequate caloric intake and early detection of evidence of protein malnutrition, which in itself may prove to be a deleterious environment and an increased risk at dialysis initiation [60]. The benefit of supplemented diets with very low protein intake (0.3–0.4 g/kg/day) has been conducted in studies with observational designs or in clinical trials whose outcomes include eGFR based on serum creatinine formula [61–63]. Given that it has been strongly demonstrated that initiating dialysis with a poor nutritional status is associated with inflammation and higher mortality, it may be questionable to try to delay progression to ESRD for a few months with excessive protein restriction [64].
6. *Holiday days for specific medications when indicated*: Routine counseling about tempo-

rary discontinuation of ACEi/ARB, diuretics, and other antihypertensive agents during intercurrent illnesses is recommended to preserve kidney autoregulation [58].

7. *Consider the risk–benefit ratio of invasive procedures, and if possible, delay:* The performance of surgeries or procedures with IV contrast application may accelerate the initiation of dialysis in patients with advanced CKD. In ESKD patients with moderate or severe myocardial ischemia, there is often controversy about the risk–benefit ratio of invasive procedures such as percutaneous coronary intervention or coronary artery bypass grafting. In the open label trial ISCHEMIA-CKD, patients with advanced CKD and concomitant chronic coronary disease who underwent an invasive coronary strategy did not reduce the risk of death or nonfatal myocardial infarction compared to an initial conservative strategy. Not only did the invasive strategy show no cardioprotective benefit, but it was also associated with a greater risk of hemorrhagic stroke. Furthermore, invasive coronary strategy was associated with an accelerated time to initiation of maintenance dialysis, with a median time of 6 months after procedure, compared to 18 months in the conservative group [65]. Although a causal mechanism remains elusive, as the intervention group had no further post-procedure AKI events, this example is reminiscent of the medical concept that "less is more" and that "not every blocked artery needs a stent" [66].

Box 38.5 What the Guidelines Say You Should Do: Retarding CKD Progression

- Define CKD progression based on one of more of the following:
  - Decline in GFR category (a certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline).
  - Rapid progression is defined as a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year.
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.

Source: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [12].

38.7 Problems in Preventing Urgent Dialysis

One of the aims of KDIGO 2012 CKD guidelines is to avoid late referral, defined as referral to specialized services less than 1 year before the start of renal replacement therapy. Late referral to a nephrologist is associated with higher morbidity and higher death risk [67]. However, *early referral to a nephrologist is not synonymous of optimal dialysis initiation*. Many patients still initiate dialysis late or suboptimally prepared, despite early referral and care for >12 months by factors such as patient-related delays, acute-on-chronic kidney disease, surgical delays, and late decision-making, among others (Box 38.6). **An important limitation to timely referral for proper preparation of a patient before dialysis is the unpredictable, nonlinear, and rapid progression to ESKD triggered by the occurrence of an AKI episode, when it occurs in patients who already have CKD.** This situation may be common among older patients [68].

The literature has demonstrated that "*late referral*" may be a direct cause of worse outcomes, but often late nephrology consultation may be a consequence of fast progressing or aggressive renal disease. For example, roughly 60% of those seeking nephology assessment <90 days prior to initiate dialysis had acute irreversible renal failure and were more likely to

have other comorbidities such as systemic vasculitis or malignancy [68]. Nevertheless, predialysis care is independently associated with lower mortality even in patients with cancer such as multiple myeloma [69]. It is important to identify this as an important bias of several publications and to understand that proper predialysis preparation in some acute or fast progressing settings is not always possible.

Many ESKD patients have many comorbidities and attend regular non-nephrology medical visits frequently, yet the precedent of having regular medical visits to general practitioners or other specialists has not been shown to improve nephrology referral or facilitate proper CKD management [70]. For many physicians, there is a large gap in medical knowledge in relation to CKD complications that needs to be addressed.

Box 38.6 What Guidelines Say You Should Do: Early Referral

- Timely referral for planning RRT in people with progressive CKD in whom the risk of kidney failure within 1 year is 10–20% or higher, as determined by validated risk prediction tools, and avoidance of late referral, defined as referral to specialist less than 1 year before start of RRT.
- Patients with progressive CKD should be managed by a multidisciplinary care team that should have access to dietary counseling and education and counseling about different RRT modalities, transplant options, vascular access surgery, as well as ethical, psychological, and social care.

Source: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [12].

38.8 Myths Associated with Dialysis

First PD, after HD.

Due to the differences in early and late survival, some have suggested using a "dual-modality" or "integrative-care" approach with initiation of RRT with PD, followed by timely transfer to HD. One study showed a survival advantage in a matched-pair analysis of patients who started on PD and were transferred to HD versus patients who started and remained on HD. Yet, another study reported that initial dialysis modality was not a significant predictor of survival after adjusting for age, sex, and primary renal diagnosis. Thus, in the absence of randomized controlled studies, definite recommendations regarding the dialysis modality based on mortality rates cannot be made, even when some data seem to suggest that starting patients on PD might be beneficial. A non-planned change from PD to HD is associated with an increased risk of hospitalization and mortality.

PD is more appropriate for patients with cardiovascular comorbidities providing hemodynamic stability and avoiding rapid fluid shifts that may be harmful to the cardiovascular system.

Nowadays there is evidence provided by some studies that the risk of death in elderly patients with diabetes, coronary artery disease, and congestive heart failure is significantly greater in patients on PD [71]. Nevertheless, we have to consider this could be due, at least in part, to a biased patient selection. Another explanation could be that fluid control is potentially more difficult in PD and fluid overload may be the main cause of death in some of these reports. What is clear is that this vision certainly contradicts the often expressed opinion that PD is more appropriate for patients with preexisting significant cardiovascular disease.

PD is the preferred dialysis modality in diabetic patients.

Some early reports suggested that PD could improve survival in diabetic ESRD patients. At present, most studies have concluded that both HD and PD appear to have similar survival in diabetic patients after adjustment of multiple variables [25]. PD has advantages in diabetic patients such as fewer episodes of hypotension during dialysis, avoidance of vascular access complications, home setting, fewer episodes of bloodborne diseases, and fewer episodes of hemorrhagic retinopathy; nevertheless, it also has disadvantages that include an increased risk of fluid overload, gain of weight precipitated by continuous glucose absorption (100–300 g of glucose in a conventional DP), and large insulin requirements when hypertonic solutions are used, among others. The majority of these disadvantages can be overcome by adequate care.

Before You Finish: Practice Pearls for the Clinician

- In each clinical visit, a CKD patient should be assessed for progression and risk of dialysis, in particular looking closely to those with eGFR <30 mL/min/1.73 m^2, high blood pressure, type of underlying renal disease (diabetes, APKD, primary glomerular disease), and development of CKD complications.
- The eGFR slope against time is useful to predict those CKD patients that will probably require dialysis in the next 1–2 years.
- The decision to start dialysis should also include a careful evaluation of symptoms and signs of uremia and other clinical conditions, and not solely eGFR.
- Patients in preparation for dialysis must preserve their veins, and cannulation of veins above the wrist in either upper extremity should be avoided.
- Vascular access should be placed in patients who have been selected to HD, with an eGFR 15–20 mL/min/1.73 m^2 or before, in those whom progression to ESKD seems likely in a short term. In HD the first option must be radio-cubital AV fistula created 1–4 months before dialysis; in peritoneal dialysis a chronic catheter should be placed approximately 1–2 weeks before dialysis.
- Retarding initiation of dialysis may be accomplished with appropriate medical care that would include optimal blood pressure control, avoidance of NSAIDs, and other measures, including discontinuing inhibitors of the renin–angiotensin system, correcting metabolic acidosis, and appropriate diet restrictions.
- In spite of early nephrology referral, many patients are not efficiently prepared for a programmed dialysis initiation as multiple factors such as patient-related delays, acute-on-chronic kidney disease, surgical delays, and late decision-making could be playing a role.
- Once kidney replacement therapy is needed, most patients can be treated with either PD or HD. The selection of dialysis modality is influenced by a number of considerations, and results of survival studies between HD and PD should not guide patient/physician selection of dialysis modality.

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Quality of Life in Chronic Kidney Disease

39

Rachael L. Morton and Angela C. Webster

Before You Start: Facts You Need to Know

- Health-related quality of life (HRQoL) relates to the measurement of how disease or treatments impact on a person's sense of subjective well-being.
- HRQoL is best measured using a validated method or 'tool', commonly self-administered questionnaires.
- Generic tools enable comparison with the general population and other groups but may be insensitive to the impact of disease-specific symptoms. Common generic tools are The Medical Outcomes Study Short Form 36 (SF-36) or the EuroQol 5 dimensions (EQ-5D).
- Disease-specific tools are more sensitive to relevant symptoms but cannot be used for comparison with other populations. Common disease-specific tools include Kidney Disease Quality of Life-Short Form (KDQOL-SF).
- HRQoL declines as a person's GFR declines. Many dialysis patients report an HRQoL equivalent to people dealing with a terminal malignancy, although HRQoL improves but does not normalise after transplantation. CKD impacts HRQoL more profoundly for younger people compared with older people.

39.1 What Is Quality of Life and What Does It Mean for CKD Patients?

Quality of life is a complex construct for which there is no agreed definition. Terms sometimes used to describe closely related constructs include subjective well-being and life satisfaction. The term 'quality of life' when applied to health refers to the effects of the disease or treatments as perceived and reported by the individuals themselves. In the case of chronic kidney disease (CKD), this includes patients, their families and caregivers. To emphasise the focus on health, it is preferable to use the term health-related quality of life (HRQoL) [1] (Box 39.1).

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Box 39.1 Glossary of Important HRQoL Terminology

Caregiver	Informal or unpaid family member or close person who provides care for the individual with chronic kidney disease
Domain	A dimension of quality of life, for example, mobility
HRQoL	Health-related quality of life
Instrument	A survey tool or questionnaire for measuring quality of life
Proxy	Someone other than the individual reporting on the individual's quality of life, for example, a doctor or family member
QALY	Quality adjusted life year
QoL	Quality of life
Tool	A survey, questionnaire, or technique for measuring quality of life
Utility	A quality of life weighting between 0 (death) and 1 (full health)
Validation	The process by which a data collection instrument is assessed for its dependability. That is, does the instrument produce data that are reliable and true?

A patient's HRQoL is influenced by their lived experience of illness across a broad range of dimensions. These dimensions, often called domains, may include symptoms of CKD and other coexisting illnesses; side effects from treatment; a person's physical functioning, their role; psychological, social, sexual, and cognitive functioning; satisfaction with care or unmet needs for information and support services; financial demands; and spiritual well-being (Fig. 39.1).

CKD can affect a patient's HRQoL in many ways. The CKD diagnosis may cause fear, anxiety, and depression. Symptoms of CKD such as fluid retention, bone pain, peripheral neuropathy, itch, or sleep disturbance as well as side effects from medication or dialysis treatments can all impact negatively on well-being and affect everyday roles and activities. Limitations on everyday activities imposed by CKD, such as fluid or dietary restrictions, and difficulty in travelling or taking holidays for those on dialysis can also affect HRQoL.

Quality of life is of direct importance to patients with CKD and for some is a more important consideration than length of life [3]. Therefore, the need to balance the benefits and harms of CKD treatments in terms of survival and quality of life provides an important reason for clinicians to assess HRQoL when evaluating the effect of new and established treatments.

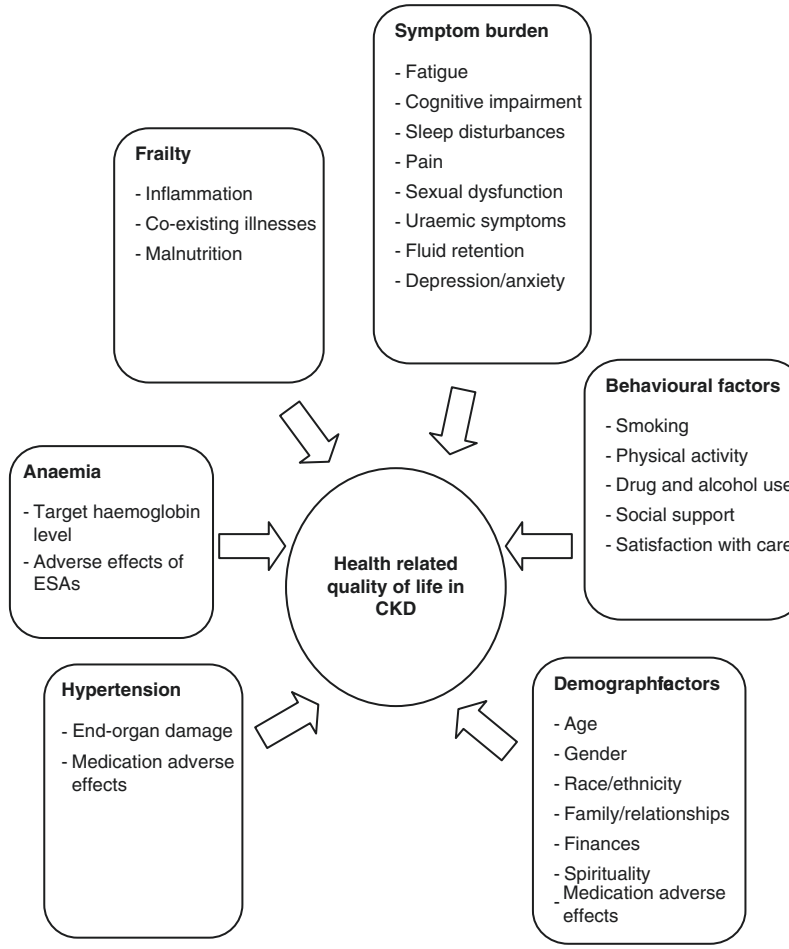

Fig. 39.1 Interaction of factors contributing to diminished HRQoL in CKD (Adapted with permission Soni et al. [2])

39.2 What Is Known About HRQoL in Kidney Disease?

Available literature indicates that HRQoL declines as GFR decreases, particularly in the domains of physical functioning. HRQoL is lower in incident and prevalent dialysis patients compared with the age-matched general population. Although age itself has a significant influence on physical function, older patients report less loss of HRQoL and greater satisfaction with life than do younger patients. On average, HRQoL of dialysis patients is similar to patients dealing with metastatic malignancy and is worse for renal patients with a high symptom burden (Box 39.2). Socio-demographic factors may also influence HRQoL. For patients with end-stage kidney disease (ESKD), treatment with transplantation yields higher HRQoL than dialysis. Considering dialysis modalities, home-based dialysis is associated with higher self-reported HRQoL than hospital-based dialysis [4].

HRQoL is one component of a broader suite of Patient Reported Outcomes Measurements (PROMs) and while symptoms of depression, cognitive impairment, or pain are relevant to overall quality of life, HRQoL instruments are not designed to diagnose these clinical conditions. The move towards building healthcare around patient-centred outcomes, and increasing consideration of individual patient preferences, means a good understanding of HRQoL measurement and interpretation is of critical importance in modern nephrology practice.

Box 39.2 Examples of Mean Health-Related Quality of Life Weights in CKD and in Other Chronic Diseases

Population or health state	Quality of life weight (utility) × [0–1 scale, where 0 = death and 1 = full health]
CKD stage 3	0.88
Kidney transplant	0.86
CKD stage 4	0.84
CKD stage 5 (pre-dialysis)	0.79
Peritoneal dialysis	0.75
In-centre haemodialysis	0.61
Hospitalised for influenza on haemodialysis	0.50
1 year on haemodialysis	0.49
Distant metastases from breast cancer	0.76
Melanoma stage IV—stable disease	0.65
Metastatic prostate cancer	0.60
Paralysis due to spinal cord injury	0.52
Bed-ridden with pressure ulcers	0.30

Source: Data from the Cost-Effectiveness Analysis Registry—Tufts University (https://research.tufts-nemc.org/cear4/) [5]

39.3 Methods to Assess Quality of Life in CKD

While HRQoL is a subjective phenomenon in that it comprises people's perceptions, the measurement techniques used to assess, analyse, and interpret HRQoL are objective. Methods to assess HRQoL include interviews, focus groups, or patient diaries; however, in the vast majority of clinical applications, HRQoL is measured by questionnaire. Patients usually self-administer the questionnaire, although there may be circumstances under which a researcher-administered questionnaire is necessary. If an HRQoL questionnaire has been rigorously developed, its constituent questions should have been selected on the basis of literature review and expert or patient opinion. It will also have been subjected to testing of its reliability and validity with the populations of interest (Box 39.3).

Box 39.3 Reliability, Validity, and Responsiveness of HRQoL Instruments

Concept	Definition
Test–retest reliability	The correlation between responses to the same questions or items administered to the same respondents at different times
Inter-rater reliability	The correlation between responses to the same items obtained by different observers, raters, or interviewers (relevant for proxy-administered questionnaires)
Internal consistency reliability	The extent to which items in a commonly accepted scale measure the same concept (often measured with Cronbach's alpha)
Content validity	The extent to which an instrument includes domains relevant to the population or study
Construct validity	Involves specifying constructs that account for variance in a proposed measure and satisfy hypothesised relationships among constructs. The agreement there is between different measures meant to measure the same concept (convergent validity) and the more they differ from those intended to measure other concepts (discriminant validity)
Criterion validity	The extent to which the measurement correlates with an external assessment, such as a previously validated measure or gold standard, for example, Karnofsky Performance Status or the Beck Depression Inventory
Responsiveness	The sensitivity of the instrument to detect changes in a patient's clinical condition

39.3.1 Generic Versus Disease-Specific Questionnaires

Questionnaires that measure HRQoL are generally referred to as instruments. Generic instruments enable a broad evaluation of overall health across many domains and are widely used. They are designed for measuring HRQoL in the general population and in doing so allow for comparisons to be made between specific groups, e.g. patients with stage 4 CKD and the general population, or patients and their caregivers (Table 39.1). One of the downsides of generic instruments is that they may be subject to positive or negative bias for particular groups in the population. For example, an instrument with an emphasis on physical functioning may rate a lower HRQoL for a person with spinal injuries than a disease-specific instrument where there is an emphasis on mobility or independence. Similarly a generic instrument may not be sensitive enough to detect a change in HRQoL if the disease-specific symptom or condition is not included. An example of this is the inability of an instrument with no domains for visual acuity to measure the impact of reduced vision in a population of patients with diabetic retinopathy.

The alternatives to generic instruments are disease-specific instruments. These are designed for patients with a specific disease, for patients with specific symptoms, or for those undergoing a particular intervention—such as dialysis (Table 39.2). These instruments detect subtle changes in common CKD symptoms such as fatigue or pruritus if these dimensions are explicitly included. A major downside of disease-specific instruments is that they do not allow comparisons between groups, i.e. those with and those without the disease and/or between people managed with different treatment modalities, e.g. dialysis versus transplantation (Table 39.2).

39.3.2 Utility-Based Quality of Life

Economic evaluations and cost-effectiveness studies of treatments in CKD often require the health outcome to be reported in quality-adjusted life years (QALYs). QALYs are a standard metric which combines the length of life with the quality of life. The quality of life is weighted in this calculation and when used in this circumstance is called a utility. Utilities are based on individuals' preferences for different health states—thereby a more desirable health state receives a greater weight. HRQoL utilities are measured on a scale ranging from 0 to 1, where 0 indicates the state 'dead' and 1 indicates 'full health'. Valuations of different health states on the 0–1 scale are available from large surveys of the general population in many countries (Table 39.3).

Table 39.1 Summary of generic HRQoL instruments commonly used in people with CKD

Name of instrument	Developed by and for whom	Validated in	Time to complete	Domains covered	Number of questions or items	Can be converted to utility?	Where do I get it?
Short Form 36 Health Survey (SF-36)	Medical Outcomes Study for HRQoL in the general population	General population and used extensively in CKD	20 min	8 (physical functioning, role—physical, bodily pain, general health, vitality, social functioning, role—emotional, mental health)	36	Not directly—but an algorithm is available to transform SF-36 scores into utilities	www.qualitymetric.com
SF-12	Rand Corporation as a shorter version of the SF-36	General population and used in CKD	5 min	8 (physical functioning, role—physical, bodily pain, general health, vitality, social functioning, role—emotional, mental health)	12	Yes—the SF-6D provides a means for using the SF-12 data by estimating a preference-based single index measure using general population values	www.qualitymetric.com http://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d
EQ-5D	EuroQol organisation for a generic instrument that describes and values HRQoL	General population with population norms from most high income countries	5 min	5 (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)	5 plus a visual analogue scale	Yes—specifically recommended for NICE submissions in the UK	www.euroquol.org
Sickness impact profile (SIP)	Johns Hopkins University to provide a descriptive profile of changes in a person's behaviour due to sickness	General population with any disease or illness	30 min	12 (sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour and communication)	136—or a shorter version with 68 questions	No	http://www.mapi-trust.org/

Table 39.2 Summary of disease-specific HRQoL instruments commonly used in CKD

Name of instrument	Developed by and for whom	Validated in	Time to complete (min)	Domains covered	Number of questions or items	Where do I get it?
KDQ	University of Western Ontario, Canada for haemodialysis patients	Haemodialysis patients	10–15	5 (physical symptoms, fatigue, depression, relationships with others, frustration)	26	Not routinely used
Kidney disease quality of life—long form (KDQOL-LF)	Kidney Disease Quality of Life Working Group for patients on dialysis	Haemodialysis patients	30	Includes the SF-36 plus 8 kidney-specific domains: Symptoms and problems, effects of kidney disease, sleep quality, burden of kidney disease, cognitive function, social support, dialysis staff, encouragement and patient satisfaction	134	www.rand.org
Kidney disease quality of life—short form (KDQOL-SF)	A shortened version of the KDQOL-LF developed by the RAND corporation	Haemodialysis patients	20	General HRQoL including the SF-36 plus 8 kidney-specific domains: Symptoms and problems, effects of kidney disease, sleep quality, burden of kidney disease, cognitive function, social support, dialysis staff encouragement and patient satisfaction	80	www.rand.org
KDQOL-36™	RAND corporation	Haemodialysis or peritoneal dialysis patients	10–15	General HRQoL including the SF-12 instrument and 3 kidney-specific domains: burden of kidney disease, symptoms/problems, effects of kidney disease	36	www.rand.org

Table 39.3 Summary of utility-based instruments for use in health economic evaluations commonly used in people with CKD

Name of instrument	Instrument type	Developed by	Population valuation weights (tariffs)	Time to complete (min)	Domains covered	Number of questions or items	Where do I get it?
EQ-5D	Multi-attribute	EuroQol	UK, USA, most European countries, Australia/New Zealand	5	5 (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)	5 each with 3 or 5 levels plus a visual analogue scale	www.euroquol.org
SF-6D	Multi-attribute	University of Sheffield, UK	UK	5	12 (need to complete the SF-12 questionnaire)	12	www.qualitymetric.com http://www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d
Health utilities Index (HUI) version 2 or 3)	Multi-attribute	Health Utilities Index, Inc	Canada, UK	8–10	9 (vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition)	15	http://www.healthutilities.com/
Assessment of quality of life (AQOL) version 4D, 6D, 7D or 8D	Multi-attribute	Monash University, Australia	Australia	Dependent on version: 2–6	Dependent on version (4–8 including independent living, happiness, mental health, coping, relationships, self worth, pain, senses)	Dependent on version (12–35 questions)	http://www.aqol.com.au/
Time trade-off (TTO)	Preference-based measure: (trading time in different health states)	Mc Master University, Canada	Not applicable	Dependent on number of time preference questions: usually 10–15	To be determined by the investigator as the time to be traded and health states are context specific	Usually 5–15 questions	Example: http://www.healthstrategy.com/tto/tto.html
Standard Gamble (SG)	Preference-based measure: (trading risk of death with time in a particular health state)	Mc Master University, Canada	Not applicable	Dependent on number of risk preference questions: usually 10–15	To be determined by the investigator as the risk of each health state is context specific	Usually 5–15 questions	Example: http://www.healthstrategy.com/sg/sg.html#anchor

39.4 What Quality of Life Measure Should I Use?

The choice of HRQoL instrument will depend on your objectives (e.g. for research or for following patients), the patient population you are working with, the treatments involved and their potential side effects and the resources available. For some measurement needs, there may not be one ideal tool—you may need to use a complementary set of instruments. If feasible, pairing a generic and a disease-specific questionnaire is recommended. For any economic evaluation, a utility-based quality of life instrument should be used [4]. There are numerous HRQoL instruments available; therefore, taking the time to choose the right measure at the outset can make all the difference between negative and positive findings. It is always a good idea to get copies of the actual questionnaire so you can see exactly how the domains are covered and what you will be asking your participants to consider.

The best instruments are ones that have been validated in your population of interest and have a track record in research with objectives and treatments similar to your own study. The chosen instrument should also have face validity for the patient. Face validity means including questions that are both appropriate and meaningful for your patient context (Tables 39.1, 39.2, and 39.3; Box 39.3).

39.5 Measuring HRQoL in Special CKD Groups: End-of-Life Care for the Elderly and Caregivers

39.5.1 The Elderly and End-of-Life Care

Elderly patients often have multiple coexisting diseases such as ischaemic heart disease, diabetes, peripheral vascular disease, or cancer which result in additional decrements in HRQoL. The initiation of dialysis therapies in elderly ESKD patients is often associated with decreased quality of life, increased hospitalisation, and functional decline. Similarly, elderly patients managed on a conservative non-dialytic pathway may also lose HRQoL with symptoms of dyspnoea, pain, and lack of energy. The goal of care at the end of life is to achieve as good a quality of life for the patient as possible, and good communication as well as proactive management of symptoms is required. There is a growing body of literature in nephrology and palliative care about practical methods to manage symptoms for ESKD patients at their end of life. Assessment of HRQoL in the elderly and palliative population requires a modified approach taking into account the illness of respondents and the particular domains of interest or importance such as spirituality and pain management. The SF-36 and the EQ-5D have been used to assess HRQoL in this population; however, newer instruments such as the ICECAP-SCM (supportive care measure) may be more sensitive to the well-being and quality-of-life needs of this population [6].

39.5.2 Caregivers

To date, the quality of life of informal caregivers of patients with CKD has rarely been targeted for intervention or measured in clinical trials. However, it is of special interest where the goal of intervention is to improve chronic care service provision such as respite for partners of home dialysis patients rather than change the severity of illness of the patient [7]. Caregivers of elderly patients on dialysis report decreased quality of life, and a substantial number also have signs of depression.

More research is needed to examine potential relationships between caregivers' quality of life and how this impacts upon the quality of care they offer and the HRQoL of the people with CKD they care for. Where the quality of life of caregivers has been measured, this has generally been done using generic questionnaires designed for measuring HRQoL in the general population (e.g. the SF-36) [8]. While this approach allows results for caregivers to be compared with those for other groups, generic measures are unlikely to cover areas that are of special importance to care-

givers—for example, burden of care, feelings of guilt, financial concerns, and family responsibility and support. In addition, such measures may not distinguish between impacts related to the health of the person with CKD being cared for and the health of the caregiver themselves—many of whom may also be suffering from chronic illness.

39.6 Detailed Review of Most Common Instruments Used to Assess HRQoL in CKD

The Medical Outcomes Study Short Form 36 (SF-36) is the most widely used generic QOL instrument for CKD patients, their caregivers, and the general population. The SF-36 v 2.0 contains 36 items and covers eight domains including physical functioning, role functioning (physical), bodily pain, general health, vitality, social functioning, role functioning (emotional), and mental health. Each domain score is transformed onto a 0–100 scale and two summary scores are calculated: the physical summary score and the mental summary score. Norms for the general population in many countries are available to enable comparisons. This instrument takes about 10 min to complete and is available in several languages and many modes of administration (e.g. paper based, online, or on a tablet). Despite no specific validation of this instrument in the CKD population, numerous studies have been published using this instrument [9].

The Short Form 12 (SF-12) v2.0 is a more recent shortened version of the SF-36 instrument discussed above. It contains 12 questions to measure physical and mental health covering the eight domains in the SF-36. The instrument uses norm-based scoring that enables comparisons with the general population. One advantage of this instrument is that the responses can also be transformed into the SF-6D, a utility-based instrument for use in economic evaluations [10]. Additionally, the SF-12 is a short one-page questionnaire that takes 2–3 min to complete.

The Sickness Impact Profile measures global health status (sleep and work, eating, rest, recreation and pastimes, home management) and physical and psychosocial health domains. According to an extensive review in CKD [11], the Sickness Impact Profile shows good evidence of both reliability and validity in the ESKD population.

The EuroQol 5 dimensions (EQ-5D) is a generic instrument developed in Europe and is widely used around the world. It contains five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Originally containing three response levels per domain, it has recently been updated with five response levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) [12]. The EQ-5D also contains a visual analogue scale (VAS). The EQ VAS records the respondent's self-rated health on a vertical, thermometer-like visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The patient's score is used as a quantitative measure of health outcome as judged by the individual respondent. Advantages of the EQ-5D are its ease of completion, availability in many languages, and ability for the scores to be transformed into utilities for economic evaluation.

An example of a disease-specific HRQoL instrument is the Kidney Disease Quality of Life-Short Form (KDQOL-SF) instrument. It includes questions from the SF-36, plus an additional 43 items specific to kidney disease. The kidney-disease-specific questions include but are not limited to burden on the family; CKD symptoms such as cramps, pruritus, dry skin, and shortness of breath; dialysis access; fluid restriction; and ability to travel. A shorter version of this instrument called the KDQOL-36 is also available, which contains the same items as in the generic SF-12 along with an additional 24 questions that are kidney-disease-specific. Many dialysis centres in the USA use the KDQOL-36 as the preferred measurement tool for its ease of administration and report relatively minimal patient and staff burden.

39.7 What Should I Do to Improve HRQoL for My Patients?

Listed below are examples of interventions to improve quality of life in patients with CKD (Table 39.4) and a summary of relevant clinical practice guidelines in nephrology (Table 39.5).

Table 39.4 Summary of suggested interventions that show improved HRQoL in CKD in research studies

Intervention	Source of evidence (ungraded)
Provide information and education to meet patient/family needs	Randomised controlled trial and several observational and qualitative studies
Cognitive behavioural therapy and/or group psychosocial intervention	Randomised controlled trials
Erythropoietin to correct anaemia	Several large randomised controlled trials and cohort studies
Structured exercise programmes	Randomised controlled trials
Treatment of depression—e.g. antidepressant medication	Cohort studies
Treatment of sleep disturbance/sleep apnoea	Randomised controlled trial and several observational studies
Improved pain management	Randomised controlled trial and 2 cohort studies
Treatment of sexual dysfunction	Randomised controlled trials
Improve patient satisfaction with CKD service provision	Cohort study
Nutritional counselling (pre-dialysis)	Randomised controlled trial
Financial assistance	Few observational and qualitative studies
Home dialysis modality	Longitudinal cohort studies, several cross-sectional studies
Frequent or extended hours haemodialysis	Randomised controlled trial, several observational cohort studies
Respite care	Cohort studies
Support for travel/vacations	Several qualitative studies
Kidney or kidney/pancreas transplantation	Several cohort studies

Table 39.5 What the guidelines say you should do: HRQoL

Guideline group[a]	Guideline	HRQoL context
Kidney Disease: Improving Global Outcomes (KDIGO)	Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD)	The gastrointestinal side effects and high pill burden required to achieve normal serum phosphorus may lead to reduction in HRQoL. There is no good evidence that vitamin D, calcitriol, vitamin D analogues, or calcimimetics improve HRQoL
Caring for Australasians with Renal Impairment (CARI)	Water and fluid in pre-dialysis patients	Sodium and water retention reduces HRQoL due to nocturnal dyspnoea and fluid overload
	Duration and frequency of haemodialysis therapy	'…Blood pressure control and quality of life improved with more frequent, shorter dialysis. Patients acted as their own controls, and total weekly Kt/V was kept constant. Blood pressure control and quality of life both improved'
		'In a cohort of 83 patients, patient survival was 81% over 5 years. Compared with short thrice-weekly dialysis, nocturnal dialysis is associated with improved salt and water control, increased solute removal, improved calcium and phosphate control, and a marked improvement in quality of life'

(continued)

Table 39.5 (continued)

Guideline group[a]	Guideline	HRQoL context
	Pre-dialysis education	'Multi-disciplinary clinics and [structured pre-dialysis] education programmes may facilitate the improved medical care of patients (for example, better control of anaemia and hypertension), greater patient involvement in the selection of the mode of dialysis, a reduction in the need for "urgent start" dialysis, and improve short-term survival and quality of life after the initiation of dialysis'
	Level of renal function at which to initiate dialysis	'Compared with patients who have timely initiation, the health-related quality of life among late starters was worse during the first 6 months after initiation, but no different at 12 months'
	Timing of referral of chronic kidney disease patients to nephrology services (adult)	'A planned first dialysis resulted in a higher QoL in the first 6 months than a late start dialysis'
	Acceptance onto dialysis—ethical considerations	'An expectation of survival with an acceptable quality of life is a useful starting point for recommending dialysis'
		'The possibility that length or quality of life will not be improved by dialysis may be a relevant factor for patients and caregivers in making decisions about whether or not to start dialysis'
	Acceptance onto dialysis—quality of life	Suggestion for clinical care (based on level III and IV evidence). A discussion of the effect of dialysis on quality of life (QOL) should be included in the decision-making process for undertaking dialysis treatment. The discussion should include effect on physical function, burden of treatment, and effect on family and social life. This is best accomplished by a multidisciplinary team of appropriate health professionals
		Age alone should not be interpreted as being predictive of poorer QoL
		Poorer physical and mental health should be considered predictive of poorer QoL on dialysis
		No single QoL measure should be used to recommend acceptance or denial of dialysis
Canadian Society of Nephrology (CSN)	Use of erythropoietic stimulating agents	Anaemia is associated with reduction in QoL
European Renal Best Practice (ERBP)	Antidepressants for depression in stage 3–5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy, and safety	'In line with the current treatment guidelines, the high prevalence of depression in patients with CKD3-5 and its negative influence on survival and quality of life, active intervention seems justified'. Intervention—treatment with antidepressants
Renal Physicians Association (US)	Shared decision-making in the appropriate initiation of and withdrawal from dialysis	'Patients whose prognosis is particularly poor should be informed that dialysis may not confer a survival advantage or improve functional status over medical management without dialysis and that dialysis entails significant burdens that may detract from their quality of life'
		Providing effective palliative care: 'To improve patient-centred outcomes, offer palliative care services and interventions to all AKI, CKD, and ESRD patients who suffer from burdens of their disease'
Renal Association (UK)		*End-of-life care*: Conservative kidney management and withdrawal of dialysis—'Quality of life for patients following a conservative pathway may be comparable to that in haemodialysis patients, though data are very limited'

Table 39.5 (continued)

Guideline group[a]	Guideline	HRQoL context
National Institute for Health and Care Excellence (NICE)	Assessment and optimisation of erythropoiesis	*Benefits of treatment with erythropoiesis stimulating agents* (*ESAs*): 'Treatment with ESAs should be offered to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function'
Australia and New Zealand Society of Nephrology (ANZSN)	Renal Supportive Care Guidelines 2013—Quality of life	What constitutes a poor QOL of life varies from person to person and the potential impact of dialysis on an individual will be unique for each person
		Patients need good information in order to allow them to assess the potential impact of renal replacement therapy on their lives
		The Short Form 36 Health Survey (SF-36) QOL questionnaire is a suitable tool to be used in dialysis and non-dialysis patients to assess QOL changes

[a] *Links to guidelines*: *KDIGO* = www.kdigo.org/, *CARI* = http://www.cari.org.au/guidelines.php, *CSN* = http://csnscn.ca, *ERBP* = http://www.european-renal-best-practice.org/, *Renal Physicians Association* (*USA*) = http://www.renalmd.org/End-Stage-Renal-Disease/, *Renal Association* (*UK*) = http://www.renal.org/clinical/guidelinessection/guidelines.aspx, *ISPD* = http://ispd.org/lang-en/treatmentguidelines/guidelines, *NICE* = http://www.nice.org.uk/guidance/index.jsp?action=byType&type=2&status=3, *ANZSN* = http://onlinelibrary.wiley.com/doi/10.1111/nep.12065/pd

Before You Finish: Practice Pearls for the Clinician

- A good understanding of HRQoL measurement and interpretation is of critical importance for decision-making in modern nephrology practice. Known HRQoL estimates can be used to help patients understand the likely impact of their disease, its progression and potential treatment interventions and can help clinicians and researchers better appreciate the impact of disease and treatments in different patient groups.
- HRQoL measurement can also inform understanding of new research findings. CKD results in considerable decrement to HRQoL, which varies by stage and renal replacement therapy. Although HRQoL for different health states may be reported as an average across patient groups, it is important to understand that each patient's experience will be unique, and some side effects or interventions may impact different people to different extents.
- While several clinical practice guidelines make reference to HRQoL, there is no specific guideline focussing on HRQoL improvement. However, there is some evidence that interventions targeting specific symptoms or aimed at supporting educational or lifestyle considerations do make a positive difference to people living with CKD.

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