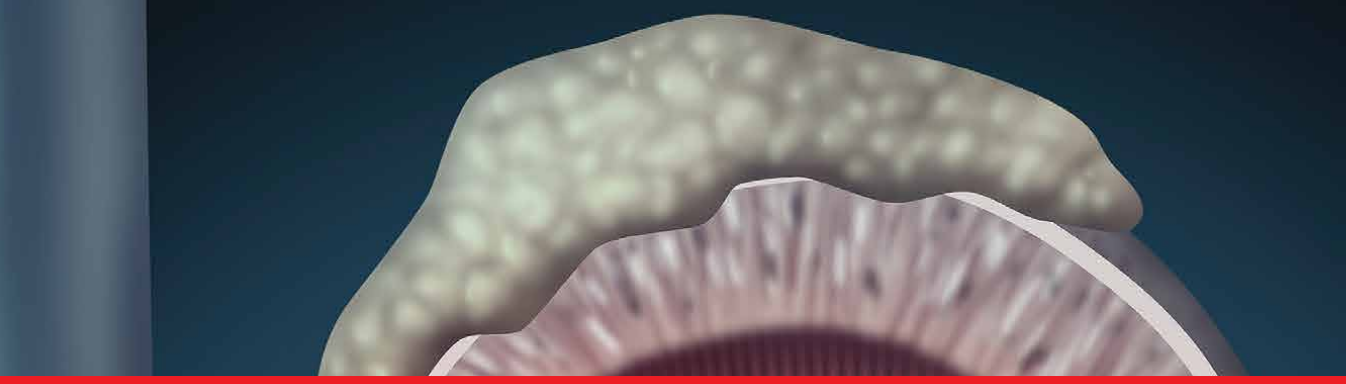

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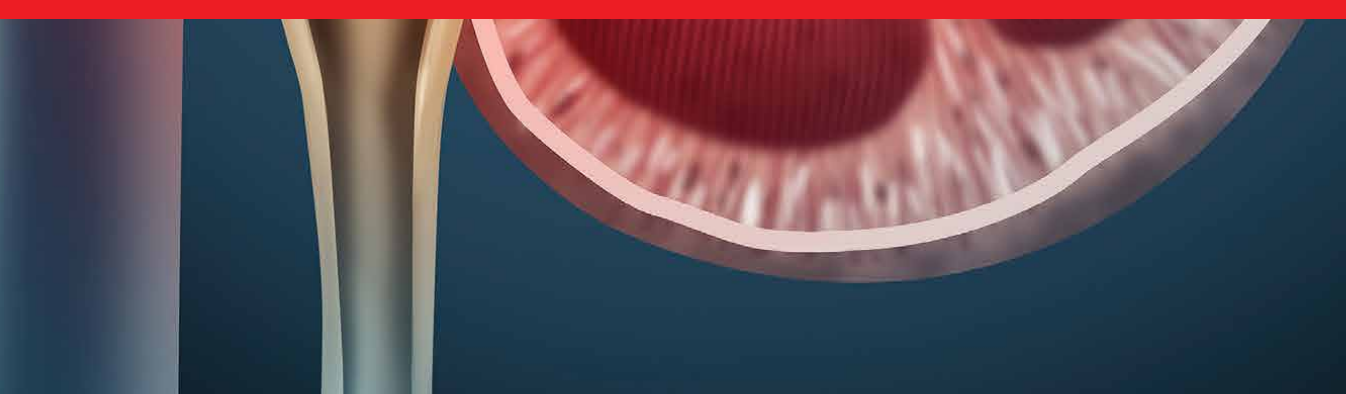
Chronic Kidney Disease

Beyond the Basics

Edited by Ane Claudia Fernandes Nunes



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Meet the editor

Dr. Ane C. F. Nunes is a geneticist with a master's degree and Ph.D. in Medical Sciences and Nephrology from the Federal University of Rio Grande do Sul (UFRGS), Brazil, with postdoctoral experiences in Renal Physiology at the Federal University of Rio de Janeiro (UFRJ), Brazil; Clinical Medicine and Nephrology at the University of São Paulo, Brazil; and Nephrology and Hypertension at the University of California Irvine, USA. She is a Professor of Medical Genetics, Human Genetics, and Molecular Biology. Her research fields are human genetic diseases, cellular and molecular biology applied to nephrology, biochemistry, and microbiology. She has worked on projects on inflammatory markers, pathology and molecular diagnosis, DNA polymorphisms, chronic kidney disease (CKD), polycystic kidney disease (PKD), Fabry disease, rare diseases, cellular and murine models for CKD, RNA processing, fluorescent image analysis, nanoparticle development, and nanomedicine.

Contents

Preface

Chronic kidney disease (CKD) is advanced renal failure, which requires renal replacement therapy in its final stage. Several disciplines in health sciences are involved in diagnosing and treating CKD. As such, this book discusses CKD from a multidisciplinary point of view. It includes four sections.

Section I: "Clinical Nephrology" includes four chapters that summarize crucial aspects for CKD patients. In Chapter 1, Olutoyin Lawal presents an updated review of cardiovascular disease in CKD patients. In Chapter 2, C. Elena Cervantes and Mohamad Hanouneh discuss diabetic kidney disease. In Chapter 3, Edwin Fernando and Subashri Mohanasundaram present an overview of palliative care in CKD. In Chapter 4, Maha Haddad presents an impressive review of the transition of clinical routine for CKD teenager patients, from pediatric to adult setups.

Section II: "Biomarkers and Molecular Biology" includes four chapters. In Chapter 5, Goce Dimeski and Oliver Treacey discuss using biochemical tests for evaluating CKD. In Chapter 6, Ludmila Milovanova et al. address the damage to cardiologic biomarkers in CKD, especially in bone and mineral disorders. In Chapter 7, Nataliia Gubina examines the role of tubulointerstitial damage biomarkers in overweight CKD patients. In Chapter 8, Hoon Chang et al. explore the relationship between vascular endothelial growth factor inhibitors and kidney disease.

Section III: "Hemodialysis and Transplantation" includes three chapters that discuss currently available renal replacement treatment options, considering transplantation as a procedure for total replacement of renal function. In Chapter 9, Hemant Mehta describes a variety of vascular access for hemodialysis patients. In Chapter 10, Shiro Fujikata describes interesting points of kidney transplantation in a patient with two distinct hereditary kidney diseases: ADPKD and MELAS. In Chapter 11, Manon Dekeyser addresses the management of immunosuppression in transplant recipient patients.

Section IV: "Basic Research and Innovation" includes four chapters that present original studies in renal disease. In Chapter 12, Eleanor Lederer et al. describe an interesting study of artificial intelligence approaches to the underpinnings of CKD and mineral bone disease. In Chapter 13, Kuljeet Singh Dhawil presents an animal model study that analyzes diagnostic biomarkers in the infectious scenario. In Chapter 14, Tessa Novic and Nidharhan Anandasivam present a study of new pharmacotherapy in diabetic nephropathy. Finally, in Chapter 15, Amel Ben Chehida et al. describe renal involvement in glycogen storage diseases.

As an editor, I am honored to have organized the studies included in this book. I thank all the authors and the staff at IntechOpen for their commitment and dedication to the project.

Ane Claudia Fernandes Nunes, Ph.D.
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Section 1

Clinical Nephrology

Chapter 1

Cardiovascular Diseases in Chronic Kidney Disease

Olutoyin Morenike Lawal

Abstract

Cardiovascular Disease in Chronic Kidney Disease. Cardiovascular Disease (CVD) is a topical issue of public health concern in Chronic Kidney Disease (CKD) Patients. Worldwide, CVDs are the leading cause of death. The burden of CKD is growing and CKD patients have been observed to develop CVD very early, contributing to the accelerated progression of the underlying kidney disease. CVD has also been found as the usual cause of death in CKD patients rather than the progression of the CKD itself. The risk factors for CKD and CVD are mutual and interwoven, hence CKD has been termed CVD risk equivalent. Early identification and intervention of CVD risk factors in CKD patients is imperative to limit the progression of disease and mitigate its attendant consequences.

Keywords: CKD, CVD, eGFR, ESRD

1. Introduction

Chronic Kidney Disease (CKD) is defined as the glomerular filtration rate (GFR) <60 ml/min/1.73m^2 or the presence of other markers of kidney damage including proteinuria or albuminuria for >3 months [1].

The kidneys are essential organs in the body; they function to filter out wastes, toxins and excess fluid. They also function as endocrine organs, producing and activating various hormones such as erythropoietin, 1, 25 dihydroxycholecalciferol, Renin angiotensin aldosterone system.

CKD is one of the non communicable diseases of public health concern. It is a cause of premature mortality, and contributes to significant morbidity and poor quality of life. It is also an independent risk factor for cardiovascular disease which is the global leading cause of premature mortality.

Stage	Description	eGFR (ml/min/1.73m^2)
Stage 1(G1)	Normal or high	≥90
Stage 2(G2)	Mildly reduced	60–89
Stage 3(G3)	Mildly to moderately reduced	45–59
Stage 3b(G3b)	Moderately to severely reduced	30–44
Stage 4(G4)	Severely reduced	15–29
Stage 5(G5)	Renal failure	<15

Abbreviations: CKD: chronic kidney disease; GFR: glomerular filteration rate.

Albuminuria stages	AER (mg/day)	Description.
A1	<30	Normal to mildly increased
A2	30 to 300	Moderately increased
A3	>300	Severely increased.

AER: albumin excretion rate.

CKD is a progressive disease and it is classified based on how well the kidney is functioning which is usually assessed by the estimated glomerular filteration rate (eGFR) and the level of protein in the urine.

GFR categories in CKD [2].

In the past, CKD staging was only limited to eGFR classification only, however albuminuria level was included to improve the prognostic value of the classification. Albuminuria greatly increases the incidence of end stage renal disease (ESRD) and has been proven to hastens the progression of CKD to ESRD [2, 3].

The essence of staging is for early detection of those with accelerated risk of renal function decline and to promptly institute treatment to halt or delay the progression.

2. Etiology of CKD

Diabetes and hypertension are the leading causes of CKD [4]. They are responsible for about 70% of the cases of CKD.

Other causes of CKD include: Glomerulonephritis, Inherited disease conditions like polycystic kidney disease, Congenital renal and urinary tract abnormality, autoimmune disease.

3. Epidemiology

The impact of kidney disease on global health is significant contributing greatly to increasing morbidity, mortality and health care costs both directly, and indirectly as an invaluable cause of cardiovascular disease (CVD).

The world wide estimated prevalence of CKD is 13.4%, 10.1% in Africa and 13.2% in sub Saharan Africa. There has been an increase in the global mortality rate of CKD [5]. The worldwide CKD mortality rate increased by approximately 40% between 1990 and 2017. In year 2017, more than 1 million people died of CKD with sub Saharan Africa recognized as one of the regions with the highest burden of the disease [4].

Early stages of CKD are asymptomatic; hence screening is important for early detection and prompt initiation of management of the disease.

The prevalence of CVD is markedly higher in CKD patients compared to the general population and it is a major contributor to premature mortality and reduced quality of care in CKD patients.

4. Symptoms

Since early stages of CKD are largely asymptomatic, diagnosis relies heavily on blood and urinary investigations. Other pointers to CKD include: hypertension, Diabetes, anemia.

5. Complications of CKD

CKD is a systemic disease and hence has numerous implications. The various complications of CKD directly or indirectly heighten cardiovascular risk hence further contributing to the adverse outcomes in CKD patients.

Increased cardiovascular risk in CKD patients is well recognized. With significant cardiovascular risks found across the various CKD stages, CKD has been termed an independent risk factor for cardiovascular disease [6]. Albuminuria greatly increases the incidence of ESRD and has been proven to hasten the progression of CKD to end stage renal disease [2, 3].

It has been well established that Cardiovascular disease such as Peripheral arterial disease, Ischemic heart disease, heart failure and stroke are unarguably commoner in CKD patients compared to the general population [7].

The various complications of CKD include: Hypertension, anemia, bone disease, heart disease, hyperlipidemia, electrolyte imbalance such hyperkalemia, hyper or hypocalcaemia, salt and water retention.

Hypertension remains one of the commonest complications of CKD [8]. Hypertension is both a cause and consequence of CKD and contributes significantly to the cardiovascular risks in CKD patients.

Anemia is defined as hemoglobin level < 13 g/dl and < 12 g/dl in men and women respectively by the WHO, [9] while the National Kidney Foundation sets a slightly higher target of <13.5 g/dl in men [10].

Anemia is a common complication in CKD patients and it develops majorly as a result of deficiency in erythropoietin synthesis. Erythropoietin is a glycoprotein produced by the kidney and plays a critical role in the formation of red blood cells. This production is significantly compromised when the kidney is damaged. Anemia plays a significant role in cardiovascular disease outcome in CKD patients contributing to IHD, left ventricular hypertrophy, fluid retention hence, worsening heart failure. and accelerating CKD progression [11]. This has formed a therapeutic target in CKD patients.

Another major function of the kidney is the regulation of calcium phosphate homeostasis, a function that is also altered when the kidney is dysfunctional. This results in disruption of this balance resulting in low calcium and excess phosphate level in the blood. Hyperphosphatemia has been established as a risk factor for cardiovascular disease, as high serum phosphate level has been associated with hypertension, vascular and cardiac calcifications, atherosclerosis, left ventricular hypertrophy and myocardial fibrosis [12].

Cardiac Disease: Various forms of cardiac diseases such as left ventricular hypertrophy, cardiac arrhythmias, cardiac valvular calcifications, IHD, heart failure, sudden cardiac death have characterized CKD outlook. Cardiac diseases are present at all CKD stages in higher proportion compared with the general population and the burden is undoubtedly higher at the advanced stages of CKD. It has been well established that cardiovascular disease rather than progression to end stage renal disease is the cause of death in majority of the CKD patients. Although, therapies to target cardiovascular diseases have been recommended, mortality outcome in CKD attributable to cardiac disease remains disproportionately high [13].

Dyslipidemia and CKD outcome: Dyslipidemia is a common complication in CKD patients and is a precursor to atherosclerosis formation. Dyslipidemia is a major modifiable risk factor for CVD in the general population and contributes significantly to the cardiovascular burden in CKD patients. Studies have shown that dyslipidemia contributes to systolic heart failure, ischemic and non ischemic cardiac dysfunction [14].

Electrolyte imbalance: The kidney functions to regulate water and electrolyte balance in the body. When there is insufficient water and electrolytes, the kidney conserves fluid as much as possible; it decreases urine output, produces concentrated urine and water intake is triggered. When there is excess, the body compensates by increasing urinary excretion.

Hyperkalemia is the most common electrolyte imbalance in CKD patients. The kidney normally excretes about 90% of the serum potassium. Hyperkalemia can trigger a life threatening arrhythmia that can result in cardiac arrest [15]. Disordered metabolism of sodium, calcium and magnesium are other important electrolyte derangement of great impact in CKD patients and they worsen outcomes in these patients [16].

Abnormal fluid status is a common finding in CKD patients with fluid overload being a major presentation in advanced CKD patients. Assessment of fluid status in CKD patients remains challenging. Various technologies to objectively evaluate fluid level to support the clinical examination method still prevalently utilized are being recommended for better assessment and improved management [17]. Fluid overload in CKD patients is associated with hypertension, LVH, heart failure, pulmonary edema [18].

The complications of CKD ultimately culminate in worsened cardiovascular outcomes and premature mortality in these patient group [19].

6. Markers in CKD

The high incidence of various cardiovascular complications in CKD patients have been linked with several pathophysiological pathways. Over the years, there have been concerns about the possible utility of markers to improve and enhance the diagnostic, prognostic and therapeutic accuracy of CVD in CKD patients. Although, this has been met with divergent viewpoints, a combination of biochemical and cardiac markers rather than any single one have been suggested as likely useful prognostic tools in these patients [20]. Some of the markers of interest include: Natriuretic peptides, Cardiac troponins, inflammatory cytokines, Fibroblast growth factor 23 (FGF 23), Asymmetric Dimethylarginine (ADMA).

Natriuretic Peptide: Studies have shown that B type natriuretic peptide (BNP) and amino – terminal pro B type natriuretic peptide (NT- proBNP) are useful markers in early identification and risk prediction of cardiac disease. Plasma BNP levels have been shown to increase progressively with declining renal function, and natriuretic peptides have shown significant correlation with heart failure severity, ischemic heart disease prevalence and left ventricular dysfunction in CKD patients [20].

Cardiac Troponins: Coronary artery disease is a frequent finding in CKD patients and is the leading cause of morbidity and mortality in them. The traditional risk factors in CKD patients accelerate atherosclerosis formation thus contributing to the high prevalence of Ischemic heart disease found in these patients [21]. Troponins T (cTnT) and I (cTnI) are useful markers of cardiac injury. They have been found to be elevated in CKD patients and are useful predictor of mortality in them [22].

CKD has been recognized as a chronic inflammatory condition with production of reactive oxygen species and other proinflammatory substances through various pathophysiologic mechanisms. The ongoing persistent inflammatory state in CKD patients has been associated with cardiovascular and all cause mortality. Various factors catalyzing the inflammatory state in CKD patients include: increased generation

and reduced clearance of reactive oxygen species and inflammatory cytokines, metabolic acidosis, impaired metabolism of adipose tissue and recurrent infections [23]. Raised Interleukin 6 (IL – 6), C reactive protein (CRP), Tumor Necrosis Factor alpha (TNF) are some of the inflammatory markers that have been reported in CKD patients, they predict CKD severity and have prognostic implications for cardiovascular diseases [24].

Calcium Phosphorus homeostasis is critical in human physiology. This delicate balance is disrupted in CKD. Vitamin D activation is impaired with kidney disease and serum phosphate excretion is disrupted resulting in low blood calcium and elevated serum phosphate. FGF 23 is a phosphorus regulating hormone. Studies have shown that high levels of FGF 23 is an independent predictor of mortality and is associated with worsening of CKD progression and cardiovascular complications [25].

ADMA is an endogenous inhibitor of nitric oxide synthase. Its presence implies reduced production of nitric oxide (NO). Nitric oxide maintains endothelial function via its vasodilatory and anti inflammatory properties. Raised ADMA levels have been found in CKD patients and is associated with endothelial dysfunction, atherosclerosis, and ultimately CVD [26].

7. Treatment

Since CKD is largely asymptomatic at inception, preventive measures and regular screening are necessary strategies to minimize its incidence and prevalence.

Healthy lifestyle is recommended. Exercise has been found to play a critical role in blood pressure and blood glucose control; it keeps body weight in check and prevents obesity. It is a very important tool in cardiovascular risk reduction [27].

Hypertension: The current KDIGO blood pressure recommendation suggests a target systolic blood pressure of <120 mmHg. This is in view of the recent evidence of enormous cardiovascular benefits that is associated with lower blood pressure reduction in high risk groups such as CKD patients [28]. Both lifestyle adjustment and pharmacological approach to blood pressure control are required to achieve optimal blood pressure control.

Blood glucose control should be individualized and tailored to individual need and target HBAic of between 6.5 and 8% has been recommended [29].

Anemia: Treating anemia with erythropoietin to a safe target of between 11 and 12 g/dl has been recommended. Values higher than this has been associated with increase morbidity and mortality [30].

Hyperphosphatemia: Owing to the association of excess phosphate level to adverse cardiovascular outcomes in CKD patients, reducing the blood phosphate levels has been considered a promising therapeutic target that might improve the prognosis of CKD patients [13]. Currently dietary and pharmacological approaches aimed at this reduction are being employed [13].

Cardiac disease: various lifestyles and pharmacologic agents have been established to improve outcome however, studies are still ongoing to ensure better and improved prognoses in CKD patients as current data still shows excess premature mortality in CKD patients attributable to cardiac complications.

Dyslipidemia: There are various means of reducing serum lipid and its effect on cardiovascular outcome especially in CKD patients. While the role of dietary control in dyslipidemia cannot be undermined, statins have been established as pharmacologic agents of choice in the treatment of dyslipidemia in CKD patients [31].

Diuretics are prescribed to eliminate excess fluid and provide symptomatic relief to fluid overload in CKD patients.

8. Conclusion

The burden of CKD is enormously huge and its impact and contributions to premature mortality, morbidity and economic loss is quite concerning. Healthy lifestyle measures should be adopted early as preventive measures and to limit CKD progression when present, prompt screening, diagnosis and early initiation of treatment of the risk factors when required will go a long way to improve outcomes of CKD.

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Chapter 2

A New Era in Diabetic Kidney Disease

Carmen Elena Cervantes and Mohamad Hanouneh

Abstract

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) worldwide, and its rising prevalence explains the significant increase in the number of patients receiving renal replacement therapy. Additionally, CKD represents a major cause of morbidity and mortality in patients with diabetes. Hyperglycemia is the cardinal feature that leads to diabetic nephropathy. In fact, elevated glucose levels initiate several inflammatory and metabolic pathways that result in activation of the renin angiotensin aldosterone system (RAAS) and dysregulation of the tubuloglomerular feedback (TGF). For decades, the standard of care to prevent or delay the progression of diabetic kidney disease has included RAAS inhibitors and optimal blood pressure and glycemic control. Fortunately, newer medications have joined the armamentarium of drugs against diabetic nephropathy. Specifically, we will review sodium glucose cotransporter 2 inhibitors (SGLT2is) and the selective mineralocorticoid receptor antagonist (MRA), finerenone, which have proven to decrease the progression of diabetic kidney disease and cardiovascular risk.

Keywords: cardiovascular disease, chronic kidney disease, diabetes mellitus, sodium glucose cotransporter 2 inhibitors, selective mineralocorticoid receptor antagonists

1. Introduction

The global burden of chronic kidney disease (CKD) was estimated to be 10–15% in 2017, which accounts for 850 million people living with this condition worldwide [1, 2]. In 2021, the Centers for Disease Control and Prevention (CDC) established that approximately one in seven adults have CKD in the United States [3]. The most common cause of CKD is in fact diabetes.

Another pressing statistic is the mortality attributed to kidney disease. In 2017, CKD ranked as the 12th leading cause of death [1]. However, besides its direct impact in morbidity and mortality, kidney disease is also an independent risk factor for cardiovascular events [4]. Globally, CKD accounted for 61.3 million disability-adjusted life-years (DALYs) with 41.6% of those being directly attributed to cardiovascular disease. DALYs mainly resulted from ischemic heart disease, stroke, and peripheral artery disease [1]. Further, a rising CKD population leads to a higher number of patients with end-stage kidney disease (ESKD). It has been predicted that the incidence of ESKD will increase

from 11 to 18% between 2015 and 2030 [5]. These trends, together with higher cardiovascular disease, will intensify the burden on healthcare systems.

2. Epidemiology

Diabetes stands as the primary cause of CKD contributing to approximately half of the cases [6]. Currently, diabetes affects roughly 460 million persons worldwide with a projected increase to around 580 and 700 million cases by 2030 and 2045 respectively [7, 8]. It was estimated that 10.5% of the US population had diabetes in 2018, with a projected increase to 14% by 2030 [9, 10].

Clustering of diabetes and diabetic kidney disease (DKD) has been observed among specific racial and ethnic groups. As such, African Americans, Native Americans, and Latinx have higher prevalence of diabetic nephropathy compared with Caucasians. This is explained not only by epigenetic factors associated with the environment and access to care but also by a genetic component [11]. Although, DKD does not represent a simple Mendelian inheritance, several genes have been identified as potential candidates that may differ between populations. This includes the glucose transporter 2, transforming growth factor β, APOL1, and endothelial nitric oxide synthase genes. Further, studies suggest a relationship between polymorphisms of the angiotensin converting enzyme (ACE) gene and DKD. Specifically, there is evidence that ACE gene may play a role in determining which patients may respond to renin angiotensin aldosterone system (RAAS) blockade therapy [12].

3. Pathophysiology and clinical course

Even though the pathogenesis of DKD involves several hemodynamic and metabolic disorders, hyperglycemia is the cardinal feature of diabetic nephropathy. Elevated blood glucose leads to activation of many biochemical pathways resulting in increased oxidative stress, advanced glycation end-products (AGE), cytokine and growth factor release, and hormonal imbalance [12]. Collectively, these factors affect glomerular endothelial, mesangial, tubular and epithelial cells, or podocytes [11].

Renal hemodynamic changes happen with diabetes onset. Even in the absence of hypertension, animal models have shown an elevated intraglomerular pressure that is mediated by angiotensin II and endothelin [13]. The main mediators between the metabolic and hemodynamic pathways are the transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) [11].

Angiotensin II is a potent hemodynamic and growth factor mediator. It increases sodium reabsorption and volume expansion in the proximal and distal nephron. In the proximal tubule, angiotensin II directly activates the sodium-hydrogen transporter, thereby increasing proximal sodium reabsorption. In addition, angiotensin II acts on the zona glomerulosa in the adrenal cortex and stimulates the release of aldosterone, which in turn increases distal sodium reabsorption and potassium excretion. Further, this vasoactive hormone causes systemic vasoconstriction through G-protein-coupled receptors. In the glomeruli, the afferent and efferent arteriole resistance increases in response to angiotensin II, although there is a greater effect in the efferent one [14]. Lastly, as a growth factor, this hormone affects the proximal tubular and the mesangial cells through direct and indirect pathways [15].

The role of angiotensin II in the tubuloglomerular feedback (TGF) is worth discussing separately. As shown in **Figure 1**, TGF is an autoregulatory mechanism within each single nephron, where specialized cells that belong to the juxtaglomerular apparatus (JGA) interact to maintain glomerular filtration rate (GFR). The JGA is formed by the macula densa, which is located between the ascending limb of the loop of Henle and the distal tubule, the juxtaglomerular cells of the afferent and efferent arterioles, and the mesangial cells. The macula densa senses distal tubular NaCl concentration. In states of reduced NaCl delivery, the macula densa releases renin resulting in efferent arteriole vasoconstriction [mediated by angiotensin II] and afferent arteriole vasodilation [mediated by a decrease in adenosine, which is a renal vasoconstrictor]. Therefore, in states of volume depletion with resulting decreased distal NaCl delivery, the net effect is an increase in single nephron GFR. In contrast, increased distal NaCl delivery decreases renin levels and stimulates the release of adenosine, which reduces single nephron GFR. **Figure 1** shows the normal physiology of the tubuloglomerular feedback [12].

The diabetic milieu alters the tubuloglomerular feedback due to an increased activity of the sodium–glucose cotransporter 2 (SGLT2) in the proximal tubule. Proximal reabsorption of Na+ and glucose via sodium glucose cotransporter 2 leads to a decreased distal delivery of NaCl, which in turn increases single nephron GFR (SNGFR) and leads to hyperfiltration as shown in **Figure 2** [12].

DKD is characterized by different phases. Hyperfiltration is the initial stage and is followed by proteinuria in most cases and a subsequent decline in GFR secondary to a loss of nephron mass [16].

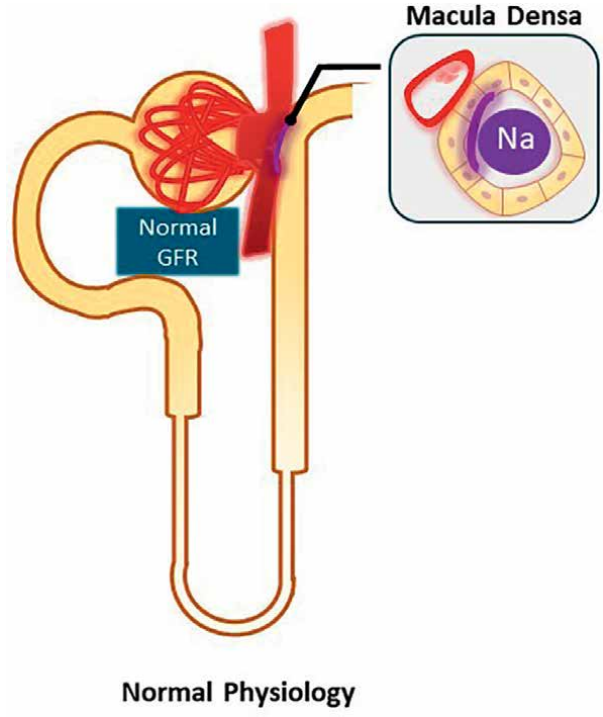

Figure 1.
Tubuloglomerular feedback. This autoregulatory mechanism is present within each single nephron. The macula densa, located in the distal nephron, senses tubular NaCl concentration and regulates the diameter of the renal arterioles to maintain GFR.

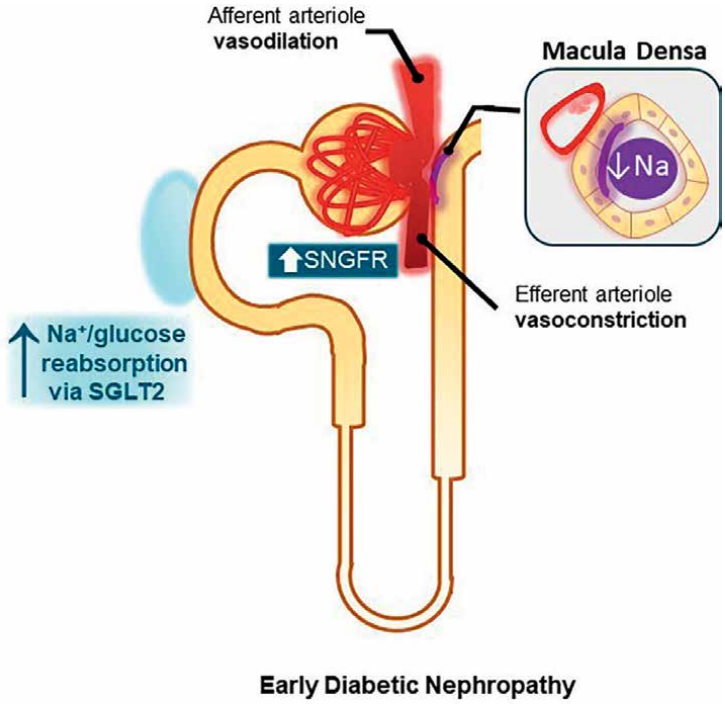

Figure 2.
Pathogenesis in diabetic nephropathy. In diabetes, there is an increased activity of the sodium glucose cotransporter 2 (SGLT2). This results in higher proximal NaCl reabsorption leading to a decreased distal delivery of NaCl. This is followed by a release of renin from the juxtaglomerular apparatus, RAAS activation with vasoconstriction of the efferent arteriole, and a decrease in adenosine that causes afferent arteriole vasodilation. The net effect is an increase in single nephron GFR (SNGFR).

Hyperfiltration is defined as a GFR of at least two standard deviations above the mean GFR from its nondiabetic counterparts. It can be present in 10–67% of patients with type 1 and 6–73% of those with type 2 diabetes [11]. Hypertension and obesity frequently coexist with diabetes and contribute to glomerular hyperfiltration by causing glomerular enlargement [17, 18]. This results in increased renal plasma flow, glomerular capillary hyperperfusion, and higher glomerular transcapillary hydrostatic pressure gradient, which collectively lead to an increase in GFR.

The structural lesions of DKD start with thickening of the glomerular basement membrane followed by mesangial expansion and podocyte damage [19–21]. These changes lead to defects in selective glomerular capillary permeability, albuminuria, and protein extravasation into the mesangium. In fact, segmental mesangiolysis and Kimmelstiel-Wilson nodules are signs of progression of DKD [22, 23]. Interstitial fibrosis and glomerulosclerosis eventually take place manifesting as a decline in GFR [24, 25].

The presence of proteinuria in DKD is the single biggest predictor of CKD progression. Approximately 25% of patients with type 2 diabetes develop moderate albuminuria by 10 years [26]. Further, any degree of albuminuria also increases cardiovascular risk in this population [27–29]. It is important to note that roughly 20% of patients with diabetes develop DKD in the absence of albuminuria, and they have shown slower rates of CKD progression [30–32].

4. Diagnosis

Diabetic nephropathy is usually identified after 5 years of diagnosis of type 1 diabetes. Because type 2 diabetes is recognized later in life and tends to be accompanied by elevated blood pressure and poor glycemic control, DKD may be evident at the time of diabetes diagnosis. Despite the differences in timing of recognition of kidney impairment, the clinical manifestations are similar in both types of diabetes [11]. Importantly, only 30–40% of patients with diabetes develop DKD, so nondiabetic glomerulopathies should also be considered in this population [33].

The natural history of DKD and the presence of other microvascular complications, such as retinopathy and/or neuropathy, can help determine the likelihood of kidney involvement. Among those, diabetic retinopathy has perhaps been the most widely used clinical feature. In fact, a population-based study in Wisconsin reported retinopathy in 98% of patients with type 1 diabetes mellitus (DM) compared with 78% of those with type 2 DM by 15 years [34, 35]. Further, in a meta-analysis of 2012 patients, the pooled positive predictive value of diabetic retinopathy for DKD was 0.72 (95% CI 0.68–0.75), while the negative predictive value was 0.69 (95% CI 0.67–0.72) [36]. In other words, diabetic retinopathy is concordant with diabetic nephropathy in almost all patients with type 1 diabetes, but it is less frequent in those with type 2 diabetes.

In regard to diabetic neuropathy, the correlation is less clear. The European Diabetes (EURODIAB) Prospective Complications Study showed that 23.5% of persons with type 1 DM had developed neuropathy by 7 years [37]. Other studies have reported that up to 50% of patients with types 1 and 2 diabetes have diabetic peripheral neuropathy [38].

However, it is important to highlight that the prevalence of nondiabetic kidney disease (NDKD) may vary between 10 and 85% depending on the study [39–41]. For example, a review of 233 kidney biopsies performed in persons with diabetes identified NDKD in 53% of the cases. The most common conditions observed included focal segmental glomerulosclerosis, minimal change disease, IgA nephropathy, and membranous glomerulonephritis [40].

Therefore, it is of utmost importance to identify when to pursue a kidney biopsy, which remains the gold standard for diagnosis. In general, a biopsy is indicated in the following clinical settings: nephrotic range proteinuria or GFR decline in the absence of diabetic retinopathy, onset of proteinuria less than 5 years from the diagnosis of type 1 diabetes, nephrotic range proteinuria with normal kidney function, active urinary sediment, such as microscopic hematuria, rapid decline in kidney function in patients with previously stable CKD [11].

5. Treatment—Standard of care

The treatment of DKD is focused on four major pillars: cardiovascular risk reduction, blood pressure and glycemic control, and inhibition of the renin angiotensin aldosterone system (RAAS). Cardiovascular risk reduction is achieved by proper blood pressure and glycemic control, management of dyslipidemia, and smoking cessation [11].

5.1 Blood pressure control

Blood pressure goals in patients with diabetes have been highly debated. The Action in Diabetes and Vascular Disease: PreterAx and Diamicron-MR Controlled Evaluation

(ADVANCE) trial showed a 21% risk reduction of kidney endpoints with systolic blood pressure levels below 135 mmHg compared with those values ~140 mm Hg [42]. Further, a review of studies showed that less GFR decline is achieved at a mean arterial pressure of 89 mm Hg (equivalent to a systolic blood pressure of 120 mm Hg and a diastolic of 75 mm Hg) [43].

The KDIGO guidelines recommend a blood pressure goal below 140/90 mmHg for DKD and a lower goal below 130/80 mmHg in the presence of albuminuria [44].

5.2 Glycemic control

Optimal glycemic control reduces CKD progression, cardiovascular events, and death. Most studies focus on targeting the hemoglobin A1c (HbA1c) since it is a surrogate of the 3-month average blood glucose. However, data have also shown that glucose variability predicts worse kidney and cardiovascular outcomes [45].

In patients with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) showed that intensive glycemic control (goal HbA1c < 6.05%) conferred a lower risk for the development of microalbuminuria by 39% and by 56% for overt proteinuria. Importantly, the median HbA1c concentration was 9.1% in the conventional group compared with 7.3% in the intensive group. Other microvascular complications were also lower in the intensive control arm [46].

In regard to patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) showed a 33% reduction in albuminuria in the group that achieved a median HbA1c of 7% compared with 7.9% in the conventional arm [47].

Further studies addressing whether lower A1c goals would have an additional benefit have shown mixed results. The ADVANCE, Action to Control Cardiovascular Risk in Diabetes (ACCORD), and VA Diabetes Trial (VADT) targeted and achieved HbA1c levels of ~6.0% compared with a control arm of ~7.0% [48–50]. ADVANCE trial showed positive kidney outcomes but no difference in cardiovascular events [48]. Contrarily, ACCORD and VADT established no cardiovascular or kidney benefit [49, 50].

Taking all this information together, the KDIGO guidelines recommend an individualized HbA1c target ranging from < 6.5 to < 8% [44].

5.3 Renin angiotensin aldosterone blockade

RAAS blockade has been the single most effective therapy for slowing the progression of DKD for decades, and it has been studied across all stages of diabetic nephropathy. As explained in the pathogenesis, RAAS is activated in diabetic nephropathy resulting in vasoconstriction of the efferent arteriole, which plays a role in increasing SNGFR. **Figure 3** shows the nephroprotective effect of RAAS [12].

In initial stages when albuminuria has not occurred, the use of RAAS inhibitors is controversial. In fact, studies conducted in patients with Type 1 diabetes have failed to show that RAAS blockade prevents the development of microalbuminuria, although this was a secondary endpoint [51, 52]. On the other hand, the Bergamo Nephrologic Diabetes Complications (BENEDICT) and the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) Trials showed that therapy prevented or delayed the development of microalbuminuria independent of blood pressure reduction [53, 54]. In 2016, a meta-analysis of 16921 patients further confirmed a potential role for RAAS blockade in the prevention of DKD, establishing a 16% risk reduction of development of microalbuminuria in patients with type 2 diabetes [55]. In regard to the cardiovascular risk associated to diabetes, the Health Outcomes and Prevention

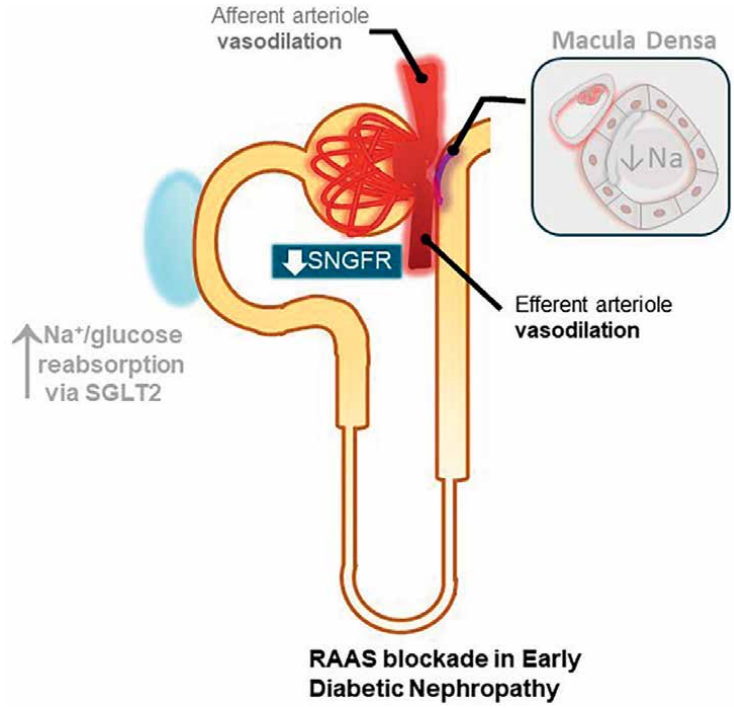

Figure 3.
Hyperfiltration in early diabetic nephropathy with concomitant RAAS blockade. Angiotensin II is a potent vasoconstrictor of both renal arterioles but predominantly of the efferent one. Therefore, Renin Angiotensin Aldosterone System (RAAS) blockade results in vasodilation of the efferent arteriole and decreases single nephron GFR (SNGFR).

Evaluation (HOPE) study established that ACE inhibition decreased the risk of cardiovascular death, stroke, and myocardial infarction in patients with and without kidney disease [56]. Overall, RAAS blockade appears to play a role in prevention of DKD and cardiovascular protection irrespective of nephropathy. It is worth mentioning that current guidelines do not yet recommend it for the prevention of DKD [44].

Once hyperfiltration ensues and microalbuminuria develops, patients are at risk for transitioning from microalbuminuria to overt proteinuria. The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) trial showed a dose-dependent effect favoring the use of irbesartan over placebo for the development of overt proteinuria, which was defined as ACR > 200 mg/day [57]. Similarly, in the Irbesartan Diabetic Nephropathy Trial (IDNT), RAAS blockade had superior kidney outcomes, independent of the effect on blood pressure, when compared with both the amlodipine and the placebo groups [58].

Maintaining RAAS blockade during the last stage of DKD where there is a progressive decline in GFR is still recommended. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed a 25% risk reduction of doubling of serum creatinine, 28% reduction of risk of ESKD, and 16% reduction in the composite endpoint, which was defined as doubling of serum creatinine or ESKD or death after 3.4 years of follow-up. Moreover, the therapy group showed 35% reduction of proteinuria assessed as secondary endpoint [59].

Another important clinical question is whether dual blockade of the RAAS provides additional benefit. Landmark trials including the ONTARGET, VA

NEPHRON-D and the ALTITUDE presented safety concerns due to significant rates of hyperkalemia, kidney injury, or hypotension [60–62]. Collectively, these studies suggest avoiding dual blockade of the RAAS system in type 2 diabetes.

The twenty-first century began with this overwhelming evidence favoring the use of RAAS inhibitors across all clinical phenotypes of DKD. Unfortunately, the prevalence of RAAS blockade agents use decreased from 45% in 2006–2008 to 36% in 2012–2014 [63].

6. Novel therapies for diabetic kidney disease

6.1 Glucagon-like peptide (GLP-1) receptor agonists

GLP-1 receptor agonists, also called incretins, are part of the arsenal of medications for the treatment of diabetes since 2005. However, only since 2019 an oral formulation has been available and approved by the FDA. GLP-1 receptor agonists initially gained popularity because of their ability to induce weight loss. They act by stimulating glucose-dependent insulin secretion and decrease glucagon secretion, gastric emptying, and appetite [64].

Another positive effect of GLP-1 receptor agonists is their cardiovascular protection. A meta-analysis of 56,004 patients with diabetes showed a significant 12% relative risk reduction in major adverse cardiovascular events [65]. In 2021, the Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes (AMPLITUDE-O) trial showed a 27% risk reduction of incident major adverse cardiovascular events in the efpeglenatide group. Even though the kidney outcomes were a secondary endpoint, a composite kidney outcome of decrease in kidney function or macroalbuminuria was 32% lower in the medication arm [66].

6.2 Sodium glucose cotransporter 2 inhibitors (SGLT2is)

The sodium glucose cotransporter 2 is responsible for the uptake of roughly 90% of glucose and majority of the sodium that is reabsorbed in the proximal tubule [12].

It has been shown that SGLT2is significantly reduce the renal threshold for glucose excretion from ~10 mmol/l (180 mg/dl) to ~ 1.2 mmol/L (21 mg/dL) in diabetic and to ~2 mmol/L (37 mg/dL) in nondiabetic subjects [67]. As a result, a better glycemic control addresses hyperglycemia, which is the main driving factor of the diabetic milieu. It is worth mentioning that glucose uptake by kidney cells is not insulin-dependent, so the effect of SGLT2is is present even in states of insulin deficiency [12].

In addition to their effect on glucosuria, the benefits of the SGLT2is result from their natriuretic action and the restoration of the tubuloglomerular feedback. The increased distal delivery of sodium ameliorates the altered TGF characteristic of diabetic nephropathy by decreasing SNGFR, hyperfiltration, and intraglomerular pressure as shown in **Figure 4** [68].

Cardiovascular outcome trials with SGLT2is inhibitors, although not powered for secondary (renal) endpoints, showed beneficial renal effects by 40–70% [69–72]. Notably, all these studies included patients with CKD, but most of them had early, if any, kidney disease. The Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes (EMPA-REG OUTCOME) trial included subjects with a mean eGFR of 74 mL/min/1.73 m^2, and 60% of the patients enrolled did not have albuminuria [69, 70]. Further, the Canagliflozin Cardiovascular Assessment Study (CANVAS)

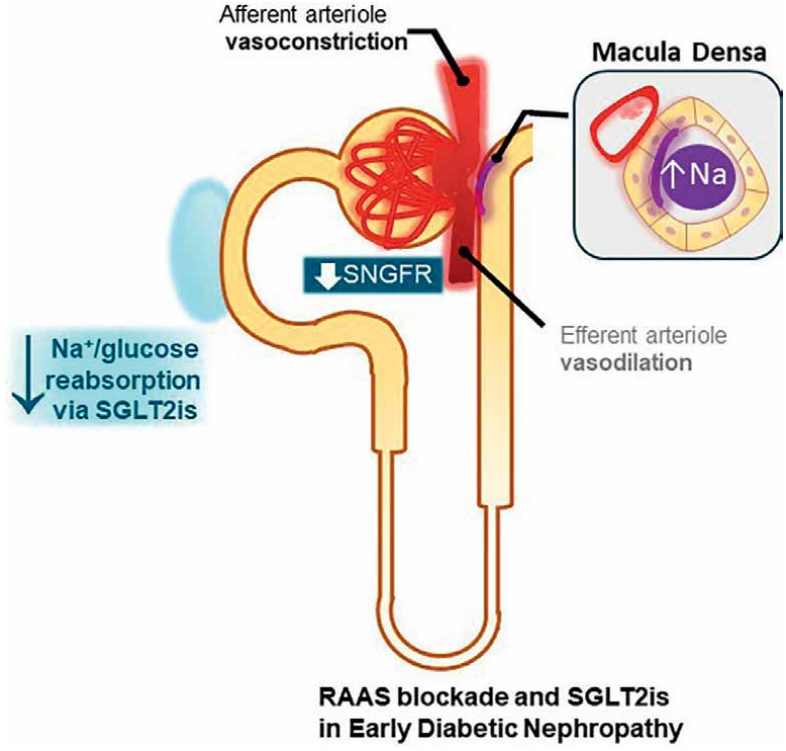

Figure 4.
Effect of RAAS blockade and SGLT2is in diabetic nephropathy. Sodium glucose cotransporter 2 inhibitors (SGLT2is) increase the distal delivery of NaCl to the macula densa, thereby restoring the tubuloglomerular feedback. Renin angiotensin aldosterone system (RAAS) blockade decreases single nephron GFR (SNGFR) through vasodilation of the efferent arteriole; however, the effect of SGLT2is lowers SNGFR further through vasoconstriction of the afferent arteriole.

observed patients with a mean eGFR of 76.5 mL/min/1.73 m^2 and a median UACR of 12 mg/g [71]. Similarly, the Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) included patients with a mean eGFR of 85 mL/min/1.73 m^2 while UACR data was not provided [72].

The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) was the first study to establish primary renal endpoints. It included patients with stage 3 CKD with a mean eGFR of 56 mL/min/1.73 m^2 and a median UACR of 927 mg/g. The CREDENCE trial showed a significant 30% risk reduction in the composite renal outcome without significant adverse events. This trial led to the FDA approval of canagliflozin for DKD [73].

In 2020, the Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trial showed a 39% risk reduction of the primary composite renal outcome in the dapagliflozin arm. Of note, the positive effect was observed across all subgroups including those with and without diabetes. The mean eGFR in this study was 43 mL/min/1.73 m^2 with a median UACR of 965 mg/g [73].

Neither CREDENCE nor DAPA-CKD showed an increased risk of amputations, hyperkalemia, or hypoglycemia. However, CREDENCE showed a significantly higher risk of diabetic ketoacidosis in the canagliflozin group. This was not observed in the DAPA-CKD [73, 74]. In addition, patients treated with dapagliflozin developed more urinary tract infections and genital infections compared with placebo.

Randomized controlled trials with dedicated kidney outcomes have shown that SGLT2is are beneficial and safe in patients with CKD and proteinuria, regardless of diabetes status [73, 74]. Even though the majority of patients from the cardiovascular outcome trials included patients without proteinuria, subgroup analysis was not provided [69–72]. Notably, the lowest GFR studied thus far is 20 mL/min/1.73 m^2 in the EMPEROR- reduced trial, which also showed positive secondary kidney endpoints [75]. Finally, an ongoing clinical trial, The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) with primary renal and cardiovascular outcomes also enrolled patients with an eGFR $\geq$ 20 mL/min/1.73 m^2. [NCT03594110]

Table 1 summarizes trials of SGLT2is and selective mineralocorticoid receptor antagonist in DKD patients.

Nonetheless, it is still recommended to avoid STGL2is in patients with recurrent genito-urinary tract infections, patients with urinary bladder catheterization or

Trial	Patient population	Intervention	Primary endpoint	Follow-up (median, years)	Results
EMPA-REG OUTCOME (2015)	N = 7020 T2DM and CVD GFR> 30 No UACR criteria 60% had a UACR < 30	Empagliflozin vs Placebo	MACE	3.1	Primary outcome: HR 0.86, 95% CI: 0.74–0.99 Secondary (renal) outcome: Incident or worsening nephropathy 39% lower in the empagliflozin group HR 0.61; 95% CI: 0.53–0.70
CANVAS (2017)	N = 10,142 T2DM and CVD GFR $\geq$ 30 No UACR criteria 70% had a UACR < 30	Canagliflozin vs Placebo	MACE	2.4	Primary outcome: MACE: HR 0.86, 95% CI: 0.75–0.97 Secondary (renal) outcomes: Composite 40% reduction in GFR, renal replacement therapy or death from renal causes: HR 0.60; 95% CI, 0.47 to 0.77 Progression of albuminuria HR 0.73, 95% CI: 0.67–0.79
CREDENCE (2019)	N = 4401 T2DM GFR 30–90 UACR 300–5000 Maxim tolerated RAS blockade	Canagliflozin vs Placebo	Composite of ESKD, doubling of serum creatinine, or kidney/CV related death	2.6	Primary outcome: HR 0.70, 95% CI: 0.59–0.82

Trial	Patient population	Intervention	Primary endpoint	Follow-up (median, years)	Results
DECLARE-TIMI 58 (2019)	N = 17,160 T2DM and CVD GFR ≥ 60 No UACR criteria	Dapagliflozin vs Placebo	MACE; Composite CV death or hospitalization for HF	4.2	Primary outcome: MACE: HR 0.93, 95% CI: 0.84–1.03 Composite CV death or hospitalization for HF HR 0.83, 95% CI: 0.73 – 0.95 Secondary (renal) outcome: Composite of >40% decrease in GFR to < 60 ml/min, ESKD, or renal death: HR 0.53, 95% CI: 0.43–0.66
DAPA-CKD (2020)	N = 4304 T2DM: 67% GFR 25 to 75 UACR 200 to 5000	Dapagliflozin vs Placebo	Composite of sustained decline in GFR of at least 50%, ESKD, or death from kidney or cardiovascular causes	2.4	Primary outcome: HR 0.61, 95% CI: 0.51–0.72 Primary outcome according to subgroups: T2DM: HR 0.64 (95% CI: 0.52–0.79) No T2DM: HR 0.50 (95% CI: 0.35–0.72)
EMPEROR-REDUCED (2020)	N = 3730 HFrEF GFR ≥ 20 No UACR criteria	Empagliflozin vs Placebo	Composite of CV death or hospitalization for HF	1.3	Primary outcome: HR 0.75, 95% CI: 0.65–0.86 Secondary (renal) outcomes: Mean slope of change in GFR (hierarchical testing): HR 1.73 (95% CI: 1.10–2.37) Composite renal outcome: HR 0.50 (95% CI: 0.32–0.77)
FIDELIO-DKD (2020)	N = 5734 T2DM GFR 25 to 75 UACR 30 to 5000	Finerenone vs Placebo	Composite of kidney failure, a sustained GFR decrease of at least 40%, or death from renal causes	2.6	Primary outcome: HR 0.82; 95% CI: 0.73–0.93 Secondary outcome: Reduction in UACR: HR 0.69; 95% CI: 0.66–0.71

MACE: Major Advere Cardiovascular Events, T2DM: Type 2 Diabetes Mellitus, CVD: Cardio Vascular Disease, and HFrEF: Heart Failure with reduced Ejection Fraction, GFR: Glomerular Filtration Rate (mL/min/1.73 m^2), UACR: Urine Albumin to Creatinine Ratio (mg/g).

Table 1.
Recent chronic kidney disease randomized clinical trials of SGLT2is and selective mineralocorticoid receptor antagonist.

suprapubic catheters, or when there is a concern for volume depletion or prolonged fasting.

6.3 Selective mineralocorticoid receptor antagonists

Aldosterone binds to the mineralocorticoid receptor (MR) of principal cells in the cortical collecting duct of the kidney and activates the epithelial sodium channel (ENaC), which will regulate salt excretion, extracellular volume, and blood pressure. MR is also present in nonepithelial cells such as cardiomyocytes, endothelial cells, vascular smooth muscle cells, mesangial cells, and podocytes. Importantly, cortisol also has high affinity to MR in nonepithelial cells due to the lack of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD-2), which converts cortisol to cortisone, the nonactive form. Activation of the mineralocorticoid receptor stimulates the formation of reactive oxygen species, endothelial exocytosis, and adhesion. These sequences stimulate an *inflammatory* response in adipocytes that contributes to insulin resistance by increasing oxidative stress. Lastly, inflammation can eventually lead to fibrosis and remodeling in multiple organs including the heart, vasculature, and kidneys [76].

As such, a novel selective MR antagonist has also been added to the armamentarium against DKD. Finerenone and eplerenone are selective MR antagonists. However, finerenone is equally saturated in the kidneys and heart tissues, while eplerenone is more saturated in the kidneys. Spironolactone is a nonselective MR antagonist, which is also more saturated in the kidneys and can bind with the estrogen receptors in the mammary glands causing gynecomastia. By the end of 2020, the Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) trial showed promising renal outcome. Finerenone had a significant 18% reduction of a primary composite of kidney failure, sustained decreased of at least 40% in eGFR, and death from renal causes. Further, it showed a 31% greater reduction in albuminuria by month 4 compared with placebo [77].

In FIDELIO-DKD trial, the incidence of all serious adverse events was similar in both groups; however, the incidence of hyperkalemia leading to discontinuation of the trial regimen was higher in the finerenone group compared with placebo (2.3% vs. 0.9%, respectively) [77].

The positive kidney and cardiovascular outcomes seen in the FIDELIO-DKD persisted irrespective of SGLT2 inhibitor status [78].

7. Conclusions

The major therapeutic breakthroughs for DKD have led to updates in the current guidelines. The KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends the use of SGLT2is in patients with Type 2 diabetes, CKD and GFR > 30 ml/min/1.73 m^2. KDIGO also suggests initiating GLP-1 receptor agonists in patients with type 2 diabetes mellitus and CKD if glycemic targets are not met despite using metformin and SGLT2is or if unable to use those medications [44].

Similarly, the American Diabetes Association (ADA) recommends using GLP1-receptor agonists or SGLT2is in persons with type 2 diabetes and cardiovascular disease. However, when CKD or heart failure are predominant, SGLT2is are the preferred option [79].

We expect those guidelines to incorporate finerenone in the management of DKD given its beneficial role in CKD progression and cardiovascular outcomes in patients with diabetes mellitus Type 2.

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Conflict of interest

Dr. Hanouneh is a speaker for AstraZeneca and Bayer.
Dr. Cervantes has no conflicts of interest.

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Chapter 3

Palliative Care in Patients with Chronic Kidney Disease

Edwin Fernando and Subashri Mohanasundaram

Abstract

Patients with chronic kidney disease (CKD) experience a high symptom burden, both physical and psychological, that is underrecognized and undertreated. The excessive symptom burden appreciably influences the existence of sufferers and their families. There is an increased prevalence of unpleasant physical and psychological symptoms in patients with CKD. These symptoms impact the Quality of life (QoL) adversely. Routine evaluation and control of those signs and symptoms for the duration of the disorder trajectory ought to be a priority. While managing symptoms, the toxicity of medications that impair residual kidney function, delayed drug clearance, and the impact of dialysis on drug clearance should be considered. The standard rule is to maintain cognitive, physical, and kidney function and deal with the symptom burden with the awareness that management priorities may change with time. Clear communication and shared decision-making need to manual deciding on conservative kidney management, advanced care planning, and psychosocial support alongside dialysis.

Keywords: palliative care, shared-decision making, terminal symptoms, chronic kidney diseasep

1. Introduction

Patients with CKD experience debilitating physical and psychological symptom burden, independent of the stage of CKD, as suggested by recent evidence [1]. With a median of five to six symptoms, this high burden harms the quality of life in these patients, similar to patients suffering from malignancies [2, 3]. Nearly 20% of dialysis patients withdraw from dialysis before the terminal event and, increasingly, older, frail patients with end-stage kidney disease (ESKD) chose not to be initiated on dialysis when its utility may be of little or no benefit and also potentially harmful [4]. Hence, treatment options for patients with eGFR category 5 CKD should include shared decision-making and holistic patient-centered care, ensuring the quality of life (QOL), active symptom management, and advanced care planning. It includes all measures that would delay the progression of kidney disease [5].

2. Definition and principles

Palliative care refers to the crucial yet comprehensive management of the physical, psychological, social, spiritual, and existential needs of patients and families in serious

illness. It is aimed at providing the best possible quality of life by ameliorating suffering, controlling symptoms, and restoring functional capacity while maintaining sensitivity towards the patient's personal, cultural and spiritual beliefs. The change of terminology from "kidney palliative care" to "kidney supportive care" reinforces this comprehensive management rather than implying a limiting belief that palliative care is directed at only patients who are at the end of life [6].

3. The need for palliative care in CKD

CKD patients who undergo comprehensive palliative care management experience less symptom burden at the end of life, receive care according to their preferences, and also are provided with the opportunity to use hospice care. These patients are less likely to die in an acute setting or an intensive care unit requiring more invasive interventions. They enjoy a better quality of life, while also reducing the cost of healthcare [7].

4. Challenges in palliative care

Enabling and integrating palliative care into routine care for CKD patients comes with several challenges, such as regional differences, deciding on the priorities at the frontline, turnover of frontline staff and administrative leadership, sensitivity to the cultural and spiritual practices. A thoughtful combination of health care- and patient-focused evidence-based strategies has to be formulated to ensure more effective care. Despite potential benefits, palliative care is underutilized by advanced CKD patients in many parts of the world, for instance, the lesser availability of such facilities to blacks. Also, the time of referral to hospice care plays a vital role, in that, patients who are referred to hospice care late, are more likely to be dependent on acute care in a hospital setting [8]. Hence, identification of the right patient, shared- decision making and advanced care planning serve to be important factors that need to be considered for effective delivery of palliative care.

5. Components of palliative care

The core components that are integral for the effective delivery of palliative care include:

- Shared decision making
- Quality of life (QoL) assessment
- Advanced care planning
- Prognosis
- Palliative & Hospice Care
- Terminal symptoms management

5.1 Shared decision making

Shared decision-making is the key factor that must be incorporated into all other components from recognizing and management of debilitating symptoms, sharing prognosis, advanced care planning to delivery of end-of-life care and bereavement support. It is essential to incorporate the patient's needs and adapt to his or her lifestyle, including family, social and cultural beliefs, in relieving suffering [9, 10].

5.2 Quality of life (QoL) assessment

Quality-of-life assessment should begin with the time of diagnosis of CKD continue typically every two months in patients on dialysis and every three months in patients with advanced CKD, yet not on dialysis until death. Symptom assessment is integral for assessing the quality of life, as these symptoms impact the patient's functional status.

Some of the commonly used validated tools are the Edmonton Symptom Assessment System (ESAS)- Revised: Renal [10, 11], Integrated Palliative Care Outcome Scale- Renal (IPOS-Renal) [12, 13], and Dialysis Symptom Index [14]. These validated questionnaires help in assessing and managing the symptoms systemically. The Edmonton Symptom Assessment-Revised: Renal, a widely used assessment tool, uses a visual analog scale(VAS) with a super-imposed 0 to 10 numerical rating scale, which assesses pain, activity level, nausea, depression, anxiety, drowsiness, appetite, wellbeing, shortness of breath, pruritus, sleep, and restless legs. A caregiver can complete several items on the questionnaire if the patient is too ill to participate in the evaluation.

In addition, assessment of frailty is particularly useful as it helps in identifying vulnerable individuals to problems involving cognition, medication use, continence, balance, and social support, all of which are common challenges for patients with advanced CKD. Frailty, initially described in the geriatric population, has now been recognized as a predictor of mortality, quality of life, and functional status in patients with advanced CKD [15]. The frailty assessment tools include Clinical Frailty Scale (CFS) [16] and the Edmonton Frail Scale (EFS) [17]. Early recognition of mild to moderate frailty in CKD patients will help in optimizing physical activity and nutrition or planning appropriate advanced care.

5.3 Advanced care planning

Advanced care planning (ACP) involves patient-centered care with the understanding and sharing of the patient's values, life goals, and preferences regarding aspects of future medical care at times of incapacity. It also helps the family members and surrogates with decision-making and lessens their distress and bereavement. Hence ACP must be incorporated into routine care for all patients with advanced CKD, and with periodic reassessment, it helps ensure that the patient has had enough time to think and make well-informed decisions regarding future care, as their health status may decline.

ACP is most needed in the following high-risk patients:

- "No" as an answer to the question: "would you be surprised if the patient died in the next 12 months?" [18].

- Frail patients, with functional or cognitive decline, or repeated unplanned admissions.

- Patients with poor tolerance of dialysis with a change in modality, those who choose or are considering conservative kidney management or withdrawal from dialysis

- Patients with poor or declining quality of life, with high physical or psychosocial symptom burden.

- Patients with decision-making difficulty regarding goals of care.

ACP primarily is based on the perspectives of patients with advanced CKD. Hence, it is essential that the patient is given adequate time to think, reflect on their decisions of advanced care. This, however, shall not be addressed in a single conversation, and hence requires periodic review to gain a full understanding of the patient's beliefs and values. Another effective way of planning involves, including the patient's family, however not making decisions solely on their perspectives.

5.4 Prognosis

The treating nephrologist needs to provide details of the prognosis to facilitate patient-centered decision-making. The available tools to assess prognosis include: Charlson comorbidity score [19], the patient's functional status, and the surprise question ("Would I be surprised if this patient died within the next year?") [18]. In spite of the lack of sensitivity and specificity of the available tools, they help in identifying high-risk patients who can be treated with specific supportive care interventions.

It is important to discuss prognosis with patients who are deciding between conservative kidney management and dialysis and with patients who are contemplating withdrawal of dialysis. Mean survival from the last dialysis treatment to death in a patient who stops dialysis is 7 to 10 days, with a range of 2 to 100 days, with longer survival in those with significant residual kidney function. Treating nephrologists need to identify patients for whom dialysis does not provide survival advantage or better QoL, as these patients may be treated with conservative kidney management.

5.5 Palliative and hospice care consultation

In patients, whose suffering (especially spiritual and psychological support) cannot be addressed by the kidney care team, palliative care consultation should be sought. Specialist palliative care services may also be sought to address considerations at the end of life, involving both symptom management and location of death. Also, referral to hospice, is particularly relevant for patients withdrawn from dialysis or who have chosen conservative kidney management and are nearing the end of life when the eGFR is typically $\leq$5 mL/min/1.73 m^2.

While there is no uniform policy about continuing dialysis for hospice patients, dialysis has to be decided on an individual basis. Also, patients with a terminal condition not related to ESKD may be eligible to receive hospice services both under the ESKD benefit and the hospice benefit. To facilitate coordinated care, it is imperative that providers should work with their local hospice agencies and palliative care

services to educate patients and families, including nephrologists, and clinic and dialysis personnel on the benefits of hospice for the advanced CKD population.

6. Terminal symptoms management

For patients with advanced CKD patients, the terminal symptoms which are described further, cause a great deal of distress and agony more than the death itself. In a study conducted by Alexsson et al. [20], out of 472 patients who were expected to die from advanced CKD, pain was the most prevalent symptom (69%), followed by others such as respiratory secretions (46%), anxiety (41%), confusion (30%), while shortness of breath (22%), and nausea (17%) were found in a lesser percentage of patients. In most other studies, pain was the most common symptom towards the end of life (in 42 to >90% of patients) [21, 22]. Other less commonly reported symptoms were weakness, agitation, depression, myoclonus or muscle twitching, dyspnea, fever, diarrhea, dysphagia, and nausea. Much emphasis is made on terminal symptoms management, as in terminal stages, patients and caregivers experience anxiety, depression, and have practical concerns.

6.1 Pain

Pain is the most common symptom experienced by almost one-third of CKD patients. The origin of pain in CKD can be musculoskeletal or neuropathic. The majority of the patients experience moderate to severe intensity of pain. Management of pain should involve medical history, primary diagnosis, comorbidities, physical examination, psychological status, functional status, and QoL.

6.1.1 Determination of pain intensity

Following are the screening tools for assessing the intensity of pain:

- Modified Edmonton Symptom Assessment Version 2 (m-ESAS v.2)
- IPOS-Renal (POS-renal)

Further follow-up can be achieved by using a separate visual pain.

6.1.2 Causes and chronicity of pain

Proper management of pain involves identifying triggers, frequency, and chronicity of pain. Patients experience recurrent pain from cannulation of arteriovenous fistula, leg cramps, steal syndrome. Management of these symptoms over some time becomes challenging as they are somatosensory or psychological.

6.1.3 Type of pain

Identifying the type of pain helps in choosing the appropriate analgesia in ameliorating the symptom. Nociceptive pain responds to non-opioid and opioid analgesics, at least in the short term. Neuropathic pain responds poorly to Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids and often requires adjuvant drugs, that

have a primary indication other than pain. Since most chronic pain in CKD is of mixed etiology, addressing the neuropathic component first with adjuvant therapy avoids inadvertent use of opioids.

6.1.4 Goals of therapy

Management of pain should lead to improved QoL, by allowing routine day-to-day work. This is achieved by having a realistic aim to reduce pain to a tolerable level (at least by 30% on the pain scale). Treating chronic pain encompasses both non-pharmacological and pharmacological measures.

Non-pharmacological measures include (not graded): aerobic exercise, acupressure, physiotherapy, local heat application, all of which help in reducing the pill burden of analgesia. Cognitive-behavioral therapy, psychotherapy, and relaxation help in reducing drug dependency among patients with neuropathic pain.

Pharmacological interventions in the management of chronic pain are usually done by following the World Health organization analgesic ladder (**Figure 1**) [23].

The five essential principles that have to be considered within the context of advanced CKD are described in **Table 1** [24].

A cautious stepwise approach to the introduction and titration of analgesics is outlined in **Table 2.**

6.2 Uremic pruritus

In advanced CKD, uremic pruritus (UP) is a common and troublesome symptom, experienced in 46% of hemodialysis patients [5, 25, 26]. It affects multiple health-related QoL outcomes such as sleep, general mood, and social function and independently affects mortality. Uremic pruritus involves itching over large surface areas, without restriction to any dermatomal pattern. The pathogenesis of UP is often multifactorial; comprising of uremic neuropathy, increase in activity of μ-opioid receptors, substance P, inflammation from chronic systemic inflammation of skin or nerves. Multiple evidence stat that only a small proportion of cases have histamine as an implicating factor. Management involves the assessment of contributory and reversible

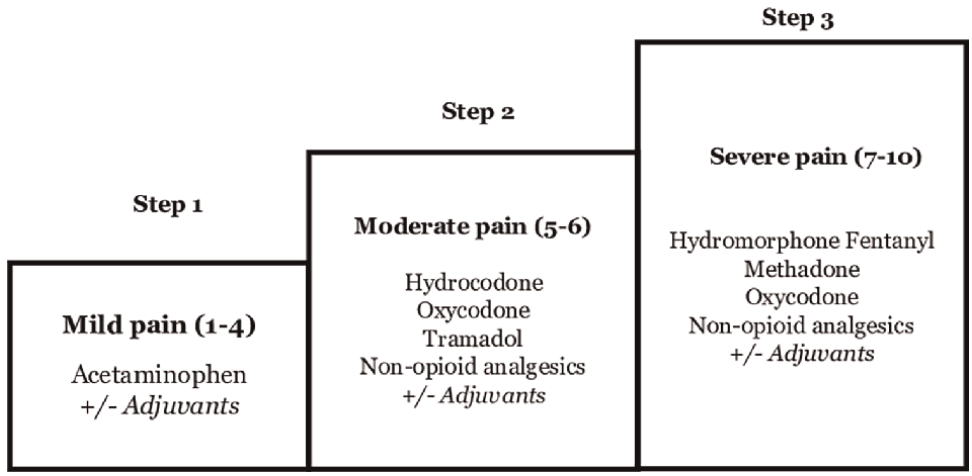

Figure 1.
The World Health Organization three-step analgesic ladder modified for patients with kidney failure.

Principle	Description	Special consideration in CKD
1. By mouth	Oral administration is the safest and preferred method. In case of uncertain ingestion or absorption, alternative routes such as transdermal, rectal or subcutaneous administration can be done.	Despite easy intravenous access in hemodialysis patients. It is usually avoided to optimize safety and minimize the risk of addiction.
2. By the clock	For continuous or predictable pain, regular medications with additional 'rescue' doses should be administered	Some patients may require dosing post-hemodialysis to relieve pain, eg, gabapentin post-hemodialysis in patients with mild to moderate intensity of pain. Gradual as well as careful titration of analgesics is essential to avoid adverse events.
3. By the ladder	Stepwise proceeding from non-opioids to low dose opioids, with the full tolerated dose being administered before moving on to next level.	Sustained release preparations are genrally not recommended, due to narrow therapeutic index, as well as increased rate of mortality with long-acting drugs.
4. For the individual	The risk–benefit ratio on an individual case basis has to be assessed. The optimum dose of strong opioids is the amount at which there are no intolerable side effects while relieving pain.	Close attention to other influencing factors like physical, psychosocial and spiritual concerns is essential for a holistic management of chronic pain.
5. Attention to detail	With changing nature of pain over time, regular reassessment becomes essential.	There are no studies on the long-term use of analgesia in CKD. Hence careful attention should be paid to efficacy and safety.

Table 1.
The five essential principles of management of pain in CKD.

factors. It is imperative to rule out a fungal skin infection, contact dermatitis, drug reactions before initiating treatment for UP. The following are the non-pharmacological and pharmacological treatment options available for CKD patients (**Table 3**).

6.3 Insomnia

The prevalence of sleep disorders in CKD ranges from 20%–83% among CKD patients and 50%–75% among ESKD patients [28–35]. Sleep disorders are present from the early stages in CKD and affect both duration and quality of sleep. The most common sleep disturbance is excessive daytime sleepiness. These sleep disturbances can decrease QoL, impair immune system impairment and have a negative impact on cardiovascular disease, and increase mortality by causing sudden cardiac death. It can also lead to disordered neurocognition with impaired attention and poor work performance. The causes of insomnia in CKD are both physical and psychological, and the available modes of treatment of insomnia are as follows (**Table 4**).

6.4 Anxiety and depression

Depression is very common among CKD patients with its prevalence being three to four times higher compared to the general population [33–43]. Depression is invariably associated with poor psychosocial and clinical outcomes and lower QoL. It is also associated with higher mortality, increased emergency department visits, hospitalizations, prolonged hospital stay, cardiovascular events, withdrawal from dialysis, and

Trial each step for 1–4 weeks before progressing, depending on the severity of the pain		
Treatment plan	**Neuropathic pain**	**Nociceptive pain**
Start with adjuvant therapy If pain persists, ↓ Add a non-opioid +/− adjuvant therapy	1st line: Gabapentin 50–100 mg p.o. at nighttime. If not effective, titrate the dose by 100 mg every 7 nights to a maximum of 300 mg at night-time 2nd line: Carbamazepine starting dose: 100 mg twice daily 3rd line: Tricyclic antidepressants, eg: amitriptyline starting at 10–25 mg daily, or doxepine starting at 10 mg daily	N/A
If pain persists, ↓ Add a non-opioid +/− adjuvant therapy ↓ Titrate slowly to ensure adequate pain relief	Acetaminophen, maximum of 3 g per day in addition to adjuvant therapy (adjuvant can be stopped if of no benefit or not tolerated)	Acetaminophen, maximum of 3 g per day Consider a topical NSAID, for eg; diclofenac gel 5% or 10% 2–3 times per day. If pain is localized to a small joint.
	e.g; hydromorphone starting at 0.5 mg PO (0.2 mg subcutaneously) q4–6 h in addition to adjuvant therapy and acetaminophen. Additionally, consider buprenorphine, fentanyl and methadone	e.g; hydromorphone starting at 0.5 mg PO (0.2 mg subcutaneously) q4–6 h Additionally, consider buprenorphine, fentanyl and methadone

Table 2.
Management of neuropathic or nociceptive pain in CKD.

Non-pharmacological treatment	Pharmacological treatment
1. Appropriate skincare: • wear gloves at night to avoid scratching • Moisturizers(e.g., baths with lukewarm water and gentle moisturizing soaps without fragrances or additives; aqueous emollients within 2 min of bath; the use of non perfume coconut oil, Aloe vera cream, Vaseline lotion, calamine lotion) 2. Topical application: • Capsaicin 0.025% or 0.03% ointment • Pramoxine 1% • Menthol/camphor/phenol 0.3% each either separately or in combination • g-linolenic acid cream 2.2% 3. Phototherapy (UVB): • 400–4800 J/m2 three timesweekly for a 3-week trial 4. Modification in dialysis: • High-flux HD and hemodiafiltration over a period of 12 weeks	1. Gabapentinoids: • Gabapentin or pregabalin Recommended dose: Gabapentin 100 mg daily (2 h before sleep) or 300 mg post HD thrice weekly • Pregabalin 50 mg thrice weekly or 75 mg twice weekly post HD. 2. Antihistamine and mast cell stabilizer: • Hydroxyzine 25 mg once daily • Montelukast 10 mg daily 3. Tricyclic antidepressants: • Doxepin 10 mg at bedtime, in patients on regular follow-up 4. Others: • κ-opioid receptor agonist nalfurafine 5 mcg • Thalidomide 100 mg daily • Difelikephalin 0.5 μg per kilogram of body weight* (phase III clinical trials) [27]

Table 3.
Treatment options for uremic pruritus.

suicide. Both biological and behavioral causes are implicated as the etiology of depression in CKD/ESKD. The recommended screening tools include a two-question approach modified from the Patient Health Questionnaire, Hospital Anxiety and

Non-pharmacological treatment	Pharmacological treatment
1. Cognitive behavioral therapy (CBT): • This includes sleep education, stimulus control, sleep restriction, relaxation training, and sleep hygiene • Treatment period over 6–8-week sessions 2. Acupressure 3. Physical exercise: Aerobic andflexibility exercise 4. Change of dialysis modality	1. Adequate management of concurrent pain, pruritus, depression, and obstructive sleep apnea. 2. If restless leg syndrome (RLS), neuropathic pain, or uremic pruritus (UP) are present, add low-dose gabapentin 50–300 mg at night. 3. Doxepin 10 mg at night as the second line for neuropathic pain or pruritus. 4. Zopiclone 3.75–5 mg, as third-line. 5. Melatonin 2–5 mg regulates and improves sleep–wake cycle in the short term but not at 1 year.

Table 4.
Treatment options for insomnia.

Depression Scale, Patient Health Questionnaire-9, and General Anxiety Disorder-7. Evidence states that approximately only 35% of those with diagnosable depression receive treatment. An improvement in depressive symptoms and psychosocial outcomes was observed when treated with a combination of antidepressants and psychotherapy.

Following **Table 5**, enumerates the available modalities to treat depression in CKD patients.

6.5 Restless leg syndrome

The definition of RLS was revised during the National Institutes of Health consensus conference (2002), Bethesda, USA, to include [44–46]:

- Urge to move the legs usually with unpleasant sensations in the legs; arms and other body parts are occasionally involved.
- Symptoms begin or worsen during periods of rest or inactivity.
- Symptoms partially or totally relieved by movement and as long as the activity continues.
- Symptoms are worse during the evening or night than during the day.

Non-pharmacological treatment	Pharmacological treatment
1. CBT 2. Exercise therapy 3. Frequent dialysis (needs more research)	1. Selective serotonin reuptake inhibitors • Sertraline 50–200 mg/day • Escitalopram 10–20 mg/day • Fluoxetine 20–60 mg/day 2. For episodic anxiety, a short trial of benzodiazepines and beta-blockers 3. Mirtazapine 15–45 mg/day in CKD 1–4. (50% dose reduction in Stage 5 CKD) 4. Duloxetine 40–120 mg/day (Better avoided once estimated glomerular filtration rate (eGFR) <30) 5. Tricyclic antidepressants(TCAs) and monoamine oxidase inhibitors—Not recommended in CKD.

Table 5.
Treatment modalities for depression in CKD:

Non-pharmacological treatment	Pharmacological treatment
1. Removal of stimulants such as alcohol, caffeine, nicotine 2. Optimization of sleep hygiene 3. Aerobic exercises 4. Pneumatic compressions 5. Regular mental alerting activities such as solving puzzles and board games 6. Correction of other contributing and reversible factors such as concurrent use of dopaminergic antagonists, iron deficiency, anemia, hyperparathyroidism, and elevated serum phosphorus	1. Gabapentin 100 mg daily (2 h before sleep) or 300 mg post HD thrice weekly 2. Synthetic dopamine agonist: • Ropinirole: To initiate with 0.25 mg, taken 1 h before bedtime with slow titrating to a maximum of 4 mg per day. • Pramipexole (only immediate-release tablet): To initiate with 0.25 mg, taken 1 h before bedtime with slow titrating to a maximum of 0.75 mg per day 3. Antioxidants Vitamin C and E 4. Others: • Levodopa (Improves symptoms but not routinely used owing to increased vomiting, agitation, headaches, dry mouth, and gastrointestinal symptoms) • Benzodiazepines (increased risk of frequent falls but considered for use in patients who cannot take oral drugs) • Iron dextran (less likely to have added benefit beyond correction of iron deficiency anemia).

Table 6.
Treatment modalities for depression in CKD.

Among the dialysis population, the prevalence of RLS ranges from 6.6–80%. Abnormalities in the dopamine pathway of the subcortex in the brain have been implicated as a major etiological factor in the pathogenesis of RLS. Other contributing factors include iron deficiency, anemia, hyperparathyroidism, elevated serum calcium and phosphorus, inadequate dialysis, and poor sleep hygiene. Nevertheless, RLS is associated with decreased QoL and increased cardiovascular morbidity and mortality (**Table 6**).

6.6 Gastrointestinal symptoms

Gastrointestinal symptoms are common, especially in patients with advanced stage of CKD, yet not on dialysis [44, 47]. Most patients after initiation of dialysis, have an improvement in symptoms and experience better appetite. If already on dialysis, adequacy of the same should be assessed and managed appropriately. Measures should be taken to correct factors contributing to inadequate dialysis and improve uremia.

6.6.1 Nausea, vomiting

Multiple factors such as uremia, drugs (e.g., opioids, antibiotics, and anticonvulsants), diabetic gastroparesis, and/or uremic gastropathy are implicated as etiological factors for nausea and vomiting in patients with CKD. The stated occurrence of nausea in advanced kidney failure is about 46%. If gastritis is a contributory factor, a short course of proton-pump inhibitors may be used. Prokinetic agents such as metoclopramide (10 mg q 8th hourly) (50% dose reduction when eGFR <40 ml/min/1.73 m^2) and itopride can be tried for gastroparesis with close monitoring for any side

effects especially extrapyramidal symptoms with metoclopramide. Haloperidol (0.5–2 mg q 12 h) or levomepromazine (12.5–25 mg q 8 h) is commonly used for nausea and gastrointestinal symptoms but requires dose reduction due to their propensity for cerebral sensitivity.

Another common symptom, xerostomia or dry mouth can be addressed using lozenges or ice chips. No specific medication is approved.

6.6.2 Constipation

Along with dietary restriction, poor appetite, drugs such as opioids, iron supplements, phosphate binders, can contribute to constipation. Non-pharmacological strategies include consuming fiber (20–38 gm/day) and fluid intake within an allowed dietary restriction and physical activity. Pharmacological recommendations include once-daily use of oral osmotic laxatives (lactulose 15–30 ml), stimulant laxatives (bisacodyl 5–15 mg PO), sodium picosulfate, and stool softeners.

6.7 Dyspnea

Dyspnea is a common worrisome symptom in patients with CKD Stage 5 [44]. Volume overload (pulmonary edema), cardiovascular cause, or anemia are attributed as causative factors.

- For volume overload: treat with a trial of loop diuretics at the higher end of recommended dosing, initiation and intensification of dialysis, slow continuous ultrafiltration

- For cardiac cause: identification of cardiac lesion and its correction, helps in relieving symptoms.

- Other contributory factors, such as anemia should be corrected promptly, with iron supplementation and erythropoietin.

As management of dyspnea at home could be very difficult for the patient and family, the patient may be admitted to the hospital for the same. In the end stage, general measures to address hypoxia such as propped-up position, inhaled oxygen, and anxiolytics.

- Small doses of opioids can be used for dyspnea end-of-life care.

- Short-acting benzodiazepines like lorazepam 0.5–1.0 mg oral or sublingual at 6–8-h interval can be tried.

- Especially at the end of life, midazolam at a dose of 1.25–2.5 mg can be given subcutaneously with close monitoring.

7. Palliative dialysis

Palliative dialysis is an approach that prioritizes quality of life over survival, by using patient-specific dialysis prescriptions. It requires integration of renal supportive

care, discussion among the patient, family, and dialysis providers. It aims at relieving symptoms such as breathlessness rather than achieving biochemical parameters that represent conventional dialysis adequacy. Palliative dialysis does not translate to less dialysis or precursor for withdrawal of dialysis. It rather implies flexibility in issues such as blood pressure control, so that care can be tailored appropriately for each patient [48].

8. Withdrawal of dialysis

Conservative kidney management (CKM) is a continuation of all other services to ameliorate terminal symptoms however without initiation or continuation of dialysis. Following are the ideal scenarios where CKM is adopted [49, 50].

- Patients who have one or more life-shortening comorbidities such as end-stage liver or heart failure.
- Frail patients with significant preexisting functional or cognitive impairment, who may have worsening impairment on dialysis.
- Patients residing in long-term care facilities.
- Patients with irremediable physical or psychological symptoms, in whom dialysis may prolong life but will also prolong suffering.
- Patients with irreversible intellectual incapacitation such that they cannot apprehend the process, risks, and benefits of dialysis in such a way that dialysis cannot be administered safely. Some examples of this include:
    - Patients without decision-making capacity whose advanced care directive or the substituted judgment of a health care proxy dictate CKM.
    - Patients who are unable to cooperate with the procedure of dialysis itself and are unable to react to specific surroundings or people, to such an extent they require restraints or sedation during dialysis
    - Patients in a persistent vegetative state.

9. Ethical issues in decision making

Ethical issues arise especially during times of withdrawal or withholding active care [51–53]. The key ethical principle, here, is non-maleficence, as the intention to either withhold or withdraw is to avoid or cease causing harm in situations where the treatment does not cause any benefits. The power of autonomy holds that patients have the right to accept or reject health care, which is medically indicated. Respecting autonomy implies respecting the patients' own set of values, goals, experiences, and social relationships, which ultimately leads to different decisions taken by different patients in the same clinical situation.

As much as important it is, to respect the patient's autonomy, especially during situations when he or she requests for withdrawal of care, it is the duty of the treating nephrologist, to identify the real motto behind the patient's decision and to address any reversible or treatable psychological factors. High-quality discussions about what is important to patients and their families promote good decision-making and patient-centered care. It allows clinicians, patients, and families to avoid disagreements that could otherwise escalate into ethical conflicts. However, treatment options cannot be dictated based solely on the surrogate's decisions.

A realistic tool that allows ethical decision making is Jonsen's "Four Box Model". The main benefit of this model is to balance medical decision-making elements that are important to health professionals with those patient-centered elements that are important to clinical decision-making, including preferences, quality of life, and other practical considerations.

10. Post-death assessment and bereavement care

As a part of routine quality assurance, some nephrology programs assess the quality of a patient's end-of-life event [21]. Such assessment promotes the focus of attention towards ensuring advance care planning, symptom control, and effective communication among treating teams, patients, and their families. Bereavement support to families and involved caregivers (eg, dialysis unit staff, transporters, etc) can be extended by dialysis unit-sponsored memorial services. Support should be provided to all families and loved ones following the death of an ESRD patient, irrespective of referral to hospice care. Condolence letters and/or call from the nephrologist or other staff, attendance by the social team at the funeral, contact with a renal social worker, annual renal memorial service are some of the ways by which post-bereavement care is provided.

11. Conclusions

Although conservative kidney management is more and more recognized as an appropriate treatment choice for patients, who are unlikely to benefit from dialysis, there is still great variation in the current understanding and reputation of conservative kidney management as a distinct modality choice. With this comes exceptional variations in clinical practice and standards of care. Many patients undergoing conservative kidney management present with complex health scenarios, and most recommendations have to be personalized. Participation from patients play a vital role in decision-making. In a shared decision-making process, ensuring that all interventions are aligned appropriately with their values, preferences, and prognosis will go a long way.

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Chapter 4

Transition of Adolescents with Chronic Kidney Disease from Pediatric to Adult Care Centers

Maha Najeeb Haddad

Abstract

Transition of care of adolescents and young adults (AYA) with chronic illness from pediatrics to adult care has been recognized as an essential part of the patient's care. Transition is a process that starts in early adolescence and prepares the AYA to use the medical care system and take care of their own medical needs independently to ensure continuity of care and improve outcomes. This chapter focuses on transition of AYA with chronic kidney disease (CKD) and kidney transplant recipients. It includes transition definition, relevant developmental aspects in adolescence and the impact of CKD on the adolescent development, the transition process, and the essential components of a successful transition.

Keywords: definition of transition, significance, components, tools, challenges of transition

1. Introduction

There has been a significant improvement in patient survival in pediatric patients with end-stage kidney disease and kidney transplant recipients. While survival rate has increased, the prevalence of major various morbidities in those children including cardiovascular and other comorbidities remains high [1, 2]. During adolescence, high-risk behaviors include substance abuse and non-adherence peak [3]. Adult clinics are facing an increased number of adolescents and young adults with serious morbidities who either get transitioned or are referred to establish care. This can be challenging to both adult care facilities and the adolescents themselves. Unlike in the adult setting where the patient is expected to be the sole advocate for their care and is expected to comprehend robust instructions, and make their own medical decision, in the pediatric setting patients are under the care of their family or guardians who make the medical decision and take the responsibility for all aspects of the patient's care. The patient and their families are usually very well known to the pediatric provider who in many instances has been taking care of the patient since birth. In addition, the pediatric providers' patient load is much less than that of adult providers. Transition of care to the adult setting can be detrimental, particularly to the patient with kidney transplant. Studies suggest an increased risk of graft loss after transitioning to adult

care, mainly due to non-adherence [4, 5]. Non-adherence stems from increased risk behavior in the adolescent and the accompanying lack of ability to assess, or even believe in the consequences of risky behaviors. Other challenges of transition of care include lapses in medical insurance. Lack of continuity of care may have negative economic consequences due to increase in cost such as when treating graft rejection or when having to start dialysis after graft loss. In one Canadian study that analyzed the benefits of a transfer clinic, attendance at a single kidney transplant transfer clinic was associated with improved adherence and renal function the year following transfer to adult care [6]. Another study indicated improved allograft and patient survival post-transfer of care in addition to improved health care cost [7].

2. Transition definition and goals

The concept of transition began to develop in the 1990s and is defined as the "purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented heath care system" [8]. A consensus policy statement on health care transition approved by the boards of the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Physicians-American Society of Internal Medicine defined the goal of transition "as is to maximize lifelong functioning and potential through the provision of high quality, developmentally appropriate heath care services that continue uninterrupted as the individual moves from adolescence to adulthood" [9, 10].

Transition is an organized process that facilitates transition preparation and integration into adult-centered health care. It focuses on the adolescent patient with the goal of educating, empowering, and promoting autonomy and independence in the patient so they can manage their own health care needs and effectively use health care services, whereas "Transfer" is the event of leaving pediatric care to adult care facilities, preferably happening at the end of a successful transition.

For the transition process to be successful, it has to take into account the patient's developmental status and the cultural beliefs of the family. The transition plan should be individualized to each patient and family.

3. Adolescent development and effects of CKD

Adolescents go through physical, social, emotional, cognitive, and moral developmental changes. Adolescence is a period of separation from parents, identity formation, and autonomy. Adolescents transit from concrete to abstract thinking. There are multiple and complex factors including genetic and environmental factors that play a role in the expression of the individual's biology and behavior [11]. Environmental factors include family, school, and peers. Cultural factors also define the norm. All those interactive factors result in variation in the adolescent development making it challenging to determine what is "normal" and difficult to define when it starts and when it ends [12].

In general, adolescence is divided into three stages: early adolescence (11–14) years of age, middle adolescence (15–17) years, and late adolescence 18–21 years. Early adolescence is characterized by marked physical changes and concrete thinking where the adolescent will know the right from the wrong. In early adolescence, the

adolescent is focused on peer acceptance, which renders the adolescence to be susceptible to peer pressure, whereas during late adolescence, self-ID and autonomy solidify [13]. One of the main psychological developments in adolescence is the development of self-image. Accepting self-image and feeling normal are crucial and are linked to the sense of belonging and acceptance. Chronic illness can have a tremendous toll on self-image. Feeling different from peers may lead to high-risk and rebellious behavior such as non-adherence with medications, difficulties in relationships, depression, poor academic performance, and substance abuse. Reassurance and acceptance from the family and care givers are crucial. The care givers and family should be keen in providing this, and should encourage the adolescent, and compliment them on their achievement and their good behavior to increase their self-esteem and sense of belonging. The physician should use open-ended questions to gain insight into the adolescent's understanding of health, adherence, high-risk behaviors, and self-esteem. Assessment of high-risk behavior in AYA with chronic kidney disease and renal failure where substance use is prevalent is an essential component of the transition process [14].

During adolescence, ongoing brain development takes place and parallels the cognitive development. Structural brain images show significant increases in the white matter that continues into early twenties. The process of myelination occurs in a caudal to rostral (back to front) matter. Prefrontal areas mature last. The prefrontal area is involved in cognitive control, regulation of emotions and decision making, and weighing risks and benefits is one of the last areas to mature [15].

Brain images and neurocognitive studies showed that children with CKD and end stage-renal disease (ESRD) have brain abnormalities and neuro-cognitive deficits despite the advances in management of CKD [16]. Several systematic reviews examined neuroimaging and described the neurological complications in patients with CKD in adults [17–19]. One systematic review of structural and functional neuroimaging findings in children and adults included 43 studies, 13 of which were on children described clear trends. Those fundings include cerebral atrophy, brain vascular and white matter abnormalities, cerebral and cortical infarction, and similarities in regional cerebral blood flow between patients with CKD and those with affective disorders [20].

In a study from Helsinki University Central hospital, the neurophysical profile of 45 children with kidney transplant was assessed and compared to a control group of matched for age, sex, and maternal education. They concluded that children with kidney transplant exhibited impairment in receptive language and visuospatial functions and in recognizing emotional states [21].

In addition to all the above challenges, pediatric patients with CKD, dialysis, and transplant miss a lot of school days due to the demand of their chronic illness.

Physicians and transition champions should take all the aforesaid patient challenges into consideration. Transition should be developmentally appropriate and individualized to each patient and family and should consider the cultural expectations and norms for each patient and family.

4. The transition process and elements

The goal of transition of the adolescents is to continue to receive high quality and uninterrupted care as they transit to adults. This can only take place if the AYA are well prepared for that. They should have good understanding of their illness and have

the skills to manage their own medical condition and general health independently. They also should have medical insurance coverage to allow them to be followed in adult facilities.

Based on the On TRAC Model principles, transition is best managed by the existing subspeciality team who are familiar with the patient's condition and know patient and family well, and in whom the family and patients have established trust. Transitioning can be integrated into the patient's follow-up visits [19]. So pediatric care providers should take the lead on transitioning their patients.

During transition, preparing the adolescent with the goal to acquire the right skills and knowledge takes place. Collaboration and communication with the adult care providers are an integral part of the transition process and should take place one year prior to the patient's transfer.

Transition is a gradual process that should start in early adolescence and continue to be carried out till the patient is ready for transfer. The concept should be introduced to the family in early adolescent years (12–14) where the transition policy is shared with the patient and family. A clear plan should be developed for each patient and should be agreed upon by the family and the care givers. Since multiple aspects of the adolescent care should be addressed, a multidisciplinary team should be involved in the transition process including the care provider, nurse, social worker, and dietician, and when possible, a pharmacist and a psychologist. Collaboration with gynecologists and urologist to offer contraception and urology care facilitates providing comprehensive medical needs to the adolescent. From the multidisciplinary team, a designated transition person should be identified. In the consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA), it is stated that it is essential to identify a champion in both the adult and pediatric clinics to coordinate and educate on transitional issues. In their statement, they published the essential components of transition [22]. The identified champion should have special interest in organizing and leading the transition process. In addition, transition should include parents, other family members, and boyfriends/girlfriends.

The transition team should have an agreed upon transition policy that the transition team is familiar with and should be shared with the patient and family at the start of the transition process.

After introducing the concept to the patient and family, the transition process should start by assessment of transition readiness. It is best to use existing and validated transition check lists such as the TRAQ [23] and STARx Questionnaire [24]. The readiness assessment questionnaire should be comprehensive and should have questions that can assess patient's understanding of their illness, knowledge of their medications, assessment of adherence and consequences of non-adherence to mediations, and in dialysis patients, consequences on non-adherence to dialysis. For children over the age of 12 years, it should include assessment of high-risk behaviors such as alcohol and drug use, smoking, sexuality, reproductive health, educational/vocational needs, their understanding of health maintenance, support system, understanding of the health care system, knowledge about diet, emergency handling, readiness for independence and self-reliance, and health insurance coverage. This will serve as a starting point for the patient and the family. The information given about transition should be given in a gradual manner appropriate to the developmental stage and intellectual ability of the patient [22].

Ongoing evaluation and tracking of transition readiness is an important component of the transition process as it identifies deficiencies and allows for tailoring the plan to each individual's needs during the transition process [25, 26]. An individualized jointly

developed goals and action plan with the youth should be documented and shared with each patient at the end of each assessment. Tracking the transition progress of each patient requires the use of individual flow sheets or registry to facilitate tracking and ease follow-up on progress. During transition, and in late adolescence, the adolescent and young adult, and while getting on going education, are coached and given the opportunity to practice supervised self-reliance such as scheduling and attending visits on their own, refilling their medications, and communicating their concerns with the health care provider and making decisions.

At least 1 year prior to transfer, communication with the adult clinic should start. During this year, insurance issues should be sorted out and the patient should be provided with a written medical summary. The patient should have an appointment with an identified adult care provider who has previous knowledge of the patient's arrival and condition, and the clinic should be expecting and ready to receive a young adult.

The adult clinic receiving the young adult they should have a transition plan. A transition point person should identify the young adults in clinic, receive them, and introduce them to the adult care facility and the multi-disciplinary team. The adult clinic should also communicate with the pediatric providers acknowledging receiving the patient and the transfer package.

While it is agreed on that the timing to initiate transition planning is early adolescence, the time of transfer and integration into adult care varies. Some pediatric programs follow the adolescent and the young adult till 21 years, while others transfer at 18 years. Regardless of patient age, transfer should not take place during crisis or if the patient's condition is unstable.

There are different transitioning models for the last year. One model is to have a dedicated joint transition clinic between pediatric and adult programs the year preceding the transfer. A joint clinic allows the transitioning adolescent to meet with the adult provider and opens the door for open communication between the pediatric and adult teams. Use of a dedicated transfer/transition clinic in adolescents and young adult kidney transplant patients has been shown to be associated with improved adherence and renal function in the year following transfer [6], and with better patient satisfaction and the lower changes in medication and care [27].

The dedicated transfer clinic can be located either in the pediatric or in the adult care center.

The other model of transitioning the year preceding the transfer particularly if it is not possible for the patient to attend the joint transfer/transition clinic such as when the patient is transferring care to a private provider is to give the transitioning patient the opportunity to see the adult provider while still being followed by the pediatric team. The patient can have alternate visits between the two providers or can be seen several times in the adult care clinic before transferring care.

A very useful online tool for transition can be found on "gottransition.org." On that website, they provide tools in both English and Spanish. They describe the six elements of transition on both the pediatric and adult sides and recommend a quality improvement approach to implement the six core elements. The six core elements include transition policy, tracking and monitoring, transition readiness, transition plan, transfer of care, and transfer completion.

I. Transition plan: Develop a written and agree upon transition policy and plan.

II. Tracking and monitoring:

Use individual flow sheets and registry and when possible, use electronic health records to track the youth's transition progress with the six core elements

III. Transition readiness:

Assess self-care needs and offer education on identified needs, and develop the plan jointly with the youth and parent/care giver document regularly in a plan of care.

IV. Transition planning:

Develop a health care transition plan with a medical summary for each patient.

V. Transfer of care:

In this step, transfer to adult care practice takes place. Transfer should only happen when the patient's condition is stable. Here, the pediatric provider should prepare a letter with the transfer package and send them to adult practice, confirm the date of the first adult provider appointment, and complete transfer package, including final transition readiness assessment, plan of care with transition goals and pending action, medical summary, and emergency care plan. The pediatric provider should confirm receipt of the transfer package and should remain responsible for the patient's care until the young adult is seen by the adult care provider.

VI. Transfer completion:

The pediatric provider confirms that the transfer is complete and elicits feedback.

5. How well are the transition principles implemented?

The process of transition requires a team effort, time, and dedication which makes it challenging to implement. In 2013, a survey of 15 European dialysis sites found suboptimal awareness of the ISN/IPA consensus statement guidelines [28]. In a survey of pediatric nephrologists across the United States where the response rate of nephrologist was 40%, 60/150, and the response rate of centers was 56%, 49/87 centers, it was found that the elements of transition were not widely followed [29]. For the question of having a transition clinic, only 23% of the responses were positive, and only 37% of the responses were positive for having a transition summary. Only 25% had a designated transition coordinator and involved adult care takers 1 year prior to transfer. The authors designed the "RISE" to transition protocol for renal transplant patients based on essential elements for a successful transition. The protocol has four competency areas including **R***ecognition* of the disease process and the health care system, **I***nsight* into the short- and long-term impact of the disease, nonadherence and emotional needs, **S***elf-reliance* in scheduling and attending appointments, refilling medications and identifying urgent changes to their health, and **E***stablish* healthy life choices, adherence to medications, follow-up, psychological skills, and educational and vocational goals [29].

In Europe, a survey on behalf of the European Society of Pediatric Nephrology (ESPN) working group "transplantation" on the management of transition and transfer to adult care in pediatric kidney transplant recipients that involved 39 centers from

24 countries accounting for 2500 children found that the IPNA and ISN guidelines were insufficiently implemented in Europe [30].

6. Conclusion

Transition from pediatric to adult care facilities in patients with CKD or patients who have received a kidney transplant remains an essential process to ensure access to care and promote outcomes. Pediatric nephrologists, with their multidisciplinary care team and a designated transition champion, lead this process that starts in the early adolescent period and ends with transfer of care. Transitioning requires the use of validated and comprehensive readiness assessment questionnaires, use of flow sheets, or the electronic health record for tracking and the collaboration and communication with the adult care providers. Transition results in improved patient satisfaction, and most studies showed improved outcomes and even cost effectiveness. Despite that, transition of care remains poorly implemented mainly due to poorly allocated time and resources. Pediatric nephrologists need to advocate for transitioning their patients.

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Section 2

Biomarkers and Molecular Biology

Chapter 5

Biochemical Tests for Diagnosing and Evaluation Stages of Chronic Kidney Disease

Goce Dimeski and Oliver Treacy

Abstract

The primary biochemical markers for the diagnosing and evaluating stages of chronic kidney disease (CKD) are serum creatinine and the estimated glomerular filtration rate (GFR). For diagnosing CKD, the GFR needs to be <60 mL/min/1.73 m^2 for more than 3 months. Less frequently used endogenous marker for estimating the GFR is cystatin C. Alternatively, exogenous markers that can be used include inulin, iotalamat, and iohexol if clarity is not achieved with creatinine or cystatin C. Globally, urinary albumin and albumin-creatinine ratio are the recommended tests from a spot collection to estimate the kidney damage. Urinary protein estimate's use is declining, especially 24-hour collections. There are several other markers discussed in brief that may be a useful adjunct in identifying causes and likely management strategies for CKD. Finally, pitfalls of the primary methodologies for the above tests are provided to guide readers in better understanding the results and their use in patient care decisions.

Keywords: creatinine, glomerular filtration rate (GFR), albuminuria, proteinuria, cystatin C

1. Introduction

Chronic kidney disease (CKD) is a significant health issue, with a global prevalence approaching 10% [1]. It is a condition associated with long-term morbidity and mortality linked to its severe impact on the cardiovascular system. In the healthcare setting, many resources are allocated toward the monitoring and treatment of CKD. These can be in the form of medical practitioner consults, allied health input, medications, dialysis, and biochemical monitoring of progression and complications.

Biochemical tests are pivotal to the diagnosis, monitoring, and management of CKD. Increased understanding of the array of methods for individual tests and the ways best to interpret result for each test can be critical in optimizing decisions for patient care. Additionally, understanding the deficiencies or pitfalls of each test with preanalytical collection and handling processes and analytical performance, including interferences, may be very useful in better understanding the accuracy of results and empowering clinical staff to interact with pathology experts and subsequently deliver improved patient care decisions.

Biochemical testing and monitoring can be used for assessing renal dysfunction, the progression of CKD staging, biochemical and endocrine sequelae of CKD, and optimizing therapy and dialysis. This chapter will endeavor to provide an overview of the biochemical analytes employed in CKD monitoring and provide laboratory considerations in the understanding of each.

2. Creatinine

Creatinine is the end metabolic product of creatine in muscle, and the amount of creatinine in the serum and urine is related to muscle mass and renal excretion. It is consistently converted into creatinine at ~2% per day by an irreversible process, freely filtered at the glomerulus, and not reabsorbed by the renal tubules, which makes it a good endogenous marker for kidney impairment detection. Its use in kidney function evaluation has limitations, which include age, sex, race, and body weight. Hence, the development of the estimated glomerular filtration rate (eGFR) and the measured glomerular filtration rate (mGFR) has been adopted. GFR estimation or measurement is utilized to determine the amount of blood passing through the kidneys per minute, and its amount can be indicative of kidney function from the clearance of endogenous biomarkers (creatinine and cystatin C) or exogenous substances, which include urine isotope collections, such as inulin, iotalamat, and iohexol, used for measuring the GFR more accurately. Although they may provide superior accuracy, they are invasive, impractical, time consuming, and expensive, including the need for specialized chromatographic test methods. The eGFR minimizes the effect of age and sex compared to a solitary creatinine level and, thus, is one of the best indicators of renal function in CKD. There are also formulas that adjust for race. Most of the formulas utilize creatinine or cystatin C, and any potential errors with both the analytes will also be propagated by the eGFR calculation. The limitations of these formulas include that they can only be used in adults greater than 18 years old, and an alternative formula, e.g., Schwarz formula, is a potential eGFR calculator that can be used in a pediatric population, although care may be needed in its application to certain ethnic groups [2]. The KDIGO guideline for CKD based on the GFR is <60 mL/min per 1.73 m^2 (**Table 1**) [3].

In an effort to standardize a creatinine result in a patient with a known gender and age, the laboratory will provide an eGFR, which provides an estimated GFR based on formulas derived from experimental models. This eGFR is mostly calculated currently using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which has the advantage over its predecessor (the Modification of Diet in Renal Disease (MDRD) formula) in that it can be used across the whole range of GFR, while the MDRD formula

GFR categories	GFR result
Normal to increased	≥90 mL/min per 1.73 m^2
Mildly reduced	68–89 mL/min per 1.73 m^2
Moderately reduced	30–59 mL/min per 1.73 m^2
Severely reduced	15–29 mL/min per 1.73 m^2
Kidney failure	<15 mL/min per 1.73 m^2

Table 1.
KDIGO-suggested GFR categories [3].

is applicable to patients with established kidney disease. This is important, as it allows for more accurate stratification of the stage of early kidney disease (stages 1 and 2). Both the formulas have inherent limitations, such as being unable to be applied to pediatric patients (less than 18-year-old) and being inaccurate at the extremes of body size and age, but the CKD-EPI has been shown to be a superior formula for estimating eGFR [4].

The measuring methods are divided into chemical and enzymatic. The chemical methods are primarily based on alkaline picrate, which was first described by Jaffe in 1886; hence, the methods are commonly referred to as Jaffe methods. Creatinine reacts with picrate in an alkaline solution to form the picrate-creatinine complex and has an orange-red color, which is measured at 490–520 nm.

This reaction is not specific for creatinine; hence, many method variations have been introduced over time. The chemical methods started as end point, which are now almost nonexistent, and they have been superseded by kinetic assays in order to minimize noncreatinine chromogens causing interferences. These noncreatinine chromogens have a different rate of color development, allowing for the separation of the rate of color development from creatinine from the interferents. Additionally, the reaction incubation temperature has influence on the reaction of the interferents, and temperatures of 25--41°C have been used to minimize interferences [5]. They are relatively inexpensive and the most widely used, but they are liable to a number of interferents, including: a) positive interferents: ascorbic acid, pyruvate, protein, glucose, creatine, various cephalosporins, acetoacetate, and fluorescein and b) negative interferents: bilirubin, hemoglobin F, and dopamine [6]. The bacterial contamination of urine samples can cause the production of substances that inhibit the Jaffe reaction.

The enzymatic methods are increasingly used in laboratories as they become more economical to improve accuracy, but they are not immune to interferences. Enzymatic methods are typically used in point-of-care (POC) devices [7]. There are three commonly used enzymatic methods: a) creatininase (creatinine amidohydrolase), which is the least used due to poor kinetics, reduced sensitivity, and poor precision; b) creatininase and creatinase are far more frequently used, and to overcome ascorbic acid interference, ascorbate oxidase is included in the reagent; and c) creatinine deaminase (creatinine iminohydrolase) that can be affected by endogenous ammonia in small amounts, for example, from protein deamination and release red cell chromogens when blood is left uncentrifuged at room or higher temperature. The bacterial contamination of urine samples can cause protein deamination.

Isotope dilution-mass spectrometry (IDMS) is the reference method of creatinine measurement. All the Jaffe and enzyme methods are standardized against the IDMS method. High-performance liquid chromatography (HPLC) methods exist, and more recently, a combination of IDMS and HPLC methods has been reported to improve turnaround time and accuracy. These methods are not practical for routine and rapid turnaround usage.

The differences between methods, calibrators, and patient samples (noncommutability) limit the transference of results between analytical methods; thus, it is important that result interpretation is based on the reference ranges provided for the method. This includes not only creatinine results but eGFR results as well.

3. Urinary albumin and total protein

The measurement of urine protein leak in urine is pivotal to the detection, diagnosis, prognosis, and treatment of kidney disease. Albumin is an abundant protein in

urine; hence, either total protein or albumin along with creatinine is routinely used as biochemical diagnostic markers. Proteinuria/albuminuria due to diabetes and/or hypertension is an early marker of kidney disease and is a leading cause of chronic kidney disease and cardiovascular incidents. In general, current guidelines recommend the measurement of an early morning random urine collection for albumin-creatinine ratio (ACR). It is calculated by dividing the albumin concentration in milligrams by creatinine concentration in millimoles. Persistent increased albumin in the urine (two positive tests over 3 or more months) is the principal marker of kidney damage.

Although the 24-hour collections have been the "gold standard," alternative methods for detecting protein excretion, such as urinary ACR, correct for variations in urinary concentration due to hydration as well as provide more convenience than that of timed urine collections. The spot specimen correlates well with 24-hour collections in adults. Australian recommendations were published [8] (**Table 2**) as part of the standardization process for primary care by a consensus working group, and these recommendations were adopted by Kidney Australia in 2013 on the limits for urinary albumin-creatinine ratio alone. The study estimated that about six million individuals (~25%) have one or more of the major risk factors for CKD and that about 1.4 million (6%) Australian adults have CKD [8]. Soon after this the KDIGO recommendations were adopted.

The most recent KDIGO guideline for CKD based on the markers of kidney damage is that the disease duration must be >3 months, which also suggested new terminology. The suggested limits of albumin and protein excretion rates AER and PER and ACR and PCR values are presented in **Table 3** [3].

In our tertiary hospital from 2010 to 2020, there has been 62% reduction in timed protein, 40% reduction in random protein requests, and 72% reduction in timed albumins requests, while there has been 22% increase in random urine requests. Time

Sex	ACR for males (mg/mmol)	ACR for females (mg/mmol)	24-hour urinary albumin (mg/day)
Normal	<2.5	<3.5	
Microalbuminuria	2.5–25	3.5–35	30–300
Macroalbuminuria	>25	>35	>300

Table 2.
Categories of albuminuria in Australia in 2012.

Albuminuria and proteinuria categories	AER, PER, ACR, and PCR results
Normal	AER <10 mg/d; ACR <10 mg/g (<1 mg/mmol)
Mild	AER 10–29 mg/d; ACR <10 mg/g (1.0–2.9 mg/mmol)
Normal to mild	AER <30 mg/d; ACR <30 mg/g (<3 mg/mmol) PER <150 mg/d; PCR <150 mg/g (<15 mg/mmol)
Moderate	AER 30–300 mg/d; ACR 30–300 mg/g (3–30 mg/mmol) PER 150–500 mg/d; PCR 150–500 mg/g (15–50 mg/mmol)
Severe	AER >300 mg/d; ACR >300 mg/g (>30 mg/mmol) PER >500 mg/d; PCR >500 mg/g (>50 mg/mmol)
Nephrotic syndrome	AER >2200 mg/d; ACR >2200 mg/g (>220 mg/mmol) PER >3500 mg/d; PCR >3500 mg/g (>350 mg/mmol)

Table 3.
KDIGO suggested albuminuria and proteinuria categories.

urine advantage is that it accounts for day night variations as well as positional or exercise variations.

Patients need to be provided with clear instruction for sample collections to mitigate any preanalytical problems, such as avoid collection if there is any bleeding (menstrual or urine), and other physiological contaminations intended (e.g., topping up with water) or unintended.

Albumin in the urine is present in variable structural forms, and it is not always as a single intact polypeptide molecule, but there is fragmented form, and it may include highly carbonylated form. The modification is by proteolysis during passage through the urinary tract, and chemical modification during specimen storage leads to the formation of albumin fragments [9]. The different molecular forms of albumin are not observed in the samples of healthy individuals or from all the patients, but these changes reflect the kidney diseases processes. These patient-specific albumin differences can lead to differences in results between assays based on the technology type of the assay and the specificity of the immunoassay. Albumin methods for urinary albumin can be: a) immunonephelometric using a specialized equipment (nephelometer) and primarily and infrequently used in large specialized laboratories; b) immunoturbidimetric assays are the most commonly used and can be set up on all the general chemistry high-throughput automated analyzers; c) point-of-care assays, where rapid turnaround of results or no laboratory exists; d) HPLC assays; and e) sensor or emerging assays. A review of the Royal Colleague of Pathologist Australasia Quality Assurance programs for 2021 showed that for albumin, 92% of the participating laboratories utilize immunoturbidimetric methods, 4.9% immunonephelometric, and only 3% other methods. For total protein, 49% utilize benzathonium chloride and 49% the pyrogallol red-molybdate methods. Almost all of the testing for urinary proteins and albumin is performed by automated methods on general chemistry analyzers.

Measuring albumin is the preferred method for defining and staging CKD. The urine of a healthy individual contains up to 150 mg of protein in total per day of which approximately 20 mg is albumin.

3.1 Urinary albumin methods

The immunoassay-based methods use either monoclonal or polyclonal antibodies. Currently, the methods are not standardized. The antibodies target specific epitopes on the albumin molecule or fragments. The target antibody epitopes can vary from method to method, and combined with the molecular complexity of urine albumin, this can lead to diminished correlation in results between methods. It is, therefore, of fundamental importance that results should be interpreted with caution if the patient is using more than one pathology service; ideally, the same method is suggested for the best management outcomes. This will minimize misclassifications of the albuminuria category for CKD. The methods are sufficiently sensitive and specific to measure concentration levels down to or below 5 mg/L and total precision of <5% (correlation coefficient), which allows for identifying patients with increased albumin excretion. Immunoturbidimetric methods measure only immunoreactive albumin and are unable to detect fragmented albumin; thus, they can underestimate albumin in biological samples. Most of the pathology laboratories will provide albumin results in less than 3 hours from the receipt of samples.

In contrast, the immunonephelometric assay has showed a marked reduction of 53 ± 4% when carbamylated and glycated albumin was present [10]. Very high albumin concentration in the sample can lead to an underestimation of albumin

concentration because it exceeds the antialbumin antibody concentration, a large amount of albumin cannot bind its antibody, and the obtained value is low, which is known as the "hook effect."

ELISA provides faster results and uses a small amount of antialbumin antibodies; however, competitive ELISA uses only one antibody and is less specific for albumin compared with sandwich ELISA. In sandwich ELISA, two antialbumin antibodies are required, offering better specificity but making the method expensive. ELISA methods are semiautomated and, therefore, not completely free from human analytical error [11].

There are numerous POC strip-based methods now available using different technologies and methodologies such as:

a. Use of immunoturbidimetric reaction.

b. Use of dye reagents on strips for detecting albuminuria (or proteinuria) at the POC.

   Reagent strip-based methods can also be applied for the quantitative estimation of protein or albumin by reflectance spectrophotometry. Result accuracy can be influenced due to interferences from, e.g., high urine protein hematuria, soaps, dyes, and some drugs. In a study, Pugia *et al.* showed 10–15% false positives when the albumin was <20 mg/L [12].

c. Immunochemical methods applied on the strip using monoclonal enzyme-labeled antialbumin antibodies or gold-nanoparticle-labeled antialbumin antibodies. Alternatively, polyclonal antialbumin antibodies may be used to detect the presence of albumin in the urine sample by the latex agglutination inhibition test [11].

   Dye-binding assay reports albumin result greater than 20 mg/L as positive, whereas immunologically immunoturbidimetry assays report results from 5 to 150 mg/L. Increasingly, the ones that provide quantitative albumin also measure creatinine to allow for the calculation of the albumin-creatinine ratio. If the POC methodology is of high quality and provides accurate quantitative results, it is unlikely that there would be a need to refer positive tests to a laboratory.

d. Currently, there is a considerable interest in developing immunosensors, which detect microalbuminuria without sample dilution. Carboxyl-enriched porous screen-printed carbon electrode is used in an immunosensor-based method to measure the microalbuminuria. It is based on the principle that the voltage gradient of the electrode decreases when antialbumin antibody immobilized on detector surface interacts with albumin in the sample. The quantitative detection is done with chronoamperometry. Its detection limit is 9.7 mg/mL. This method is rapid, sensitive, and highly reproducible [13].

e. Newer systems use a dye-binding-based albumin test strip assay in combination with a complementary metal-oxide semiconductor (CMOS) sensor technology (Sysmex UFC 3500 reader + CMOS). It showed a strong correlation (r = 0.92) compared with immunonephelometric assay with a limit of detection limit being as low as 5 mg/L. The effect of urinary pH on test results was negligible. Carbamylated, glycated, and partially hydrolyzed isoforms of albumin were detected [10].

Unlike immunoassay-based methods, high-pressure liquid chromatography (HPLC) can detect both the fragmented and immunounreactive albumin present in the urine sample, which produces higher results particularly in samples with low concentrations leading to higher rates of patients with microalbuminuria. The transition to use of tandem mass spectrometry and combined with HPLC provides ability to detect very low concentrations of albumin as it takes into account all its physicochemical properties. This provides the ability to establish standards, which will significantly improve the traceability and standardization of methods. Although they are more precise and accurate, however, instrumentation is specialized and costly, which limits their use for routine use. The human serum albumin standard ERM-DA470, which is serum matrix, is the most frequently used standard by manufacturers.

3.2 Total urine protein

There is no recognized reference method for measuring total urine proteins. The mix of different proteins in urine makes it impossible to optimize the current methodologies to provide consistent comparative response to the concentrations of different proteins. The two methods that are equally used are either pyrogallol red molybdate (colourimetric method) or benzethonium chloride (turbidimetric method). Both of these methods are easily adoptable on high-throughput general chemistry analyzers and have similar performance characteristics. The variability in protein composition and other compounds and concentration plus choice of standards has been found to be the factor in comparability between the two methods. Additionally, the concentration of protein in urine taken from patients can vary widely depending on dieting, exercising, and time of the day a patient urinated. In healthy individuals, Tamm-Horsfall (TH) protein (also known as uromodulin) is the most abundant protein in urine (50%), followed by albumin (20%) and immunoglobulin (5%) [14]. Tamm-Horsfall (TH) protein is apparently not significantly detected by these automated assays. Either human or bovine albumin, e.g., NIST SRM 927, is used as standard by manufacturers.

In the pyrogallol method, proteins form colored complexes, and these are spectrophotometrically measured. The presence of Bence-Jones protein can cause negative interference. Positive interference has been reported in patient receiving colloidal-based fillers, but this can be minimized if the reagent has added sodium dodecyl sulfate.

The benzethonium chloride method causes the precipitation of the proteins; turbidity and absorbance are directly related to the concentration of the urine proteins. Positive interferences have been observed in patients taking drugs, e.g., levodopa and methyldopa, while negative interference has been reported with gelatin-based plasma substitutes and one method in patients receiving contrast agent, povidone-iodine (PVP-iodine) solution.

POCT methods use a dye that changes in color. It is recommended that strips should be used to measure albumin not total proteins due to the increased accuracy. Alkaline urine (e.g., infection) can lead to false-positive results. The presence of highly colored urine (e.g., high bilirubin, other colored compounds) can make the reading of the strip more difficult. These strips may not be reactive to Bence-Jones proteins. The use of urine dipstick protein may help in CKD screening, staging, and prognosis.

Routinely, in laboratories, only turbid urines (e.g., urinary infection) are centrifugated to remove insoluble material before sample analysis. Centrifugation is recommended with all the samples for protein analysis [15]. The effect is greater at low protein concentration and the benzethonium (turbidimetric) methods being more affected due to turbidity being removed during centrifugation; hence, protein values

near the cutoff ~140 mg/L without centrifugation can lead to false-positive results and subsequently impact on diagnosis [16].

Results must be interpreted against reference or cutoff limits provided in the report. The differences in results among urine protein and albumin methods can be significant and alter risk classification and treatment decisions for individuals with kidney disease.

4. Cystatin-C (serum)

Cystatin C is an alternative to the widely available creatinine in determining renal function with the eGFR. It is a small protein produced by all the nucleated cells, which is freely filtered at the glomerulus. The production rate is relatively constant from 4 months to 70 years and is proportional to the GFR. Its clearance is predominantly renal, and since it is not reabsorbed from the renal tubular lumen, its level is directly proportional to the glomerular infiltrate. The concentration levels are not greatly influenced by height, weight, sex, race, and changes in muscle mass or nutrition [17].

Since creatinine is so widely available, has a lot of guidelines and data reinforcing its use, and is very cheap to run in laboratories, cystatin C has not been widely implemented in most commercial laboratory test catalogs. Its use is mostly confined to confirming renal function in situations where creatinined use is contraindicated, such as reduced skeletal muscle mass or to confirm the presence of a creatinine interferent as an alternative test. In the context of CKD, no clinical advantage has been found in using cystatin C over creatinine except in very exceptional situations [18]. However, some studies do note that cystatin C may be more sensitive in early CKD, where the eGFR is between 60 and 90 mL/min/1.73 m^2 [19]. In cases where there is suspected renal dysfunction, the cystatin-C-based eGFR should be calculated, since it gives more accurate and less biased estimates than the creatinine-based eGFR, and should be confirmed by the mGFR (iohexol) to reduce systematic or random variation.

Analytically, cystatin C levels are determined with immunoassays, so they are liable to all the same theoretical interferences, such as heterophilic antibodies. The immunoassay technique utilizes turbidimetric or nephelometric principles, and the analytical error can also be caused by analytes causing turbidity, such as hypertriglyceridemia. *In vivo* cystatin C levels can be increased in corticosteroid use, hyperthyroidism, increased cell turnover, and malignancy; therefore, unexpectedly high results may require these conditions to be ruled out [20, 21]. Finally, results must be interpreted based on the reference ranges provided by the specific method.

5. Urea

Urea (blood urea nitrogen) is a marker of renal function. It is the body's primary marker of nitrogenous excretion. It is produced by the liver during protein catabolism through the urea cycle, and > 90% is excreted via the kidneys. It is less utilized than creatinine though as a marker of direct renal function, because it cannot be used to accurately estimate the glomerular filtration rate. To be a marker of glomerular filtration, the analyte has to be completely filtered at the glomerulus and not reabsorbed or secreted by the tubules. While urea is completely filtered at the glomerulus, it is able to be excreted, and 40–50% is reabsorbed through the tubules by passive diffusion, limiting its utility as a specific glomerular filtration marker [22]. Furthermore, its excretion in urine can be

affected by the urine flow rate, which explains why plasma levels are increased in dehydration, since the reduced urine flow rate allows for more urea to be reabsorbed from the tubular lumen to the interstitial space and ultimately back into the blood. A number of other factors influence urea levels, including protein loading, gut bleeds, catabolism, malignancy (increase urea), starvation, and urea cycle defects (decrease urea) [23].

Urea is analyzed in the laboratory using either a chemical method or an enzymatic method. The chemical method involves the reaction of the urea present in the specimen with diacetyl to form diazine, which absorbs light at 540 nm, which is detected using a spectrophotometer. Chemical methods are no longer in use. The enzymatic method utilizes the specificity of urease for urea, which produces ammonia. The ammonia, then, reacts in an indicator reaction with α-ketoglutarate and the enzyme glutamate dehydrogenase (GLDH), with this reaction oxidizing NADH to NAD^+, which produces a change in light absorbance at 340 nm [24]. The enzymatic method can be affected by endogenous ammonia, which can be increased in urine specimens with aged specimens and patients with metabolic diseases, including urea cycle defects. CKD is associated with significant elevations in urea; however, its utility in determining renal function has been largely superseded by creatinine and the eGFR.

6. Fibroblast growth factor 23 (FGF23)

FGF23 is a phosphatonin that reduces the level of phosphate in the medium-to-long term. Hyperphosphatemia is a significant problem in chronic kidney disease, and it can be very resistant to treatment. It is postulated that FGF23 is an excellent marker in predicting deterioration in CKD [25]. It acts by binding to α-Klotho, a transmembrane FGF receptor predominantly expressed by the proximal tubules. The effect of FGF23 binding to the α-Klotho transmembrane complex is reduction in the insertion in sodium proximal tubular transporter 2a into the renal tubular membrane, which is involved in renal phosphate reabsorption. In the kidneys, it also reduces calcitriol (1, 25-dihydroxy vitamin D) production by suppressing 1a-hydroxylase and stimulating 24 hydroxylase. This results in less active vitamin D, which limits phosphate absorption from the gut and phosphate reabsorption from the kidney [26]. This would result in a reduced phosphate level in normal physiology.

CKD results in an elevation in FGF23. FGF23 production is stimulated by calcitriol, phosphate, and parathyroid hormone (PTH) [27], the latter two of which are already raised in CKD. Elevations in FGF23 are not specific for CKD, with elevations also occurring in genetic forms of rickets (X-linked, autosomal dominant, and autosomal recessive rickets), oncogenic osteomalacia, and fibrous dysplasia, but these tend to be readily differentiated clinically from CKD and are associated with hypophosphatemia. FGF23 looks to be a particularly useful marker in predicting refractory hyperparathyroidism, with its predictive ability superior to that of the PTH [28]. CKD begins to increase very early in kidney dysfunction, with end-stage renal failure associated with 1000fold increases. In CKD, FGF23 is correlated with endothelial dysfunction, CKD progression, and mortality [29].

FGF23 levels are typically done using immunoassay techniques and, as such, can be affected by the various causes of analytical issues of immunoassays, such as heterophile antibodies and high-molecular-weight interferents that can cause nonspecific binding to a molecularly similar epitope, as well as the theoretical risk of hook effects at very high levels. An FGF23 specific analytical issue is related to the availability of different assays. Some detect the C-terminal peptide (cFGF23), while others detect the whole

or intact FGF23 molecule. The difference between these molecules means that results between different assays are not interchangeable and must be interpreted in the context of the quoted reference interval. This difference in molecular FGF23 can be important to consider in renal failure, as iron deficiency, which is also common in relatively common in CKD, can falsely elevate cFGF23, while iFGF23 is unaffected [26].

7. Parathyroid hormone (PTH)

Parathyroid hormone is a principal mediator in calcium and phosphate biochemistry. It is a hormone that is secreted by the parathyroid glands on the back of the thyroid and responds to ionized calcium through the calcium sensing receptor. Hence, clinical units frequently request the estimation of the ionized calcium. The PTH performs a number of actions, including increased bone resorption of calcium and phosphate, increased renal calcium reabsorption, and decreased phosphate renal reabsorption and indirectly increases calcium and phosphate absorption from the small intestine by inducing active vitamin D production (calcitriol, 1, 25-dihydroxyvitamin D) through the induction of 1alpha hydroxylase in the kidneys [26].

In CKD, the regulation of calcium and phosphate is deranged due to the central role of the kidney in the homeostasis of these compounds. The kidneys play a pivotal role in the maintenance of calcium levels by eliminating and regulating solutes that can precipitate calcium out of solution, such as oxalate and phosphate, as well as contributing to the control of the acid–base status. This can lead to calcification throughout the body termed CKD-mineral and bone disorder, renal osteodystrophy, and adynamic bone disease [30]. It is in this setting that the PTH can prove useful in CKD. As the GFR deteriorates, the PTH levels also increase exponentially [31]. This is to compensate for the declining ionized calcium that results because of the reduced loss of oxalate and phosphate. The more the PTH goes up and the longer it does, the more likely of developing tertiary hyperparathyroidism, which is essentially a secondary hyperparathyroidism that has transitioned to autonomous PTH production. However, if the PTH is kept too low, patients are then at risk of developing adynamic bone disease [32]. Thus, CKD patients who are not on dialysis should have their PTH regularly monitored, and vitamin D status assessed and replaced if deficient. If the patient is on dialysis, the PTH should be maintained within two to nine times the upper limit of normal for the assay [33].

PTH is performed in the laboratory using immunoassays. Historically, many PTH immunoassays were susceptible to cross interference with the inactive PTH C-terminal metabolite, which would accumulate in CKD. Current assays are more specific for the intact, biologically active PTH molecule, with the immunoassay antibodies recognizing the biologically active N-terminus [26]. Being an immunoassay, it is liable to all the same interference types common to all immunoassays, such as heterophile antibody interference. Hook effect is rare in modern day immunoassays, but warrants theoretical consideration if a much lower PTH result than expected is produced. Care must be taken to ensure that the specimen is promptly separated from cells and analyzed to avoid *in vitro* lowering of levels [34].

8. Conclusion

Biochemical analysis is essential to the diagnosis, management, and monitoring of CKD. This chapter has served as a primer to such testing, looking at the analytes and

laboratory techniques that commonly make up renal function testing. It has not gone into depth in the hematological testing, endocrine testing, or dynamic function testing commonly employed in CKD management. However, even routine renal function testing warrants vigilance in interpretation. The laboratory is a suitable place to assist in these matters.

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Chapter 6

The Biomarkers of Cardiovascular Complications in Chronic Kidney Disease - Mineral and Bone Disorders, Literature Review

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Abstract

Despite the successes achieved in the management of patients with chronic kidney disease (CKD) in recent years, cardiovascular complications (CVCs) still remain the leading cause of death in this cohort. Accumulating evidence suggest CKD–mineral and bone disorders (CKD-MBDs) are closely connected with mortality from CVCs. Clarification of the possible early biomarkers of CKD-MBDs has led to interest in FGF-23, Klotho, and Sclerostin. It is now well established that the effects of these factors in CKD go beyond bone metabolism disorders only. Significantly elevated FGF-23 serum levels in CKD have been shown to be associated with increased mortality from cardiovascular causes. In addition, it was found that a decrease in Klotho serum levels is associated with early and progressive vascular calcification in CKD. In recent years, the data were accumulated on the important role of Sclerostin in the blood vessels pathophysiology in CKD. This chapter summarizes current evidence of the probable association of CVCs with known (phosphate, parathyroid hormone, and vitamin D) and new (FGF-23, Klotho, and Sclerostin) CKD-MBD biomarkers. In addition the review pays attention to possible impact of CKD therapy on the studied biomarkers and thus reducing the risk of CVCs in CKD patients.

Keywords: chronic kidney disease (CKD), FGF-23, Klotho, cardiovascular remodeling, vascular calcification, sclerostin

1. Introduction

Chronic kidney disease (CKD) is a huge public health problem, associated with a high mortality risk [1, 2]. Cardiovascular complications (CVCs) are the most common cause of death in this group of patients [3]. As compared with general population, mortality rate due to CVCs in patients with chronic renal failure is 10 times higher, and in young people, this risk is higher by 100 or more times. Damage of the

cardiovascular system begins already in the early CKD stages and is found in about 80–90% of dialysis patients [3, 4].

The complex relationship between cardiovascular disease (CVD) and kidney disease results from the interaction of conventional, unconventional CVD risk factors modified by CKD and new CKD-related risk factors such as uremic toxins, and mineral and bone disorders (MBDs) markers in CKD [4–6]. Uremic toxins with suspected cardiovascular toxicity, including FGF-23, start to accumulate in the body in the early CKD stages [4, 5, 7].

The studies revealed that CVCs in CKD largely result from accelerated arteriosclerosis (vascular tunica media calcification followed by extended Monckeberg sclerosis accompanied by increased vascular stiffness) and uremic heart remodeling (left ventricular hypertrophy (LVH) and uremic cardiomyopathy) which together lead to an urgently high cardiovascular (CV) mortality in patients with CKD [4, 5, 8, 9].

CKD-associated heart remodeling and vascular calcification (VC) have a multifactorial genesis [3–5]. In recent years, more and more data have been accumulating that the effects of CKD-MBD biomarkers go beyond bone disorders only. The CKD-MBD pathogenesis was originally described as a decrease in the levels of 1.25-dihydroxyvitamin D [1.25 $(OH)_2$ D_3], synthesized in the kidneys, that leads to the development of hypocalcemia since vitamin D (VD) regulates intestinal calcium absorption [3, 4]. On the other hand, a decrease in glomerular filtration rate (GFR) leads to phosphate (P) retention. Hyperphosphatemia (HP) along with hypocalcemia stimulate the production of parathyroid hormone (PTH), which is considered as a uremic toxin primarily due to its adverse effects on the heart (development of diffuse heart interstitial fibrosis) and bone tissue (leads to bone resorption with the development of fibrous osteitis). Vitamin D deficiency, increased serum PTH levels with the development of secondary hyperparathyroidism (SHPT), and HP were considered to be the main contributors to the development of CVD in CKD [3, 7, 10]. However, in recent years, new factors have been identified (FGF-23, Klotho, and Sclerostin), which has led to a revision of CKD-MBD pathogenesis [7, 8]. FGF-23 serum levels increase from the early stages of CKD in response to P retention and lead to increased excretion of P (phosphaturic hormone), thereby maintaining normal serum P levels. To realize its phosphaturic effect, FGF-23 requires the Klotho cofactor. Klotho is synthesized in the proximal renal tubules. Klotho is a very sensitive factor, and its level begins to decline from the early stages of CKD and progressively decreases as nephrosclerosis progresses. So an increase in serum FGF-23 in the early stages of CKD is an adaptive mechanism, however, with a progressive decline in renal function (eGFR less than 30 ml/min/1.73 m^2) FGF-23 can no longer provide sufficient P excretion, despite its high concentration in serum, and HP develops [10].

In turn, significantly elevated FGF-23 levels in CKD have been shown to be associated with increased mortality from cardiovascular causes (development of LVH and uremic cardiomyopathy) [8, 10]. In addition, it was found that a decrease in Klotho serum level is associated with early and progressive VC in CKD [7, 9, 11, 12]. In recent years, the data were accumulated on the important role of Sclerostin glycoprotein in CKD. Today, Sclerostin is an established regulator of bone mineralization, while its role in the blood vessels pathophysiology in CKD is actively studied [7, 8, 12].

It is discussed that FGF-23, Klotho, and Sclerostin can be used as early biomarkers to predict the CVC risk in CKD [7–9]. Furthermore, the accumulated recently data allow to consider these factors as a possible therapeutic option for reducing mortality in CKD patients [8, 10].

In this review, we summarize the recent literature data, concerning the association of CKD-related CVCs with the better known – "old" (PTH, P, and vitamin D) and newer (FGF-23, Klotho, and Sclerostin) biomarkers of CKD-MBD, and the possibilities for correction of these disorders.

2. The biomarkers of cardiovascular complications in CKD-MBD

2.1 The role of unconventional CVC risk factors modified by CKD

2.1.1 Phosphate in CKD-MBD, vascular calcification, and uremic cardiomyopathy

Hyperphosphatemia (HP) is a well-established manifestation of CKD. In the early stages of CKD, P retention leads to an increase in serum FGF-23 levels, which enhances phosphaturia (**Table 1**).

In addition, FGF-23 blocks 1-alpha-hydroxylase, thereby reducing the synthesis of the active form of vitamin D in the kidneys, which leads to a decrease in the absorption of P and calcium (Ca) in the gastrointestinal tract [10]. In the early stages of CKD,

Biomarkers	Bone Metabolism	Vascular Calcification	Uremic Cardiomyopathy
Phosphate	Major trigger in CKD-MBD ↑P → ↑FGF23 → ↓Vit D → ↓ Ca ↑P + ↓Ca → ↑PTH → ↑Ca	Promotes VC ↑P affects the VSMC transition into osteoblast phenotype	Increased LV mass Cardiac fibrosis
PTH	Key mediator of bone turnover Regulates P and Ca homeostasis	SHPT correlates with an increased calcium content in the myocardium and impaired systolic and diastolic ventricular function	Cardiomyocyte hypertrophy Cardiac interstitial fibrosis
Vit D	Key role in Ca and P homeostasis Depletion promote sHPTH and osteitis fibrosis	Biphasic curve of vit D on calcification	↓Vit D → impairs contractile function Increases cardiac mass, activated renin gene expression
Klotho	Acts as a Wnt inhibitor Modify bone metabolism	Inhibitor of VC Klotho deficiency→ impair endothelial function	Klotho deficiency→ LVH Cardiac fibrosis
FGF-23	Posphaturic hormone Acts through α-klotho	Is not clear if it has a direct effect on VC The effect of FGF-23 on fetuin-A level	Trigger factor in the pathogenesis of uremic cardiomyopathy LV hypertrophy induction by activating FGFR-4
Sclerostin	Inhibits bone turnover	Marker of vascular calcification	There are no conclusive data

Abbreviations: VC, vascular calcification; P, phosphate; LVH, left ventricular hypertrophy; SHPT, secondary hyperparathyroidism; VSMC, vascular smooth muscle cells; LV mass, left ventricular mass; →, brings to; ↓, decrease; ↑, increase.

Table 1.
CKD-MBD biomarkers, role in bone metabolism, vascular calcification, and uremic cardiomyopathy.

this plays an adaptive role and helps to maintain normal serum P levels. However, as CKD progresses, these adaptive mechanisms become ineffective, that followed by HP and marked increase in FGF-23 and PTH serum levels (**Table 1**).

In recent decades, the role of HP in the development and progression of vascular calcification (VC) has been actively studied. HP is thought to affect the vascular smooth muscle cells (VSMCs) transition into osteoblast phenotype [11, 12]. PiT-1 phosphate transporter is believed to be a key mediator in the phosphate-induced rearrangement of VSMCs, activating the expression of genes associated with bone formation and VSMCs osteochondrogenic differentiation [7, 11–13]. Vascular mineralization, especially in the coronary arteries, is closely associated with CKD patients' mortality. The studies revealed that the level of coronary arteries mineralization in hemodialysis patients is five times higher than in patients without CKD and dialysis. Besides that increased mineralization, HP directly affects the valve calcification progression [14–16]. Increased serum P level was associated with increasing vascular and valvular calcification in study of 439 patients with moderate CKD without previous clinical CVD [17]. Moreover, a study in 286 End Stage Kidney Disease patients undergoing chronic hemodialysis demonstrated increased calcification of aortic arch, which was strongly tied with the degree of HP [18]. In the model of human vessel culture, prolonged exposition with P led to reinforced calcification in vessels from CKD 5 stage patients compared with controls [19].

In addition, it is being discussed a direct effect of HP on cardiomyocytes (CMC). HP is connected with growth of left ventricular mass (LV mass) and prevalence of LVH, independent of GFR [10]. Serum P levels correlated with the growth of LVH in 4005 young adults in the CARDIA study [20]. Likewise, higher dietary P consumption correlated with a growth of LV mass in 4494 participants without previous CVD [21]. Patients with intermediate CKD also demonstrated a correlation of increased serum P levels and LV mass growth [22, 23]. A restriction of these studies was that examinations of FGF-23 serum levels were often not explored. However, the observed LVH might be provoked by P-induced increase of serum FGF-23 as well.

The phosphate-induced LVH can be warned by a knockout of FGFR-4 [24]. This is consistent with the hypothesis that P promotes LVH by stimulating FGF-23, which instigate LVH via FGFR-4.

P levels outside the physiological range were also often associated with the induction of interstitial fibrosis in experimental studies [25, 26]. Myocardial fibrosis can contribute to increased LV wall stiffness and diastolic dysfunction (**Table 1**). In addition, fibrosis interrupts electrical signals, making the tissue more arrhythmogenic [25, 26]. Cardiomarkers and parameters of myocardial function were consistently higher in the group of patients with higher serum P levels compared to the group with normal serum P [27].

2.1.2 Parathyroid hormone (PTH) in CKD-MBD, uremic cardiomyopathy, and vascular calcification

An increase in serum PTH levels in CKD develops in response to HP (P retention and ineffectiveness of FGF-23 phosphaturic effect), and hypocalcemia (decreased synthesis of vitamin D in the kidneys leads to decreased intestinal absorption of Ca) and is a common complication of advanced CKD stages. Long-term increase in PTH leads to the induction of parathyroid hyperplasia and SHPT [4, 7].

Besides the regulation of Ca and P homeostasis, elevated PTH levels affect the cardiovascular system [28]. The experimental data suggest that PTH can directly

affect the myocardium. PTH affected rat myocardial cells, causing their early death due to an increased Ca supply to myocardiocytes [29]. Ca ions are critical for the connection between excitation and contraction of the myocardium and contraction and relaxation of the heart [5, 30]. The presence of SHPT correlates with an increased Ca content in the myocardium and impaired systolic and diastolic ventricular function (**Table 1**) [31].

In addition, there is a correlation of PTH levels, LVH, and mortality in SHPT patients [32]. The study with 2040 patients showed PTH as a substantial LVH predictor [32].

The experimental rat CKD model revealed that continuous infusion of supraphysiologic doses of synthetic PTH in parathyroid-ectomized animals was associated with extensive progression of interstitial myocardial fibrosis, regardless of serum P level or uremia [29]. Moreover, higher PTH levels produce a direct trophic effect on cardiomyocytes, interstitial fibroblasts, and smooth muscle cells of intramyocardial arterioles, contributing to LVH and fibrosis. PTH activates fibroblasts and regulates profibrotic factors such as aldosterone and angiotensin II (PTH stimulates the secretion of aldosterone and angiotensin II) [28].

It was found an association of PTH serum levels and arterial hypertension (AH) [33]. A trial with 1784 participants with moderate CKD or normal eGFR, observed for 7 years, revealed that PTH serum level was able to forecast AH [34]. Besides, a meta-analysis, including 18,994 individuals, demonstrated that elevated PTH level may be connected with a higher level of AH [35].

PTH impact on cardiomyocytes induces an elevation in production of fetal-type proteins via protein kinase C activation and exerts on cardiomyocyte function [36].

There is the evidence suggesting PTH produces an effect on blood vessels, affecting endothelial dysfunction and the increased serum levels of endothelin-1 and IL-6 [34]. The other study demonstrated the PTH effect as a major determinant of coronary artery disease ranging from the elastic plate rupture to arterial tunica media calcification [37].

Despite the theoretical inverse relationship between serum PTH level and LV function, parathyroidectomy was not always connected with an amelioration in cardiac contractile function [38–41]. This allows to suggest that the changes caused by PTH may be irreversible in the case of prolonged severe SHPT, or other factors, contributing to myocardial dysfunction, may be more important than excessive PTH level.

2.1.3 Vitamin D in CKD-MBD, vascular calcification, and uremic cardiomyopathy

CKD progression, increased FGF-23 levels, and HP are accompanied by a decrease in vitamin D (VD) synthesis in the kidneys, which leads to hypocalcemia and activation of PTH synthesis (**Table 1**). In addition, it has been found that VD deficiency is associated with CVD directly, including carotid intima-media thickness, VC, cardiovascular (CV) events, and mortality [40, 42]. VD demonstrated anti-inflammatory and antioxidant effects and renin expression reduction [43–45].

VD was suggested to protect against CVD; however, the observed effects of VD on CKD patients' outcomes are controversial [43–45].

The experimental data suggest a direct VD effect on endothelial function associated with a reduced oxidative stress and increased endothelial nitric oxide synthase (eNOS) levels. These findings correlate with several randomized clinical trials (RCTs) findings that demonstrated the beneficial effects of VD or paricalcitol

supplementation on endothelial function in CKD stages 3–4 [46, 47]. The studies revealed other beneficial effects of VD supplementation on the markers of inflammation, intracellular adhesion molecule, vascular cell adhesion molecule, PTH, E-selectin, and arterial stiffness [7, 47, 48].

The studies on a specially designed mouse model revealed that targeted deletion of the VD receptor gene increases the size of cardiomyocytes and LV mass without fibrosis [49]. Similarly, the previous studies found the association between VD deficiency and increased myocardial collagen content, impaired cardiac contractility, and increased LV mass [50]. On the other hand, the positive effect of VD active metabolites treatment on the LVH regression and the heart failure prevention [51] revealed in the experimental models was not confirmed in clinical Primo and Opera studies. The studies found no LVH regression and improve LV systolic and diastolic dysfunction in CKD stage 3–5 patients following 48-week and 52-week paricalcitol treatments, respectively, at a dose that adequately controlled SHPT [52, 53]. Thus, the promising effect of reducing CKD-related CVDs with treatment with VD-active metabolites requires further clarification.

In the same time, it has been suggested that VD supplementation may protect cardiovascular system through modulation of the renin-angiotensin system (RAAS) [54, 55]. Li et al. [56, 57] suggested that VD was a negative endocrine regulator of renin biosynthesis in vivo, since renin mRNA and protein levels in the kidney of both vitamin D receptor knockout mice and 25-hydroxyvitamin D1 α-hydroxylase knockout mice were found to be significantly increased. Moreover, it has been observed that VD receptor knockout mice developed AH and LVH as a result of RAAS dysregulation [56, 58]. The results of numerous studies confirmed that 1,25-dihydroxyvitamin D3 directly suppressed renin gene expression, and this effect was independent of VD influence on Ca metabolism [56, 58].

2.2 The role of new CKD-MBD biomarkers in the assessment of cardiovascular risk in CKD

The significant risk of CVD and mortality in CKD patients suggests an urgent need to find a reliable biomarker that would timely not only detect kidney disease but also identify patients with a higher risk of cardiovascular mortality.

Compared with the "old" CKD-MBD biomarkers and already established in clinical practice (P, PTH, and vitamin D), whose blood elevated levels unfortunately indicate the advanced stages of CKD, the study of newer biomarkers (FGF-23, Klotho, and Sclerostin) is promising as their serum levels rise is found in the early stages of CKD [7, 8].

2.2.1 Fibroblast growth factor-23 (FGF-23)

FGF-23, a glycoprotein synthesized by osteocytes, has been identified as a phosphaturic hormone whose serum levels rise earlier in CKD (CKD stage 2–3A) than PTH (CKD stage 4–5).

Under physiological conditions, FGF-23 maintains normal blood P levels by inhibiting sodium phosphate (NaPi) co-transporters in renal tubules and thus reducing renal phosphate reabsorption [8, 59, 60]. In addition, FGF-23 inhibits 1-α-hydroxylase in the proximal tubules (the enzyme responsible for the conversion of 25-OH-vitamin D into its active form, 1.25 $(OH)_2$-vitamin D_3) [59]. Thus, FGF-23

regulates serum P levels both directly through NaPi co-transporters and indirectly through vitamin D metabolism, which regulates intestinal P absorption (**Table 1**).

The clinical studies have demonstrated that serum FGF-23 levels begin to rise early, around stage 2-3A of CKD [7, 8, 10]. FGF-23 secretion is stimulated by P retention due to GFR decline and a decrease in Klotho expression in the renal tubular cells. The phosphaturic effect of FGF-23 leads to the normalization of serum P levels in the early stages of CKD. However, later, as a decrease in eGFR to 30 ml/min/1.73 m^2, HP still develops, despite a significantly increased FGF-23 serum levels. Patients in the pre-dialysis stage of CKD have a 100- to 200-fold increased FGF-23. HP leads to increase secretion of PTH [7, 8, 10].

Given the high CVD mortality in CKD patients, FGF-23 effect on CVD mortality was intensively studied both in experimental and in clinical settings. The recent meta-analysis found that significantly elevated FGF-23 levels are directly associated with cardiovascular (CV) events and all-cause mortality in dialysis patients [61]. FGF-23-level measurement in CKD patients over time may help to identify a subpopulation of patients with a higher mortality risk. The studies revealed that patients with a slower increase in FGF-23 levels over 5 years demonstrated a fivefold higher risk of death, and with a rapid increase in FGF-23 levels, the risk of death was 15 times higher than in patients with stable FGF-23 level [62]. These data indicate that an increased level of FGF-23 acts as a uremic toxin, earlier than PTH. Most of the studies investigating the relationship between FGF-23 and mortality in CKD patients analyzed the presence of LVH and the activation of the renin-angiotensin-aldosterone system (RAAS). In patients with diabetic nephropathy and early CKD (stages 2 and 3), lower plasma Klotho levels and higher FGF-23 levels were associated with a higher risk of LVH and, therefore, higher CV hospitalization rate [63].

As for LVH development, the experimental data suggest that FGF-23 can affect the heart and cause myocytes hypertrophy without Klotho [64]. FGF-23 demonstrated direct LVH induction by activating fibroblast growth factor receptor-4 (FGFR-4) in the heart in the absence of membrane Klotho [65].

The pathogenetic relationship between FGF-23 serum level and LVH was fully confirmed in the clinical work of Faul and Ansel [66] which showed that an increase in serum FGF-23 levels can directly lead to LVH development in CKD patients. The study consists of several stages; at the first stage, more than 3000 patients with renal insufficiency were examined for serum FGF-23 and echocardiography (EchoCG) at baseline and 1 year later. Each increase in serum FGF-23 on 1 logarithmic unit was associated with an increase in LVMI on 1.5 g/m^2. After 2.9 $\pm$ 0.5 years, the researchers re-examined 411 patients who had normal EchoCG parameters at the beginning of the study. In 84 (20%) patients with normal blood pressure (BP) levels, LVH was firstly detected. At the same time, each increase in FGF-23 on 1 logarithmic unit led to an increase in the frequency of LVH de novo detection by 4.4 times; and significantly high levels of FGF-23 caused a sevenfold increase in the frequency of LVH detection, independent of the AH.

Besides, FGF-23 is thought to contribute to the development of AH by modulating the RAAS. Experimental studies indicate that FGF-23-mediated $1,25(OH)_2D_3$ deficiency activates the RAAS. Disruption of $1,25(OH)_2D_3$ signaling in vitamin D receptor null mice promotes renal renin expression and subsequent production of the vasoconstrictor angiotensin II [10].

Moreover, FGF-23 also increases the production of transforming growth factor-β (TGF-β), lipocalin-2, and tumor necrosis factor-α (TNF-α), which are well-known markers of inflammation [7, 67].

Therefore, FGF-23 increases the risk of CVD both directly (by affecting the heart) and/or indirectly (through the RAAS activation, and inflammation) [68].

The clinical evidence suggests an association between FGF-23 levels and an increased CVD risk at all stages of CKD. FGF-23 was associated with an increased risk of CV events and mortality in diabetic patients, even with normal or moderately impaired renal function [69]. Moreover, FGF-23 levels directly correlated with LVH and inversely with left ventricular ejection fraction in hemodialysis patients, in whom FGF-23 was an independent overall mortality predictor [70]. However the authors indicate that the predictive potential of FGF-23 in relation to CVD mortality is higher in patients with intermediate GFR (mean value 60 ml/min) [71].

According to clinical data [72], an increase in serum FGF-23 levels was associated with a moderately elevated level of troponin I. In the same time, serum troponin I correlated with left ventricular mass index (LVMI) in patients with CKD.

In addition, it was established [73] that an increase in serum FGF-23 levels accelerated the development of vascular arteriosclerosis almost by sixfold, with the direct correlation with VC. However, in multivariate analysis, this relationship was statistically weak, which may indicate a possible indirect effect of FGF-23 on VC. Further obtained data indicate the effect of FGF-23 on fetuin-A level, which is known to be synthesized by osteoblasts and is an inhibitor of vascular smooth muscle cells (VSMC) calcification [73, 74].

In another prospective of the mild-to-moderate kidney disease (MMKD) study [75] involving 227 patients with nondiabetic CKD 1–4 stages, the patients were followed up for 53 months to assess the progression of the nephropathy. Based on the results, an independent direct relationship between increased serum FGF-23 level and CKD progression rate was established. FGF-23 was recognized as an important independent predictor of adverse renal and CV prognosis, and in addition, in the regression Cox analysis, P levels lost prognostic value after adjustment to serum FGF-23 level.

On the other hand, experimental evidence suggests that the progression of LVH in CKD can be delayed. The studies reveal that specific blockade of FGFR-4 in a rat model slows down LVH progression [24, 76]. Besides that, the experimental data in uremic rats also indicate that vitamin D treatment reduced the LVH severity and FGFR-4 expression suggesting calcitriol cardioprotective effects [77]. Therefore, LVH in CKD can be treated and the risk of CVD can be reduced either by lowering FGF-23 levels or by inhibiting its effect on FGFR-4.

Accumulating recently data allow considering FGF-23 as an earlier and important predictor of mortality than serum P and PTH levels in patients with CKD. Elevated serum FGF-23 level is currently considered as an independent trigger factor in the pathogenesis of uremic cardiomyopathy that served as the basis for suggesting FGF-23 as a new uremic toxin, earlier than PTH [78].

2.2.2 Klotho

Klotho is synthesized in the proximal renal tubules. There are two main forms of Klotho protein: transmembrane (a coreceptor for FGF-23) and secreted (soluble Klotho). The last one enters into the bloodstream and performs endocrine functions, including cardioprotection.

Deficit of Klotho causes development of multiple systemic manifestations (i.e. premature aging syndrome), an integral part of which is severe cardiovascular impairments [7–9, 79].

Patients with CKD develop Klotho deficiency contributes to high CVD mortality. Decreases in Klotho levels in CKD can be found at stage 2, and urine tests reveal decreased Klotho level at stage 1 [79, 80].

In vitro studies have shown that along with the increase in phosphaturia, stabilization of GFR, and regulation of vascular endothelial permeability, serum Klotho suppresses Na-dependent capture of P by the endothelium and VSMCs and prevents differentiation of VSMCs and mineralization induced by HP [80, 81].

In an experiment, Klotho overexpression slowed down CKD advancement, improves P metabolism, and protects the vasculature from calcification [79–81]. The experimental studies revealed that Klotho circulating form produces a cardioprotective effect also by inhibiting TRPC6 channels in the heart [82]. Klotho-deficient mice with CKD demonstrated a more pronounced LVH than wild-type mice with CKD, even after serum P and FGF-23 levels normalization [83]. Klotho deficiency in CKD results in cardiac fibrosis besides hypertrophy. The studies demonstrated endogenous Klotho expression by both human cardiomyocytes (CMC) and cardiac fibroblasts. Uremic serum or TGF-β1 inhibits Klotho expression in CMC [84]. Klotho upregulation inhibits TGF-β-induced fibrosis and pathogenic Wnt/β-catenin signaling in CMC (**Table 1**) [84].

The clinical studies support the experimental evidence of Klotho cardioprotective role. In patients with stage 3 CKD, changes in the FGF-23/Klotho ratio correlated with changes in the LV mass [85]. In hemodialysis patients, low Klotho levels were associated with CV events independent of other CKD-MBD factors [86]. According to the KNOW-CKD study, serum Klotho was demonstrated as an independent biomarker of LV mass index in CKD patients [87].

Li F. et al. found that patients with calcified aortic valves had lower serum levels of Klotho, and that treatment with recombinant Klotho reduced the high P-induced osteogenic activity in interstitial cells of the human aortic valve [88]. Another study revealed that Klotho administration reduced the severity of high P-induced renal and cardiac fibrosis and improved both renal and cardiac function (in the absence of prior kidney disease) [89]. Given the available experimental data, it can be assumed that the treatment of Klotho deficiency in CKD may inhibit the development of CVCs.

Taking into account the impairment of Klotho/FGF-23 axis, Klotho deficiency, and high levels of FGF-23 in patients with CKD, it has been suggested that the Klotho/FGF-23 axis may not only be a diagnostic and prognostic biomarker of CVD in CKD, but also a therapeutic target, since these disorders contribute to progression of CKD and CVD [89, 90].

2.2.3 Sclerostin

In recent years, the data were accumulated on the important role of Sclerostin (Scn) glycoprotein in CKD [91, 92]. Scn, a protein produced by osteocytes and encoded by the SOST gene on chromosome 17q12-q21, is an inhibitor of the integration pathway (Wnt) in osteoblasts, which is responsible for osteoblastogenesis [93]. Thus, in healthy people, Scn inhibits bone formation (**Table 1**). Interestingly, the SOST gene is also expressed in tissues and organs other than bones, mainly in the heart, lungs, aorta, and kidneys [7, 94, 95]. Given these data, Scn is no longer considered only a bone-specific protein and a marker of bone metabolism but became the focus of further research aimed at elucidating its role in tissues and organs. Unfortunately, the exact causes of tissue Scn synthesis both in healthy people and in CKD patients remain unclear. Today, Scn is an established regulator of bone mineralization, while its role in the blood vessels pathophysiology in CKD is actively studied [91, 96].

It is important to determine the clinical significance of Scn metabolism changes in CKD, since the relationship between adynamic bone disease and heart and blood vessels calcification in CKD patients is considered to be established [97]. At the same time, the publications available to date on the role of Scn in ectopic calcification are still controversial [91, 92, 96, 98, 99].

Increased serum Scn levels are assumed to slow down osteogenesis in CKD. At the same time, there is reason to believe that this mechanism is blocked in CKD, and the increased Scn level is mainly aimed at inhibiting extraosseous calcification [8, 91, 98, 99].

The meta-analysis by Kanbay et al. revealed that serum Scn was not associated with all-cause mortality and CVD mortality [99]. Previously, serum Scn values were found to be associated with lethal and nonfatal CV events in CKD patients without dialysis [100]. On the other hand, the NECOSAD study revealed that dialysis patients with elevated Scn levels demonstrated better CV survival [101].

Our data are consistent with the findings of the authors who demonstrated Scn protective effect on calcification in CKD [91, 98, 99, 102]. Scn inhibitory effect on osteogenesis and the negative correlation between Scn and PTH level as a uremic toxin may support these data (**Figure 1**) [98, 99, 102].

The recent studies indicate that Wnt pathway plays a certain role in vascular biology, including VC, angiogenesis, and atherosclerosis [103]. The Wnt pathway is involved in many aspects of biology, including cell survival, stem cell development, and cell differentiation, including bone and blood vessels [103, 104]. Scn slows down the canonical Wnt signaling pathway and inhibits osteoblast activity and bone formation [103, 104]. Deceleration of the Wnt signaling pathway reduces VSMC proliferation.

Given the fact that atherosclerosis and calcification are actively regulated and progressive processes, we can hypothesize that high levels of Scn may indicate some kind of protective mechanism that could inhibit Wnt pathway activation and restore Wnt signaling observed in healthy people [99, 104].

Register et al. [98] found that high levels of Scn were associated with less calcification of carotid plaques in diabetic males and were not associated with aorta or coronary arteries calcification. The authors suggested that Scn overproduction might be a physiological adaptation to increased calcification.

At the same time, further studies to confirm the role of Scn in the FGF-23-Klotho-Scn system as protection against the pathogenic transformation of VSMCs, triggered by P and FGF-23, are considered as priorities. Scn is likely to counteract the effects of

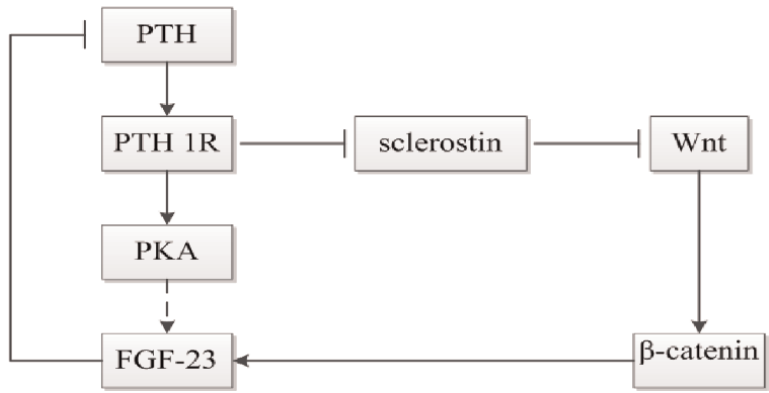

Figure 1.
The relationship between PTH, FGF-23, and Scn [8].

low Klotho levels and high FGF-23 levels enabling temporary compensatory balance in the FGF-23-Klotho-Scn system. Increased Scn level in CKD is probably aimed at calcification inhibition but cannot completely suppress it, since a decrease in Klotho can be a much more powerful stimulus for calcification, and an increased level of PTH inhibits Scn (**Figure 1**). Since Scn levels increase and Klotho levels decrease as CKD progresses, several authors may misinterpret the role of Scn as a factor that enhances calcification. In fact (results of multivariate analysis), a sharp drop in Klotho level during the progression of CKD is likely to negate Scn protective effects [99, 102].

We can view all three factors (FGF-23-Klotho-Scn) as a discrete system of factors that influence CV risk. Apparently, such a high CVD risk is determined by the combined action of all these three factors, which begin to manifest themselves at the early stages of CKD and are associated not only with each other, but also with unconventional CKD factors (P, PTH, and vitamin D3), which emerge as CKD progresses, and rapidly increase, potentiating each other and thereby greatly increase CVD overall mortality risk. The influence of each group of these factors can make a different contribution depending on CKD stage. It is noteworthy that many data do indicate that the FGF-23-Klotho-Scn axis may be a potentially new early target in cardiorenal medicine.

The identification of the real physiological and pathophysiological role of Scn in cardiovascular diseases in CKD patients requires new research in this field, which will determine future therapeutic strategies.

3. CKD-MBD correction and new biomarkers (FGF-23, Klotho, and Sclerostin)

The publication of preliminary findings of several clinical studies indicates the possibility of the influence of the main renoprotective therapy aspects, such as early treatment of arterial hypertension (AH), hyperphosphatemia (HP), anemia, elevated PTH levels, and impaired nutritional status, on Klotho protein synthesis maintenance and FGF-23 overproduction inhibition [8, 105–107].

Since serum FGF-23 level (as an earlier marker of MBD than PTH and P in CKD) increases in response to P retention, prophylactic reduction of dietary P in CKD patients with increased FGF-23 levels and use of phosphate binders (Pbs) became an important therapeutic challenge in patients with CKD. This can contribute to the prevention of SHPT and CVD in CKD [8, 108–111]. Study in healthy individuals demonstrated that low-dietary P uptake reduced FGF-23 levels, while an elevated P uptake increased serum FGF-23 [108–110]. In uremic rats, feeding of a plant-based diet substantially decreased FGF-23 levels as opposed to a meat-based diet [112].

Clinical researches in CKD patients showed a FGF-23 decreasing effect of vegetarian diets [113–117]. Moe et al. showed that the vegetarian diet diminishes serum P levels as well [113].

Some clinical study findings suggest [106] that low-protein diet (LPD) in combination with keto/amino acids for at least 12 months in patients with stages 3b-4 of CKD can prevent the development of nutritional status disorders as well as maintain Klotho expression and inhibit FGF-23 increased production.

Moreover, some findings suggest that the stage 3b-4 CKD patients with LPD (0.6 g of protein per kg of body weight/day) and calcium salts of keto acids could achieve and maintain the target serum P and Ca level taking lower doses of Pbs compared to patients used LPD but did not take keto/amino acids [106].

Pbs sequester P thus warn its gastrointestinal absorption. The non-Ca-based Pb sevelamer carbonate lowers FGF-23 levels in CKD patients, whereas lanthanum carbonate does not demonstrate a compatible effect in FGF-23 levels. But none have evidence of true CV outcomes [118–123].

Ca-containing Pbs did not decrease or even elevate serum FGF-23 levels and induce VC progression [123]. Hence, Ca-containing Pbs are rather unsuitable to use in CKD patients. Clinical trials exploring the actual cardiac outcome of a Pb therapy in CKD patients are still insufficient.

Recent studies demonstrate useful effects of ferric citrate (Fc) treatment for CKD patients [124–126]. Block et al. indicated a placebo-controlled clinical trial in non-dialysis CKD patients that Fc significantly reduces intact FGF-23 and serum P levels among patients with increased baseline P (≥4.5 mg/dL) [124]. As demonstrated by Francis et al., Fc not only reduces FGF-23 and P levels but also ameliorates the renal and cardiac function in the Col4a3 knockout mouse model of advanced CKD.

Col4a3 knockout mice receiving Fc also exposed lesser renal interstitial fibrosis and tubular atrophy than Col4a3 knockout control mice. Moreover, the Col4a3 knockout mice developed severe cardiac dysfunctions which could be improved by Fc therapy. Without therapy, the Col4a3 knockout had an average ejection fraction of 48%, which was ameliorate to 65% in treated mice. This might be connected with the reduced FGF-23 levels, because Fc treatment decreased circulating FGF-23 and the cardiac expression of FGFR-4 and subsequent hypertrophic target genes in the heart. Overall, Fc delays the progression of CKD and ameliorated the survival of CKD mice. It was noticed that the beneficial effects of Fc were more pronounced when the Col4a3 knockout mice were treated in the early CKD stages compared with the later onset of therapy [125].

In our study [105], the group of patients with CKD 5D who managed to achieve and maintain the target serum P level (0.9–1.45 mmol/L), compared with a matched group of patients with uncorrected HP (> 1.45 mmol/L), demonstrated a lower serum levels of FGF-23 and PTH ($p < 0.01$ and $p < 0.05$, respectively), mainly those patients who took non-Ca Pbs (sevelamer hydrochloride) for HP correction.

Nicotinamide (niacin and vitamin B_3) (NA) reduces the dietary P absorption by suppressing the expression of the intestinal P transporter NaPi-2b [127, 128]. Several clinical studies showed that 8–12 weeks of NA treatment efficiently lowers serum P levels by 12–34% in ESKD end stage kidney disease patients on dialysis [129–133]. Besides the P reduction, Rao et al. demonstrated a FGF-23-lowering effect of NA in a randomized, placebo-controlled trial. NA treatment for 24 weeks decreased serum FGF-23 levels by 11% among patients with CKD stages 2–3b (eGFR 30–74 mL/min/1.73 m^2) [10]. But NA has not been proven to reduce CV outcomes and may even be associated with some adverse CV outcomes in early CKD [127, 128].

The experimental studies revealed that an increase in Klotho expression was accompanied by a decrease in proteinuria and a significant decrease in angiotensin II in mice with hypertensive chronic glomerulonephritis [134, 135]. The studies revealed that by initiating an oxidative stress, angiotensin II and aldosterone can reduce Klotho expression in rat kidney even at minimal concentrations, while the infusion of exogenous sKlotho contributed to the inversion of renal damage caused by angiotensin II [135].

In clinical study, the hypertensive patients with CKD stages 1–3b [107, 136] whose target blood pressure was achieved predominantly with angiotensin II receptor blockers demonstrated the higher serum levels of Klotho protein compared with those who took drugs of a different groups or did not reach the target blood pressure level ($p = 0.008$, $p = 0.025$).

A number of studies revealed that anemia-related hypoxia is an independent factor of the decreased sKlotho protein production with CKD progression [8, 137]. Our study revealed a slowdown of the sKlotho protein serum level decrease in the patients with CKD and with anemia who managed to achieve and sustain the target hemoglobin level with epoetin and iron and consequently to eliminate hypoxia of vital organs, including the kidneys [137].

W.L. Lau et al. [138] tested two vitamin D receptor agonists (VDRAs) in a mouse CKD model where dietary P loading induced aortic medial calcification. Mice were given intraperitoneal calcitriol or paricalcitol three times per week for 3 weeks. In the setting of a high P diet, serum PTH and Ca levels were not significantly altered by treatment. VDRA therapy was associated with increased serum and urine Klotho levels, increased phosphaturia, correction of HP, and lowering of serum FGF-23. There was no effect on elastin remodeling or inflammation; however, the expression of the anti-calcification factor, osteopontin, in aortic medial cells was increased. Paricalcitol upregulated osteopontin secretion from mouse VSMCs in culture. Thus, Klotho and osteopontin were upregulated by VDRA therapy in CKD, independent of changes in serum PTH and Ca.

Maintaining targeted serum P and Ca levels may be a factor that inhibits excessive FGF-23 production and reduces the risk of FGF-23-dependent LVH in stages 3b-4 CKD.

Although the use of antibodies against Scn improved bone density and reduced the risk of fractures in osteoporosis [139], important evidence indicates that such treatment may increase the risk of CVD in patients with primary osteoporosis and CKD.

4. Conclusion

Understanding the role of MBD biomarkers in CKD, including new factors – Klotho, FGF-23, and Scn – in the genesis of CVDs is important for the development of new therapeutic strategies aimed at reducing CVCs and mortality.

It was shown that the initial MBD in CKD begins early at stage 2-3A with an increased FGF-23 and Scn serum levels and a decreased Klotho level. The clinical manifestation of these early changes may be increased daily P excretion. At this point, CV risk rises, although serum P and PTH levels are usually still normal.

The role of ischemia, oxidative stress, and angiotensin II level increase contributes to decreased renal Klotho expression. These changes require careful treatment to maintain Klotho production as a potent cardiorenoprotective factor.

The accumulated data suggest that FGF-23/Klotho/Scn ratio is one of the early markers of CKD progression, mineral metabolism disorders, and CVD prediction. VC, cardiac remodeling, and an increased CVD mortality risk regardless of serum P and PTH levels accompany changes in the serum FGF-23/sKlotho/Scn ratio as CKD progresses.

The preliminary findings of the positive effect of the arterial hypertension and anemia correction on the maintenance of sKlotho protein production as well as the possibility of FGF-23 overproduction inhibition by HP correction demonstrate the need an individual approach to the selection of cardiorenoprotective therapy. Analysis of changes in MBD biomarkers in the early CKD stages including those assessed by the degree of morphogenetic proteins and Sclerostin dysfunction opens up prospects for research into a new aspect of cardiorenoprotective strategy.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 7

Perspective Chapter: The Level of Lipocalin-2 in Patients with Early Stages of Chronic Kidney Disease against the Background of Obesity

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Abstract

Chronic kidney disease (CKD) is an important contributor to morbidity and mortality from noncommunicable diseases. To date, other markers of early diagnosis of kidney disease have been used, in particular those that do not depend on their filtration function and indicate tubulointerstitial damage. Lipocalin-2, as a new marker of immunity and acute phase response to infectious lesions, is actively involved in fatty acid transport, inflammation modeling, and metabolic homeostasis. Neutrophil-gelatinase-associated lipocalin (NGAL) is also considered an early marker of tubulointestinal damage. Studies have shown an increase in the secretion of lipocalin-2 in the urine, especially with a higher body mass index of patients with CKD. NGAL is positively correlated with cystatin C levels and may be a significant predictor of albuminuria. A close correlation between NGAL levels and markers of systemic inflammation, such as C-reactive protein and tumor necrosis factor-alpha (TNF-α), and an increase in microalbuminuria has been shown to indicate a progressive decline in renal function.

Keywords: chronic kidney disease, obesity, lipocalin-2 (NGAL), microalbuminuria, cystatin C, endothelin-1, C-reactive protein, tumor necrosis factor-α

1. Introduction

Chronic kidney disease (CKD) is an important factor, contributing to morbidity and mortality from noncommunicable diseases. Large-scale screening research in different countries around the world has shown that the common causes of CKD are hypertension, diabetes, obesity, gout, and, more rarely, exposure to toxins, heavy metals, HIV, etc. [1]. To date, a lot of epidemiological research studies have shown that indicators such as glomerular filtration rate (GFR) and the ratio of albuminuria/creatinine, which are the markers of decreased renal function progression [2], are used for the diagnosis of CKD. However, a proper renal function test, especially in the presence of risk factors and comorbidities, has primary importance for recognizing the initial signs of kidney damage, therapy supervision, and deciding on prevention measures in patients with CKD [3]. Therefore, other markers of the early diagnosis

of kidney damage are currently used, in particular those that do not depend on their filtration function and indicate tubulointerstitial damage [4]. One such marker is lipocalin-2 or neutrophil-gelatinase-associated lipocalin (NGAL).

Lipocalin-2 is produced in many tissues, such as kidneys, liver, immune cells, uterus, and chondrocytes [5], and according to other research studies, its main source is white adipose tissue [6]. Currently, NGAL in the blood is described as a new component of immunity and acute phase response to infectious lesions [7]. Lipocalin-2 is also involved in fatty acid transport, hematopoietic cell apoptosis, inflammation modeling, and metabolic homeostasis [8]. In recent years, it has been found that serum lipocalin and urinary lipocalin are the early markers of acute renal damage [9]. However, recent publications and research show that NGAL levels increase against the background of inflammation and increased immune activity, which are the main pathogenetic factors in the pathogenesis of CKD. The change of this marker indicates that acute kidney damage is a prelude to its chronic disease, and lipocalin-2 is a mediator of CKD progression [10]. Research comparing serum lipocalin (sNGAL) and urinary lipocalin (uNGAL) has shown that urinary lipocalin has a negative correlation with GFR at all stages of CKD in patients with GFR < 90 mL/min with different etiologies of CKD, and in patients with proteinuria, it correlated more with its severity compared with serum lipocalin [11]. Based on this research, it was concluded that uNGAL level is a better biomarker of CKD than serum lipocalin.

Endothelial dysfunction also plays an important role in the development and progression of CKD [12]. The impairment of endothelium vasomotor function and a disequilibrium toward vasoconstriction leads to the formation of vasospasm, impairment of microcirculation, and local renal ischemia. According to current data, reduction in the formation of nitric oxide (NO), increase in the tubular reabsorption of water, and increase in the concentration of sodium ions help reduce the glomerular filtration rate (GFR), which ultimately leads to glomerular sclerosis [13]. It is also known that the decrease in NO synthesis due to chronic decreased blood flow in the kidneys increases the level of proinflammatory cytokines, endothelin-1 (ET-1), and other vasoconstrictors [14]. According to Khan and Pandey, chronic hypoxia of renal tissue is the main cause of the tubulointestinal system damage and leads to the progression of CKD [15].

The high prevalence of obesity today is a serious medical and social problem. Research in recent years has shown that the risk of chronic kidney disease, cardiovascular disease (CVD), and diabetes depends not only on the volume of adipose tissue, but also on its hormonal and metabolic activity [16]. It is proved that an increase in body mass index (BMI) by 10% enhances the probability of a steady decrease in GFR by 1.27 times [17]. The appearance of microalbuminuria (MAU) is an early marker of glomerular disorders and an indicator of endothelial dysfunction [18]. Thus, the diagnosis of glomerular and tubular dysfunction is insufficiently studied in patients with the early stages of CKD against the background of obesity and will assess the kidney damage in the early stages.

The purpose of the research is to evaluate the level of lipocalin-2 as a marker of the early diagnosis of tubular lesions and its relationship with the endothelial dysfunction marker, endothelin-1, and indicators of low-intensity inflammation markers in patients with the early stages of CKD against the background of obesity.

2. Materials and methods

A total of 158 patients (67 women and 91 men) with chronic kidney disease, who were hospitalized in the Department of Arterial Hypertension of Communal

noncommercial enterprise "Ivano-Frankivsk Regional Clinical Cardiological Centre of Ivano-Frankivsk Regional Council" and Urological and Cardiological Departments of Communal noncommercial enterprise "Central City Clinical Hospital of Ivano-Frankivsk City Council" in Ivano-Frankivsk City, Ukraine, were examined. The average age of the examined was 55.36 ± 2.02 years in women and 47.45 ± 2.66 years in men.

Body mass index was calculated by the Kettle formula (kg/m^2): BMI = body weight (kg)/height (m^2). Stage 1 of CKD was diagnosed in 70 patients (31 women and 39 men) (the average age was 46.43 ± 3.77 years), and stage 2 was diagnosed in 88 patients (36 women and 52 men) (the average age was 53.07 ± 2.61 years). Patients were divided into two groups: 1-a (70)—patients with stage 1 of CKD and obesity, and 2-a (88)—patients with stage 2 CKD and obesity. The control group consisted of 10 healthy individuals (three women and seven men), whose average age was 36.7 ± 8.6 years.

The reasons for the development of CKD are as follows: infections of the upper urinary system were in 11.8%, urolithiasis was in 19.89%, glomerulonephritis with symptomatic renoparenchymal hypertension was in 15.76%, abnormalities in the development of urogenital system were in 6.9%, essential arterial hypertension (AH) was in 29.1%, and coronary heart disease with heart failure was in 18.89%. The duration of CKD was on average 7.1 years. Exclusionary criteria were diabetes, hypothalamic and endocrine obesity, acute myocardial infarction, stages 3 and 4 of New York Heart Association congestive heart failure, hepatic failure, and stages 3–5 of CKD.

General clinical examinations were conducted for all patients. Albumin in daily urine was examined by the turbometric method, using the diagnostic kit "Microalbumin" (Germany) and evaluated in mg/day. The glomerular filtration rate was calculated according to the chronic kidney disease epidemiology collaboration (CKD-EPI) formula based on creatinine and cystatin C levels and their combination (CKD-EPIcysC/cr) (mL/min/1.73 m^2) using a calculator of the U.S. National Renal Fund (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm). Serum cystatin C levels (0.79–2.15 mg/L in healthy individuals) were examined by enzyme-linked immunosorbent assay using Human Cystatin C ELISA kit (Czech Republic) on the STAT FAX analyzer (No. 7898). The level of neutrophil-gelatinase-associated lipocalin (NGAL) (ng/mL) was examined by sandwich enzyme-linked immunosorbent assay in urine (0.16–10 ng/mL in healthy individuals) using the HUMAN NGAL ELISA Kit (USA). The concentration of tumor necrosis factor-alpha (TNF-α) in serum (0.02–2.3 pg./mL) was determined by solid-phase enzyme-linked immunosorbent assay using Vector BEST kit (Belarus). The quantitative determination of C-reactive protein (CRP) (0.07–2.5 μg/mL in healthy individuals) in serum was determined by enzyme-linked immunosorbent assay using the Accu-Bind ELISA Microwells kit (USA). The level of endothelin-1 (reference values within 2.5–7.8 pg./mL) in serum was examined by enzyme-linked immunosorbent assay using the Human ET-1 (Endothelin-1) ELISA Kit (USA). All enzyme-linked immunosorbent assays were performed on STAT FAX analyzers (No. 7898).

The research protocol was approved by the Ethics Commission of Ivano-Frankivsk National Medical University, protocol No. 97/17 of October 19, 2017. All patients gave informed consent to participate in it. The research was conducted in accordance with the principles of Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study" No. 900_005 of October 1, 2008.

The statistical analysis of the results was performed using the statistical software package Statistica 6.0 using Student's t-test. Correlation was assessed by Spearman's rank correlation coefficient. The discrepancy of the results at $p < 0.05$ was considered statistically significant.

3. Results

Currently, the clinic is considering new biomarkers for the early diagnosis of CKD of various etiologies. According to Melnikov et al., NGAL is expressed by tubular epithelial cells in response to inflammation, trauma, and tubulointerstitial damage [19]. According to the results of our research, the excretion of lipocalin-2 in the urine in the patients of groups 1 and 2 exceeded that in healthy individuals by 3.6 and 6.3 times, respectively ($p_{1,2} < 0.001$). The increase of the NGAL excretion in urine was greater in the patients of group 2, who had a higher body mass index. Thus, comparing u-NGAL in the patients of both the groups, it was found that in patients with stage 2 CKD against the background of obesity, it was 1.8 times higher ($p < 0.05$) than in patients with stage 1 of CKD against the background of obesity (**Table 1**). The level of daily microalbuminuria in the patients of groups 1 and 2 also exceeded that in healthy individuals by 7.4 and 8.9 times, respectively ($p_{1,2} < 0.001$). Comparing the indexes of daily microalbuminuria in the patients of both the groups, it was found that MAU in patients with stage 2 CKD against the background of obesity was 1.2 times higher ($p > 0.05$) than in patients with stage 1 of CKD against the background of obesity. Increasing NGAL level in urine has been shown to be a significant predictor of albuminuria, especially in the patients of group 2. The level of cystatin C also exceeded the indexes of healthy individuals in both the groups by 1.8 and 2.29 times, respectively ($p_{1,2} < 0.001$). The level of cystatin C in the patients of group 2 was higher by 1.25 times than in the patients of group 1 ($p > 0.05$). The increase of cystatin C in serum reflects the state of glomerular filtration and the degree of renal function decrease [20]. GFR calculated according to the formula CKD-EPIcysC/cr indicates the decrease of this index by 1.5 times ($p < 0.001$) in the patients of group 2 compared with group 1, which confirms decreased kidney function, despite normal creatinine values.

A positive average correlation was found between NGAL and BMI in both the groups ($r_1 = 0.45$ and $r_2 = 0.58$; $p_{1,2} < 0.05$), between NGAL and microalbuminuria ($r_1 = 0.45$ and $r_2 = 0.48$; $p_{1,2} < 0.05$), and between NGAL and cystatin C ($r_1 = 0.46$ and $r_2 = 0.68$; $p_{1,2} < 0.05$). In the patients of group 2, a direct average correlation was found between daily albuminuria and BMI ($r = 0.56$; $p < 0.05$), which indicates a

Indices	Health, n = 10	Group 1, n = 70	Group 2, n = 88
Age, years	36.7 ± 8.6	46.43 ± 3.77	53.07 ± 2.61
BMI, kg/m^2	21.44 ± 0.39	34.15 ± 1.1	37.59 ± 0.82
Albuminuria, mg/day	19.0 ± 0.96	141.1 ± 12.66*	170.05 ± 17.6*
Cystatin C, mg/L	0.78 ± 0.02	1.43 ± 0.13*	1.79 ± 0.13*
Creatinine, μmol/L	77.71 ± 1.48	94.26 ± 2.32*	105.03 ± 1.56*°
GFR, mL/min/1.73 m^2 CRD-EPIcysC/cr	103.3 ± 1.27	95.09 ± 2.76*	64.5 ± 2.07*
CRP, μg/mL	1.31 ± 0.42	7.73 ± 2.19*	12.85 ± 4.14*
TNF-α, pg/mL	0.73 ± 0.15	2.66 ± 0.29*	4.27 ± 0.57*°
Endothelin, pg/mL	3.4 ± 0.29	5.87 ± 0.48*	9.04 ± 0.38*°
NGAL, ng/mL	3.83 ± 0.56	13.6 ± 0.62*	24.13 ± 0.91*°

**Reliable when compared to the healthy.*
°Reliable when comparing groups 1 and 2.

Table 1.
Clinical and laboratory characteristics of the examined patients.

deterioration in the functional state of the kidneys against the background of obesity. In both the groups, there was a negative mean correlation between NGAL and GFR (CKD-EPIcysC/cr) ($r_1 = -0.56$ and $r_2 = -0.58$; $p_{1,2} < 0.05$), indicating a violation of tubular functions even in the early stages of CKD.

According to recent studies, endothelin-1 is considered a marker for the diagnosis of endothelial dysfunction in a variety of vascular pathology, including kidney disease [21]. In both the groups, we found an increase in endothelin-1 by 1.7 and 2.7 times, respectively ($p_{1,2} < 0.05$) in contrast to the control group. As GFR decreased and body weight increased, there was a 1.6-fold increase in endothelin-1 levels in group 2 patients in contrast to group 1 patients ($p < 0.05$). In the patients of both the groups, there was a positive correlation between the level of lipocalin-2 and endothelin-1 ($r_1 = 0.49$ and $r_2 = 0.44$; $p_{1,2} < 0.05$). In both the groups, there was also a negative average correlation between glomerular filtration rate and ET-1 ($r_1 = -0.44$ and $r_2 = -0.63$ ($p_{1,2} < 0.05$) and a positive strong correlation between albuminuria and ET-1 in patients with stage 2 CKD against the background of obesity ($r_2 = 0.74$; $p < 0.001$). Our data are consistent with the studies of Davenport et al., who found that increased levels of ET-1 can damage renal podocytes, cause structural changes, and reduce their function, and an increase in NGAL indicates the early signs of tubulointerstitial sclerosis [14].

We found an increased CRP level in both the groups by 5.9 and 9.8 times, respectively, in contrast to the healthy ($p_{1,2} < 0.05$). There was a weak reverse correlation between GFR and CRP levels in the patients of group 1 ($r_1 = -0.34$; $p > 0.05$) and an average reverse correlation between these indicators in the patients of group 2 ($r_2 = -0.45$; $p < 0.05$). A positive correlation was also found between the levels of CRP and BMI ($r_1 = 0.66$ and $r_2 = 0.78$; $p_{1,2} < 0.05$) and between CRP and NGAL ($r_1 = 0.46$ and $r_2 = 0.58$; $p_{1,2} < 0.05$). According to Rysz et al., an increase in the level of C-reactive protein by more than 3 mg/L contributes to a high risk of cardiovascular events, and when the GFR falls below 89 mL/min, the risk of cardiac events increases markedly [22]. According to Lumlertgul et al., uNGAL is produced in the kidney epithelium and leukocytes, and its level increases in response to prolonged tubular damage and systemic inflammation [23]. Tumor necrosis factor-α (TNF-α), a proinflammatory cytokine required for the regulation of inflammation, apoptosis, and renal oxidative stress, also increases in CKD and obesity [24]. We found an elevated level of TNF-α by 3.6 times in the patients of group 1 and by 5.8 times in the patients of group 2 in contrast to the healthy ($p_{1.2} < 0.001$). In the patients of group 2, the level of TNF-α was 1.6 times higher than in the patients of group 1 ($p_2 < 0.05$). We also found the average positive correlation between TNF-α and BMI in the patients of group 1 ($r_1 = 0.60$; $p_1 < 0.01$) and group 2 ($r_2 = 0.69$; $p_2 < 0.05$) and the average reverse correlation between GFR and TNF-α levels in the patients of group 2 ($r_2 = 0.67$; $p_2 < 0.05$). At the same time, a strong correlation was found between the levels of NGAL and TNF-α in the patients of group 2 ($r_2 = 0.72$; $p_2 < 0.05$) and between microalbuminuria and TNF-α in the patients of groups 1 and 2 ($r_1 = 0.46$; $p_1 < 0.05$ and $r_2 = 0.72$; $p_2 < 0.05$). Our results showed that TNF-α and u-NGAL levels were elevated and independently correlated with albuminuria status, suggesting that they may be used as the markers of CKD progression against the background of obesity, which is consistent with the research of Darde et al. [25].

4. Discussion

The problem of obesity in recent years has attracted the attention of a wide range of professionals. The prevalence of this multifactorial disease, connected with the excessive

accumulation of adipose tissue in the body, in all the age groups is steadily increasing, according to the National Health and Nutrition Examination Survey (NHANES) [26]. There is growing evidence that the kidneys, along with the cardiovascular system, are vulnerable target organs in obesity, and the irreversible process of changes in them occurs even in the absence of arterial hypertension (AH) and diabetes mellitus (DM) or in compensation for these conditions [27]. Thus, an increase in body mass index (BMI) by 10% increases the probability of a steady decrease in glomerular filtration rate (GFR) by 1.27 times [28]. In routine clinical practice, kidney damage is usually detected by changes in serum creatinine and creatinine-based GFR, as well as by protein excretion. However, recently, much attention has been paid to the study of the tubulointerstitial apparatus, which is involved in the pathological process of inflammatory or ischemic lesions before the glomerulus and is a marker of tubular kidney damage in preclinical stages [29]. In particular, NGAL is considered an early marker of kidney damage, the expression of which is enhanced in response to inflammation or damage to the endothelium in the renal tubules and leads to the proliferation of new epithelial cells [30]. According to Lim et al., NGAL is also a marker of disease severity and clinical outcomes in patients with CKD, in particular, in 45 patients with CKD stages 2–4, systemic NGAL concentrations were significantly related to GFR [31]. And according to research by Malyszko et al., in 92 patients without diabetes mellitus with CKD stages 2–4, both the systemic and urinary NGAL correlated with GFR and the systemic NGAL/NGAL ratio in urine showed the best correlation [32]. Current data also treat microalbuminuria as a marker of early renal dysfunction. We found that a decrease in GFR was accompanied by an increase in microalbuminuria, and an increasing level of NGAL in the urine was a significant predictor of albuminuria, especially in the patients of group 2. An increase in serum cystatin C levels is also associated with the initial manifestations of tubulointestinal lesions [33]. Cystatin C in the blood and NGAL in the urine may confirm chronic renal impairment earlier than serum creatinine monitoring. We found a positive average correlation between NGAL and cystatin C and between NGAL and BMI in the patients of both the groups and, at the same time, a negative average correlation between NGAL and GFR (CKD-EPIcysC/cr) in both the groups, indicating impaired tubular function even in the initial stages of CKD. According to Gharishvandi et al., serum and urine NGAL levels were significantly higher in obese people, and compared to creatinine and GFR, increased cystatin C and u-NGAL provides information on a worse prognosis in patients with renal disease and increasing body weight [34].

Endothelial dysfunction is considered the first stage in the development of systemic atherosclerosis, and endothelin-1 is a marker of its dysfunction in chronic kidney disease [35]. It is thought to be an early, noninvasive marker of kidney damage that can be detected before clear clinical manifestations. With the increasing concentration of ET-1, vasospasm is formed, which causes systemic changes in the microcirculatory tract, promotes ischemia, and increases the permeability of glomerular vessels, which subsequently causes proteinuria [36]. According to our data, the patients of both the groups had a positive correlation between the levels of lipocalin-2 and endothelin-1 ($p_{1,2} < 0.05$), a negative average correlation between the glomerular filtration rate and ET-1 ($p_{1,2} < 0.05$), and a positive strong correlation between the levels of albuminuria and ET-1 in patients with stage 2 CKD against the background of obesity. According to Karol et al., chronic renal tissue hypoxia and decreased GFR against the background of increasing body weight is one of the causes of damage to the tubulointerstitial apparatus, leading to the progression of CKD, and the main markers of this process are albuminuria, as well as levels of cystatin C and interleukin-18 (IL-18), including lipocalin-2 [37].

CRP is a recognized risk factor in CVD and mortality in the general population, as well as in patients with CKD. CRP plays a multifaceted role, as it is a highly sensitive marker of inflammation and tissue destruction, and is considered a "new" proatherogenic, proinflammatory adipokine, whose source is adipocytes, and its level in the blood may correlate with BMI and visceral adipose tissue [38]. According to Shankar et al., TNF-α and IL-6, more than CRP, are associated with a prevalence and severity of CKD, regardless of other identified risk factors, a history of CVD [39]. We found a strong positive correlation between the levels of NGAL and TNF-α in the patients of group 2 ($p_2 < 0.05$) and between microalbuminuria and TNF-α in the patients of both the groups ($p_2 < 0.05$), the average positive correlation between TNF-α and BMI in the patients of groups 1 and 2, and the average inverse correlation between GFR and TNF-α levels in the patients of group 2. According to Flannery et al. [40], TNF-α is a proinflammatory cytokine required for the regulation of inflammation, apoptosis, and oxidative stress in the kidneys, and the increase in serum and NGAL levels in urine correlates with kidney damage and glomerular permeability barrier in patients with chronic kidney disease, and the correlation between NGAL levels and albuminuria indicates that glomeruli and tubules may be affected at the same time.

Thus, lipocalin-2, as a new marker of immunity and acute phase response to infectious lesions, is actively involved in fatty acid transport, inflammation modeling, and metabolic homeostasis. NGAL is also considered an early marker of tubulointerstitial damage. Research has shown an increase in the secretion of lipocalin-2 in the urine, especially with a higher body mass index, in patients with CKD. It can be a significant predictor of albuminuria and positively correlates with cystatin C levels. There is a close correlation between NGAL levels and markers of systemic inflammation, including C-reactive protein and TNF-α, and an increase in microalbuminuria indicates a progressive decline in renal function.

Conflict of interest

The author declare that there is no conflict of interest.

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Chapter 8

The Vascular Endothelial Growth Factor (VEGF) Pathway Inhibition and Associated Nephrotoxicities

Hoon Chang, Shanshan Gustafson and Tulsi Mehta

Abstract

Angiogenesis is pivotal for tumor growth and the development of metastases. Thus, vascular endothelial growth factor (VEGF) plays an integral role in angiogenesis and is often overexpressed in most solid cancers making it an attractive target for treatment. As the use of VEGF inhibitors is expanding in cancer therapy, it is increasingly recognized that these medications may result in significant adverse renal toxicities, including hypertension, proteinuria, thrombotic microangiopathy, and other glomerular diseases. In this chapter, we will discuss the importance of VEGF signaling in maintaining renal integrity, the various classes of VEGF inhibitors, and the adverse effects that affect the kidneys.

Keywords: VEGF inhibitor, mTKI, hypertension, proteinuria, thrombotic microangiopathy, minimal change nephrotic syndrome, focal segmental glomerulosclerosis

1. Introduction

Pathological angiogenesis plays a key role in the growth and metastasis of malignancies. This process is largely driven by vascular endothelial growth factor (VEGF) produced by tumor cells. This signal protein acts through the VEGF receptor that stimulates endothelial cells to proliferate and migrate [1]. This signaling pathway is a therapeutic target in the management of many solid organ cancers as well as various retinal diseases. VEGF pathway inhibitors are first-line agents in the treatment of advanced colorectal cancer, metastatic breast cancer, and metastatic renal cell carcinoma [2, 3]. Intravitreal injection of anti-VEGF agents is the first line to treat age-related macular degeneration and diabetic macular edema [4]. New drugs are continuously in development, and their therapeutic benefits, as well as adverse events, are a topic of investigation. Nephrotoxicity is reported in 10–20% of patients and can result in a wide range of abnormalities. Clinical manifestations of anti-VEGF treatment range from asymptomatic proteinuria to renal failure. In this chapter, we will focus on the effects of systemic and intravitreal administration of VEGF inhibitors on kidney function.

2. The VEGF signaling pathway in the kidney

The vascular endothelial growth factor (VEGF) signaling pathway is one of the major pathways of angiogenesis. VEGF-A, which is the most well-studied isoform within the VEGF family, is a proangiogenic peptide that exerts mitogenic effects specifically on vascular endothelial cells, thus promoting angiogenesis and increasing vascular permeability. The expression of VEGF-A increases in response to hypoxia, oncogene activation, and cytokine stimulation [5, 6].

In the kidney, the VEGF-A is mainly expressed by glomerular podocytes and, to a lesser degree, by renal tubular cells [5–9]. The effect of the VEGF-A is mediated by its binding to receptor tyrosine kinases (RTKs) called VEGFR-1 and VEGFR-2 [5, 10]. The VEGFR1 has a higher affinity for VEGF-A compared to VEGFR-2 [11]; however, it has a less proangiogenic effect. In fact, the circulating soluble form of VEGFR1 (sVEGFR1) acts as a decoy receptor, inhibiting VEGF-A signaling [12]. VEGFR2 has been more extensively studied and is recognized as the most important receptor, responsible for the majority of VEGFA signaling (**Figure 1**).

The VEGFR2 is mainly expressed on the surface of both endothelial cells and podocytes, although the presence of the receptors at the podocytes for autocrine effect is controversial. While some studies have established that VEGFR2 is expressed in adult mouse podocytes and glomerular endothelial cells [13, 14], others have failed to detect any expression of VEGFR2 in podocytes—suggesting that paracrine signaling may play a bigger role in VEGF-VEGFR signaling [15].

All RTKs, such as VEGFR2, share similar molecular structures with a ligand-binding site in the extracellular domain, a transmembrane region, and a cytoplasmic region that contains the protein kinase domain with an ATP-binding site [16]. The binding of VEGF-A to VEGFR2 leads to dimerization of the receptors and subsequent phosphorylation of tyrosine kinases in the cytoplasmic domain. Such interaction

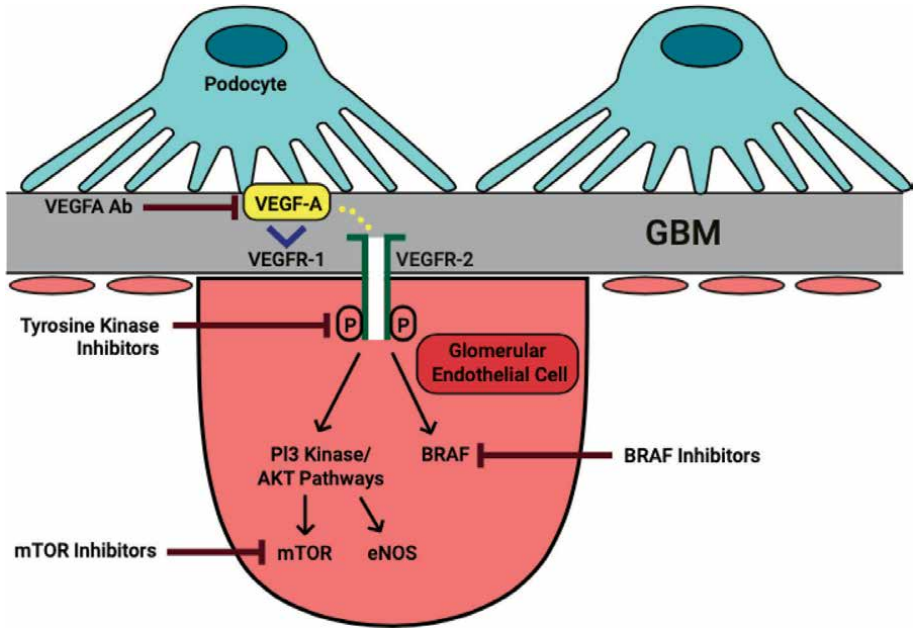

Figure 1.
VEGFA-VEGFR2 signaling pathways and various therapeutic targets.

leads to activation of downstream signaling pathways such as the RAF/MAPK/ERK pathway, endothelial nitric oxide synthase (eNOS) pathway, and mammalian target of rapamycin (mTOR) pathway. While angiogenesis does not occur in normal adult kidneys, a delicate balance between proangiogenic and antiangiogenic factors is crucial for the normal structure and function of the glomerulus [8, 10].

The structural integrity at the renal capillary bed, consisting of endothelial cells, basement membrane, and the podocyte, is critical for maintaining proper glomerular filtration. The VEGF-mediated epithelial-endothelial crosstalk is an integral process for maintaining glomerular integrity [17–19].

Depending on the level of expression, VEGF-A can exert a varying range of effects. For example, multiple murine studies demonstrated that the knockout of *Vegfa* during embryogenesis is uniformly lethal at or before birth [20, 21]. In adult mice, *Vegfa* knockout mice can induce thrombotic microangiopathy (TMA) [18]. A clinical example of reduced VEGF-A signaling in the kidney is preeclampsia. Preeclampsia is a syndrome of pregnancy that is characterized by hypertension (HTN), proteinuria, and injury to various organs including the kidney. The renal histological features of preeclampsia involve the development of glomerular capillary endotheliosis. It has been found that patients with preeclampsia have increased levels of soluble VEGFR1/sFlt-1 and an overall decreased level of free VEGF and PlGF (placental growth factor), leading to disruption of the epithelial-endothelial crosstalk.

On the contrary, overexpression of VEGF-A and an unregulated increase in the downstream signaling pathway can lead to a different set of problems. A clinical example of renal overexpression of VEGF and its receptors is diabetic nephropathy. The increased VEGF signaling induces new vessel formation in the kidney, stimulates renal hypertrophy, and leads to proteinuria [6, 22].

3. Current drugs that target VEGF signaling pathway

Molecularly targeted therapies are the cornerstone of precision medicine and have greatly advanced the treatment of many cancers. Unlike traditional chemotherapy, these agents spare damage to healthy cells and can cause fewer side effects compared to conventional treatments. Pathological angiogenesis plays a key role in solid tumor growth and metastasis [23]. The VEGF pathway is one of the most potent promoters of angiogenesis and has become a key target in antiangiogenic therapies to treat various cancers. Numerous drug classes exist to inhibit VEGF and VEGFR signaling. Major classes include monoclonal antibodies (mAbs) against VEGF, receptor tyrosine kinase inhibitors (TKIs), and downstream inhibitors of the VEGF pathway [24]. The toxicity profiles associated with targeted inhibitors of the VEGF pathway differ from those seen with traditional cytotoxic chemotherapy. As a class, inhibitors of the VEGF pathway can cause damage to the glomerulus, tubules, and vasculature, causing various clinical outcomes such as hypertension, proteinuria, nephrotic syndrome, acute kidney injury, and electrolyte abnormalities.

3.1 Anti-VEGF MAB

Agents that inhibit VEGF-A activity through antibody binding include bevacizumab, ranibizumab, aflibercept, and ramucirumab. Bevacizumab and ranibizumab are monoclonal antibodies (mAbs) that inhibit angiogenesis by binding all isoforms of VEGF-A. Aflibercept is a recombinant soluble decoy receptor composed of extracellular binding domains of VEGFR1 and VEGFR-2 and the Fc portion of IgG that binds to VEGFRs. Like

bevacizumab and ranibizumab, aflibercept binds all isoforms of VEGFA, but in addition, it binds related VEGFR1 ligands, VEGFB, and PIGF. Ramucirumab is a fully humanized mAB that specifically inhibits VEGFR-2. The renal toxicities associated with direct VEGF inhibition include hypertension and proteinuria. Bevacizumab was the first anti-VEGF drug introduced to clinical practice and is the focus of many clinical trials investigating anti-VEGF ligand blockade. Multiple meta-analyses have found a dose-dependent increase in the risk of hypertension and proteinuria in patients taking bevacizumab [25, 26]. Hypertension can occur any time after therapy initiation and may persist after prolonged treatment. Proteinuria is typically asymptomatic and decreases after treatment completion or dose reduction. Wu, et al. found that combination therapy of bevacizumab with chemotherapy was associated with a significantly increased risk for high-grade proteinuria (Grade 3 or above: urine protein ≥3.5 g/24 h or dipstick ≥4+ or nephrotic syndrome) and nephrotic syndrome compared to chemotherapy alone [27]. Multiple cases of biopsy-confirmed thrombotic microangiopathy (TMA) have been reported in patients treated with bevacizumab. In murine models, local genetic ablation of VEGF in kidney podocytes has been shown to lead to the development of microvascular injury and thrombotic microangiopathy [18]. Intravitreal administration of bevacizumab (off-label use), ranibizumab, and aflibercept are used to treat vision-threatening retinal diseases such as neovascular age-related macular degeneration, diabetic retinopathy, diabetic macular edema, and retinal vein occlusion [28]. Intravitreal injection of VEGF inhibitors has shown to cause significant depletion of circulating VEGF levels and can have systemic effects. Reizer et al. found that patients with and without preexisting hypertension both had significant elevations in blood pressure 3 weeks after intravitreal bevacizumab injection. Drug-induced hypertension resolved by week 6 for patients without baseline hypertension but persisted for those with preexisting hypertension and on the antihypertensive therapy [29].

3.2 Tyrosine kinase inhibitors of VEGF signaling

Tyrosine kinase inhibitors (TKIs) can interfere with various families of structurally similar RTKs, including VEGFR, platelet-derived growth factor (PDGF) receptor, epidermal growth factor (EGF) receptor, and fibroblast growth factor (FGF) receptor. They are commonly called multitargeted TKIs, and their effects depend on their specificities for different RTKs. TKIs directed at VEGFR include sorafenib, sunitinib, pazopanib, vandetanib, axitinib, regorafenib, cabozantinib, nintedanib, lenvatinib, dasatinib, and ponatinib. In contrast with anti-VEGF ligands and aflibercept, MTKIs are associated with increased risk for podocytopathies, including minimal change disease (MCN) and collapsing focal sclerosing glomerulosclerosis (cFSGN) [30]. MTKIs also result in dose-dependent increases in blood pressure. More potent MTKIs such as axitinib have shown higher rates of hypertension compared to sorafenib and sunitinib at the maximum tolerated doses [31, 32]. Proteinuria also depends on the specificity and potency of TKI. In a phase II trial of axitinib, a potent and specific VEGF-R TKI, 32% of patients (17 of 52) with renal cell carcinoma developed Grade 2 or higher proteinuria (measured by dipstick) and two patients had proteinuria >1 g per 24 hours.

3.3 Downstream inhibitors: b-Raf inhibitors, mTOR signaling, and eNOS inhibition

Angiogenesis can also be inhibited by targeting the downstream signaling pathways of VEGFR.

3.3.1 MAPK/ERK pathway

VEFG induces ERK1/2 signaling of the mitogen-activated protein kinase (MAPK) cascade. This pathway is important in regulating endothelial differentiation and proliferation. Novel chemotherapies targeting various portions of the MAPK/ERK pathway are currently in development. Vemurafenib and dabrafenib target B-Raf, an upstream component of the MEPK/ERK intracellular pathway, are approved agents for the management of melanoma. B-Raf inhibitors can lead to podocytopathy, slit diaphragm dysfunction, and subsequent proteinuria. A retrospective study by Muzet et al. found that 78% of patients (58 of 74) receiving vemurafenib for the treatment of metastatic melanoma developed AKI. Kidney biopsies were performed on three of the patients and showed tubular toxicity and interstitial fibrosis. Changes were chronic in two of the three cases [33]. In multiple studies, AKI on vemurafenib showed a male predominance [33, 34]. There is fewer data regarding the renal toxicity profile of dabrafenib. According to the US Food and Drug Administration (FDA) drug information packet, renal failure was present in 4% of patients (2 of 55) receiving a combination treatment of dabrafenib and trametinib (MEK inhibitor) for metastatic melanoma. Renal failure was typically associated with fever, chills, and dehydration and responded well to dose interruption and general supportive measures [35]. Hypophosphatemia has also been reported for both vemurafenib and dabrafenib [36].

3.3.2 eNOS pathway

Nitric oxide (NO) produced by endothelial cells is an essential molecule in modulating the proangiogenic properties of VEGF. VEGF activation of VEGFR-2 results in the activation of endothelial nitric oxide synthase (eNOS) and NO-induced vasodilation. Pharmacologic VEGFR blockade results in a reduction in downstream NO production, leading to reduced sodium excretion and endothelial injury, and vascular toxicities such as hypertension, thromboembolism, and pulmonary arterial hypertension [37].

3.3.3 mTOR inhibitors

The mammalian target of rapamycin (mTOR) of the phosphatidylinositol-3-kinase (Pi3K)/Akt signaling pathway is another important downstream RTK target. Inhibition of this pathway reduces VEGF-mediated angiogenesis and endothelial cell proliferation by both reducing VEGF synthesis and the VEGFR2-mediated signaling [38]. mTOR is also responsible for maintaining podocyte integrity via regulation of the autophagy [39]. mTOR inhibitors were initially developed as immunosuppressive agents and are still widely used in the setting of organ transplants. Currently, temsirolimus, ridaforolimus, and everolimus are approved for the treatment of various cancers such as renal cell carcinoma, neuroendocrine tumors, and hormone-receptor-positive breast cancer [40]. Everolimus is associated with proteinuria, and reported incidence varies widely between 3 and 36% [41]. Sirolimus is associated with de novo TMA in kidney transplant patients that developed in the absence of calcineurin inhibitors [39]. The proposed mechanism of nephrotoxicity of mTOR inhibitors involves the downregulation of VEGF signaling and disruption of the autophagic pathway (**Table 1**) [42].

Drug	Mechanism	Target	Indication	Renal manifestations (incidence)	Sources
Bevacizumab	mAB	VEGFA	CRC, NSCLC, GMB, RCC, cervical cancer, epithelial ovarian cancer, fallopian cancer, ocular diseases	Hypertension Proteinuria TMA MCN/cFSGN	[43] [18] [25] [26]
Ranibizumab	mAB	VEGFA	Ocular diseases	TMA Proteinuria	[44] [45]
Aflibercept	Recombinant fusion protein	VEGFA, VEGFB, PLGF	CRC, ocular diseases	Hypertension Proteinuria TMA	[46] [47] [48]
Ramucirumab	mAB	VEGFR2	CRC, NSCLC, GC	Hypertension Proteinuria TMA	[46] [47]
Sorafenib	MTKI	VEGFR, PDGFR, RAF, c-Kit, FLT3, Ret	RCC, HCC, thyroid cancer	Hypertension Proteinuria MCN/cFSGN TMA	[30] [49] [50]
Sunitinib	MTKI	VEGFR, PDGFR, FLT3, CSF1R, Ret	RCC, pNETs, GIST	Hypertension MCN/cFSGN Nephrotic syndrome	[43] [49] [50]
Regorafenib	MTKI	VEGFR, PDGFR, FGFR, Tie2, c-Kit, Ret, RAF	GIST, MCC, HCC	Hypertension Proteinuria	[49] [50]
Pazopanib	MTKI	VEGFR, PDGFR, FGFR1, c-Kit	RCC, soft tissue sarcoma	Hypertension Proteinuria	[49] [50]
Axitinib	MTKI	VEGFR, PDGFR, c-Kit	RCC	Hypertension Proteinuria	[49] [50]
Vandetanib	MTKI	VEGFR, EGFR, Ret	MTC	Hypertension Proteinuria	[49] [50]
Lenvatinib	MTKI	VEGFR, FGFR, PDGFRa, Ret, c-Kit	Thyroid cancer, RCC, HCC	Hypertension Proteinuria	[51] [52] [53]
Cabozantinib	MTKI	VEGFR, c-Met, AXL, c-Kit, FLT3, Ret	MTC, RCC	Hypertension Proteinuria	[49]
Nintedanib	MTKI	VEGFR, PDGFR, FGFR, SRC	Idiopathic pulmonary fibrosis, NSCLC	Hypertension Proteinuria	[54]

Dasatinib	MTKI	BCR-ABL, SRC, LCK, YES, FYN, c-Kit, VEGFR, PDGFR	CML, Ph + ALL	Proteinuria Hyponatremia	[55]

CML: chronic myeloid leukemia; CRC: colorectal cancer; CSF1R: colony-stimulating factor 1 receptor; FGFR: fibroblast growth factor receptor; FLT3: fms-like tyrosine kinase 3; GBM: glioblastoma multiforme; GC: gastric cancer; GIST: gastrointestinal stromal tumor; HCC: hepatocellular carcinoma; HTN: hypertension; LCK: lymphocyte-specific protein tyrosine kinase; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; PDGFR: platelet-derived growth factor; Ph + ALL: Philadelphia-chromosome-positive acute lymphoblastic leukemia; pNETs: progressive pancreatic neuroendocrine tumors; RAF: rapidly accelerated fibrosarcoma; and RCC: renal cell carcinoma.

Table 1.
Clinical manifestations of anti-angiogenic targeted therapies.

4. Adverse effects of VEGF signaling inhibition related to renal function

4.1 Hypertension

Hypertension (HTN) is one of the most frequently reported adverse side effects related to therapeutic inhibition of VEGF signaling. Depending on the specific medication, the incidence and severity of hypertension may vary. For example, in one systematic review regarding Bevacizumab [26], the incidence of all-grade hypertension (Grade 1: asymptomatic, transient increase greater than 20 mmHg diastolic or greater than 150/100 mmHg; Grade 2 recurrent or persistent or symptomatic increase greater than 20 mmHg diastolic or greater than 150/100 mmHg) was as high as 32% in the low-dose group (Bevacizumab 3, 5, or 7.5 mg/kg/dose) and up to 36% in the high-dose group (Bevacizumab 10 or 15 mg/kg/dose). Interestingly, about 8.7 and 16% developed Grade 3 hypertension (defined as requiring more than one drug or more intensive therapy than previously) in the low-dose and high-dose groups, respectively. Among patients receiving the TKIs, the total incidence of all-grade or high-grade hypertension (Grade 3 or 4; Grade 4 is defined as a hypertensive crisis) was 23.0 and 4.4%, respectively [49].

The overall risk of hypertension was increased with combination therapy compared to monotherapy with antiangiogenesis therapy [56, 57]. As such, the development of HTN may lead to discontinuation of the drug and limited clinical use. Hypertension that develops in the setting of antiangiogenesis treatment is often a dose-dependent effect [26, 58, 59]. While the exact molecular processes for HTN related to VEGF inhibition remain elusive, several different mechanisms have been proposed.

First, the HTN from VEGF inhibition may be due to decreased levels of nitric oxide and prostacyclin, which are potent vasodilators [26, 59–61]. As briefly mentioned before, one of the downstream pathways of VEGF signaling is the eNOS pathway. VEGF-VEGFR activation stimulates the endothelial NO synthase via recruitment of phosphoinositide 3-kinase and mediates activation of Akt and eNOS and production of nitric oxide (NO) [59, 62]. The VIVA trial (VEGF in Ischemia for Vascular Angiogenesis) infused recombinant human VEGF, both intravenously and intra-coronary, and demonstrated a dose-dependent reduction in blood pressure [63]. Therefore, antagonism of VEGF is considered high risk for hypertension as it could lead to subsequent downregulation of the eNOS pathway, causing less NO production and elevation in vascular resistance. In addition to the direct vasodilatory effect, NO also participates in tubuloglomerular feedback, pressure natriuresis, and sodium balance [64, 65].

Another explanation is the dose-dependent release of a potent vasoconstrictor, endothelin 1 (ET-1), that is associated with VEGF inhibition [66–68]. TKIs, such as regorafenib and sunitinib, were associated with increased circulating endothelin-1 levels and subsequent elevations in the blood pressure. ET-1 exerts its vasoconstrictor effect via interactions with ETA/ETB receptors. Kappers et al. were able to demonstrate that the HTN from the VEGF inhibition can be reversed to the pretreatment level with the administration of ETA/ETB receptor blocker, tezosentan.

Vascular rarefaction, which is the decreased capillary density, has also been proposed as a contributor to VEGF-inhibition-related HTN. Because microvessels (arterioles and capillaries) are important contributors of peripheral vascular resistance, disruption of this may lead to hypertension. Several studies have shown that vascular rarefactions, either functional or structural rarefactions, are associated with the use of VEGF inhibitors [69–71].

Other proposed mechanisms also exist; however, the current evidence is conflicting. For example, it has been proposed that VEGF inhibition may reduce renal fractional excretion of sodium (FENa) and cause subsequent volume-dependent hypertension. The sodium reabsorption occurs via the sodium chloride co-transporter (NCC) in the distal tubule and the epithelial sodium channel (ENaC) in the collecting duct, respectively. It was hypothesized that inhibition of VEGFR2, which is expressed throughout the distal tubule and collecting duct [72], would cause increased ENaC and NCC expression and lead to decreased diuresis, natriuresis, and increased sodium reabsorption. While one study was able to demonstrate the proposed effect [73], the other study was not able to show a significant difference in the amount of ENaC and NCC expression in the VEGF inhibition group [74].

Although there have been speculations that VEGF inhibition may exaggerate the severity of angiotensin II-dependent hypertension, the HTN from VEGF inhibition was associated with reductions in renin mRNA expression [59, 68] and urinary aldosterone excretion [59]. Suppression of renin may be an early compensatory response to the increase in BP caused by VEGF signaling inhibition.

Interestingly, it has been suggested that the development of hypertension is linked to the treatment efficacy of the VEGF inhibition, especially in patients with renal cell carcinoma and osteosarcoma [2, 62, 75–77]. Given the improved clinical outcomes without significant HTN-associated adverse events, HTN can potentially serve as an efficacy biomarker for antiangiogenesis therapies.

4.2 Proteinuria

Proteinuria is another common adverse effect that is associated with VEGF inhibitors. The development of proteinuria often occurs due to disruption of the glomerular filtration barrier. The incidence and degree of proteinuria may vary. In most studies, grading for proteinuria was defined as the following: Grade 1—dipstick 1+ or 0.15 to 1.00 g/24 h; Grade 2—dipstick 2+ to 3+ or 1.0 to 3.5 g/24 h; Grade 3—dipstick 4+ or > 3.5 g/24 h; Grade 4—nephrotic syndrome; and Grade 5—death. The same systematic review by Zhu et al. reported that the incidence of all-grade proteinuria was as high as 63%. Grade 3 proteinuria was significantly lower at 1.8% (even in the high-dose bevacizumab group) [26]. Among patients who are receiving TKIs, the incidence of all-grade and high-grade (Grade 3 or higher) proteinuria was 18.7 and 2.4%, respectively, in another systematic review [50]. As with hypertension, the VEGF inhibitor-induced proteinuria appears to be a dose-dependent effect.

Among patients who develop proteinuria after VEGF inhibition, some may develop endothelial lesions or podocytopathies. Typically, anti-VEGF antibodies (such as Bevacizumab) have been associated with "thrombotic microangiopathy (TMA)-like" endothelial lesions (also known as pseudo-thrombi), while the TKIs have been generally associated with minimal change nephrotic syndrome (MCNS) or focal segmental glomerulosclerosis (FSGS). Although there is a case report of TMA and subsequent development of collapsing FSGS (cFSGS) [78], most patients do not develop both entities concomitantly [30, 78].

Unlike the usual systemic TMA that presents with thrombocytopenia and hemolytic anemia, the bevacizumab-induced injuries are limited to the kidneys only. A unique pattern that is specific to bevacizumab-related TMA is the hyaline occlusive glomerular microangiopathy, which is likely arising from endothelial leakage followed by subendothelial accumulation of serum proteins. The glomeruli undergo duplication of the glomerular basement membrane, loss of fenestration, and detachment of endothelial cells from the basement membrane [18]. Then, over time, the accumulated serum proteins cause the formation of microaneurysms. Solidifying of these leads to the formation of hyalinosis that is also known as "pseudo-thrombi" [79–81]. Such an entity must be considered in proteinuric cancer patients who are treated with anti-VEGF therapies.

Recent evidence suggests that complement alternative pathway may contribute to endothelial injury in the cases of TMA. Complement factor H (CFH) is considered the most important inhibitor of the alternative pathway and acts to prevent endothelial injury from the complement pathway. In one study, VEGF inhibition decreases local CFH and other complement regulators, thus making the endothelial cells more vulnerable to complement activation [80, 82].

Podocytopathy, mainly minimal change nephrotic syndrome and focal segmental glomerulosclerosis, is another renal structural injury associated with VEGF inhibitors, especially the TKIs. MCNS and FSGS are characterized by podocyte foot effacement. Such structural changes can lead to actin cytoskeleton disorganization and subsequent nephrotic range proteinuria. The podocyte injuries can be the result of changes in podocyte-associated proteins including those that assemble and stabilize the slit diaphragm and those that anchor the foot process to the glomerular basement membrane. Examples of those proteins include nephrin, podocin, synaptopodin, and podoplanin [83].

Nephrin phosphorylation has been found to be essential to maintaining slit diaphragm integrity. Nephrin interacts in vivo with VEGFR2 and activates downstream the Akt/PI3K pathway and regulates actin polymerization and stress fiber formation. Disruption of this crosstalk between VEGF and nephrin signaling has been associated with podocyte injuries [83, 84].

Another mechanism for glomerular injury and proteinuria with TKI use is the role of endothelial-to-mesenchymal transition (EndoMT). EndoMT is a novel source of myofibroblasts and contributes to renal fibrosis and subsequent development of chronic kidney disease. During the EndoMT, endothelial cells tend to change their phenotypes into a mesenchymal phenotype [83, 85]. Several studies already have demonstrated that EndoMT plays a crucial role in glomerular injury and subsequent albuminuria in diabetic nephropathy [86, 87]. The study done by Stavniichuck et al. was able to demonstrate that TKI use (Sorafenib) decreased renal cortical endothelial marker WT-1 mRNA expression while increasing the mesenchymal marker expression by 2–3-fold in a murine study.

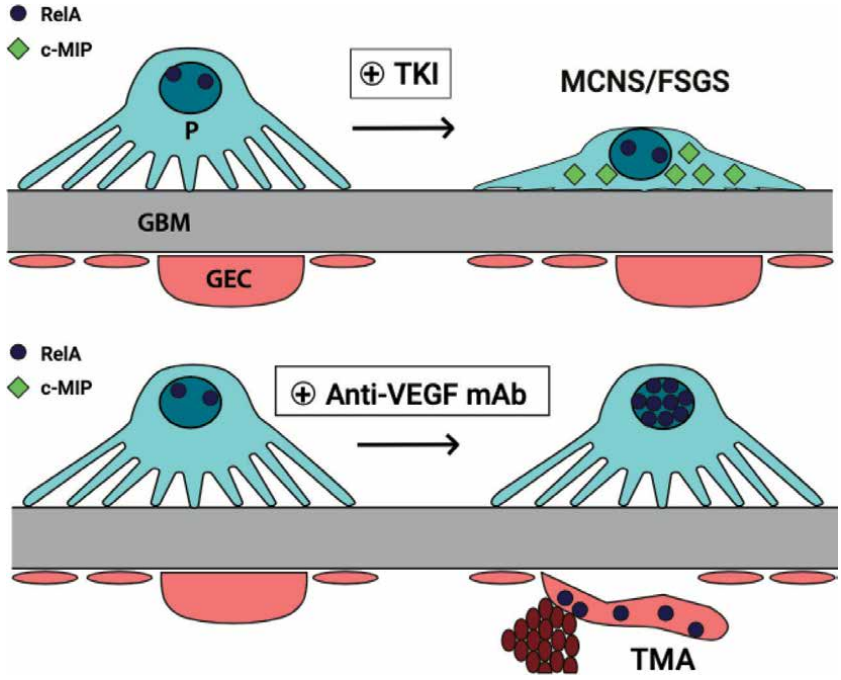

Figure 2.
The effect of TKI vs. anti-VEGF mAb on the balance of intracellular proteins, c-MIP and RelA, and associated structural injuries.

The balance between two intracellular proteins, c-MIP (C-Maf-inducing protein) and RelA (NF-kB transcription factor, also known as p65), has been associated with either the podocytopathy or the endothelial injuries associated with different VEGF inhibitors. TMA due to anti-VEGF therapy has been associated with increased expression of RelA with no detection of c-MIP. This leads to subsequent activation of the pro-inflammatory cascade, leading to endothelial injuries. On the contrary, MCNS/FSGS were only associated with C-MIP overexpression without significant detection of RelA. Overexpression of c-MIP has been associated with MCNS and FSGS, as the c-MIP interferes with the nephrin/Akt signaling pathway and causes subsequent podocyte injuries [43, 81] (**Figure 2**).

4.3 Other clinical considerations

Due to the frequent comorbidities that are concurrently present (such as hypertension and diabetes), cancer patients are at an increased risk of developing acute kidney injury and chronic kidney disease. Patients who are receiving antiangiogenic therapy may be at increased risk of kidney injury as these agents may induce direct cellular toxicity on endothelial cells and/or podocytes. The effect on kidney function can further be complicated if there is a simultaneous use of other systemic chemotherapies and/or if the patient underwent nephrectomy (which remains the gold standard treatment for non-metastatic renal cell carcinoma (RCC)) [81].

Contrast-induced nephropathy (CIN) appears to be more frequent in cancer patients who are receiving VEGF inhibitors. A small prospective cross-sectional study was able to show that the prevalence of CIN was significantly higher in the

anti-VEDGF/R treatment group compared to the control group. No one type or specific VEGF inhibitor seemed to cause more CIN than the others [88].

Patients with previously stable proteinuria and chronic kidney diseases are at risk of developing worsening renal function after initiating VEGF inhibitors. In one study, the authors reported cases of worsening kidney function with biopsy-proven acute interstitial nephritis, diabetic nephropathy, and collapsing FSGS [47].

Unfortunately, research concerning the long-term renal function and chronic kidney disease with chronic VEGF inhibitor use in cancer patients is scarce. Patients who receive these therapies often have advanced cancers with many comorbidities. Long-term follow-up may not be feasible in many cases. It is also more difficult to perform kidney biopsies for histopathological examinations given the stability of these patient populations.

Some of the available currently regarding long-term effects on eGFR after VEGF inhibition show conflicting conclusions. In one study [89], a retrospective review of patients revealed that chronic use of intravitreal VEGF inhibitor (ranibizumab) did not significantly alter the rate of change in eGFR and/or albumin-to-creatinine ratio with an increasing number of treatment injections in patients with and without diabetic kidney disease. All of the participants had diabetic macular edema and received an average of 26.8 intravitreal anti-VEGF injections per patient over 31 months.

In contrast, a different study showed that chronic use of lenvatinib can induce a decline in eGFR, leading to the development of chronic kidney disease, especially with a duration greater than 2 years. This effect was observed regardless of the baseline eGFR. The presence of proteinuria was a risk factor for the decline in eGFR. Of note, patients with better baseline renal function were able to prolong the clinical outcome [90].

Of course, the amount of systemic circulation of the VEGF inhibitors is likely much higher in the study with lenvatinib (used for patients with thyroid cancer compared to intravitreal injections). It can be speculated that the impact on eGFR and subsequent development of chronic kidney disease may be a dose-dependent phenomenon.

4.4 Electrolyte disorders and cell damages

Various electrolyte disorders may occur with VEGF inhibitors as they may have direct nephrotoxic effects on tubular transporters. Of note, hypophosphatemia and hyponatremia are the most reported electrolyte disturbances associated with VEGF inhibitors. In some cases, hypomagnesemia, hypocalcemia, and hypokalemia may also occur [81].

VEGF inhibitors are also suspected to cause cell damage via several mechanisms including disruption of the cytoskeleton [91], tubular cell apoptosis [92], and autophagy [81].

5. Preventive strategies for minimizing nephrotoxicity

Renal toxicities associated with VEGF inhibition are an area of ongoing research as new therapeutic agents are constantly in development. The National Cancer Institute's Investigational Drug Steering Committee published guidelines in 2010 advising to conduct a formal risk assessment for cardiovascular complications prior to starting treatment. Patients with preexisting hypertension should be identified and addressed before starting therapy, since they are expected to have an exacerbation of

hypertension after starting treatment. Blood pressure should be measured throughout the treatment course and managed aggressively to a goal of under 140/90 mmHg. VEGF inhibition may need to be held if BP control is not achieved [93]. Calcium channel blockers (CCBs), potassium-sparing diuretics, and HCTZ are associated with the greatest decrease in BP in patients receiving anti-VEGF TKIs therapy [74, 94].

Renal function should be assessed prior to receiving antiangiogenic therapy. Patients should undergo a screening urinalysis to quantify proteinuria prior to beginning therapy and throughout the treatment course. Patients with preexisting proteinuria should be referred to a nephrologist for possible renal biopsy to determine the histological diagnosis. Inhibition of the RAAS system is first-line therapy for treating patients with proteinuria and hypertension on anti-VEGF agents. Though this remains to be validated in randomized, controlled trials. Of note, the use of ACE-I/ARB should be considered only if the patient has concurrent HTN and proteinuria as the RAAS is downregulated in VEGF inhibitor-induced hypertension [59]. Significant proteinuria, nephrotic syndrome, and TMA are indications for stopping therapy and obtaining a kidney biopsy. Patient education and awareness of expected systemic toxicities and management are important for promoting optimal use and adherence to therapy.

6. Future perspectives

Molecularly targeted therapeutic agents have become a mainstay in the treatment of cancers. Anti-VEGF agents are commonly used in combination with other modalities such as traditional chemotherapy, radiotherapy, and immunotherapy. New antiangiogenic targets and combinations are under investigation. Delta-like ligand 4 (DLL4) is a component of the Notch signaling pathway and is highly expressed in actively growing vessels. It is a key negative regulator downstream of the VEGF signaling pathway and thus a promising target of antiangiogenesis therapy to augment the effects of VEGF inhibitors [95]. Currently, therapies against DLL4 alone and in combination with VEGF pathway inhibitors are being developed. ABT-165 is a bispecific anti-DLLF/VEGF antibody that has shown to be superior to single anti-VEGF treatment in preclinical models of colon cancer, breast cancer, and glioma when used alone and in combination with standard-of-care chemotherapeutics [96].

Currently, there are no set guidelines in the management of renal toxicities from anti-VEGF agents. Cancer patients who require these therapies are often at higher risk for kidney injury due to preexisting kidney disease and concomitant use of nephrotoxic chemotherapeutics. Patients who require intravitreal injection for diabetic macular edema and macular degeneration are also typically older and have some level of baseline renal dysfunction. Further research into the incidence and mechanisms of renal toxicity of antiangiogenic agents would help with the management. The development of early markers of vascular injury can help identify patients at risk for hypertension and proteinuria before they develop. Early recognition may allow for medication dose adjustment rather than premature discontinuation of a potentially beneficial anticancer therapy.

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Section 3

Hemodialysis and Transplantation

Chapter 9

Overcoming the Achilles' Heel of Hemodialysis Vascular Access: From Creation, Maintenance and Salvage

Hemant J. Mehta

Abstract

Vascular access (VA) is the life line for hemodialysis (HD) but also Achilles' heel. VA consists of HD catheters, arterio-venous fistula and arterio-venous grafts. From the earlier 'Fistula First' initiative, we later moved to 'Fistula First, catheter last' approach and have now realized that we need to follow the recommendation for End Stage Kidney Disease (ESKD) patients, given by Kidney Disease Outcome Quality Initiative (KDOQI). It says, "Patient First: ESKD Life-Plan" to attain the "right access, in the right patient, at the right time, for the right reasons". However, this applies to the creation of VA. It is essential to monitor and do VA surveillance to maintain the VA, as it can malfunction. When the VA malfunctions, it needs intervention. Depending upon the type of VA, the intervention varies. It could be endovascular or surgical. These issues will be highlighted in this chapter.

Keywords: chronic kidney disease, hemodialysis vascular access, hemodialysis catheters, arterio-venous fistula for hemodialysis, arterio-venous grafts for hemodialysis, problems of vascular access for hemodialysis

1. Introduction

A better HD VA leads to better survival, the ideal HD conduit is elusive and one has to really strive hard to capitalize on the already scare resource of vascular estate. HD VA remains the leading cause of morbidity and mortality among HD patients. The types of VA include HD catheters (non-cuffed and tunneled cuffed), arterio-venous (AV) shunt, AV fistula (AVF) and AV graft (AVG). The heroes and themes of Greek mythology have had a great impact in the medical literature. For example, we use the term hydra-headed for the kind of problem caused by VA, which is like a multifarious evil, not to be overcome by a single effort, a problem that poses more problems. One would call it Herculean task, that's difficult and needs enormous strength. It's a process that once begun has potential to generate many complicated problems, like Pandora's Box. HD access related problems are called Achilles' heel, a term used to describe the weak point. Recently another term has been added, dedicated to

disentanglement of factors hindering our efforts to create a perfect VA for dialysis—a truly Sisyphean task [1].

In the 1950's, though the technical devices were available for regular HD treatments like Kolff's twin-coil kidney [2], the Achilles heel was a reliable access to the circulation for multiple use which did not exist. The VA situation has not changed over the years. One has to create, allow it to mature (AVF, AVG), maintain it and salvage in case of malfunction before ultimately deciding to abandon it. The earlier VA guidelines of last decade have been replaced by end stage kidney disease (ESKD) life plan [3], where the emphasis is on the individualization of VA care on the basis of patient and disease characteristics. With increasing observation that AVF-prioritized care is particularly ineffective in certain patient groups, these latest VA guidelines have shifted recommendations from a standardized to a customized approach, recommending placement of the "right access, in the right patient, at the right time, for the right reasons". In this chapter, we shall deal with VAs creation, maintenance and salvage, except AV shunts. One has to keep local practice factors, values, preferences and varying clinical needs in mind while considering all the aspects.

Sometimes, VA is created for urgent start HD, or as a bridge to AV fistula maturation or kidney transplantation. An ideal bridge device would allow for immediate use following placement, provide blood flow rates sufficient to ensure adequate HD, have a low complication rate, and have sufficient length of technical survival to allow AVF development and maturation without the need for device replacement [4]. There were various devices. Scribner's shunt in 1960, had external silicone rubber/Teflon tubing connected to a vein and artery at the wrist enabling relatively high rates of blood for HD. In 1964, Dr. Shaldon used two single lumen catheters in the femoral vein as an HD access for daily home dialysis for acute renal failure. 1980s saw development of hybrid transcutaneous access devices comprising an AVG and a port, and totally implanted blood ports for HD treatment were introduced in 1996. The shunts and ports are no more used.

In 1965, Drs. Cimino and Brescia described AVF [5] and in 1976, chronic HD with an expanded polytetrafluroethylene graft (ePTFE) was described [6]. 1982 saw development of double lumen non cuffed double 'D' configuration HD catheter, and 1987 saw availability of Dacron cuffed double lumen HD catheters. Both these could be used immediately, whereas, after the creation of AVF and AVG, maturation occurs in the form of morphological changes in the body (venous remodeling for AVF) and these accesses should be used for HD only after they have matured. Recently, early cannulation AVG are in use with median time to first cannulation of 3 days [7]. HeRO Graft ® (Hemodialysis Reliable Outflow) is a fully subcutaneous AV access device currently available to maintain long-term access for HD patients with **central venous stenosis (CVS)**. Though it is classified as a graft, but has no venous anastomosis and hence different from conventional AVG. This could be used for catheter dependent patients or those with failing AVF or AVG and CVS, but it cannot be used immediately.

2. The 'temporary' non-cuffed, non-tunneled acute HD catheters: (non-TCC)

2.1 Creation

There is no timing for creation of this access as this is for 'emergency' HD, though it is also used for elective HD. The usual sites are internal jugular vein or femoral vein, with tip position in superior (SVC) or inferior vena cava (IVC). The use of non-TCC

dialysis catheters in acute situations can be justified. The use of non-cuffed catheters should be restricted to critically ill intensive care unit patients or for "in and out" purpose of those with temporary loss of a permanent access. Use of femoral non-TCC should be restricted to those unable to lie down, and for not more than 7 days. Many centers across the world use internal jugular vein (IJV) catheters for acute situations and for initiation of chronic HD as per local factors and customs [8]. Internal jugular catheters may be left in place for up to 3 weeks without a high risk of bacteremia, but femoral catheters should be removed after 1 week [9]. There should be a plan to discontinue or convert any short-term catheter to a long-term catheter. These catheters should not be used as stop gap access while waiting for AV fistula to mature, because the AV fistula, if created after initiation of dialysis in ESKD situation will take at least 6 weeks to mature. There is a great variability of the vein caliber and its position in relation to the common carotid artery. Ultrasound guidance is therefore strongly recommended during insertion to reduce the 7–10% risk of carotid puncture to virtually zero.

2.2 Problems during creation

Risks of arterial puncture, hematoma, tracheal compression, pneumothorax (**Figure 1**) or hemothorax, injury to local structures, air embolism and catheter malposition (**Figure 2**) are well described complications. Problem of guide wire breaking and catheter tip banding was encountered by the author (**Figure 3**). This is a rare complication, which was recognized immediately, otherwise it could have caused the embolization of the broken piece of the guide wire and more complications. The clue to avoid such complications is to ensure that the entry and movement of the wire while inside the vein should be very smooth, and stop if any resistance is encountered. Always check the shape of the guide wire once it comes out of the body, it should be straight and almost in the original shape, to ensure that no complication of the kind described has happened. Proper length should be chosen to place the tip of non-TCC in the SVC for IJV catheters or within the IVC above the confluence of iliac veins for femoral HD catheters and the tip of the catheter should be in the middle of the vein away from the vessel wall so that the 'arterial' end of the catheter (withdrawal lumen – which is under negative pressure), does not cause flow problems during HD by becoming occluded due to the vessel wall being sucked across it. If shorter length is used by mistake, especially for left IJV site, it could touch the wall of SVC and cause flow problems. The femoral non-TCC could also cause flow problem in obese patients.

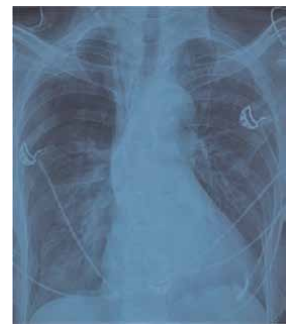


Figure 1.
Pneumothorax with non-TCC.

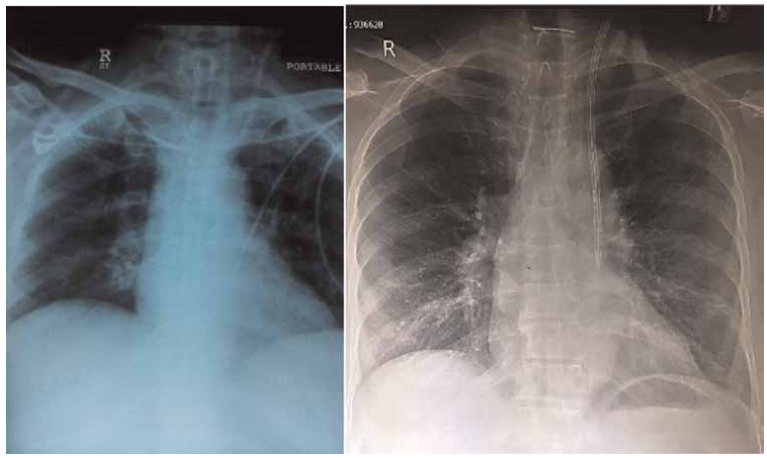


Figure 2.
IJV non-TCC tip malposition (more common with left sided non-TCC).

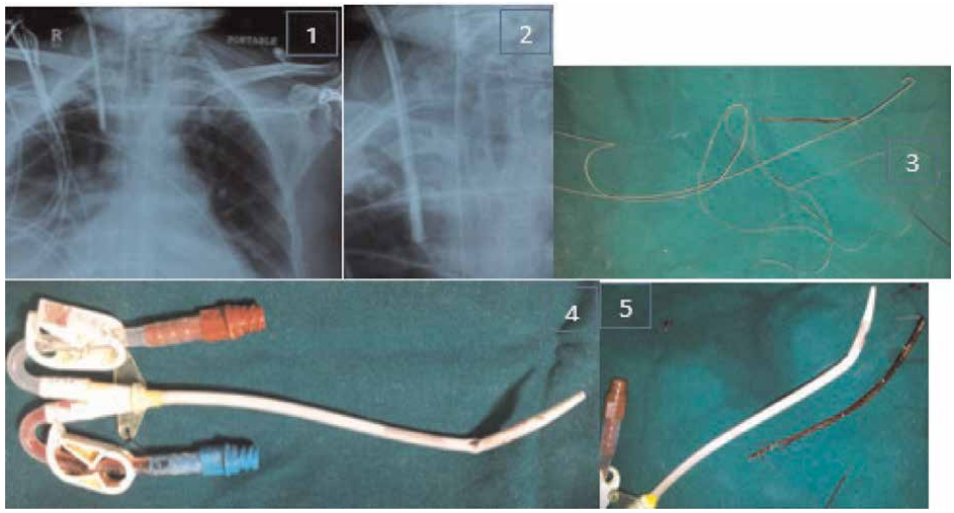


Figure 3.
Complication of non-TCC insertion. 1) chest X-ray after insertion, showed that the tip was blunted (which should be tapering, as per the catheter design). 2) close look at the X-ray, something visible within the lumen and jutting out of the catheter. 3) broken guide wire. 4) the catheter bend. 5) the broken and retained piece of guide wire, corresponding to the catheter bend.

2.3 Maintenance

The catheter care is required to prevent infection and clotting. The catheter dressing should be clean and dry. The caps and clamps of the catheters should be kept tightly closed to prevent bleeding and air embolism. The 'scrub the hub' protocol suggested by 'Making dialysis safer coalition' and Center for disease control, USA, should be followed during connection and disconnection process. The caps of the catheter should kept in a sterile bowl containing compatible antimicrobial solution during the duration of HD. To maintain patency of the catheter between the dialysis

treatments, heparin is instilled into the lumens. The amount of heparin to be filled is mentioned on the catheter and varies by manufacturer and by the size of the catheter. The concentration of heparin used could be 1000 to 5000 units per ml as per center protocol.

2.4 Salvage

If the non-TCCs are kept in place within stipulated time interval, usually they work well. However, they can develop problems of poor flows and infection if not handled properly, within 1–2 weeks also. Thrombosis occurs due to infection or due to improperly placed catheter tip touching the vessel wall. If such situations have occurred, it is advisable to change catheter (may be railroaded) to appropriate size and proper tip position. Infected non-TCC should be removed immediately and re-sited. Exchange of infected non-TCC over a wire should be avoided.

3. The tunneled cuff HD catheters (TCC)

3.1 Creation

A high proportion of ESKD patients (>50%) need to be initiated on HD urgently by a central venous catheter. The 'Fistula First' initiative was meant to increase the AVF prevalence and reduce catheter dependency, introduced by Centers for Medicare and Medicaid Services (CMS) and End Stage Renal Disease (ESRD) network in 2003, which transitioned to Fistula First Breakthrough Initiative (FFBI) in 2005, and in 2007, the proposal was to have "Fistula First, Catheter Last' initiative. This was necessary, because the success of Fistula First initiative had a downside of increased HD catheters incidence, probably because the focus on increasing fistulas may have inadvertently diverted attention away from decreasing dependence on HD catheters [10]. In spite of all efforts, around 80% of patients get initiated on HD with catheters, in USA [11] and remain on catheters beyond 90 days. It is apparent that TCCs are going to be around till all CKD patients have AV fistula created in the pre HD stage. Complete avoidance of TCCs seem unlikely at this moment, and it's like sleeping with the enemy. The catheter conundrum exists where one hates living with them but cannot live without them [12]. Hence it is necessary that nephrologist's must be aware about its insertion techniques, usage and tackle complications, from first day of insertion so as to improve TCC performance and prolong its life, to reduce the morbidity, mortality, and overall cost of the catheters, but with an aim to avoid extended catheter use.

3.2 Insertion of TCCs

As per the KDOQI vascular access guidelines of 2019 [3], it is considered reasonable in valid clinical circumstances to use TCCs for short-term or long-term durations for incident patients. The indications of insertion are varied and include ESKD patient starting on planned long term HD without AV fistula in place, or as a bridge to transplantation. It could also be used for elderly patients if it fits into the patient's ESKD L-I-F-E plan (Patient Life-Plan First then Access Needs). Another situation where it is used is for likely prolonged recovery from AKI, or patients requiring prolonged extra-corporeal therapies, like plasma exchange etc.

Short term duration for TCCs includes AVF or AVG created but not ready for use and dialysis is required, acute transplant rejection or other complications requiring dialysis, peritoneal dialysis (PD) patient with complications that require time-limited peritoneal rest or resolution of complication (e.g. pleural leak), patient has a living donor transplant confirmed with an operation date in the near future (<90 days), and AVF or AVG complication such as major infiltration injury or cellulitis that results in temporary nonuse until problem is resolved. As per the same guidelines, long-term or indefinite duration TCC indications include multiple prior failed VA with no available VA creation options, limited life expectancy, valid patient preference and special medical circumstances. KDOQI considers it reasonable to use TCC in preference to non-TCC due to the lower infection risk with TCC.

The insertion should be in the sterile environment with standard aseptic precautions. The Center for Disease Control (CDC) guidelines for the prevention of intravascular catheter related infections (2011) states that use maximal sterile barrier precautions, including the use of a cap, mask, sterile gown, sterile gloves, and a sterile full body drape, for the insertion or guide wire exchange. The COVID 19 mitigation measures have shown further reduction in catheter related blood stream infection (CRBSI) during the pandemic, superimposed on the non-pandemic related reductions in some facilities before the pandemic, emphasizing the role of aseptic measures. Even after the pandemic, it may be prudent to continue COVID 19 mitigation measures to prevent CRBSI [13].

Use of USG guidance and image intensifier is mandatory. Contrary to this recommendation, COVID 19 pandemic has brought out studies on bed side TCC insertion and its safety [14], where authors concluded that bedside right internal jugular TCC placement in COVID-19 patients, using ultrasound and anatomic landmarks without fluoroscopic guidance, may potentially reduce the risk of COVID-19 transmission among healthcare workers without compromising patient safety or catheter function. In another study, the authors concluded that bedside TCC placement has served to conserve resources, prevent complications with transport to and from the operating room, and decrease personnel exposure during the COVID-19 pandemic. This strategy warrants further consideration and could be used in critically ill patients regardless of COVID status [15]. In the pre-COVID era, a study showed that the placement of TCC by Nephrologist, with the help of USG Doppler & post placement x-ray chest was found to be a safe procedure where access to fluoroscopy was not available [16]. The TCC is recommended to be inserted (in order of preference), in the internal jugular veins (IJV), external jugular veins (EJV), femoral veins, subclavian veins, trans lumbar, trans renal and trans hepatic locations. These are adaptations as per circumstances and cannot be generalized. Except for right IJV insertions, (and rarely left IJV, authors' personal experience) other sites cannot be used for insertion without fluoroscopic guidance. Fluoroscopic guidance is also required as left sided SVC or double SVC are known (**Figure 4**).

The length and diameter of the TCC should be appropriate and chosen keeping Hagen-Poiseuille equation in mind, which states that flow is inversely proportional to length. The resistance to blood flow is directly related to catheter length and inversely proportional to the fourth power of the diameter of the hemodialysis catheter. A slight increase in the inner diameter of the arterial and venous lumens will result in a large increase in the rate of blood flow through the catheter [17]. So the chosen catheter should be long enough that the tip can reach the intended target site, but it should otherwise be as short as possible to minimize resistance to flow. As per Dr. Gerald Beathard, father of interventional nephrology in USA, (personal data), diameter is the

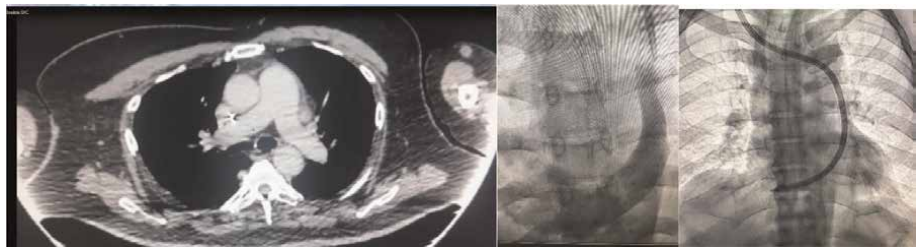


Figure 4.
Double SVC, left sided SVC.

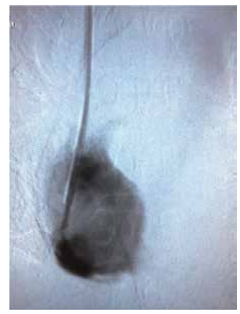


Figure 5.
The proper tip of TCC.

major factor and 19% increase in diameter leads to increase in the flow by 2 times and 50% increase in diameter by 5 times. Increasing the diameter from 2 to 2.1 mm will increase the flow by 21%. Catheter length is less important, as 19% increase in diameter will compensate for doubling of length. The mechanical catheter design helps improve rheology. The ideal catheter should give maximum flow, and reduce the risks of clotting or fibrin sheath formation. This needs good tip design. Various tip designs are available e.g. step tip, split tip, symmetrical tip etc.

TCC tip design and position plays very important role in the working of the catheters. Catheter tip should ideally be in the right atrium, such that it moves within the atrium during breathing or patient sitting up during dialysis (**Figure 5**). The problem of TCC getting pulled up in the SVC, causing flow problem during dialysis is encountered more with staggered tip TCC when the tip is not placed within RA, and the proximal arterial end abutting against the SVC wall during inspiration and due to ultrafiltration. We should be aware that the right atrial morphology, configuration and geometry varies among individuals.

3.3 Problems during insertion

Experience in practice placement and referral to interventional nephrologists would decrease complication rate and may decrease subclavian vein usage for catheter placement. However, complications like pneumo or hemothorax do happen, as also air-embolism, bleeding from local site or cardiac arrhythmias. There is a chance of arterial puncture in spite of USG guidance (**Figure 6**), catheter malposition in the posterior mediastinum (**Figure 7**), tip in the azygous vein, outside SVC, or have a kink inside the SVC when fluoroscopic guidance is not used (**Figure 8a** and **b**). A kink in

Figure 6.
TCC in the arterial system (courtesy Dr. Ravindra Madraki, Bijapur, India).

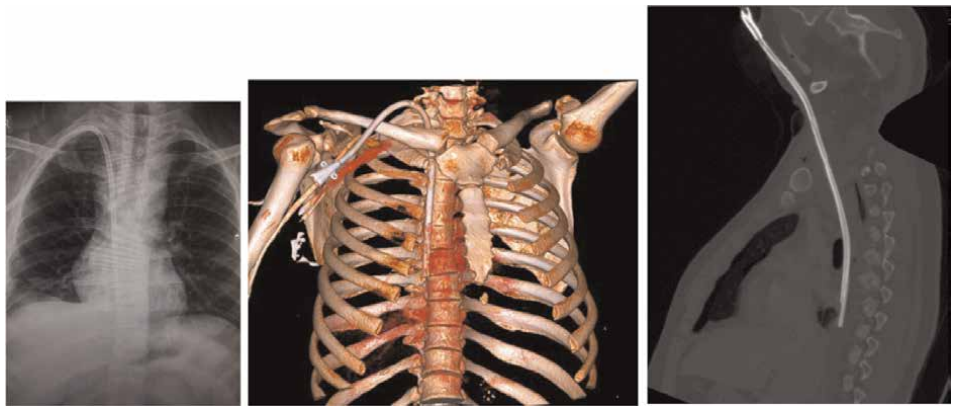


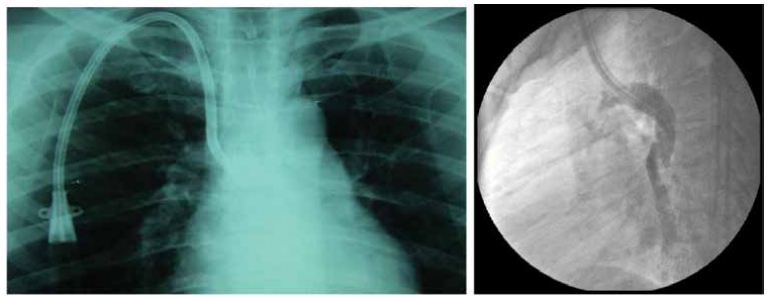
Figure 7.
TCC appeared to be well placed is actually in the posterior mediastinum, with hydro pneumothorax.

the catheter after insertion would not give a proper flow (**Figure 9**). TCC re-inserted in the vein which already had a catheter, which malfunctioned, could result in problems of flow (**Figure 10**), where the inserted TCC malfunctioned within few days, due to presence of a clot around the catheter tip and in the SVC, with a suspicious catheter related sheath (CRS, also called fibrin sheath), probably both pre-existing. Improper size of catheter (**Figure 11**) would cause flow problems immediately or after few days.

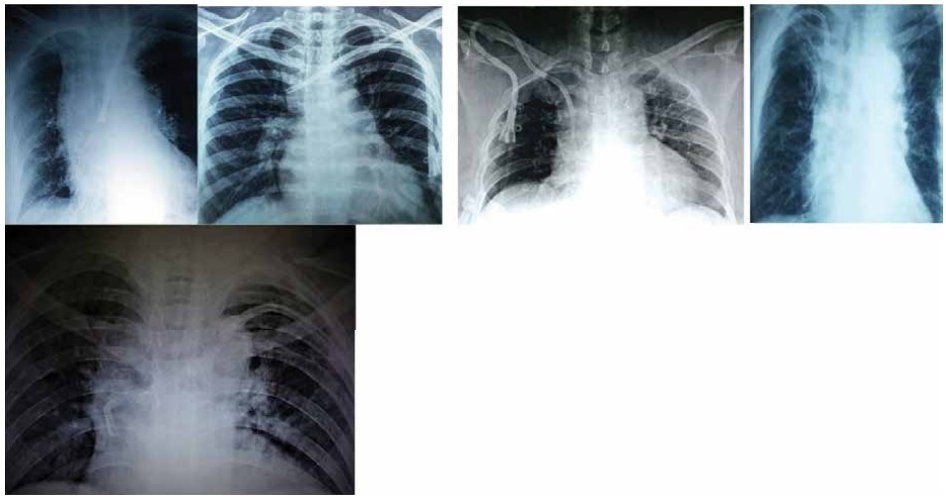
As a general rule, when the TCC insertion is planned with prior use of the same vein in the past, one should always be prepared to perform angiography to delineate the venous system (**Figure 12**). In such situations, it would be ideal to use Surfacer® device if available for in-side out venous access. In absence of the same, authors have used long Chiba needle to puncture the completely occluded venous segment to gain the guide wire entry, do angioplasty and insert TCC.

3.4 Maintenance of TCC

Complications of TCC are CRBSI and clot and cause poor TCC performance. The sterile precautions mentioned while handling non-TCC also apply to TCC during connection and disconnection process of HD. Catheter dysfunction leading to inadequate dialysis has been defined based solely upon blood flow measurement. However, there is concern that using the blood flow rate as the only criterion can be misleading and has the potential to result in a significant number of unnecessary interventions. Other



(a)



(b)

Figure 8.
A: Catheter tip misplaced in the azygous vein (courtesy Dr. Sampath Kumar, Madurai, India). b: Catheter tip misplacement, right IJV catheter in the wrong positions, left subclavian catheter left out of the right atrium.

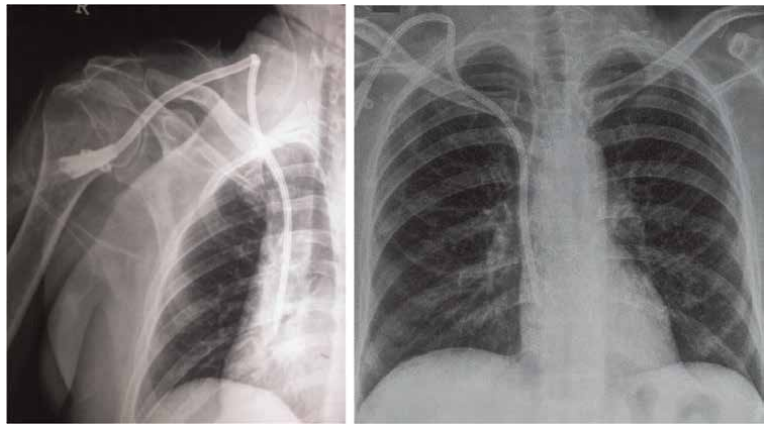


Figure 9.
Catheter kink TCC in right EJV, corrected.

Figure 10.
TCC with poor flow, due to clot in SVC and around catheter tip, with double shadow on right side of TCC suggestive of CRS (catheter related sheath, also known as fibrin sheath) (figure courtesy Dr. Nikhil Rathi, Pune, India).

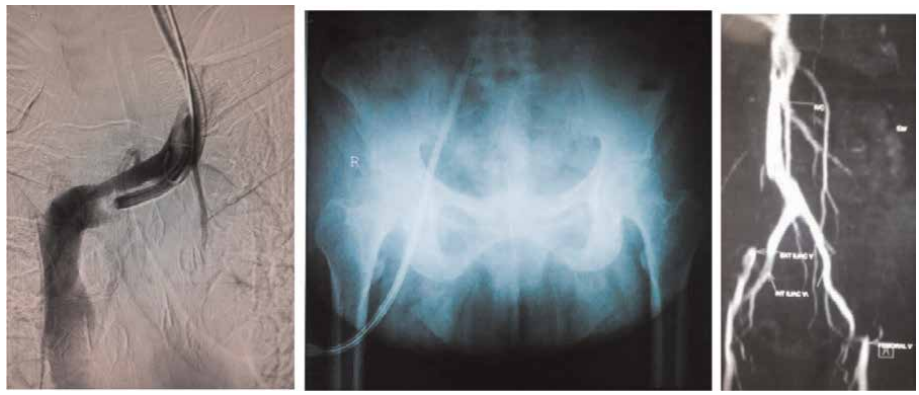


Figure 11.
Improper size of TCC in left IJV with clot and (removed) short length TCC in right femoral vein resulting in complete thrombosis of right external iliac vein.

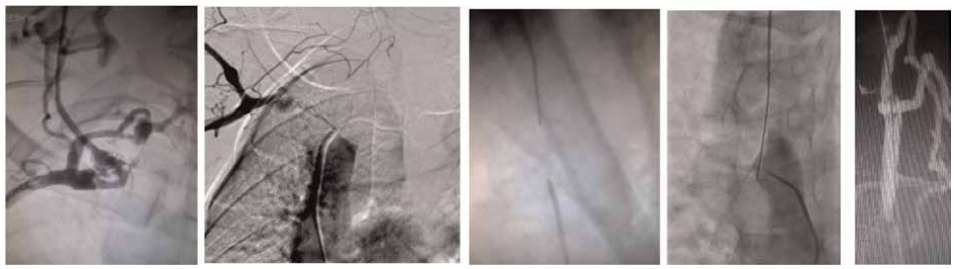


Figure 12.
Crossing the CTO with Chiba needle to get the wire across for TCC insertion.

factors besides blood flow rate that are important for determining the adequacy of hemodialysis include the weight of the patient, recirculation, ultrafiltration variables, duration of hemodialysis, and frequency of hemodialysis [18].

As the blood flow decreases, the delivered dialysis dose (measured as kt/v) decreases, and leads to reduced quality of life and increased morbidity and mortality risk. The reduced blood flow also increases the thrombosis, which in turn leads to infection. Heparin is used as a catheter locking solution to prevent thrombosis and hence infection. The TCC has 2–5 fold higher risk of infection compared to AVF or graft. Catheter related infections include exit site infection, tunnel infection and bacteremia. The TCC has 15 fold higher risk of catheter related blood stream infection (CRBSI) and all-cause mortality rate of 12–25%. Bacterial biofilm is a key reason for the contamination of medical devices like TCC and the generation of microbial and chronic infections in the body. The critical adherence of the organisms to the catheter surface initiates the common pathway of biofilm formation which has microorganisms protected by exopolysaccharide matrix. The organisms include Staphylococcus, Pseudomonas, and Candida among others. An aseptic handling provided, the citrate 4% might be the best catheter lock solution [19]. If the local risk of CRBSI is high the taurolidine + citrate + heparin lock should be used [20]. When malfunction prevails the alteplase/ urokinase block combined with citrate + taurolidine will have advantages [21]. In centers where both complications must be addressed the taurolidine + urokinase + heparin lock could be preferred [22]. The taurolidine-citrate-heparin lock solution effectively eradicated pathogens from nontunneled and tunneled catheter biofilms and helped to maintain catheter lumen sterility [23]. 60% Ethanol alone or 30% ethanol with 4% citrate and ethylene EDTA have also been tried as lock solutions.

In healthcare organizations providing dialysis services, where the case mix includes a lower proportion of patients using catheter-based dialysis, those patients may experience higher rates of catheter-associated infections [24]. Infection control measures may be stronger in organizations dealing with higher proportions of this patient group.

Another way to reduce infection is to use Curos® caps containing 70% isopropyl alcohol, which is to be attached to Tego® hemodialysis connector. ClearGuard HD antimicrobial barrier caps have a rod which is coated with dry chlorhexidine, as are the threads of the cap, and have been found to reduce CRBSI. Tego-Curos caps used with The Arrow-Clark™ *VectorFlow® Catheter reduces infection by 3 times compared to Tego-Curos caps used with Medcomp Ash Split® catheter [personal communication, Timothy Clark,* Director of *Interventional Radiology* at Penn Presbyterian Medical Center, USA].

The catheter exit site should be covered by a dressing which should be routinely changed, and patient instructed to maintain hygiene and integrity of the dressing and not to soil it.

Catheter tip can get migrated after several months of TCC working (**Figure 13**). TCC can develop a crack in the 'Y' limb of external part of catheter or in the sub-cutaneous tunnel, between the cuff and the exit site or at the 'Y' end of TCC and the 'silver ion sleeve' of the TCC. The cuff can get extruded or the skin over the tunnel can get eroded

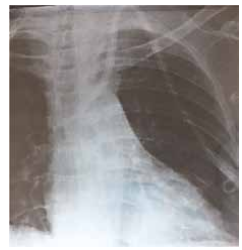


Figure 13.
Catheter tip migration after several months of functioning TCC.

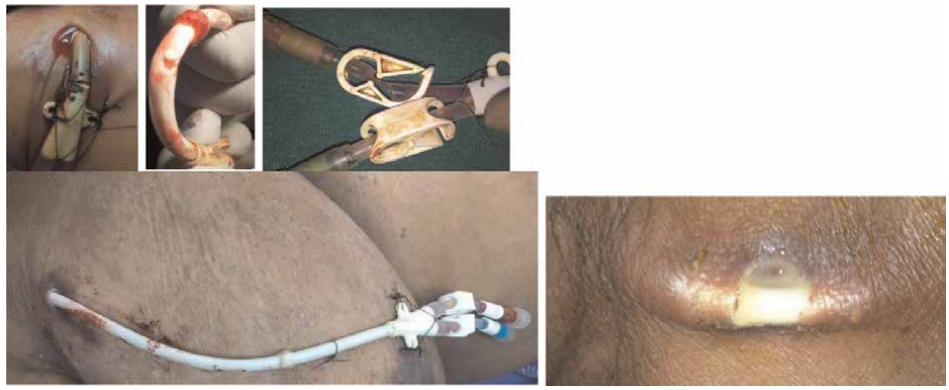


Figure 14.
Cracks in the TCC a) at the junction of silver ion sleeve with TCC b) on the TCC within the subcutaneous tunnel, cuff extrusion and erosion of skin over the tunnel.

(**Figure 14**). It can develop CRS and / or CRAT to cause catheter malfunction. The CRS should always be suspected whenever TCC malfunctions, especially with inability to aspirate but easy to inject. There may be a thrombus at the tip responsible for TCC malfunction. CRAT may or may not cause TCC malfunction, but it's a risk for pulmonary embolism. The CRAT could be infected which can cause septic emboli to lungs. The CRAT can be tackled as per the algorithm [Abstract at Annual conference of American Society of Diagnostic and Interventional Nephrology, 2018, and published in Journal of Vascular Access, doi:10.1177/1129729818780571]. The CRS can be tackled with balloon disruption or snared out (**Figure 15**).

3.5 TCC salvage

TCC can malfunction at any time after being in regular use. The situations to salvage the TCC arises when it malfunctions due to CRS, CRAT, combination of CRS and CRAT and SVC stenosis around the TCC tip in SVC (**Figure 16**), or clot at the tip (**Figure 17**), when the presentation is with poor flow. Infected TCC causes fever, or rigors during HD but no fever on non-HD days.

An infected TCC causing CRBSI sometimes needs to be removed but can also be exchanged over a guide wire, and has been found to be safe [25]. This is necessary when the existing TCC is the only dedicated vascular access and there is no other alternative option available for the continuation of HD. Antibiotics locks have been shown to be effective adjunctive therapy to systemic antibiotics in the treatment of CRBSIs [26]. Antibiotic locks should be used when immediate catheter removal is not possible and when catheter needs to be salvaged.

A meta-analysis of hemodialysis patients with TCC, with CRBSI, compared 3 treatment protocols for CRBSIs: (1) systemic antibiotics alone, (2) systemic antibiotics plus antibiotic lock (catheter not removed), and (3) systemic antibiotics plus guide wire exchange. It included 28 retrospective and prospective studies, with a total of 1596 patients. Patients treated with systemic antibiotics and antibiotic lock had similar cure rates to those treated with systemic antibiotics and guide wire exchange, and both were superior to the rates obtained when antibiotics were used alone. Recurrence of infection with the same organism was not different between the systemic antibiotics plus antibiotic lock group and the systemic antibiotics plus guide wire exchange but was much higher in patients treated with systemic antibiotics alone, which further

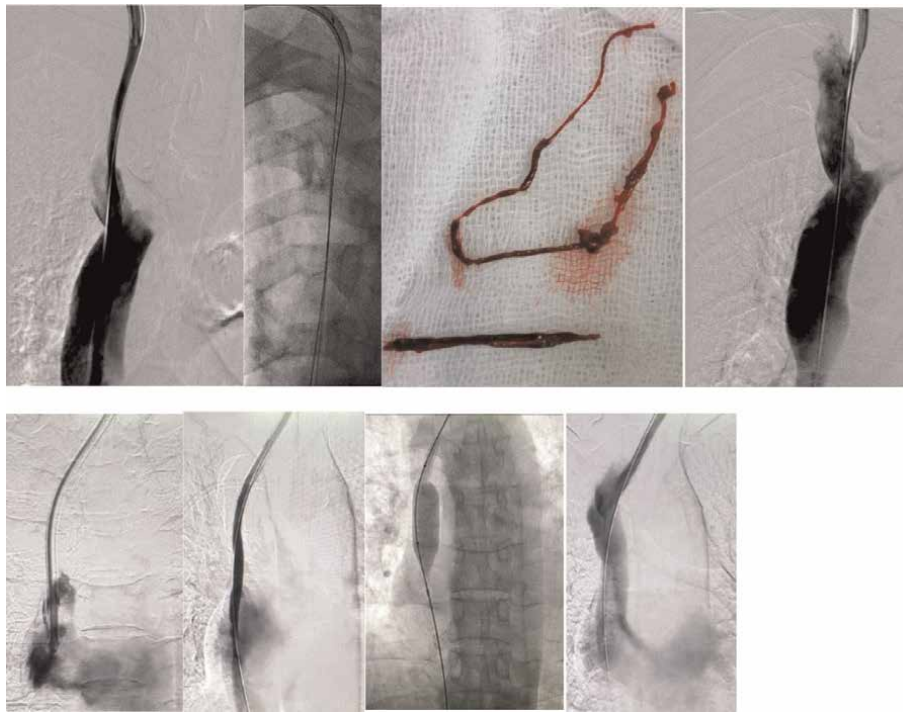


Figure 15.
CRS (fibrin sheath), snared out or balloon disrupted.

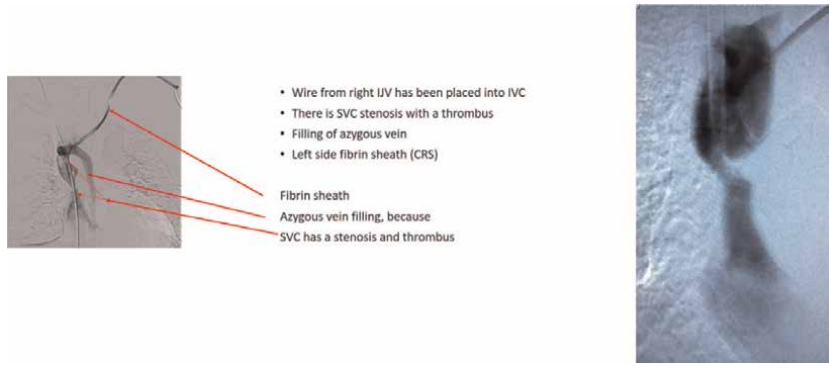


Figure 16.
The reason for left IJV TCC malfunction; stenosis at SVC-RA junction.

Figure 17.
Clots at tip of TCC.

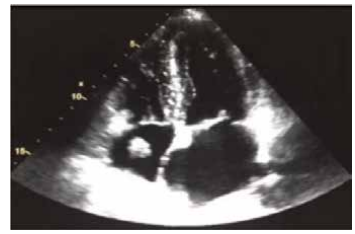


Figure 18.
CRAT, thrombolysed with alteplase.

supports the practice to use an antibiotic lock or guide wire exchange in conjunction with systemic antibiotics [27]. Prompt catheter removal with delayed placement of a new TCC is a good option provided it is also viable with alternative venous site availability. All CRBSIs require a minimum 2 to 3 weeks' systemic antibiotic therapy. However, *Staphylococcus aureus* CRBSIs and complicated infections should be treated with systemic antibiotic therapy for minimum 4 to 6 weeks. Patients who are hemodynamically unstable or have severe sepsis, metastatic infection or exit site infection with pus pouring out of the site should be hospitalized. If the patient is otherwise clinically stable without evidence of a metastatic infection, then the management can be continued in the outpatient setting. The TCC with candidemia should always be exchanged. The candedemia due to Candida parapsilosis or albicans can also cause infective endocarditis, which would ideally require surgical repair of the valve, however, one may attempt to preserve the valve with aggressive antifungal therapy.

CRAT either alone or with CRS is another cause when TCC salvage is necessary. The CRAT, if minor and causing TCC dysfunction can be resolved by removal of catheter itself. A bigger clot of >0.5 cm or a CRAT attached to the TCC tip by a thin peduncle hanging in the right atrium carries the risk of detachment and embolization if TCC is attempted to be pulled back. In such cases, thrombolysis with alteplase after negative blood cultures have been attempted with success (**Figure 18**). Alteplase is given at 0.1 mg/kg/hour for 6 hours in each lumen and may have to be repeated at incremental dose at 0.15, 0.20 and up to .025 mg/kg/hour for 6 hours (18 cases, personal experience). Chronic CRAT with functioning TCC can be treated with oral anticoagulants for 6 months if it works. Large CRAT (>6 cm) needs either surgical removal or using Angiovac® device (Angiodynamics) which is an alternative method to manage intra-atrial or intravenous thrombi. Patients with hypercoagulable states and unsuitable for any intervention needs lifelong anticoagulation if the patient continues to receive HD through TCC. The TCC malfunction due to stenosis around catheter tip, usually at SVC-RA junction or in the SVC is tackled with TCC removal, venous angioplasty and new TCC insertion with tip placement in the RA. The venous stenosis can also occur when there is presence of lead (cardiac rhythm device) and TCC in the same vein (**Figure 19**).

3.6 Complications of TCC removal

TCC is removed when not required to be used or when infected or clotted. The removal is done after cuff dissection. One has to be careful as instances of TCC getting cut inadvertently and lodging in heart or IVC while removing or fracture of the catheter have been known. Author has personal experience of two cases, one in which the broken piece of TCC was retrieved with endovascular device and delivered

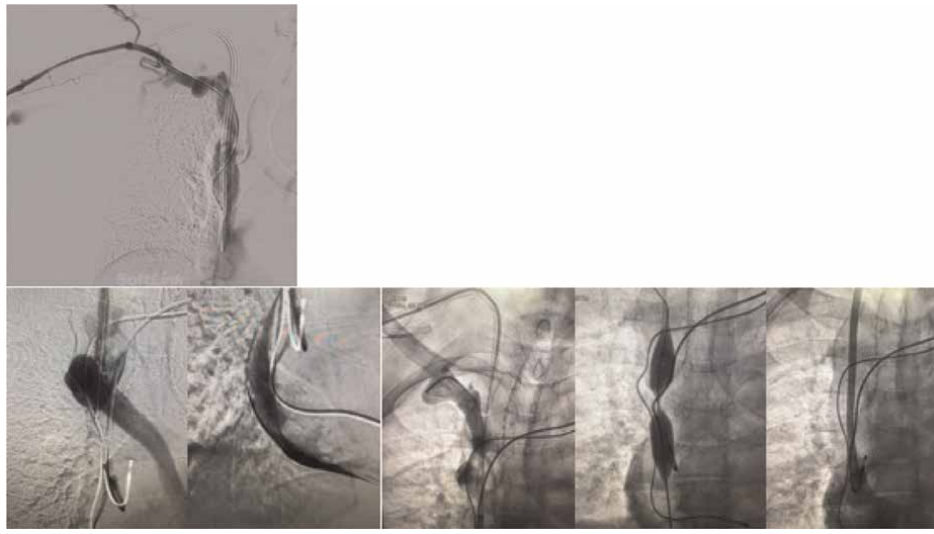


Figure 19.
SVC stenosis with pace-maker leads the azygos vein usually originates from the posterior aspect of the inferior vena cava, at the level of the renal veins. It ascends within the posterior mediastinum to the level of T4 before it arches above the right pulmonary hilum. It drains into the superior vena cava just before it pierces the pericardium, which has been illustrated above.

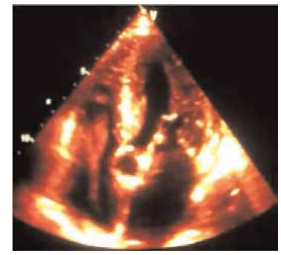


Figure 20.
Retained piece of TCC.

through femoral vein venotomy, whereas another patient required thoracotomy for removal of fractured end of TCC. Also, while removal, one has to be gentle and aware that CRS could be existing and should be pulled out along with catheter pull back. In once such instance where the TCC was removed due to CRBSI at another center before patient presented to us, the 2 D echocardiography showed retained piece of CRS (**Figure 20**).

4. Surgical AV fistula

AVF are the preferred mode of dialysis VA due to low long-term rates of infection and stenosis. In 1943, Willem Kolff did successful dialysis, but regular HD through a reliable access was made possible with the advent of the externalized Quinton-Scribner shunt in 1960 introduced by Scribner, Dillard and Quinton, from the University of Washington. First human surgical AVF was created on 19 February 1965, followed by 14

others till 21 June 1966, leading to publication 'Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula', which became widely known as 'Cimino-Brescia AV fistula', both of whom were nephrologists, and the surgery was performed by Dr. Apple [5]. Twelve out of these 14 AV fistulae resumed primary function without complications, two never functioned showing an early failure rate which would be admirably low even today [28]. Other types of external devices like winged-in-line shunt of Ramirez, subcutaneous shunt of Buselmeier, femoral shunt of Thomas and Allen Brown shunt for femoral vessels were used for urgent start and chronic HD, however, they all have been abandoned and replaced by TCC.

An AVF is closest to the ideal model of VA, better than grafts and TCC. The most important complications of fistulae for HD are lymphedema, infection, aneurysm, stenosis, congestive heart failure, steal syndrome, ischemic neuropathy and thrombosis. AV fistulae are known to fail, due to juxta anastomotic venous stenosis secondary to venous neointimal hyperplasia. It is important to do surveillance of AV fistula once it is created to gain information about early clinical symptoms of AVF dysfunction, so as to diagnose and adequately treat potential complications early before the access fails.

4.1 Creation

Failure to mature AVF is a huge problem and increases cost and morbidity. A fistula that fails early is one that either never develops adequately to support dialysis or fails within the first 3 months of its use. When dealing with AVF, one would follow rule of 3 for creation of AV fistula (personal data, Prof. Ramesh Tripathi, A/Professor at Faculty of Medicine, School of Biomedical Sciences, University of Queensland, Brisbane City, Australia) which includes anatomical parts (inflow, conduit, outflow), stages of AV fistula development (selection, creation, maturation), types of AV fistula failure (thrombosis, failure to mature, late failure), and AV fistula care providers (nephrologists, vascular surgeons, interventional radiologists). Not to forget the role of dialysis staff who are the back bone of any dialysis unit for perfect care of AVF.

Multiple steps vary for the creation of different types of fistulas. The steps in creating any fistula involve preoperative evaluation of the vasculature, the possible harvest of a vessel for transposition or use of autogenous graft, the creation of an anastomosis, and ligation of branch vessels and wound closure. Artery should be looked at for diameter, wall calcification and anatomical variation. For the vein, look at diameter, pre-existing thrombus or narrowing, distensibility and anatomical variation are necessary.

Risk Equation Determining Unsuccessful Cannulation Events and Failure to Maturation (FTM) in Arteriovenous Fistulas (REDUCE FTM I) was a study which proposed the risk equation to determine the likelihood of AVF failure in individual patients [29]. It gave scores based on age (+2 for >65), white race (−3), peripheral vascular disease (+3), coronary artery disease (+2.5), and base line score of 3 to all patients. So the total score could range from 0 to 10.5. FTM predicted risk categories as per the scores were as follow: Score < 2 is low risk (<25%), score of 2.0–3.0 is moderate risk (35%), score of 3.1–6.9 is high risk (50%), and score > 7% is very high risk (70%). These factors vary from population to population, and have different interpretation and outcome among the non-white population. It is important to investigate local rates of AVF FTM and associated predictors of AVF patency in order to guide appropriate VA decision making. Clinical predictors of AVF FTM may not be sufficient on their own to improve vascular access functional patency rates and it is suggested that the FTM score be revised as per

population, and the categories be changed as follow for non-white population: Low to moderate, moderate to high and very high risk categories.

The anastomosis can be completed between artery and vein on one of two techniques. These techniques include side to side anastomosis or artery side to vein end anastomosis. Proximity and diameter of the vasculature are determinants in consideration of either technique used for anastomosis. Dr. Appel in the 'Cimino-Brescia AV fistula' did a side-to-side-anastomosis between the radial artery and the cephalic antebrachial vein at the wrist after a 3–5mm incision had been made in the corresponding lateral surfaces of the artery and the vein. The suturing was using arterial silk in continuous fashion. An end to end anastomosis is no longer used as it requires ligation of distal flow, and has a higher rate of complication. The artery-side--to-vein-end-anastomosis has become a standard procedure. The handling of the artery and the 'free end' of the vein should be done with utmost care without pull or stretch as the torsion and kinking of the vessel are common errors that predispose to fistula failure. The mechanical trauma will chronically lead to juxta-anastomotic segment stenosis. There is a risk of kinking if venous segment is excessive and it increases further during maturation of the AV fistula, as the vein will further elongate secondary to the increase in blood flow rate and vascular remodeling.

Various measures are in place to minimize the occurrence of juxta-anastomotic stenosis, which is due to neointimal hyperplasia (NIH). This is to improve hemodynamic flow and reduce areas of low wall shear stress. One such way is to look at the angle of anastomosis between radial artery and cephalic vein of 'end-to-side' (end of vein to side of artery) AV fistula and reduce low wall shear stress. Among the four geometries of 30°, 45°, 60° and 90°, the smaller angle (30°) would be the preferred choice that minimizes the development of NIH [30].

The AVF is described as per the type of creation as surgical or percutaneous fistula. The surgical fistulae are described as per its location as wrist fistula (radio-cephalic including snuffbox fistula, radio-basilic, ulno-basilic, proximal radio-cephalic below the elbow, the Gracz elbow fistula with proximal radial artery to deep communicating vein AVF, upper arm AVF (brachio cephalic/brachio basilic) and brachial artery-brachial vein AVF, and lower extremity AVF - superficial femoral artery and the saphenous or femoral/femoral or popliteal vein in the thigh. The brachiobasilic fistula (basilic vein transposition) requires a more extensive surgery to create either as single stage or two stage surgery, involving superficialization as the second stage. Similarly brachio-brachial AVF is also performed as single stage or two stage transposition.

Sometime, there is a high bifurcation of radial artery up in the arm, and elbow AVF is created without knowledge of such situation. What is thought to be brachio-cephalic AVF is actually proximal radio-cephalic AVF (**Figure 21**).

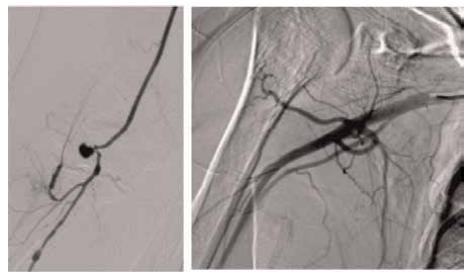


Figure 21.
High radial artery bifurcation, resulting in proximal RC AVF, and not BC AVF.

The percutaneous AV fistula is available as Ellipsys and WavelinQ devices, which use specially designed catheters to join the walls of the artery and vein to create the fistula. These techniques are only beginning to be used on a larger scale. The configuration of Gracz fistula is same as in Ellipsys percutaneous AV fistula. These were compared and the conclusion showed that both Ellipsys percutaneous AVF and Gracz-type surgical AVF demonstrate 100% technical success with similarly high cumulative patency rates [31].

4.2 Maintenance

Once the AV fistula is created, it must mature to a point of being used for HD with repeated needle cannulation. They need clinical monitoring and if indicated, surveillance with a device to see the progress in maturation. The physical examination should include inspection, palpation, auscultation, augmentation test for inflow stenosis and hand raising test to look for outflow stenosis. If not maturing, imaging and early intervention is required to rescue the AV fistula which are failing to mature. For non-maturing fistulae, KDOQI suggests that the use of adjuvant Far-infrared therapy to improve AVF primary patency be based on individual circumstances, feasibility, and the clinician's best judgment and expertise. Fish oil, aspirin, clopidogrel, prostacycline, simvastatin or ezetimibe are not recommended for maturation.

AVF should also be examined for recirculation, as the most common cause of recirculation is high grade venous stenosis and moderate to severe recirculation can be picked up. To test for recirculation on physical examination, the examiner should occlude the fistula between the two needles during dialysis and observe the venous and arterial pressure gauges. If the needles have been placed too closely together, this examination will not be possible. A hard object such as a closed hemostat occludes the fistula more efficiently than a finger. With a normal fistula, very little or no change is observed in either the venous or arterial pressure readings.

If recirculation is secondary to outflow venous stenosis, the pressure will increase in the venous return because the lower-resistance recirculation route has been occluded. As pressure limits are exceeded, the alarm will sound, and the blood pump will quickly stop. The arterial pressure may become slightly more negative as the pressure head generated by the venous side is no longer transmitted through the occluded site in the fistula.

If recirculation is due to poor inflow (arterial stenosis or insufficiency), the occlusion will cause a decrease in pressure since the blood pump will demand more blood than is available (since the recirculation route will have been occluded). In this instance, the arterial alarm will sound very quickly, but the venous pressure may change very little.

4.2.1 Cannulation

The four cannulation techniques, rope ladder (RL), area puncture (AP), buttonhole with blunt needles (BHb), and buttonhole with sharp needles (BHs), affects the arteriovenous fistula (AVF) in different ways. AP should not be used because it cause complications such as aneurysms and bleeding. Other complications include stenosis, thrombosis, infiltration, cannulation difficulty and infection.

Fistula should be cannulated and decannulated by experienced staff with standard techniques. Difficult cannulation should be attempted with duplex ultrasound guidance. Failed cannulation should be attempted after rest to the part. In between dialysis sessions, patients are instructed to keep the fistula clean and avoid blood pressure measurements,

vein puncture, wearing any watch, clothing, jewelry, or other activities that can put pressure to the fistula and restrict the flow, and sometimes, AVF closure.

4.3 Salvage

4.3.1 Nonmaturing AV fistula

Gold standard of salvage is percutaneous trans luminal angioplasty (PTA) or surgical revision. There are stimulatory (promote dilatation and/or wall thickening) and inhibitory (prevents or inhibits NIH) approaches which can either salvage a dysfunctional AV fistula or help prevent future malfunction which would require salvage procedure. The stimulatory approach includes balloon assisted maturation (BAM) of juxta-anastomotic lesion (**Figure 22**) as we practice, cutting balloon angioplasty, angioplasty with stent (**Figure 23**), elastase therapy etc. the inhibitory approach includes drug eluting angioplasty, cryoplasty, brachytherapy, adventitial wraps, mechanical support devices (The VasQ® device for improved outward and inward remodeling) and gene therapy.

4.3.2 Bam

in the true sense is a more aggressive approach to AVF maturation failure in which repeated long segment angioplasty procedures are used to sequentially dilate up the

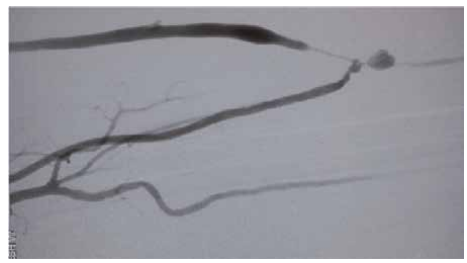


Figure 22.
Balloon assisted maturation angioplasty (v/s new AVF proximal to the juxta-anastomotic venous stenosis?).

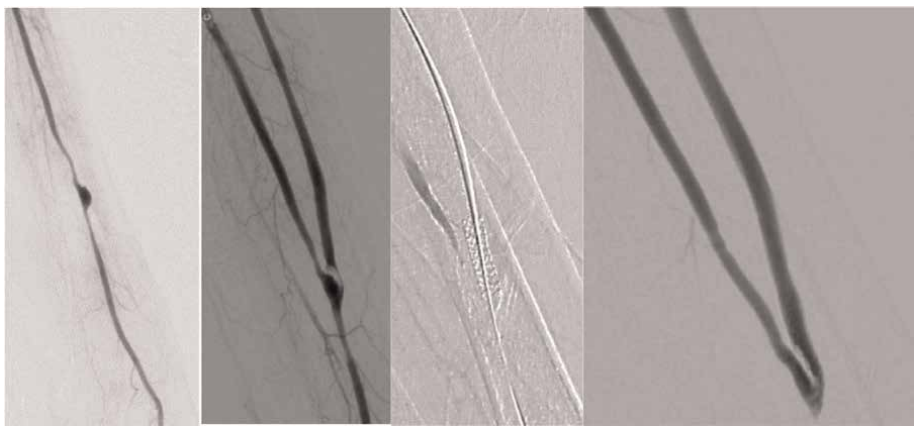


Figure 23.
Acute thrombosis in AVF treated with stent.

peri-anastomotic venous segment, converting it at times into a "collagen tube". Although arterial angioplasty is generally angioplasty of the lumen, intima, and media, when the venous angioplasty is performed for the purpose of fistula maturation, it involves rupture of the entire vessel wall with a reliance on subcutaneous tissue to contain fistula flow and pressure.

4.3.3 High risk AV fistula: Thrombosis

Factors which can cause fistula dysfunction and thrombosis include pre-existing stenotic lesion/s, cannulation injury due to same site puncture or more frequent cannulations (daily HD), infiltration, hematoma and pseudoaneurysm. The AVF can thrombose overnight or gradually. The sudden thrombosis is sometimes associated with high hematocrit values (over dose of erythropoiesis stimulating agent). Gradual thrombosis will have prior sessions of poor flows, high venous pressure or prolonged bleeding after needle removal at the end of dialysis. AVF thrombosis is treated with infusion of a thrombolytic such as tissue plasminogen activator, tPA in conjunction with using a lacerating device or a balloon catheter to remove the clot. Following mechanical or pharmacologic thrombolysis, an angioplasty is done to correct any underlying stenosis.

4.3.4 Venous stenotic lesions

These can occur along the venous outflow segment. Commonest lesions are juxta-anastomotic, but it could be elsewhere also. The cephalic arch stenosis occurs most commonly with BC AVF, rarely with RC AVF (**Figure 24**).

Thrombosis without identified stenotic lesion are tackled either with catheter directed thrombolysis with tPA, thrombosuction or mechanical thrombectomy (**Figures 25** and **26**).

4.3.5 AV fistula with aneurysm

It is a common but difficult to treat complication of AVF and is defined by an expansion of the intimal, medial and adventitial layers of the vessel wall to a diameter of more than 18 mm. and classify it on the basis of true aneurysm or false (pseudo) aneurysm, location (arterial/venous/graft) and site (anastomotic/puncture site/native vessel and whole outflow vein). Patient can be observed if asymptomatic and AVF is

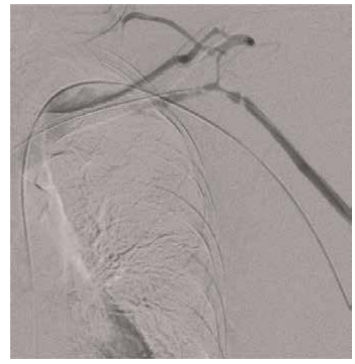


Figure 24.
Cephalic arch stenosis.

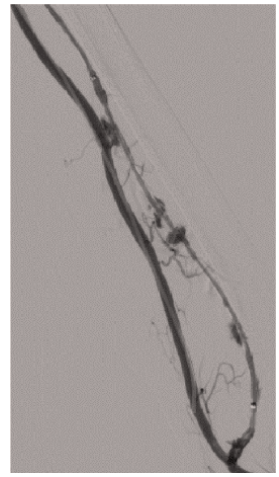


Figure 25.
Catheter directed thrombolytic therapy required.

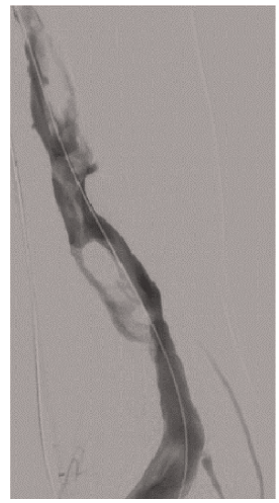


Figure 26.
Chronic thrombus, mechanical thrombectomy with Angio-jet® required.

working well, or treat if there is pain, risk of bleeding and flow issues (either low or high flow). If infected or risk of rupture, it can be surgically repaired. Infected but no immediate risk of rupture aneurysm can be treated with covered graft as shown in our case (**Figure 27**).

4.3.6 Infected fistula

Superficial infection is generally around a cannulation site. Deep infections cause swelling, redness, tenderness, and pus formation. Deep infection can cause venous thrombosis, leading to life threatening pulmonary thromboembolism [personal experience].

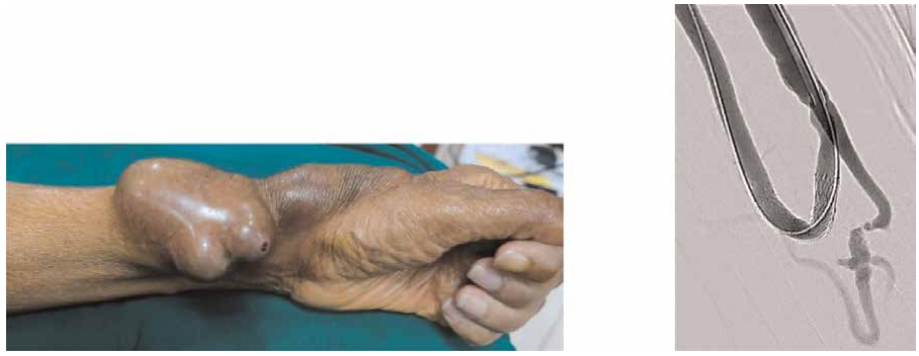


Figure 27.
AVF aneurysm with functioning fistula, treated with covered stent, after treating blood cultures positive for Staphylococcus aureus.

4.3.7 Extremity ischemia

Two clinical variants are recognized, both with characteristic findings on physical examination. Dialysis access related ischemic steal syndrome (DASS) has four stages of presentation. Stage I: Pale/blue/cool hand without pain and no or slight cyanosis of nail beds, mild coldness of skin or hand, reduced arterial pulsations at the wrist, reduced systolic finger pressures. Stage II: Pain during hand exercise and/or with dialysis or pain, cramps, numbness or disturbing coldness in fingers or hand. Stage III: Pain at rest or motor dysfunction of fingers or hand. Stage IV: Tissue loss, including ulcers, necrosis or gangrene. It is also known as distal hand hypoperfusion ischemia syndrome (DHHIS).

Second variety is called Ischemic monomelic neuropathy (IMN), it presents with severe pain, numbness, diffuse motor weakness, usually in the absence of significant ischemic changes in the tissues of the hand and fingers.

4.3.8 High flow fistula

Though the ideal flow through AVF should be about 600–800 ml/minute, sometimes, it can become high flow fistula with blood flow in the range of 3–4 liters/

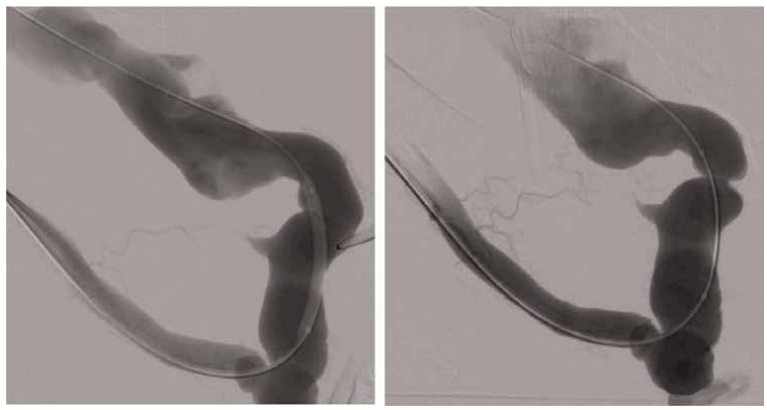


Figure 28.
MILLER's banding: Flow volume reduced from 4 liters/minute to 800 ml/minute.

minute. It can be repaired surgically or endovascularly with MILLER's (Minimally Invasive Limited Ligation Endoluminal-assisted Revision) banding procedure (**Figure 28**). MILLER's banding is also used to treat DASS.

5. AV graft

AVG are divided as biological grafts (xenografts) (bovine mesenteric vein, bovine carotid artery, bovine ureter), or synthetic grafts (Dacron, PTFE, ePTFE, polyurethane and polyether urethane urea). PTFE grafts are the most common type of graft and are considered to be the graft of choice for HD access around the world. Allografts with cryopreserved femoral vein and human mesenchymal cell engineered graft (when available) are other options. Variations among PTFE grafts are available. Use of saphenous vein translocation to the upper limb (autograft) for creation of AVF is an option.

The primary failure rate for grafts is less than that for fistulas but the risk of infection (up to 4 times higher risk than AVF) and clotting is higher. Also, given the increased number of interventions required for graft maintenance, the primary patency rate for grafts is less than that for fistulas.

5.1 Creation

The ePTFE grafts can be cannulated after 2 weeks following placement, but new generation grafts with early cannulation properties are available, allowing use as an alternative to central venous catheters for prompt access.

AVG are described as per anatomic location. Inflow artery, outflow vein, graft material, and graft configuration are considered for AVG along with location as looped forearm (brachial artery to cephalic vein), straight forearm (radial artery to cephalic vein), looped upper arm (axillary artery to axillary vein), and straight upper arm (brachial artery to axillary vein). Lower extremity grafts, looped chest grafts, axillary-axillary (necklace) grafts, and axillary-atrial grafts have also been constructed but are uncommon [32]. Like in AVF, graft to vessel angle of 30° has been found optimal.

Complications related to AVG creation can be either local problems e.g. bleeding, seroma, infection, pseudoaneurysm, and neuropathy; or access flow-related problems like swelling of graft arm, cardiopulmonary problems, DASS, IMN; or due to AVG dysfunction and failure due to thrombosis and / or infection. Thrombosis can occur in AVG, immediately after creation (technical issues) or later due to stenosis. Local antiproliferative drugs like sirolimus eluting stents or paclitaxel wrap are being studied for stenosis prevention.

5.1.1 Hemodialysis reliable outflow (HeRO) grafts

It consists of two parts, 6 mm ePTFE portion and nitinol-reinforced silicone single-lumen outflow catheter, meant to provide outflow to patients with central venous stenosis. It is fully subcutaneous VA. However, it is considered as last resort for VA. The ePTFE portion is anastomosed to brachial or other inflow artery and the central tip is positioned in the middle of right atrium. HeRO graft could be an acceptable option for complex dialysis patients who are catheter dependent.

5.2 Maintenance

Physical examination can assist in the early detection of thrombosis and stenosis in AVGs. Proper graft maintenance and graft cannulation technique are important for preventing complications. Self-examination for a thrill over AVG should be taught to the patients. Preventing thrombosis with prophylactic antithrombotic medications (antiplatelet or anticoagulation) have not been found to be useful. Warfarin may be used in presence of hypercoagulable state with strict monitoring for bleeding complications.

5.3 Salvage

Besides thrombosis, other causes of AVG failure include primary or recurrent stenosis after angioplasty, cannulation injury, infiltration, hematoma, thrombosis of

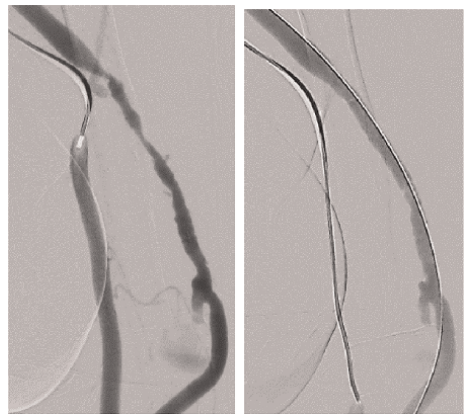


Figure 29.
AVG stenosis at venous end anastomosis with the vein. Before and after angioplasty.

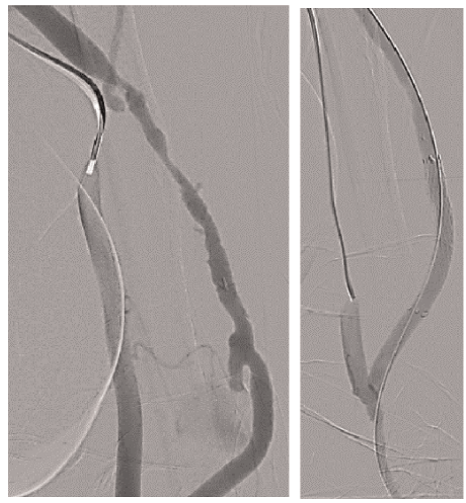


Figure 30.
Traumatic aneurysm in AV graft, covered stent deployed.

pseudo aneurysm, hypercoagulable states and presence of stent. Thrombosis is tackled with percutaneous thrombolysis or thrombectomy, mechanical or surgical. Stenosis usually occurs at vein-graft anastomosis site (**Figure 29**), but could occur along the draining vein or even the central vein. Stenosis could also be in the inflow or intra-graft. Salvage is attempted with balloon angioplasty. Stenting may be required for graft-vein anastomotic junction stenosis or for the traumatic aneurysm in the AVG (**Figure 30**). Recurrent stenosis may need surgical (alone or combined with endovascular) revision of AVG, though drug eluting balloon using paclitaxel have been used to prevent restenosis.

6. Conclusion

The profile of kidney failure has changed over last 6 decades, with advances in the VA. Starting from Scribner's shunt to endovascular AVF has changed the epidemiology of ESKD. However, none of these are failure proof, and involves cost for its maintenance and salvage. These modalities should be cost effective, and should result in improved patient outcome. Also, these should be widely available. Better understanding of VA pathophysiology, and involvement of VA as a curriculum in the basic nephrology training may lead to more nephrologists getting interested in the VA care and result in better delivery of dialysis, so as to achieve maximum rehabilitation of the patients (social and economic) and provide high quality patient centered care. VA is an exciting field and more nephrologist should join it and work as a team with vascular surgeons and interventional radiologists.

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Conflict of interest

The author declares no conflict of interest related to this presentation.

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Chapter 10

Renal Transplantation in Autosomal Dominant Polycystic Kidney Disease with Melas

Shiro Fujikata

Abstract

We report that mitochondrial encephalomyopathy, lactic acidosis, and stroke-like eposodes (MELAS) was also present in a patient with a preemptive living renal transplantation who had autosomal dominant polycystic kidney disease (ADPKD) as a primary disease. A 20-years-old female was referred to our hospital from a nearby hospital 4 years ago for preemptive living renal transplantation (Donor: her mother blood type incompatible A → O type) for chronic renal failure due to ADPKD. She was hospitalized X-3 years for renal transplantation. Since the rate of GFR decline was 18 ml/min/1.73 mm^2/year and the progression of renal function was fast for ADPKD, detailed examination of other diseases was performed. The sensory deafness, impaired glucose tolerance and dilated heart were recognized, and the presence of MELAS was confirmed, and renal transplantation was postponed and hemodialysis was introduced. The donor was also diagnosed with mitochondrial abnormality, but it was judged that abnormality was slight and donation was possible. Recipients are expected to improve ADL by renal transplantation, after approval by the ethics committee, living renal transplantation was performed 2 years ago. At present, the general condition is stable and the renal function is stable at Cr 0.67 mg/dl. There are few reports of renal transplantation in patients with MELAS and we report a rare case with some review of the literature.

Keywords: autosomal dominant polycystic kidney disease (ADPKD), mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), renal transplantation

1. Introduction

Preemptive kidney transplantation (PEKT) is on the rise, with 42% of living donor kidney transplants performed in Japan in 2018 [1]. A large portion of patients with chronic renal failure due to autosomal dominant polycystic kidney disease (ADPKD) as a primary disease are reportedly eligible for PEKT because of the slow progression of renal function [2]. ADPKD is a mutation of the PKD gene that causes tubular cells to dilate, resulting in cysts. With age, renal function progressively declines, and about half of patients develop end-stage renal failure by the age of 60 [3, 4]. Glomerular filtration rate (GFR) begins to decline at around 40 years of age, with an

average decline rate of 4.4 to 5.9 ml/min/year, and genetic factors, renal volume, and hypertension may affect the rate of decline in renal function [5]. In this case, the total renal volume capacity was 541 ml and less than 750 ml, the age was less than 30 years, and ADPKD classification was 1D. Despite the rate of decline in GFR predicted to be 3.48 ml/min/1.73 mm^2/year [6], the rate of decline in GFR in the past year was as fast as 18 ml/min/1.73 mm^2/year. A close examination of concomitant diseases as a cause of decreased renal function revealed sensorineural hearing loss, short stature, hypertension, glucose intolerance, and cardiac enlargement. Further examination revealed Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS). MELAS causes Central nervous system symptoms and muscle diseases due to mitochondrial dysfunction caused by mitochondrial gene mutations, and also decreased renal function in some cases [7, 8]. We report a case of a patient who underwent living donor kidney transplantation after hemodialysis with a good outcome.

2. Case

Patient Female, 20 years old.

Complaint General malaise, weakness attacks, headache, vomiting.

Family medical history Father, ADPKD, living donor kidney transplant.

Past medical history 19 years old, chronic glomerulonephritis, 19 years old, ADPKD.

History of present illness The patient was diagnosed as ADPKD by a nearby doctor after proteinuria was detected in her school medical examination, and was referred to our hospital in X-4 for a prior kidney transplant with her mother as the donor (blood type incompatible donor type A → recipient type O) for chronic renal failure due to ADPKD. After outpatient follow-up, the patient was admitted for renal transplantation in X-3. The rate of decline in GFR was fast for ADPKD, 18 ml/min/1.73 mm^2/year, and general malaise and weakness attacks appeared just before admission. A close examination of concomitant diseases as a cause of decreased renal function revealed sensorineural hearing loss, short stature, hypertension, glucose intolerance, and cardiac enlargement. Further examination revealed MELAS. Renal transplantation was postponed and hemodialysis was started.

Illness on admission Height 135 cm, Weight 29.8 kg, Physical examination Moderate sensorineural hearing loss, Intermittent weakness attacks in both upper and lower limbs.

Blood pressure 150/100 (carvedilol 20 mg, amlodipine 2.5 mg), pulse 52 bpm.

Finding on admission CT scan showed multiple cysts in both kidneys. Renal volume was 228 ml in the right kidney and 313 ml in the left kidney (**Figure 1**). Blood tests (**Table 1**) showed mild anemia, decreased renal function, and high levels of lactate 29.8 mg/dl (reference value 4.2–17), pyruvate 1.6 mg/dl (0.3–0.9), and myoglobin 327.4 ng/ml (below 60). CSF findings showed a significantly high lactate level of 29.8 mg/dl. General chest imaging showed significant cardiac enlargement and bilateral pleural effusions. Cardiac ultrasonography showed cardiac ejection fraction of 33%, wall thickening and granular sparkling, and a diagnosis of cardiomyopathy. MRI showed cerebellar atrophy and EEG showed phase reversal of a spike in the right occipital lobe. Audiological examination revealed sensorineural hearing loss (average hearing level of 53.8 dB on the right and 56.3 dB on the left according to the quadrant method).

Muscle biopsy showed ragged-red-fibers (RRF) with red-purple staining of enlarged mitochondria by Gomori-Trichrome staining, and strong SDH-reactive blood vessels (SSV) by Succinate dehydrogenase (SDH) staining, consistent with MELAS.

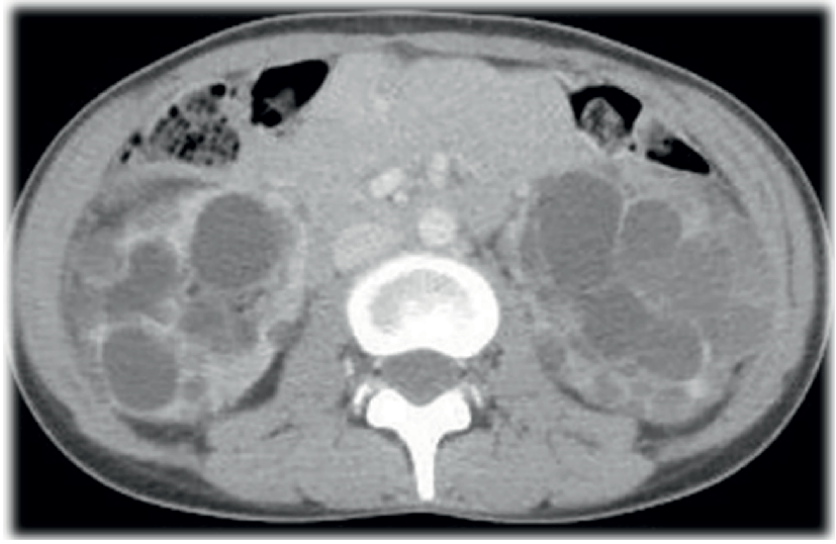

Figure 1.
Abdominal enhanced CT shows a polycystic kidney (kidney volume Rt 228 ml/Lt 313 ml).

(Complete blood count)		**(Biochemistry test)**			**(Other tests)**	
WBC	**3800/μl**	**Na**	**141 mEq/l**	**PR3-ANCA**		**<10 EU**
RBC	439*104/μl	K	4.4 mEq/l	MPO-ANCA		<10EU
Hb	10.9 g/dl	Cl	105 mEq/l	Lactic acid		29.8 mg/dl
Ht	32.00%	TP	6.6 g/dl	Myoglobin		327 ng/ml
Plt	21.7*104/μl	ALB	3.8 g/dl	Carnitine		53.9 μmol/l
		BUN	69.3 mg/dl	Urinary myoglobin		252 ng/ml
(Urinalysis)		Cr	6.84 mg/dl			
SG	1.015	AST	IU/L	(CSF test)		
pH	6	ALT	IU/L	TP	44 mg/dl	
Protein	3+	LDH	IU/L	Glu	62 mg/dl	
UP/Cr	1.9 g/gCr	Glu	189 mg/dl	Cl	128 mol/dl	
RBC	10–30/hpf	HbA1c	4.90%	IgG	4.4 mg/dl	
		CRP	0.05 mg/dl	Pyruvic acid	1.6 mg/dl	
				Lactic acid	29.8 mg/dl	

Table 1.
Laboratory data on admission.

3. Course

With the suspected MELAS based on the clinical symptoms, blood samples, spinal fluid examination, and imaging studies, we performed genetic testing after obtaining written consent from the patient and guardian. The mitochondrial gene

3243 A > G mutation was found (mutation rate 50%), and together with the clinical symptoms, MELAS was diagnosed. Since the disease is maternally inherited, the mother, as the donor, also underwent genetic testing and was found to have a 3243 A > G mutation in the mitochondrial gene. However, the mutation rate was low at 6%, and the clinical symptoms were only mild deafness and glucose intolerance, which were not diagnosed as mitochondrial disease (**Table 2**), but as mitochondrial dyscrasia. Renal transplantation was postponed, and hemodialysis was started. After 6 months of hemodialysis, we confirmed the recipient's stable general condition. We reconfirmed her intention to undergo renal transplantation, and both the patient and her mother were very eager to undergo renal transplantation. For the problems of the recipients, the prognosis of MELAS is grim, with a mean age of death of 40 years in the adult form, and there is a risk of malignant hyperthermia, prolonged action of muscle relaxants and anesthetics, and hyperlactatemia during general anesthesia management [9, 10]. A joint conference was held with neurology, anesthesiology, and cardiology, and confirmed that although the patient already had cerebral atrophy and cardiac disease, ADL could be improved by renal transplantation, and that perioperative management could be addressed by devising anesthetics and infusions (using bicarbonate Ringer's solution). No other donor candidates were found, and although the mother had mitochondrial abnormalities, she did not meet the diagnostic criteria for mitochondrial disease. Taken together, the risk of renal function progression was judged to be low. After obtaining approval from the ethics committee of our hospital, we explained the risks to the patient and her family again, confirmed their willingness to undergo transplantation, and decided to proceed with the kidney transplantation.

1. Main symptoms
① Progressive muscle weakness, deafness, diabetes mellitus or external ophthalmoplegia
② One or more of the following Central nervous system symptoms: intellectual regression, memory impairment, seizures, psychiatric symptoms, aphasia/phasia, severe vision loss, transient paralysis, hemianopsia/cortical blindness, myoclonus, dystonia, cerebellar ataxia
③ One or more of the following: cardiac symptoms such as cardiac transmission disorder and cardiomyopathy, renal symptoms such as glomerulosclerosis and renal tubular dysfunction, hematologic symptoms such as severe anemia, and hepatic symptoms of moderate severity or greater.
2. Examination and imaging findings
① Repeatedly high lactate levels in serum or CSF at rest or lying down, or a clear lactate peak in the lesion area on MR spectroscopy
② Brain CT/MRI showing infarct-like lesions, cerebral or cerebellar atrophy, or bilateral symmetrical lesions in the basal ganglia or brainstem
③ Muscle biopsy or abnormal mitochondrial morphology in the symptomatic organ
④ Deficiency of mitochondria-related enzymes or deficiency of intermediate metabolites such as coenzyme Q10
⑤ Qualitative or quantitative abnormalities of mitochondrial DNA or mitochondria-related nuclear gene mutations.
Diagnosis of mitochondrial disease
Definite cases: at least one of (1) ① to ③ and at least two of (2) ① to ⑤
Suspicious cases: at least one of (1) ① to ③ and at least one of (2) ① to ⑤

Table 2.
Diagnostic criteria for mitochondrial disease.

3.1 Perioperative course

The blood group antibody titer was 64-fold in an incompatible blood type living donor kidney transplant (donor type A and recipient type O). Anti-donor specific antibodies were negative. Preoperatively, the patient underwent one double-membrane filtration plasma exchange and one simple plasma exchange, and rituximab 200 mg/body was administered preoperatively. Immunosuppressive drugs such as tacrolimus 0.15 mg/kg, Cellcept 500 mg/body, and methylprednisolone 10 mg/body were started 1 week before surgery, and the patient underwent living donor kidney transplantation in X-2 years. For anesthesia, intravenous anesthetics (propofol and remifentanil) were used instead of inhalation anesthetics and muscle relaxants, and lactate Ringer's solution was used instead of starting solution and bicarbonate Ringer's solution to prevent lactate level from rising. The operation time was 368 minutes, the anesthesia time was 501 minutes, the total blood loss was 73 minutes and 43 seconds, and the blood loss was 322 ml. First urination was immediately observed, and there was no delay in postoperative awakening or prolonged respiratory depression. Although a weakness seizure appeared on postoperative day 4, the symptoms resolved with conservative treatment. Her renal function stabilized at 0.77 mg/dl of Cr without rejection, and she was discharged on postoperative day 35. Two years after the surgery, no rejection was observed, her renal function was 0.67 mg/dl and no proteinuria was observed, and her MELAS was stable with no exacerbation of stroke symptoms such as convulsions and paralysis, although she complained of intermittent headaches.

4. Discussion

ADPKD reportedly occurs in 1 in 1000 people, and is a good indication for renal transplantation because of the better survival rate of renal transplantation than that of non-ADPKD patients, and is also a good indication for PEKT because of the slow progression of renal function [11]. In this case, mitochondrial disease (MELAS) was found during the examination of concomitant diseases due to rapid progression of renal function. Mitochondria exist in all cells in the body except red blood cells, while mitochondrial disease is a systemic disease caused by mitochondrial dysfunction mainly due to mitochondrial gene mutations [12].

Mitochondrial dysfunction causes abnormalities in energy production and apoptosis, resulting in symptoms in various organs throughout the body, especially in the brain, heart, and skeletal muscles, requiring energy, and is often associated with diabetes and nephropathy (**Table 2**) [13]. In addition to MELAS, myoclonic epilepsy with ragged red fibers (MERRF), chronic progressive external ophthalmoplegia (Kearns-Sayre syndrome), and myoclonic epilepsy with ragged red fibers (MELAS) are classified according to the combination of characteristic symptoms. In addition to MELAS, there are chronic progressive external ophthalmoplegia/Kearns-Sayre syndrome (CPEO/KSS) and Leigh's encephalopathy, and MELAS is the most common, accounting for 30% [14].

The diagnostic criteria for mitochondrial disease are shown in **Table 2** [15]. In this case, the main symptoms were muscle weakness, cardiomyopathy, hearing loss, glucose intolerance, and renal symptoms, and the examination and imaging findings were high blood and spinal fluid lactate levels, cerebellar atrophy on MRI, abnormal mitochondrial morphology on muscle biopsy, and mitochondria-related gene mutations. The patient was diagnosed as mitochondrial disease, meeting the three criteria for mitochondrial disease and the four criteria for laboratory and imaging findings. In

A. Clinical findings of stroke
1. Headache/vomiting 2.Convulsion 3.Hemiplegia
4.homonymous hemianopsia or cortical blindness
5. Abnormal brain localization on brain imaging (CT, MRI, etc.)
B. Evidence of mitochondrial abnormality
1. Repeatedly high lactate levels in blood or CSF, or deficiency of mitochondria-related enzymes
2. Abnormal mitochondrial morphology (e.g., ragged-red fibers) on muscle biopsy
3. Known genetic abnormality (MELAS-related) (A3243G abnormality)
• Certification criteria/Definite cases
Two items in A and two items in B above (at least 4 items in total)
• Certification criteria/Suspicious cases
Two items in A and one item in B above (at least three items in total)

Table 3.
Diagnostic criteria for MELAS.

addition, according to the diagnostic criteria for MELAS (**Table 3**), the patient showed symptoms of headache, vomiting, and cerebellar atrophy, as well as high lactate levels, abnormal mitochondrial morphology, and mitochondrial gene mutation (A3243G mutation) on muscle biopsy. Taken together, she was diagnosed as having MELAS, fulfilling two items in A and three items in B [16]. ATP deficiency due to mitochondrial disorders reportedly causes tubular damage, and furthermore, glomerulosclerosis due to podocyte dysfunction and microvascular damage, which can lead to Fanconi syndrome, tubulointerstitial nephritis, and secondary focal glomerulosclerosis [8, 17]. The possibility of mitochondrial disease, including MELAS, should be actively suspected in patients with progressive renal dysfunction refractory to treatment, renal biopsy findings of tubular damage and secondary focal glomerulosclerosis, multiple organ abnormalities other than renal, growth abnormalities and growth retardation, and suspected maternal inheritance. Since the symptoms of headache and vomiting may overlap with those of uremia, it is often difficult to differentiate between the two, as there have been case reports of renal failure preceding multi-organ symptoms [18].

In this case, the patient's father also had chronic renal failure due to ADPKD and had received a kidney transplant. The patient was also diagnosed with chronic renal failure due to ADPKD, and the delay in examining other diseases may have contributed to the delay in diagnosis. For MELAS, without fundamental treatment to improve mitochondrial function, symptomatic treatment of symptoms in each organ has been the mainstay of treatment [12]. Recently, oral L-arginine reportedly improves the unbalanced distribution of blood flow in the brain and prevent stroke-like attacks, and taurine replacement therapy for abnormal taurine modification of tRNA in MELAS with mitochondrial gene mutation (A3243G mutation) prevents recurrence of stroke-like attacks, and has been started in this case [19–21]. Regarding renal replacement therapy for patients with end-stage renal failure due to mitochondrial disease, it has been reported that patients with cardiomyopathy often have difficulty in continuing hemodialysis due to circulatory instability, and have been shifted to peritoneal dialysis [22]. Regarding the reports of renal transplantation for end-stage renal failure with mitochondrial disease as the primary disease, Paul et al. reported that all 11 observable cases (including 0 cases with MELAS) survived and transplanted kidneys were

attached (observation period: 5.6 years). In contrast, two cases of renal transplantation in patients with MELAS-induced renal failure have been reported, although all of them reported only the perioperative course and not the prognosis [23–25]. Perioperative precautions include the onset of malignant hyperthermia caused by inhalational anesthetics, prolonged action of muscle relaxants and anesthetics, and hyperlactatemia [10, 21]. In this case, we did not use inhalational anesthetics or muscle relaxants, but used a total intravenous anesthetic with propofol [10, 21]. For infusion, lactated Ringer's solution was not used to prevent lactate level from rising, but mainly starting solution was used. After autonomic urination, bicarbonate Ringer's solution was also used, and the infusion volume was about 80% of that of normal renal transplant patients (10 ml/kg/hr) to avoid cardiac stress. Awakening from anesthesia was normal, and blood lactate level after extubation was as high as 30.6 mg/dl. However, without exacerbation of MELAS symptoms such as shivering, headache, muscle weakness, and epileptic seizures, Cr was stable at 0.77 mg/dl. Two years have passed since the kidney transplantation, without clinical deterioration of MELAS, and the renal function is stable. We will need to continue to monitor her closely.

5. Conclusion

We reported that mitochondrial encephalomyopathy, lactic acidosis, and stroke-like eposodes (MELAS) was also present in a patient with a preemptive living renal transplantation who had autosomal dominant polycystic kidney disease (ADPKD) as a primary disease. At present, the patient is taking arginine and taurine, and her general condition is stable, including renal function, without any stroke attacks. We will need to continue to monitor her closely. In cases of unexplained progressive renal hypofunction with multiple organ abnormalities, growth abnormalities, and growth retardation, it is important to consider mitochondrial disease (including MELAS) as a differential when maternal inheritance is suspected.

Conflict of interest

The authors have no COI to disclose.

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Chapter 11

Immunosuppressive Drug Management in Kidney Transplant Recipients

Manon Dekeyser

Abstract

Kidney transplantation is considered the best treatment option for end-stage kidney disease, as it provides significant improvements over dialysis in terms of both survival and quality of life. Various developments in the field of immunosuppression have greatly improved graft survival, and the immunosuppressive treatments currently used include molecules inducing T cell depletion and molecules able to control the activation and proliferation of T cells. Combinations of calcineurin inhibitors, antimetabolites, and glucocorticoids remain the gold standard for kidney transplantation. However, novel molecules designed to minimize renal toxicity, through calcineurin inhibitor sparing, are increasingly being identified. These molecules and the existing combination strategies are discussed here, together with novel therapeutic protocols for mitigating the individual risk of graft rejection and adverse events related to long-term immunosuppression.

Keywords: kidney transplantation, immunosuppressive drugs, management of immunosuppression

1. Introduction

Kidney transplantation is now the standard treatment for patients with end-stage renal disease, as it outperforms dialysis in terms of quality of life and survival [1–3]. In 2019, kidney transplantation was the leading type of solid organ transplantation worldwide, with 107,540 new kidney graft transplantations (rate of 14.01 per million people—data source: GODT—transplant-observatory). Successful kidney transplantation depends as much on the optimal management of immunosuppression as on meticulous clinical care. Historically, graft rejection was the first barrier to successful transplantation. Graft rejection is an immunological response directed against alloantigens present on the graft and mediated by both the cellular and humoral arms of the immune system. Patients undergoing solid organ transplantation require long-term immunosuppression to inhibit T-cell activation and limit the development of antiallograft effector T cells and antibodies, to prevent graft rejection. Various developments in the field of immunosuppression have led to considerable progress in terms of short-term graft survival, with a decrease in the frequency of acute rejection. However, long-term graft survival has remained stable in

recent decades. In the United States, the five-year survival for transplanted kidney grafts was 74.4% for cadaveric donor transplants and 85.6% for living donor transplants for the 2008–2015 period (data source: OPTN—optn.transplant.hrsa.gov). The overall graft failure rate after 10 years was 20% [4].

Powerful immunosuppressive drugs can prevent alloimmune responses, but this benefit must be balanced against several adverse effects. Mortality has decreased significantly over the last 20 years, reaching 1.9 per 100 patient-years in 2015–2018, with improvement most marked for the acute post-transplant period (0–3 months after transplantation). However, death rates over time follow a U-shaped curve, reflecting the existence of two periods of particularly high risk—the first 3 months after the death and a progressive increase in the risk of death from 5 years after transplantation. Cardiovascular disease (36.3%), cancers (27.5%), and infections (16.9%) are the main causes of death [5].

2. The alloimmune response

T cells play a key role in establishing the alloimmune response and are, therefore, the main target of immunosuppressive treatment (**Figure 1**). T-cell activation requires the presence of an antigen within the peptide-binding groove of major histocompatibility complex (MHC) molecules.

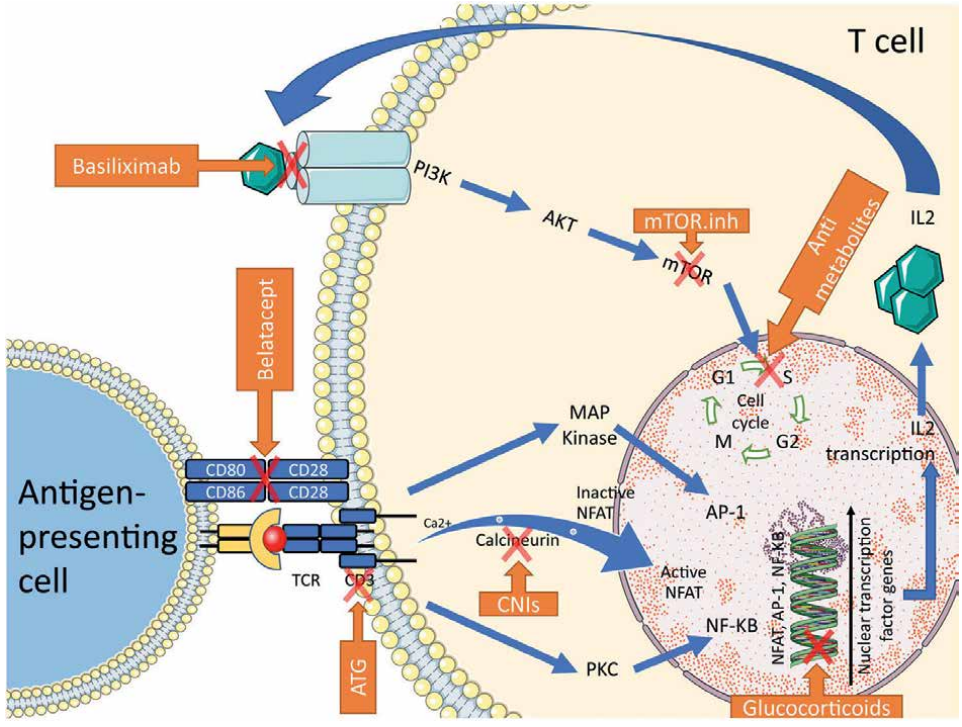

Figure 1.
T-cell activation and sites of action of immunosuppressive agents. ATG: Anti-thymocyte globulins; AP-1: Activator protein 1; CNIs: Calcineurin inhibitors; IL2: Interleukin-2; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; mTOR.Inh: Mammalian target of rapamycin inhibitors; NFAT: Nuclear factor of activated T cells, NF-κB: Nuclear factor kappa B; PI3K: Phosphatidylinositol 3 kinases; PKC: Protein kinase C; TCR: T-cell receptor. (Servier medical art – Creative commons attribution 3.0 France license).

Lymphocyte activation requires three signals and results in clonal expansion. The first signal is the interaction between the T cell and an antigen-presenting cell (APC) presenting an allopeptide to the T-cell receptor via its type I or type II MHC. The second costimulatory signal is provided by the interaction between CD28 on the T cell and CD80/CD86 on the APC. These two signals activate the calcium/calcineurin, RAS/MAP-kinase, NFAT, and NFκB pathways, leading to (i) CD40 ligand expression, (ii) the production of various cytokines, including interleukin 2 (IL-2), the key cytokine for T-cell proliferation, and (iii) transcription of the alpha chain of the IL-2 receptor (α-CD25), improving the affinity of IL-2 for its receptor. The third signal involves IL-2 binding to its receptor via an autocrine/paracrine pathway. This binding leads to activation of the Pi3K/AKT/mTOR pathway and the lymphocyte proliferation signal [6].

3. Available immunosuppressants

3.1 Balancing the risk of graft rejection against the risk of infection

Most transplants are allografts. It is almost impossible to obtain a perfect match between donor and recipient, and powerful immunosuppressive drugs are, therefore, needed to limit immunological rejection. In clinical practice, the need to balance the risk of graft rejection against that of infection tends to lead to the personalization of immunosuppression protocols [7].

Calcineurin inhibitors (CNIs) probably provide the best immune protection during the first year of treatment, but in the long term, this advantage is outweighed by chronic renal toxicity and adverse metabolic effects. Novel molecules have been developed to minimize the toxicity of immunosuppressive treatment. However, only a few of these molecules are considered suitable as alternatives to CNIs as their benefits are frequently outweighed by disappointing results in terms of allograft rejection or adverse effects.

3.2 Therapeutic arsenal

Various molecules for eliminating T cells or inhibiting lymphocyte activation and proliferation have been developed (**Figure 1**).

3.2.1 Anti-thymocyte globulins (ATG)

Anti-thymocyte globulins (ATG) are a mix of polyclonal immunoglobulins G from rabbits or horses directed against human thymocytes and T-cell lines. Its broad antigen targets result in a depletion of T and B cells through complement-mediated or activation-associated death. This approach has been shown to prevent acute rejection in highly sensitized patients [8]. However, its lack of specificity, associated with a need for higher doses, increases the risk of adverse effects [9, 10]. Immune reconstitution takes place over a period of months or years following the initial perfusion, with memory T cells reappearing more rapidly than naive T cells. Prolonged CD4 T-cell lymphopenia has been reported after the administration of ATG. This prolonged lymphopenia was associated with morbidity and mortality [11], with atherosclerosis and cardiovascular events, in particular [12].

3.2.2 Monoclonal anti-CD25 antagonist (anti-IL2 receptor antibody): basiliximab

IL-2 receptor (rIL2) activation leads to T-cell proliferation (**Figure 1**). Basiliximab (anti-rIL2) is a chimeric antagonist antibody targeting the α-CD25 chain of the IL-2

receptor. This interaction leads to the competitive inhibition of IL-2 binding to the IL-2 receptor, thus inhibiting T-cell proliferation.

3.2.3 Glucocorticoids

Glucocorticoids exert immunosuppressive effects by inhibiting the production of various proinflammatory cytokines, such as IL-1, IL-2, IL-6, and IFNγ. They bind to cytosolic glucocorticoid receptors, resulting in migration toward the nucleus, where they downregulate the expression of genes encoding transcription factors, such as AP1 or NF-κB. At high concentrations, glucocorticoids regulate adaptive immunity by inhibiting lymphocyte activation and promoting lymphocyte apoptosis. They also suppress CD4 T-cell activation indirectly, by modulating dendritic cell function (antigen presentation, costimulation, and cytokine production) [13].

3.2.4 Calcineurin inhibitors (CNIs): cyclosporine-A and tacrolimus

Since their discovery in the 1980s, CNIs have been the cornerstone of immunosuppressive treatment. Two molecules are available—cyclosporine-A (CsA) and tacrolimus. These small molecules interact with cytosolic proteins called immunophilins. CsA binds cyclophilins, whereas tacrolimus binds FKBP12. These interactions lead to the competitive inhibition of calcineurin, a phosphatase responsible for dephosphorylation of the transcription factor NFAT. By inhibiting calcineurin, both drugs block the transcription of NFAT, resulting in the inhibition of the T-cell activation cascade [14].

Tacrolimus has been shown to be superior to CsA. In a seven-year follow-up study, the proportion of patients free from acute rejection was 77% in the tacrolimus arm, but only 59.9% in the CsA arm, with better graft survival in the tacrolimus arm (60.2% in the tacrolimus arm versus 47.0% in the CsA arm; $p < 0.0001$) [15].

However, some redundancy in this pathway has been observed, and the combination of other molecules with CNIs is required to prevent graft rejection. CNIs have a narrow therapeutic window, requiring constant monitoring to improve their efficacy and reduce their toxicity. Their nephrotoxicity remains a major issue. CNIs cause direct reversible vasoconstriction, which can lead to acute kidney injury. They have also been implicated in chronic vascular lesions, such as arteriole hyalinosis, tubulointerstitial fibrosis, and thrombotic microangiopathy, probably through direct endothelial cell injury. They have also been associated with a higher risk of developing hypertension, dyslipidemia, and de novo diabetes, all of which are associated with cardiovascular risk factors and mortality [16, 17].

3.2.5 Belatacept

Belatacept is a cytotoxic T-lymphocyte-associated protein-4-immunoglobulin fusion protein (CTLA4-Ig). It selectively blocks the CD28-CD80/CD86 pathway, thereby preventing the costimulation required for T-cell activation [18]. The main advantage of this molecule is the absence of nonimmune adverse events, including nephrotoxicity in particular. The phase III BENEFIT study [19, 20] showed significant improvements in the glomerular filtration rate in patients on belatacept. Seven-year follow-up data confirmed these findings, with improvements in allograft kidney function and survival in the longer term. Belatacept also seems to improve the metabolic profile [21]. Interestingly, the frequency of *de novo* donor-specific antibody (DSA) production has been reported to be lower in patients treated with belatacept.

This effect can be explained by a disruption of germinal center responses and the inhibition of B-cell maturation [22, 23]. However, the widespread use of this promising drug has been tempered by its adverse effects.

Persistent viral infections have recently been reported in patients on belatacept. During the initial phase of development, a higher incidence of Epstein–Barr virus (EBV) associated post-transplantation lymphoproliferative disorder (PTLD) related to primary infection with EBV was observed in recipients. The use of belatacept has, therefore, generally been restricted to EBV-seropositive patients. A frequency of opportunistic infections of 12% was recently reported in a retrospective cohort, essentially due to Cytomegalovirus (CMV) reactivation and pneumocystis pneumonia [24]. In CMV-seronegative recipients receiving an organ from a seropositive donor, belatacept use was shown to be associated with a higher incidence of CMV viremia, a higher rate of first-line treatment failure, a longer time to viral clearance, and cases of severe CMV retinitis [25–27]. Some cases of deadly progressive multifocal leukoencephalopathy related to the JC polyomavirus reactivation have also been described in patients on belatacept [20, 28, 29]. This possible increase in the risk of infection requires confirmation in a larger case–control study, but the available data nevertheless suggest that such events should be monitored very carefully. Belatacept is a CD28-CD80/CD86 costimulation blocker, and, as such, it can induce T-cell anergy. T-cell anergy is defined as a long-term state of T-cell hyporesponsiveness in response to suboptimal activation, including a lack of costimulation due to CD28-CD80/CD86 blockade [30]. It can be very challenging to treat viral infections related to immunological mechanisms of T-cell anergy because we currently have no means of reversing T-cell anergy [31]. Thus, the use of belatacept [32] and future biotherapies capable of inducing T-cell anergy may lead to the emergence of a subset of viral infections that are extremely difficult to manage.

3.2.6 Antimetabolites: azathioprine and mycophenolate mofetil

Azathioprine was the first antimetabolite drug to be developed. It is metabolized to 6-mercaptopurine (6-MP). The thiopurine S-methyltransferase (TPMT) enzyme then catalyzes the metabolism of 6-MP to generate three metabolites—two inactive metabolites and the active 6-thioguanine nucleotide (TGN) metabolite. TGNs are incorporated into the DNA of replicating cells, leading to an inhibition of DNA synthesis, and the impairment of B- and T-cell proliferation. TGNs can also decrease the number of circulating monocytes by inhibiting the cell cycle in bone marrow promyelocytes. Some genetic polymorphisms within the TPMT gene can lead to a decrease in TPMT enzyme activity, or even its total abolition, resulting in higher levels of TGNs and a higher risk of severe bone marrow suppression [33, 34].

The use of azathioprine has decreased considerably since the turn of the century, and this molecule has been largely replaced by mycophenolate mofetil (MMF). MMF is a reversible inhibitor of inosine monophosphate dehydrogenase (IMDPH) isoform 2, an enzyme required for the *de novo* synthesis of purine bases. This molecule has made a major contribution to improvements in kidney graft survival. IMDPH inhibition impairs purine synthesis in T cells but also has wide-ranging effects in B cells, dendritic cells, monocytes, and macrophages [35]. MMF also can induce T-lymphocyte apoptosis, suppress dendritic cell maturation, and inhibit the expression of adhesion molecules, thereby impairing the recruitment of lymphocytes and monocytes. Unlike calcineurin inhibitors, MMF is not nephrotoxic and does not induce the production of transforming growth factor-beta, which is fibrogenic. MMF does not increase blood pressure, cholesterol, or triglyceride levels [36]. Nevertheless,

MMF treatment is not without complications, the principal of which is digestive and hematological toxicity; MMF also increases the risk of infection, with viruses in particular [37]. In addition, its metabolism depends on several factors, including ethnicity, rendering its pharmacodynamics complex. Individual drug exposure is not easy to evaluate and requires a calculation of the area under the curve (AUC) or mini-AUC, which is complex to achieve during patient follow-up in real life [38].

3.2.7 Mammalian target of rapamycin inhibitors (mTOR.Inh): sirolimus and everolimus

Mammalian target of rapamycin inhibitors (mTOR.inh) blocks T-cell progression through the cell cycle by inhibiting the mTOR kinase. mTOR.inh bind FKBP-12 and inhibit the mTOR kinase, resulting in cell-cycle arrest in the G1-S phase. This effect leads to the inhibition of the T-cell proliferation signal [39].

Two molecules are currently available—sirolimus and everolimus. Despite the antiviral properties of these molecules and their potential value compared to CNI, the generalized use of mTor.inh has been limited by their adverse effects and the higher incidence of acute rejection in pivotal clinical trials. In the SYMPHONY study, the rate of acute rejection in patients treated with rapamycin was 60% higher than that in patients treated with low doses of cyclosporine with the same associated immunosuppressive therapies, and twice that in patients treated with low doses of tacrolimus [40]. In addition, mTOR.inh may cause renal lesions via various mechanisms, including proteinuria and microangiopathy. The key benefits of mTOR.inh treatment may be the antiproliferative effects of these drugs, which are beneficial in the long term for preventing chronic graft dysfunction and reducing the risk of cancers [41, 42]. Several studies have highlighted the effect of these drugs in reducing tumor development or preventing cancer recurrence.

4. Conventional protocols

Immunosuppression protocols are based on the rational combination of multiple immunosuppressive drugs with different mechanisms of action on T cells. The choice of immunosuppression protocol should be made after an individual assessment of the risks of rejection and opportunistic infection and based on the adverse effects of the drugs concerned. The variables usually considered are the immunological risk and the age of the recipient, the type of donor (living or deceased), HLA matching, and the presence of comorbid conditions and infections.

Current protocols usually combine (i) induction therapy and (ii) maintenance therapy based on corticosteroids, CNIs, and antimetabolites. Traditionally, the immunological risk of the recipient has dictated the intensity of immunosuppression. Patients are therefore classified as described below:

- Recipients with low immunological risk: Antibody induction may not be necessary for recipients of organs from HLA-identical donors. Moreover, protocols without continuous exposure to CNIs or steroids can also be used in such patients [43–45]. Nevertheless, physicians should be aware that less intensive treatment, particularly with a secondary minimization of immunosuppression, may result in acute rejection, highlighting the need for meticulousness when trying to minimize immunosuppression [43].

- Recipients with a standard risk: This category includes recipients without HLA sensitization, and with a first isolated kidney transplant from a non-identical HLA donor. In these patients, anti-rIL2 antibodies have been shown to prevent acute rejection effectively, and generally have a better tolerability profile than that reported for anti-thymocyte globulin [46, 47]. Moreover, anti-rIL2 induction makes it possible to reduce the CNI dose. In the SYMPHONY trial [40], induction with an anti-rIL2 antibody in association with low doses of CsA gave similar acute rejection rates to a standard dose of CsA without rIL2 induction. Nevertheless, as basiliximab is not a depleting antibody and induces milder immunosuppression than ATG, it is considered to be associated with a higher immunological risk and is not advised in highly sensitized patients [48].

- Recipients with high immunological risk: This category includes recipients with high levels of PRA (panel reactive antibodies—usually ≥85%), DSA, or who have undergone re-transplantation or simultaneous (kidney and another organ) transplantation, and have delayed graft function. In these patients, more intense immunosuppression is required, through the use of anti-thymocyte globulin induction and a combination of potent immunosuppressive drugs [49, 50].

- Recipients with a very high immunological risk: This category includes ABO-incompatible transplant recipients, patients with positive cross-matching, and patients undergoing HLA desensitization. These patients require very complex management due to the high risk of severe hyperacute rejection. Powerful immunosuppression protocols are available, including the use of polyclonal immunoglobulins, plasmapheresis, rituximab, anti-thymocyte globulin induction, and maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and corticosteroids [51, 52].

4.1 Induction therapy

The aim of induction therapy is to prevent the activation of the immune system provoked by new alloantigens. ATG and anti-rIL2 antibodies are typically used. High doses of corticosteroids are also part of the induction treatment, as they decrease the initial phase of inflammation by remodeling the innate and adaptive immune responses.

In addition to increasing the risk of neoplasia and infection, the use of ATG has been associated with higher cardiovascular mortality [53]. Based on these limitations, it seems reasonable to reserve this treatment, as far as possible, for patients with a high immunological risk, and to prefer basiliximab for more general use, particularly given the increasing evidence of its safety.

4.2 Maintenance therapy

Long-term maintenance therapy is crucial to maintain control over the immune system so as to avoid allograft rejection. Maintenance therapy usually consists of a combination of CNIs, typically tacrolimus, an antimetabolite molecule, as mycophenolate mofetil and corticosteroids. The combination of these different molecules blocks T-cell activation via different pathways simultaneously, making it possible to decrease the dose of each treatment, thereby limiting the toxicity of individual molecules.

4.3 Treatment of allograft rejection episodes

Three main types of allograft rejection have been described based on the time course of their development:

- Hyperacute rejection – resulting from pre-existing DSA reacting with the endothelium. This type of rejection can occur within minutes of transplantation, following massive complement activation. Remarkable advances in our understanding of HLA and correct management of immunosuppression have greatly decreased the risk of hyperacute rejection.

- Acute rejection – acute rejection is an immunological response mediated primarily by T cells. Treatments based on corticosteroids and ATG are, therefore, usually effective for the treatment of acute cellular rejection.

- Chronic rejection – chronic rejection may occur over a period of months or years after transplantation. It involves several immunological mechanisms, including, in particular, humoral immunity, with activation of the complement pathway. The success of current immunosuppression regimes has resulted in the survival of more than 90% of kidney allografts 1 year after transplantation. However, chronic rejection remains a major issue and its treatment is still a matter of debate. Plasma exchange, polyclonal immunoglobulins, corticosteroids, and rituximab are the most common treatments, but the standard of care practices have not yet been clearly defined [54].

5. New developments

5.1 CNI minimization or sparing with mTOR inhibitors

An alternative protocol based on a combination of mTOR.inh, MMF, and steroids was initially developed for CNI sparing. Unfortunately, rejection rates were significantly higher for patients treated with this protocol than for patients receiving CNIs [40, 55]. The risk of *de novo* DSA development was also higher [40]. These disappointing results led to the abandonment of CNI-sparing strategies based on mTOR.inh.

However, mTOR.inh can be used in cases of CNI minimization. In several studies, the authors chose to keep CNI doses as low as possible, whilst adding mTOR.inh treatment. These studies showed this strategy to be effective [56–58]. Moreover, viral infection rates were 60% lower for CMV infections and 45% lower for BK polyomavirus-associated nephropathy [59]. These results led many teams to review their protocols and to propose similar CNI minimization strategies for patients at low immunological risk. An optimal everolimus concentration ($\geq$3 ng/mL) was found to be associated with significantly lower rates of acute rejection [60]. In addition, mTOR.inh blocks the cell cycle in many different cell types and has been shown to decrease the incidence of skin cancer recurrence, suggesting potential additional benefits of this treatment for preventing tumors in transplant patients.

5.2 CNI sparing by immunotherapy

Belatacept is the first biotherapy to be used as an alternative to CNIs in kidney transplantation. Its lack of nephrotoxicity and better metabolic profile are the main

benefits of this molecule. Furthermore, belatacept is administered as intravenous perfusion, which makes it easier to ensure that it is administered effectively, thereby decreasing the risk of occult nonadherence.

Since 2010, belatacept has been tested in combination with MMF and steroids, in association with anti-rIL2 induction therapy. Two studies, BENEFIT (for donors with standard criteria [19]) and BENEFIT EXT (for donors with extended criteria [61]), have compared the *de novo* introduction of this molecule, without CNIs, to standard triple therapy, including CsA. Long-term renal function has been shown to be better for belatacept than for a CsA-based regimen. Belatacept also results in a lower incidence of *de novo* DSA production and is associated with a lower risk of new-onset diabetes after transplantation.

Surprisingly, higher rates of acute cellular rejection have been reported in patients on belatacept, and various effector memory T-cell phenotypes have been observed [62, 63]. Several studies have identified "risky" memory T-cell subsets associated with belatacept-resistant rejection, including CD4 T cells with a $CD28^+$ effector-memory phenotype or a $CD57^+$ $PD1^-$ profile. TIGIT, an immune checkpoint receptor, is expressed on these memory CD4 T-cell subsets. The use of a neutralizing anti-TIGIT antibody significantly increased apoptotic cell death rates for these cells [64]. Recently, it has also been shown that the proliferation of belatacept-resistant T cells requires early IFNα pathway activation. The inhibition of type I IFN or IL-6 reduces the proliferation of belatacept-resistant T cells [65]. These new developments will pave the way for the identification of new therapeutic targets for preventing belatacept-resistant rejection after kidney transplantation.

5.3 Viral infection and the management of immunosuppression

Viral infections remain a challenging issue after transplantation. Usually, treatment includes antiviral agents if available and/or a decrease in the intensity of immunosuppression. The principal goal is the restoration of effective antiviral immunity without increasing the risk of rejection. In solid organ transplantation, the individual risk of viral infection is determined largely by the "net state of immune deficiency". Many parameters, including immunosuppression regimen, contribute to this state, and other individual predisposing factors, such as immune-aging, concomitant viral infection, and antiviral T-cell efficiency, are also involved [66].

CD8 T cells play a key role in controlling viral infection. Clinicians, therefore, decrease the intensity of immunosuppression by initially decreasing or withdrawing antimetabolites and/or CNIs, but this may increase the risk of graft rejection. A change in the "standard" regimen to another protocol for controlling or preventing viral infection has been proposed. As the mTOR pathway is largely involved in viral replication [67], there are several lines of evidence suggesting that mTOR.inh have antiviral properties, with a lower risk of CMV, polyomavirus, and Human herpes virus-8 (HHV8) infection than for standard protocols [68–70].

Various acute and recurrent viral infections may occur after kidney transplantation, but two viruses predominate CMV and BK polyomavirus (BKv). Despite recent advances, CMV infection is still associated with progressive disease, graft loss, morbidity and mortality, and antiviral drug resistance. CMV is usually efficiently controlled by specific antiviral therapy. Immunosuppression is not, therefore, systematically reduced, but such reductions may be proposed in cases of severe CMV disease, antiviral drug resistance, or inadequate clinical response [71].

In the last 20 years, BKv infection has emerged as a major complication of kidney transplantation, causing BKv-associated nephropathy, which has a prevalence of 10% and leads to graft loss in >50% of cases. The worldwide seroprevalence for BKv is more than 90%. Nevertheless, BKv disease is particularly frequent in the context of kidney transplantation but rare in non-kidney solid organ transplantation. In the absence of a specific antiviral treatment, a reduction of immunosuppression intensity is recommended for recipients with sustained plasma BKv reactivation or in cases of proven BKv-associated nephropathy. However, in the absence of randomized clinical trials, there are no standardized protocols for immunosuppressant minimization. A decrease in CNI exposure (CNI dose decrease of 25–50%), associated with or followed by a decrease in the dose (by 50%) of the antiproliferative drug, or its complete withdrawal, is proposed. This strong reduction of immunosuppression intensity may expose the patient to a higher risk of graft rejection. Some authors have also suggested switching patients from tacrolimus to low-dose CsA, and/or from mycophenolate mofetil to mTOR.inh. No recommendations have been made concerning the addition of intravenous immunoglobulins, leflunomide, or cidofovir [72].

5.4 Immunovirological monitoring to mitigate the risk of viral infection

An innovative approach to mitigating the viral risk, without increasing the risk of rejection, involves assessing the ability of the antiviral cellular immune response to control viral reactivation [73]. Functional specific antiviral T cells can control viral replication in cases of CMV infection [74, 75]. For example, CMV-specific T-cell monitoring has been shown to predict CMV control after solid organ transplantation [76]. Accordingly, CMV immune monitoring can be added to standard follow-up to improve CMV management. Similarly, the BKv-specific cellular immune response is crucial for the control and clearance of BKv. BKv-specific T-cell dysfunction increases the risk of uncontrolled BKv infection, whereas an increase in the number of BKv-specific CD8 T cells is associated with a better prognosis for BKv-associated nephropathy [77]. Various tools have been developed used to assess the quality of antiviral T-cell responses, but few are currently available in clinical practice. Additional studies are required to determine the potential utility of these tools for predicting infection risk after transplantation.

5.5 Transplantation in the context of cancer

Neoplastic complications are, unfortunately, among the most frequent and severe adverse events occurring after kidney transplantation, constituting the second leading cause of post-transplantation death [5]. Skin cancers are the most frequent post-transplantation tumors, with non-melanoma skin cancer particularly prevalent [78].

CNIs are directly involved in cancer pathogenesis, and their ability to promote the development of cancer cells has been clearly demonstrated in a mouse model [79]. It is, therefore, tempting to stop CNI treatment in the context of cancer.

mTOR.inh inhibit the mTOR pathway, which is involved in cancer cell growth. These molecules are, therefore, the treatment of choice in cases of cancer, as they can decrease the frequency of non-melanoma skin cancer without increasing the risk of acute rejection [80]. Similarly, mTOR.inh-based immunosuppression has been shown to be associated with lower rates of cancer and non-melanoma skin cancer, particularly in cases of late conversion from a standard immunosuppression regimen [81, 82]. In these initial reports, mTOR.inh was used in place of CNIs. However, recent

observations of a higher risk of *de novo* DSA occurrence in patients treated with mTOR.inh without CNIs have suggested that the combination of a mTOR.inh with a low dose of CNIs may be a better option [56, 83]. The effect of belatacept on neoplasia remains unknown.

5.6 Transplantation in the context of pregnancy

End-stage kidney disease is often associated with infertility and high-risk pregnancies. In women of reproductive age, kidney transplantation generally restores fertility, and more than 14,000 pregnancies in the context of kidney transplantation have already been reported worldwide [84]. However, complications, such as pre-eclampsia, hypertension, low-birth weight, preterm birth, and gestational diabetes, are more common in kidney transplant recipients than in women who have not undergone transplantation. Furthermore, acute rejection can occur during pregnancy, at rates similar to those in the non-pregnant transplant recipient population. Pregnancies in the context of kidney transplantation require careful monitoring, with joint management by an obstetrician with experience in managing high-risk pregnancies [85]. It is generally recommended to wait at least 1 year after transplantation before trying to conceive, due to the risk of graft failure. Conception can be considered safe if graft function is stable, with no recent episodes of graft rejection, a serum creatinine concentration < 1.5 mg/dL, proteinuria <500 mg a day, and normal blood pressure or well-controlled hypertension [84].

Immunosuppressive treatment and antihypertensive medication must be carefully managed. Immunosuppressive treatment modification should occur about 3 months before planned conception, to minimize the risk of graft rejection and adverse events due to treatment modification. CNIs are usually considered safe and should be continued throughout pregnancy. However, the levels of these drugs in the blood may fluctuate due to the physiological increase in blood volume. Careful monitoring is, therefore, required to ensure that the patient is not under-treated and exposed to a risk of rejection. By contrast, MMF is teratogenic and should be replaced by azathioprine at least a few weeks before any attempt at conception. Limited evidence is available concerning the safety of belatacept during pregnancy. mTOR.inh should be stopped as soon as possible, due to the involvement of the mTOR pathway in embryonic development and growth [86]. Finally, prednisone may be used safely in pregnant women. The preferred regimen during pregnancy is, therefore, a combination of CNIs, azathioprine, and prednisolone. For patients with hypertension, the optimal management of blood pressure is crucial to ensure a safe pregnancy. Nevertheless, renin-angiotensin-aldosterone system inhibitors should be stopped during pregnancy, due to the risk of renal agenesis.

5.7 Management of immunosuppressive drugs in the context of a loss of graft function and a return to dialysis

Returning to dialysis after transplantation is a complex transition, associated with an increase in morbidity and mortality [87]. Large numbers of transplant recipients eventually need a new graft. There may, therefore, be an indication for maintaining low doses of immunosuppression in this population to minimize the risk of alloimmunization. The benefits of pursuing immunosuppressive treatment after a return to dialysis must be weighed up against the risks of long-term immunosuppression. Several parameters must be considered, including the prospect of retransplantation,

the prevention of graft intolerance, and immunosuppression-related adverse events. When managing immunosuppressive drugs, physicians should initially consider withdrawing antimetabolites. A schedule of CNI tapering can then be proposed and personalized on the basis of the benefit–risk ratio of pursuing such treatments. Slow tapering of CNIs over a period of 6 months following the recommencement of dialysis is recommended. If a new transplant is expected, pursuing low-dose CNI treatment is probably a better option than the complete withdrawal of these drugs. mTOR.inh can be tapered slowly, much like CNIs. There are no recommendations concerning the decreasing of prednisone dose [88].

6. Conclusion

Kidney transplantation is now the standard treatment for patients with end-stage renal disease. Current protocols usually combine (i) induction therapy and (ii) maintenance therapy based on corticosteroids, CNIs, and antimetabolite drugs. Nevertheless, new combinations of therapies are emerging as potential alternatives to the standard of care, with the hope of decreasing CNI toxicity, the occurrence of infections or tumors, and the occurrence of antibody-mediated rejection. In this context, mTOR.inh and belatacept are promising emerging candidates for inclusion in new combinations of molecules. New trials will be required to confirm the encouraging results reported and to adapt treatments to the diversity of patients undergoing kidney transplantation.

Competing interests

The author has no competing interests to declare.

Abbreviations

6-MP	6-mercaptopurine
α-CD25	Alpha chain of the IL-2 receptor
APC	Antigen-presenting cell
ATG	Anti-thymocyte globulins
AUC	Area under the curve
BKv	BK polyomavirus
CMV	Cytomegalovirus
CNI	Calcineurin inhibitors
CsA	Cyclosporine-A
CTLA4-Ig	Cytotoxic T-lymphocyte associated protein-4-immunoglobulin
DSA	Donor-specific antibody
EBV	Epstein–Barr virus
HHV	Human herpesvirus
HLA	Human leukocyte antigen
IFNγ	Interferon γ
IL	Interleukin
IMDPH	Inosine monophosphate dehydrogenase
MHC	Major histocompatibility complex

MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin
mTOR.inh	Mammalian target of rapamycin inhibitors
PTLD	Post-transplantation lymphoproliferative disorder
rIL2	Interleukin-2 receptor
TGN	Thioguanine nucleotide
TPMT	Thiopurine S-methyltransferase

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Section 4

Basic Research and Innovation

Chapter 12

Artificial Intelligence Approaches to Chronic Kidney Disease-Mineral Bone Disorder

Eleanor Lederer, Michael E. Brier and Adam E. Gaweda

Abstract

Chronic Kidney Disease: Mineral Bone Disorder (CKD-MBD) is a complex syndrome, encompassing biochemical, skeletal, and cardiovascular complications. The heterogeneity of individual manifestations, the multitude of contributory factors, and the absence of biomarkers to identify the complications and intervene early in the course have resulted in the current clinical approach, where clinicians are addressing primarily biochemical abnormalities in the advanced stages of chronic kidney disease. The late intervention and the use of surrogate targets that are far removed from the relevant clinical outcomes of fracture and accelerated cardiovascular disease, causes the poor survival of individuals with CKD. The identification of early events in the development of CKD-MBD and the recognition of novel mediators of CKD-associated skeletal and cardiovascular disease are setting the stage for a revolution in how we approach and treat CKD-MBD. The complexity of CKD-MBD lends itself to an alternative approach to management using an artificial intelligence approach combined with a sophisticated mathematical model of the disease to help clinicians target disease complications in a personalized fashion.

Keywords: chronic kidney disease, renal osteodystrophy, cardiovascular events, artificial intelligence

1. Introduction

The derangements of mineral metabolism that occur as chronic kidney disease (CKD) progresses encompass far more than mere biochemical abnormalities of calcium and phosphorus. Recognition of the full manifestation of the syndrome was acknowledged by the international guideline development organization, Kidney Disease: Improving Global Outcomes in 2006. Named Chronic Kidney Disease: Mineral and Bone Disorder (CKD-MDB), this complex syndrome includes the biochemical abnormalities (hyperphosphatemia, hypocalcemia, secondary hyperparathyroidism), the skeletal abnormalities (renal osteodystrophy), and the development of soft tissue calcification, especially in the vasculature [1].

CKD-MBD has effects far beyond the balance of minerals, with the two major clinical sequelae of CKD-MBD being fractures and accelerated cardiovascular disease (**Figure 1**) [2–4]. Individuals with CKD develop bone fragility due to decreased mineralization and

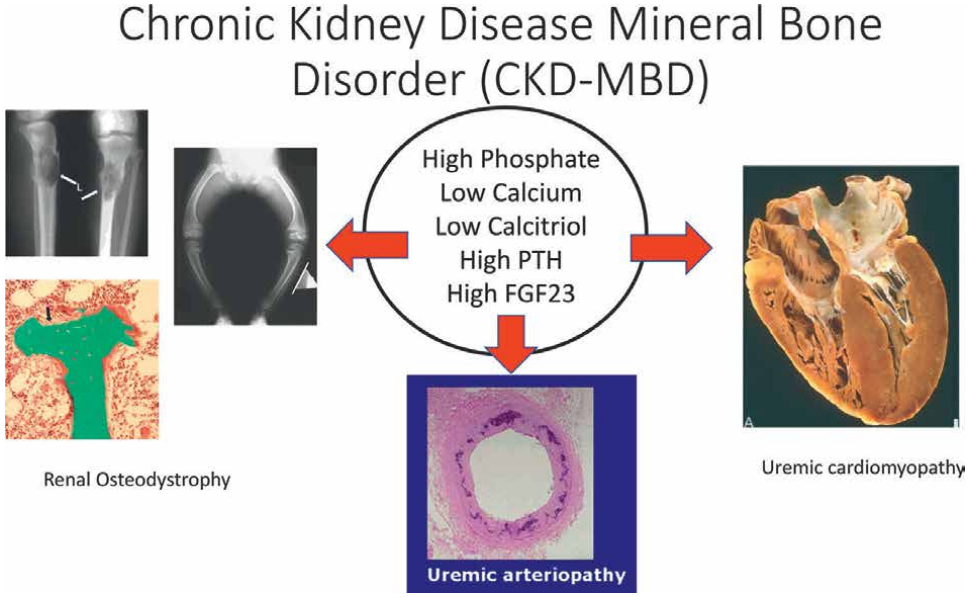

Figure 1.
Definition of chronic kidney disease mineral bone disorder. This figure graphically depicts the major components of CKD-MBD.

abnormal bone structure. The incidence of "osteoporosis" in individuals with CKD is not truly known as few large-scale studies have systematically assessed bone density; however, multiple studies have shown that the incidence of fracture is higher in CKD patients when compared to the general population [5–11]. The other major sequela of CKD-MBD is accelerated cardiovascular disease manifested as cardiomyopathy, cardiac arrhythmias, sudden cardiac death, calcific valvular heart disease, pulmonary hypertension, and vascular smooth muscle calcification, also known as uremic or medical arteriolar calcification [12–22]. These complications contribute heavily to the poor survival of patients with CKD. The increased mortality can be seen as early as stage 1 CKD. While the decrease in survival is modest with stage 1 CKD, this mortality effect is amplified with each increasing stage of CKD with the greatest effect seen in younger patients. For example, a recent study observed that a 30-year-old individual starting dialysis would have an expected life span of only 12 years, markedly decreasing from the expected 45–50 years of a healthy individual [12]. As the stage of CKD progresses the fraction of patients dying of cardiovascular disease increases to as high as 50% of all deaths [12, 13]. Undergoing kidney transplantation, our best therapy for end-stage kidney disease (kidney failure), improves but does not confer a normal life span. In fact, the individual who receives a kidney transplant can expect a survival comparable to an individual with stage 3 CKD [22].

Although life-saving, individuals with complete kidney failure treated with either dialysis or transplantation do not enjoy a normal lifespan. Notably, these therapies are for complete kidney failure, suggesting that interventions late in the course of CKD are inadequate to achieve the optimal impact on the morbidity and mortality of CKD. Disappointingly, the application of interventions such as statins, blood pressure control, and weight control in these individuals have failed to change materially the outcome for these individuals with complete kidney failure, confirming the observation that late intervention is ineffective [23–26]. Although renal osteodystrophy as a sequela of CKD has been recognized for over 60 years, the impact of abnormal mineral metabolism on

the cardiovascular system has only been recently appreciated [15, 16]. Recent advances in the field have uncovered previously unknown mediators of mineral metabolism such as klotho, activin A, DKK1 (dickkopf 1), FGF23, and sclerostin, to name just a few, that have an impact on skeleton and cardiovascular systems to produce the chronic complications known as CKD-MBD [27–37]. Alterations in the regulation of many of these mediators occur at the earliest stages of CKD. Within the past few years, several investigators have conducted trials intervening earlier in the course of CKD to ameliorate the skeletal and cardiovascular manifestation of CKD-MBD, generally targeting single discrete targets. These studies are in preliminary stages and the results have been decidedly mixed. For example, one group of investigators tested the hypothesis that limiting phosphate absorption early in the course of kidney disease before serum phosphate was frankly elevated could ameliorate the long-term outcomes [38]. In this relatively short-term trial, the outcomes were changes in urine phosphate and serum levels of FGF23. Unfortunately, the primary outcomes were not achieved. On the other hand, interventions to ameliorate the acidosis associated with CKD by giving either a higher fruit/vegetable diet, supplemental bicarbonate, or an acid-binding polymer suggest slower deterioration of kidney function [39–41]. The effects on skeletal and cardiovascular outcomes have not been reported as yet. Another interesting study demonstrated that administration of an inhibitor of the inflammatory cytokine, IL-1, decreased biochemical markers of inflammation and improved markers of vascular health [42] but had no discernible effects on markers of mineral metabolism. The long-term effects are not yet available. However, these and other studies justify the ongoing investigation into the identification of earlier mediators of the development of CKD-MBD that could become therapeutic targets to improve outcomes [43–47].

The recognition of the systemic nature of the pathogenesis of CKD-MBD has led to a greater awareness of the marked heterogeneity in the manifestations of CKD-MBD and difficulty in identifying individual pathology, particularly with regard to bone health [48–63]. At this time, the absence of clear evidence from clinical trials for early interventions has hindered the development of clinical guidelines for evaluation of skeletal and cardiovascular status or risk factors in individuals with CKD. No standardized assessments of skeletal and cardiovascular health have been established. Phenotypic classification to define individual risks has not been accomplished. For the individual patient, a clinician is unable to predict which complications will likely occur. The result is that all patients with CKD are approached similarly with the same tools and the same targets, which are primarily the biochemical targets of CKD-MBD – calcium, phosphorus, and PTH levels. Overall, these considerations have led to the inevitable conclusion that as a medical community, we need to 1) treat patients with CKD earlier in the course to prevent the deadly complications, 2) identify the best biomarkers to predict adverse complications, 3) develop new therapies for CKD-MBD based on pathogenesis, 4) target the clinically significant sequelae of CKD-MBD, and 5) tailor therapies to the individual patient. The complexity of CKD-MBD makes it an ideal condition to apply artificial intelligence techniques to improve the outcomes for individuals afflicted with this deadly disorder.

2. Pathogenesis of CKD-MBD

The initiating event thought to trigger the development of CKD-MBD is the challenge of maintaining phosphate balance in the setting of declining kidney function [64, 65]. Dietary intake and absorption of phosphate are well in excess of daily needs. The kidneys are primarily responsible for maintaining phosphate balance by altering tubular

reabsorption of phosphate from glomerular ultrafiltrate [66]. Even at the earliest stage of CKD, an orchestrated series of changes occur to ensure that the kidneys can excrete the daily load of phosphate. These changes include decreased expression of transport proteins in the kidney that reabsorb filtered phosphate through the activation of a hormone called fibroblast growth factor 23 (FGF23). FGF23 is a hormone, made by osteocytes primarily in response to a phosphate load that interacts with FGF receptors on the kidney proximal tubule in conjunction with its essential cofactor, klotho, a glucuronidase made almost exclusively in kidney [32–36, 67, 68]. The result is the activation of a signaling cascade that reduces the expression of sodium-coupled phosphate transporters on kidney proximal tubule cells and increased the excretion of phosphate by those nephrons. The other major phosphaturic hormone, parathyroid hormone (PTH), also contributes to the enhancement of kidney excretion of phosphate at the single nephron level by reducing the expression of phosphate transporters [66, 69, 70]. While immediate and transient changes in FGF23 and PTH can be elicited in individuals without CKD by providing a phosphate load, the presence of CKD leads to early (stage 1 CKD) sustained increases in FGF23 followed by sustained increases in PTH, generally beginning late stage 3 CKD. The other major effect of FGF23 that influences phosphate homeostasis is the downregulation of the formation of 1,25 dihydroxy vitamin D, the active form of vitamin D that is responsible for enhancing intestinal absorption of both calcium and phosphate, necessary for normal bone mineralization [32–36, 67, 71]. The final activating step of vitamin D occurs in the kidney. FGF23 suppresses the formation of active vitamin D by decreasing the production of 1 alpha-hydroxylase (CYP27B1), the activating enzyme. Simultaneously, FGF23 promotes inactivation of vitamin D through the increased production of 24 hydroxylase (CYP24A1), one of the vitamin D inactivating enzymes. Together, these two effects of FGF23 to decrease intestinal absorption of phosphate and decrease kidney reabsorption of phosphate serve to maintain phosphate balance through the early stages of CKD. Patients with CKD do not become hyperphosphatemic until the late stages of CKD, while the increase in FGF23 and the decrease in calcitriol occur very early. Importantly, neither FGF23 nor calcitriol is routinely measured parameters in patients with CKD.

In addition to a loss of excretory function, kidney injury leads to the elaboration and release of additional circulating substances that influence mineral metabolism [27–31]. Two of these substances, DKK1 and activin A, are released from injured kidneys into the circulation, stimulating the release of sclerostin from osteocytes. Sclerostin, in turn, inhibits bone formation. Additional molecules released by injured kidney cells, damage-associated molecular patterns (DAMPs) or alarmins, stimulate the release of inflammatory cytokines that also have a direct effect on bone turnover, indirect effects through their detrimental effects on muscle, and increase FGF23 production [72–76]. The expression of klotho, the essential cofactor for FGF23 signaling in the kidney proximal tubule, decreases at the onset of CKD, resulting in impaired FGF23 signaling [36]. This consequence then leads to increased stimulation of FGF23 to accomplish the primary task of blocking kidney phosphate reabsorption. Klotho also has anti-inflammatory and anti-oxidant properties; thus, the loss of klotho amplifies the inflammatory response, additionally contributing to FGF23 release. The development of anemia associated with CKD also has an effect on FGF23 release, thought to be mediated by the abnormalities in iron utilization [77, 78]. Anemia increases both the production and the cleavage of FGF23. The current understanding of FGF23 effects is that intact FGF23 is the active entity; however, the cleaved products may also have as yet unknown effects on mineral metabolism.

The consequences of the accelerating pace of FGF23 generation are manifold. Calcitriol production and expression continue to decline. FGF23 at very high levels

also appears to interact with FGF receptors on the heart which can be activated in the absence of klotho. The results of FGF23 stimulation of heart FGF receptors is cardiac muscle remodeling leading to left ventricular hypertrophy and eventual heart failure [32, 33, 68, 79, 80]. The markedly increased FGF23 levels have been implicated in the development of vascular calcification. FGF23 inhibition of calcitriol expression coupled with the presence of high levels of sclerostin impairs bone formation and turnover, leading to defects in skeletal structure and mineralization [27, 31]. Active vitamin D has also been implicated in vascular health; thus, the decrease in active vitamin D levels may also contribute to uremic vasculopathy [81, 82].

As CKD progresses, the ability of the body to maintain relatively normal levels of serum phosphate, calcium, and PTH falters. Eventually, serum phosphate rises and serum calcium falls. Secondary hyperparathyroidism develops due to the combination of hyperphosphatemia, hypocalcemia, and low calcitriol levels. Despite attainment of PTH levels well in excess of the upper limits of normal, calcitriol levels remain low. PTH, in part, combats the decrease in bone formation mediated by sclerostin but the alterations in bone turnover and mineralization persist. The interplay between the high bone turnover effects of hyperparathyroidism and the low bone turnover effects of high sclerostin and low calcitriol yields divergent clinical sequelae, which are nearly impossible to distinguish without bone biopsy. Some individuals show predominantly high turnover bone disease, others low turnover and yet others demonstrate a combined picture. Irrespective of bone histology, these individuals are at high risk for fracture. An additional consequence of the prolonged and increasingly deranged mineral metabolism is that the smooth muscle cells of the vasculature undergo a transformation by which they gain properties of osteoblasts, i.e., increased expression of osteoblast genes and proteins such as collagen, osteocalcin, alkaline phosphatase, and the phosphate transporter PiT-1 and decreased expression of the inhibitor of soft tissue calcification, matrix GLA protein [80, 83, 84]. The consequence is the elaboration of matrix vesicles that promote vascular smooth muscle calcification, a consequence that has been implicated in the development of severe vascular complications including peripheral tissue gangrene and calciphylaxis.

Figure 2 summarizes the pathogenesis of CKD-MBD from the skeletal and cardiovascular perspectives. Two fundamental processes merge to produce the complex picture of CKD-MBD: renal excretory failure involving primarily challenges to maintaining phosphate homeostasis and the kidney cell injury response leading to the release of circulating factors that affect skeletal health, systemic inflammatory status, and oxidative stress. The tissue level results are bone fragility, cardiomyopathy, and vasculopathy. The clinical consequences experienced by the patients are fractures, heart failure, arrhythmias, peripheral gangrene, valvular heart disease, and calciphylaxis. This extensive review of the pathogenesis sets the stage for appreciating the complexity of the pathogenesis and the varied clinical manifestations that have defied effective therapy for decades. Clearly, the current targets for therapy of CKD-MBD, i.e., control of the abnormal biochemical parameters calcium, phosphorus, and PTH, do not address the fundamental pathogenesis of CKD-MBD. Significant effort has been exerted to control serum phosphate and combat phosphate retention through diet, phosphate binders, and dialysis. A variety of active vitamin D analogs to treat secondary hyperparathyroidism have been developed and compared. The advent of the use of calcium-sensing receptor agonists as an alternative means to control PTH without raising serum calcium was met with great enthusiasm. Trials describing the use of and comparing these agents have verified that PTH can be controlled but have not resulted in a meaningful increase in survival for individuals with CKD. These targets for therapy are biochemical markers that become abnormal late in the

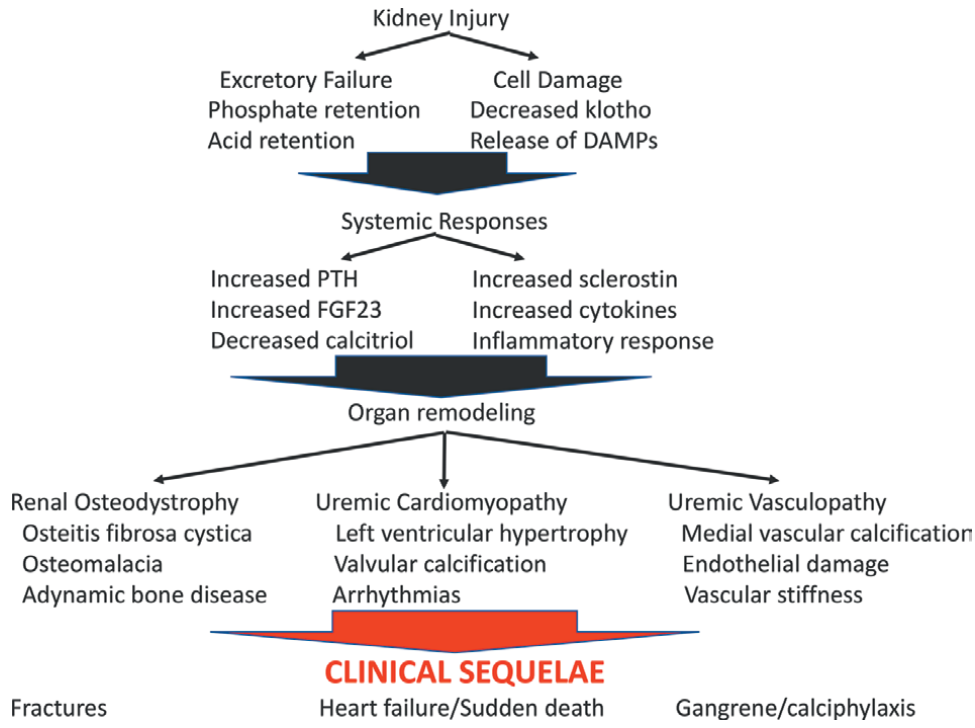

Figure 2.
Pathogenesis of CKD-MBD. This figure depicts, in simplified form, the major features outlining the development of CKD-MBD from the initial insult (kidney injury) to the clinical sequelae.

course of kidney disease and are far removed from the meaningful clinical sequelae of CKD-MBD – renal osteodystrophy, uremic cardiomyopathy, and uremic vasculopathy. It is our contention that the complexity of CKD-MBD mandates a sophisticated approach employing artificial intelligence techniques that will allow clinicians to identify individuals at high risk for specific complications of CKD-MBD and will facilitate the development of effective and personalized therapies early in the course of disease to ameliorate the complications and thus the accelerated mortality associated with CKD-MBD.

3. Artificial intelligence applications to kidney disease

The preceding section has outlined the complexity of CKD-MBD where the interplay of multiple bowel chemical factors working in concert or counter to other factors makes treatment multidimensional. This multi-dimensionality is naively addressed during drug development without a requirement for an existing drug to be optimized following the introduction of a new therapeutic agent or biochemical factors more directly related to the outcomes of interest. The use of artificial intelligence in combination with advanced mathematical modeling can be applied to solve this dilemma.

The concept of applying Artificial Intelligence (AI) to assist in diagnosing and treating kidney diseases is not a new idea but has been underexplored. Artificial Intelligence methods are merely computational models of cognitive and learning functions inherent to human beings (**Table 1**). Important in this definition is the assertion that at the current state of the art the AI tools are there to aid, not replace,

AI methods	Application Area
Supervised Learning: Decision Trees Neural Networks	Diagnostics Predictive Modeling Information Mining
Unsupervised Learning: Clustering Self-Organizing MapsPrincipal Component Analysis	Image Segmentation Phenotypic Classification
Reinforcement Learning: Q-Learning Policy Gradient Actor-Critic	Treatment Planning Treatment Optimization

Table 1.
Commonly Used AI Methods in Medicine and Their Applications.

the clinician and the implication that AI can enhance human capabilities but cannot act autonomously. Of all AI branches, Machine Learning (ML) has been the family of methods most commonly applied in nephrology. The basic underpinning of ML is the principle that a computational system using a human-like learning process can be trained to recognize and predict patterns known (supervised learning) or unknown (unsupervised learning) to human users. However, we wish to move past the thesis of Turing in 1950 where he proposed the question "can machine think?" [85]. It is simply not the goal of these advanced mathematical techniques to "fool" the user and believe that treatment recommendations are coming from a human. To this end, we wish to create new knowledge and use that knowledge represented as a mathematical equation to describe the process we wish to improve and two understand the repercussions of multiple drug therapies on the process we wish to control.

In general terms, Supervised Learning recapitulates and generalizes human knowledge encoded in data. A good example of supervised learning is a diagnostic application where the machine is trained to "read" histology slides of biopsies from human kidneys previously labeled by a human expert. Several publications document the utility of AI methods in this realm. The machine or "agent" is presented with a large number of kidney biopsy slides demonstrating the range of pathology and is trained to recognize specific pathologic findings as would be performed by a human pathologist. With appropriate "training", a supervised learning agent can provide very rapid and reproducible histopathologic diagnoses. The application of this form of ML can dramatically increase the diagnostic throughput of cases, enabling more rapid reading of slides and transmission of the diagnoses to the referring physicians. Supervised Learning AI methods have been applied to the identification of kidney transplant rejection and multiple forms of glomerular disease. Malcolm Gladwell has famously stated that an individual needs to devote 10,000 hours to become an expert [86]. For a clinician, this goal may require years or even decades to achieve. For the computer, this process can be compressed into hours.

Unsupervised Learning is a technique that can be used to autonomously discover patterns in data. Importantly, these patterns may or may not be previously known to the human operator. Similar to supervised learning, the machine is provided with data from a large number of subjects, encompassing the spectrum of the disease process to be studied. The machine can organize the subjects into different categories using measures of similarity specified by the human operator. For example, a common clinical question that has been addressed with unsupervised ML is the prediction of acute kidney injury in

the intensive care unit. While intensivists have attempted to identify patients at high risk for the development of acute kidney injury, the usual parameters that have been tested have demonstrated poor sensitivity and specificity. Being able to determine who is most likely to develop acute kidney injury in this setting could lead to preventive measures such as avoiding nonsteroidal anti-inflammatory drugs or other nephrotoxic drugs. Thus, Unsupervised Learning is useful for clinical questions that have been previously unexplored or unresolved The advantage of applying AI methods to this type of scenario is that the computational capacity allows the processing of much larger amounts of information than can be processed by the human brain, enabling the machine to organize the analyzed variables in various different ways. That being said, it cannot be emphasized enough that although the learning process itself is free of bias, the quality of the output produced is dependent on the data being provided. Clearly, data generated through human intervention contain multiple sources of bias, leaving open the possibility that important factors to address the specific question may not be included in the dataset provided to the computational system. Incorporating additional AI applications into systems with greater computational capacity can address this potential deficiency to some degree. For example, including information from patient records through Natural Language Processing (NLP) can markedly enrich the source information and potentially lead to real breakthroughs in the understanding disease process. For example, inclusion of patient symptomatology from the electronic medical record in addition to easily digitized patient information has led to the discovery that the prevalence of genetic disorders is more common than previously recognized [87, 88]. Several other examples of the use of AI for data fusion to identify new patterns of disease presentation or prevalence include the eMERGE initiative, the Million Veteran Program, and Vanderbilt University's Synthetic Derivative database.

These examples leverage the vast quantities of data stored in the electronic medical record and the advances in image processing that allow a digital image to be obtained. Most endeavors of this type have demonstrated almost no difference in recognition of disease over the current clinical practice. In areas where the economic cost of humans performing this work is high, an artificial intelligence approach may prove beneficial. However, our goal should be to leverage this data and the associations, whether known or unknown, between observation and outcome to exceed current clinical care.

4. Application of artificial intelligence techniques to CKD-MBD

The arguments for considering the application of AI to CKD-MBD have been touched on. CKD-MBD is an extraordinarily complex clinical syndrome. The pathophysiology is incompletely understood but recent studies have uncovered novel mediators such as FGF23 and sclerostin that present very early during kidney disease. These mediators are not routinely measured, but some are actually targets of new therapies for bone disease. Determining if these new therapies could be used for the treatment of CKD-MBD is a timely question. In fact, the treatment of CKD-MBD has not materially changed in decades. The targets remain control of serum phosphate, control of serum calcium, and control of parathyroid hormone levels. The current guidelines provide little guidance on the evaluation and treatment of CKD-MBD in the early stages CKD primarily because of a dearth of clinical research. Consequently, clinicians have been unable to materially improve the outcomes of individuals with CKD. The survival of patients with CKD remains unacceptably poor.

Several groups of investigators have looked into methods of using large databases to develop a phenotypic characterization of individuals with CKD and predictive

models for some specific outcomes such as progression of CKD to ESRD or development of cardiovascular events. The research program in the Nephrology Division at the University of Louisville School of Medicine and the affiliated Department of Veterans Affairs Robley Rex VA Medical Center has focused on the development of a comprehensive Systems Biology approach to the complications of CKD over the past 20 years. The goal of the initial project was to develop a tool that would individualize the therapy of the anemia of kidney disease in dialysis patients. For this project, the investigators employed an Artificial Neural Network (ANN) combined with Model Predictive Control. The ANN is a complex nonlinear regression model, originally created as a way of mimicking the structure of human brain that can be used to replicate complex relationships encoded in large data sets using Supervised Learning. Model Predictive Control is a modern automatic control methodology that, in the context of anemia control, uses a model of the patient to predict the response to erythropoietin therapy. Based on the predicted patient responses to specific drug manipulations, optimal dose adjustments are found that optimize the likelihood of maintaining the relevant blood parameters within defined guideline levels. The model can be capable of "learning" each individual patient's pattern of response to therapy thus enabling treatment personalization. This approach was highly successful, resulting in avoidance of wide swings in hematocrit and more efficient utilization of erythropoietic therapy. As stated previously, these investigators reached the goal of improving anemia management over current clinical practice through the publication of two double-blind, randomized, clinical trials [89, 90]. Hemoglobin variability was significantly decreased using an artificial intelligence approach. In a follow-up publication on long-term use of the artificial intelligence approach, the researchers also were able to demonstrate a 25% decrease in erythropoietin exposure [91].

Based on the success of this project, the group next tackled the challenge of individualization of therapy of CKD-MBD, initially focusing on the achievement of published guidelines for calcium, phosphorus, and PTH levels in dialysis patients. This project represented a significant escalation in complexity. First, three separate but interconnected goals of therapy are targeted. Second, multiple therapies are available for use: dialysis prescription, intestinal phosphate binders, active vitamin D analogues, and calcium-sensing receptor agonists. Third, patient behavioral issues significantly influence the outcomes. Adherence to phosphate binder therapy is entirely under patient control. Many of the vitamin D analogs and the calcium-sensing receptor agonists are also oral agents, and thus their efficacy is impacted by patient adherence to the regimen. The solution applied to this project differed somewhat from the previously described AI techniques. A model to describe the evolution of CKD-MBD as kidney failure progresses was developed and validated (**Figure 3**) [92]. This model, based on a previously published model of mineral metabolism in healthy individuals, was modified to describe the changes in mineral metabolism, bone turnover, and soft tissue calcification that occur through ordinary differential Equations [93]. The challenge of optimal CKD-MBD treatment was addressed using an AI technique called Reinforcement Learning (RL). This ML modality is a hybrid between Supervised and Unsupervised Learning that incorporates a reward system inherent to trial-and-error human learning in order to let an intelligent agent discover the optimal pattern of behavior on its own (**Figure 4**). Using a systems biology model of a disease, an RL agent can be trained by exposure to a wide variety of simulated patient data that describe the spectrum of disease, in this case, calcium, phosphorus, and PTH in dialysis patients. The agent is provided by the human operator with the goals of therapy for all three biochemical parameters, for example, the targets defined by the published guidelines. By mimicking the human trial-and-error learning, the agent discovers which drugs to use, when, and in

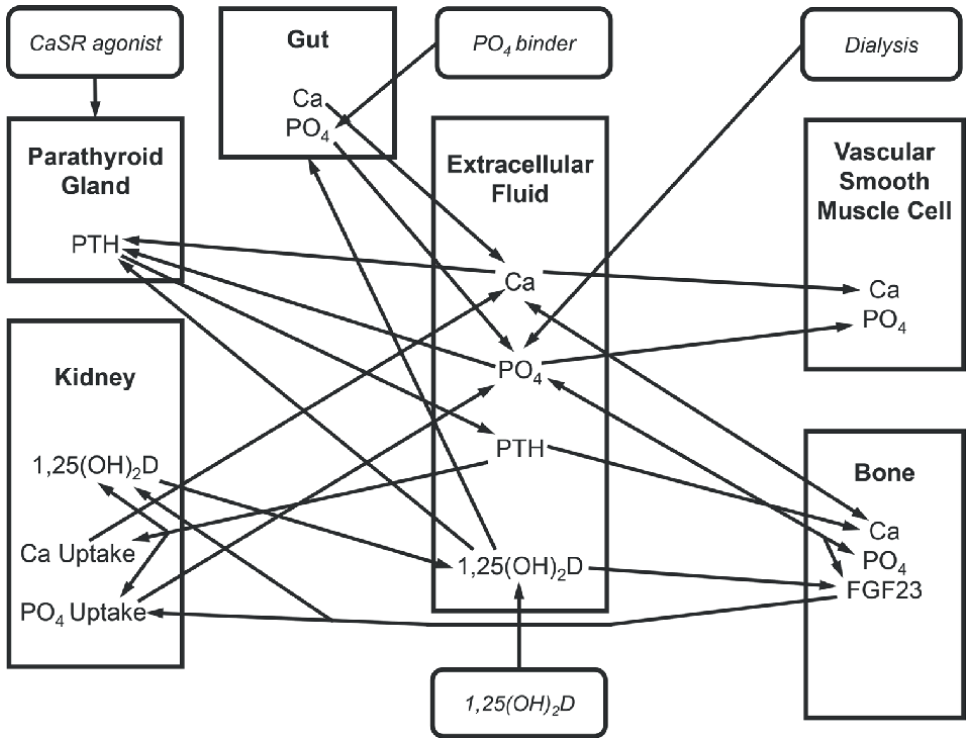

Figure 3.
Block diagram model of CKD-MBD. This figure depicts a simplified version of the systems biology model of CKD-MBD encompassing the major organs involved (kidney, intestine, bone, parathyroid), the biochemical features (Ca [calcium], PO_4 [phosphate], PTH [parathyroid hormone], 1,25 vitamin D [calcitriol], FGF23 [fibroblast growth factor 23]), and the interventions (CaSR agonist, 1,25 $(OH)_2$, dialysis). The arrows designate relationships between components. The final model consists of over 100 different parameters, the relationships described as ordinary differential equations.

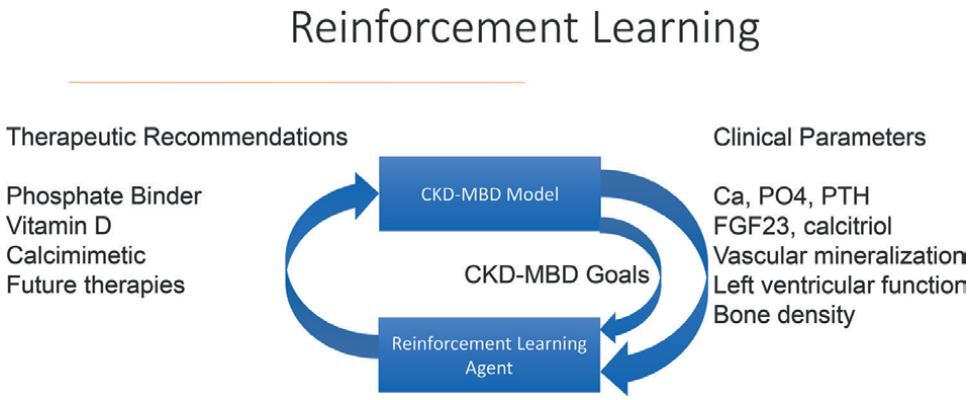

Figure 4.
Schema of reinforcement learning. This figure depicts the iterative and exploratory process of reinforcement learning. The agent is provided with therapies (depicted on the left-hand side), clinical parameters (depicted on the right-hand side), and the goals of therapy (CKD-MBD goal). The agent then chooses a therapy, runs it through the model to assess the outcome, and makes a therapeutic recommendation. If the outcome measured against the goal is favorable, the agent receives a "reward" which reinforces the specific approach. In contrast, if the outcome from the therapeutic recommendation does not come closer to achieving the pre-set goals of therapy, the agent does not receive a "reward" and alters the therapeutic recommendation.

what dose amounts, to achieve these goals. One advantage of this approach, especially in the case of complex diseases such as CKD-MBD, is the ability to discover new, previously unknown treatment strategies without exposing human subjects to unnecessary risk. In experiments using simulated subjects, achievement of the guideline goals of therapy occurred more rapidly using the Reinforcement Learning approach as opposed to a standard-of-care approach. The merger of an artificial intelligence approach (reinforcement learning) and a quantitative systems pharmacology (QSP) model of CKD-MBD creates a powerful tool. Although time-consuming to develop, the QSP model allows for extrapolation outside of the collected data that may exist in an electronic medical record. Substitution of the QSP model with another technique like an artificial neural network would significantly constrain the scope of the system, as the artificial neural network which is not capable of performing such extrapolations would likely respond to dose combinations at the edges of the data space with nonsensical results. Adding reinforcement learning allows rigorous probing of the entire data space to discover new unrecognized treatment approaches. Further, this approach is scalable when new biochemical markers are discovered, and new therapeutic agents are developed to target those markers.

The development of the comprehensive model that recapitulated the progression of CKD-MBD throughout the spectrum of CKD stages yielded additional interesting considerations. The model included changes in the levels of calcitriol (active vitamin D) and FGF23 with the progression of CKD, biochemical parameters that are not routinely measured. The model also included equations that described the movement of calcium and phosphorus in and out of bone and in and out of soft tissue. These features of CKD-MBD are not measurable but represent the processes that result in the clinically relevant outcomes including increased fracture risk and vascular disease. The model predicted changes in calcitriol and FGF23 at the onset of CKD, corresponding to published literature on the subject. More significantly, the model predicted that the loss of bone minerals and the increase in vascular calcification started at the earliest stages of CKD and accelerated throughout the course of CKD. The model also predicted that the application of the Reinforcement Learning agent to achieve the goals of CKD-MBD for calcium, phosphorus, and PTH resulted in improvement in calcitriol and FGF23 levels and a reduction in bone mineral loss that was superior to the results seen with the Supervised agent (i.e., standard of care).

The capabilities of this artificial intelligence approach combining the comprehensive model of CKD-MBD with Reinforcement Learning make it possible to examine different approaches to CKD-MBD through *in silico* clinical trials, targeting the relevant clinical outcomes of fracture, cardiomyopathy, and peripheral vascular disease. For example, instead of setting specific levels of calcium, phosphorus, and PTH as the goals of therapy, the goals can be minimization of bone mineral loss or minimization of vascular smooth muscle calcification. Setting these goals may yield vastly different recommendations for the use of the calcium-sensing receptor agonists or vitamin D. Additionally, the model has the flexibility to incorporate additional parameters. For example, the effects of sclerostin, activin A, and inflammatory markers can be incorporated into the model as additional mediators of CKD-MBD. Many currently available treatments such as the monoclonal antibodies directed against sclerostin (romosuzamab) used for osteoporosis or FGF23 (burosumab) used for genetic forms of rickets can be tested for their effects on the biochemical parameters, the mineralization abnormalities, and the cardiomyopathy of CKD-MBD *in silico*. The results from these simulations could then be used to inform the development of clinical trials. One additional advantage of the *in-silico* approach is that multiple interventions can be tested both simultaneously and singly very rapidly. It is quite difficult to develop clinical trials testing multiple interventions because of the

number of subjects needed to achieve adequate power and the difficulties in interpretation in the setting of multiple interventions. The application of this approach is expected to result in potentially paradigm-changing concepts of the pathogenesis as well as the treatment of CKD-MBD. For decades, the cornerstone of therapy of CKD-MBD has been the use of phosphate binders for limiting intestinal absorption. Yet a recent extensive review clarified that no trials have demonstrated a survival benefit with the use of any phosphate binder [94]. On the surface, this would suggest that phosphate binders have no role in the therapy of CKD. On the other hand, another study identified a link between phosphate control and a beneficial effect of statins in advanced CKD, suggesting that examining more complex patterns of disease development and therapy may yield better results [95]. This type of approach can be significantly facilitated by the application of AI.

5. Conclusion

Artificial intelligence techniques are powerful tools that hold the promise of revolutionizing the delivery of medical care. The complexity, profound clinical impact, and rapidly evolving understanding of CKD-MBD suggest that artificial intelligence could accelerate the development of newer effective therapies for this deadly disorder. Challenges remain. Refinement of the model to ensure the accurate and complete representation of all aspects of CKD-MBD is an ongoing project. Validation of the predictions and recommendations from this computational system will require human trials. Finally, provider and patient acceptance of a computer program contributing to medical care may not be immediate. Despite these challenges, the use of a variety of artificial intelligence applications in multiple clinical settings is increasing and is increasingly accepted. More to come.

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Chapter 13

Studies on Infectious Etiologies of Canine Chronic Renal Failure with Emphasis on Diagnostic Biomarkers

Kuljeet Singh Dhaliwal

Abstract

Ongoing renal disappointment results from a moderate and irreversible loss of working of nephrons, and the reason is frequently hard to determine. The reasons for renal disappointment can be intrinsic or extrinsic. Extrinsic incorporates cardiovascular sickness, over weight, diabetes, sepsis and respiratory and hepatic disappointment. Intrinsic causes incorporate glomerular nephritis, polycystic renal illness, renal fibrosis, tubular cell death and stones. Common aetiology identified As: Bacteria (*Lyme borelliosis*, urinary tract infection, *Leptospira*), Viruses (canine adenovirus), Hemoprotozoan and Rickettsia (*Leishmania infantum*, *Ehrlichia canis*, *Anaplasma platysine*, *Babesia canis vogeli*, *Hepatozoan canis*) or dietary (proteins rich in sulphur-containing amino acids). Serum biomarkers like SDMA, ADMA, NGAL and Cystatin-c are of much diagnostic aid, that even 25% of renal insult can be identified.

Keywords: canine, renal failure, biomarkers, early diagnosis, SDMA, NGAL

1. Introduction

Renal failure is the loss of ability of kidneys to excrete wastes, concentrate urine, conserve electrolytes and maintain fluid balance. It is of two types, acute renal failure (ARF) or acute kidney injury (AKI) and chronic renal failure (CRF) or chronic kidney disease (CKD) [1]. Renal failure is the major cause of death in young and older dogs. 15% prevalence for renal failure has been observed in dogs over 10 years of age and up to 31% in cats over 15 years of age [2].

Acute kidney injury (AKI) is characterised by sudden decrease in renal filtration resulting in high levels of serum creatinine, acute uraemia and decrease in the volume of urine. AKI affects humans, dogs and cats, which may result from one or more contributing causes and it may differ in severity [3]. Nephrotoxins and ischemia are the most common causes of renal diseases in dogs. Common nephrotoxicants are aminoglycosides, vitamin D, nonsteroidal anti-inflammatory drugs, lilies, raisins, grapes, etc. [4]. Ischemia usually occurs due to shock, dehydration, decreased cardiac output,

renal vasculature thrombosis and hypotension. Major infectious causes of acute renal failure are leptospirosis, ehrlichiosis, babesiosis and pyelonephritis [5].

Mild AKI generally goes unnoticed and generally recognised in advanced stages and is clinically characterised by anorexia, depression, oral ulceration, vomiting and/or diarrhoea, or oliguria. Chronic kidney disease (CKD) is due to loss of functional renal tissue due to a prolonged (≥2 months), usually progressive, process. CKD often smoulders for many months or years before it becomes clinically apparent, and it is invariably irreversible and frequently progressive. Because AKI may progress to a chronic condition, any cause of AKI is also a possible cause of CKD. CKD should be distinguished from the more readily reversible acute disease by history, physical examination and laboratory findings, although a renal biopsy may be required [6].

Chronic renal failure results from a progressive and irreversible loss of functioning of nephrons, and the cause is often difficult to determine. CRF in dogs is characterised by polyuria, polydipsia, anorexia, diarrhoea, weight loss, pallor mucous membrane, oral ulceration, halitosis, acute blindness, etc. CRF is caused by several risk factors including old age, diverse breeds, small body size, peridontal disease, obesity, etc. [7]. Kidney disease which is present for 3 months or longer can be regarded as chronic. The duration of CKD can be determined from medical records or can be assessed by physical examination or renal structural changes by imaging or renal pathology [2].

CKD is generally classified into 1 to 4 stages. Generally, no clinical signs are seen until ≥75% of nephron function has been impaired (Stages 3 and 4). In Stage 1, a process is damaging the kidneys but azotemia and clinical signs have not developed. In Stage 2, the disease has progressed, GFR has fallen to <25% of normal, and azotemia is present, but clinical signs are not yet seen but there may be impaired urine-concentrating ability and increased urine volume. In stage 3, GFR has declined further, azotemia is present, and clinical signs are often seen. In stage 4, there is severe azotemia with clinical signs. Usually, the earliest clinical signs in CKD are polydipsia and polyuria (late Stage 2 or early Stage 3). In Stages 1 and 2 of CKD, diagnosis is often missed or made incidentally. In Stages 3 and 4, the BUN, serum creatinine, and Pi are increased and K is generally decreased. However, hyperkalemia may be associated with oliguria and anuria. The urine specific gravity may range from 1.001 to 1.060 in dogs. In animals with dehydration and normal renal function, it should be >1.030. The inability to produce concentrated urine in dehydration is an early sign of CKD but concentrated urine is rarely seen when the serum creatinine is >4 mg/dL in an animal with azotemia of renal origin [6].

The complete history, physical examination, urinalysis, haematology, serum biochemistry, and nephrosonography provide a realistic way to diagnose CRF in dog. Early diagnosis, systematic approach to CRF diagnosis and therapeutic management can delay the progression of illnesses in dogs [2].

Serum creatinine is considered as the diagnostic tool for detecting renal failure but it has certain drawbacks such as low sensitivity and low specificity during early disease and is affected by muscle mass. Recently, novel serum and urine biomarkers have been reported which have been found to be more specific and sensitive indicators to diagnose both ARF and CKD in human and veterinary patients. These biomarkers can differentiate different processes such as glomerular damage, reduced GFR and tubular dysfunction that lead to renal disorders [8].

Some markers can be used in the detection of glomerular or tubular dysfunction earlier than conventional methods. An ideal biomarker should be specific, non-invasive, sensitive to allow early detection, specific of the extent/severity of disease, be suitable for monitoring progression, informative w.r.t. the localization of the injury and the clinical outcome, inexpensive and readily available from a reference

laboratory [9, 10]. Protein markers of tubular function damage and dysfunction e.g. retinol binding protein (RBP), neutrophil gelatinase-associated lipocalin (NGAL), Kidney Injury Molecule 1 (KIM-1) and enzymes can be markedly increased in the urine due to reduced tubular reabsorption [11].

For early detection and more specific and sensitive diagnostic capability in renal diseases, novel serum and urine biomarkers are being tested in both human and veterinary patients. An ideal biomarker is that which is specific for the detection of kidney disease (both AKI and CKD), sensitive for detecting early disease, non-invasive, low cost, able to monitor disease progression, reveal injury location and severity of disease and predict clinical outcome [8]. Asymmetric Dimethylarginine (ADMA) is an endogenously generated methylated arginine that has been associated with endothelial dysfunction and kidney damage. Symmetric Dimethylarginine (SDMA) concentration is highly correlated with inulin and creatinine clearance in man with CKD. Kidney Injury Molecule-1 (KIM) concentration is highly specific for detection of proximal tubular injury in kidneys and is used primarily to detect AKI. Cystatin C is freely filtered at the glomerulus and is absorbed and catabolised in proximal tubule cells with decreased tubular secretion [12].

2. Etiopathogenesis

The glomerulus is interposed inside the renal cortex, between an afferent and efferent arteriole, and is the source of water filtration and blood solutes. This filtrate travels through the space of Bowman, and is then significantly altered as it passes through the renal tubule. The functions of the different segments of the renal tubule are expressed in the epithelial cells which line the tubule's having functional and structural specialisations [13].

Major function of kidney is to maintain homeostasis of body i.e. regulation of electrolyte & acid-base balance, water balance, arterial blood pressure and excretion of metabolic wastes, hormone and exogenous compounds (e.g. drugs). It synthesises erythropoietin and active vitamin D. It helps in gluconeogenesis during fasting. The juxtaglomerular cell produces the hormone renin in response to reduced circulating volume to kidneys. The renin plays an important role in sodium, extracellular fluid volume, and blood pressure homeostasis [14].

The glomerular basement membrane serves as a filtration barrier between the bloodstream and tubular lumen of nephrons. Plasma flowing through glomerular capillaries is filtered into the Bowman's space. The glomerular filtration barrier allows all free proteins of molecular weight lower than approximately 30 kDa and radius lower than 20 Å [15]. Glucose and amino acids, such as cystine, ornithine, lysine and arginine are almost completely reabsorbed in the proximal tubule [16].

The mechanism responsible for acute increase in renal blood flow and GFR is responsible for continuous hyper filtration and accompanying renal hypertrophy due to long-term protein intake [17]. The renal cortex receives 90% of the renal blood flow and contains the large endothelial surface area of the glomerular capillaries which is susceptible to blood-borne toxicant exposure. In the renal cortex, the epithelial cells of proximal tubule and thick ascending loop of Henle are most affected by ischemic and toxicant-induced injury [18].

Chronic kidney disease (CKD) has been defined and classified in various ways over time, but current international guidelines define it as decreased kidney function manifested by the glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 sq.m [19].

The major pathophysiologic mechanisms contributing in CRF includes decreased renal perfusion pressure, decreased filtration coefficient, high intratubular pressure, acute tubular necrosis (ATN), interstitial nephritis and interstitial oedema [20]. ATN is caused by a variety of factors, including pre-renal azotemia, urinary tract obstruction, vasculitis, glomerulonephritis and acute interstitial nephritis, leading to acute renal failure. However, ischemic or toxic ATN is the leading cause of acute renal failure [21].

Deposition of amyloid (protein) in glomeruli, blood vessels and cortical tubules is the cause of proteinuria leading to chronic renal failure. Primary amyloidosis is associated with osteolytic multiple myeloma and the development of nodules in organs. Secondary amyloidosis is associated with persistent infections [22]. Chronic renal failure has been occasionally associated with hypercalcemia in dogs and cats. In patients with chronic renal failure, the combination of hyperphosphatemia, decreased renal calcitriol output, and decreased plasma ionised calcium concentrations promotes PTH secretion in an attempt to preserve normal calcium homeostasis [23]. Progression to chronic renal disease is linked to etiologies that cause glomerular hypertension, elevated systemic hypertension and chronic interstitial nephritis [24].

Proximal tubular cell reabsorbing proteins from the tubular fluid leads to the possibility that proteins or associated molecules adversely affect the biological status of the tubular cell leading to proteinuria [25]. Long continued proteinuria can lead to permanent structural changes in the nephron leading to impaired renal function. Erythropoietin is derived from peritubular interstitial cells in the renal cortex and the outer renal medulla in the kidneys. The lack of renal erythropoietin leads to anaemia in chronic interstitial nephritis [26]. Heiene *et al.* [27] studied renal histomorphology in dogs with Pyometra and long-term clinical outcome with respect to signs of renal disease and concluded that Pyometra is one of the causes of renal disorders in canines. Endotoxin generated in the uterus due to pathogenic bacteria reach the kidney via systemic circulation and cause interstitial inflammation and tubular atrophy leading to nephritis and renal failure.

Mishinam and Watanabe [28] concluded that the activation of the rennin angiotensin aldosterone system in chronic renal failure causes hypertension in dogs and attributed this to loss of functional nephrons. Grauer [29] stated that the pathophysiology of CKD could be regarded at both the organ and systemic levels. At the level of the kidneys, the main pathology of CKD was loss of nephrons and decreased glomerular filtration which leads to increased plasma concentration of substances that are normally cleared by renal excretion. Chew *et al.* [30] stated that intraglomerular hypertension and hyper filtration were compensatory mechanisms leading to the progression of CKD. Hyper filtration primarily results from increased glomerular ultrafiltration coefficient (Kf) and increased Trans glomerular capillary pressure. Proteinuria and glomerulosclerosis are consequences of this hyper-filtration [31].

CKD includes diseases of the macrovascular compartment (such as systemic hypertension, coagulopathy and chronic hypoperfusion), microvascular compartment (such as systemic and glomerular hypertension), interstitial compartment (such as pyelonephritis, neoplasia, obstructive uropathy, allergic and immune- nephritis) glomerulonephritis, developmental disorders, congenital collagen defects and amyloidosis [32]. Prostaglandins play a role in the kidney, such as control of renal blood flow, glomerular filtration, renin release and sodium excretion. NSAIDs interfer with prostaglandin production and lead to disease progression [33].

CKD aetiology is largely unknown as it is thought to be due to various causes including oxidative stress, inflammation, cardiac and endothelial dysfunction, metabolic disorders other than primary renal dysfunction [34].

The disease tends to progress in dogs with IRIS CKD Stages 3 and 4. The majority of dogs with this severe CKD will die or be euthanized as a result of their illness [35].

Dogs with IRIS CKD Stages 3 and 4 normally live for few months to a year or two, depending on the severity of their kidney disease, but with early diagnosis and thus successful treatment, survival periods may be significantly increased [36].

The presence or absence of kidney damage, urine output, hypertension and changes in GFR are all key factors determining the prognosis as well as course of the disease in dogs [37].

3. Prevalence

3.1 World wide

Sosnar *et al.* [38] studied 1099 cases admitted between 1990 and 2001 to the University of Veterinary and Pharmaceutical Science, Brno and recorded 139 cases (111 dogs & 28 cats) of renal failure with prevalence of 12.7%. O'Neill *et al.* [39] reported the apparent prevalence of chronic kidney disease of 0.21% and total prevalence of 0.37% in a merged clinical database of 107,214 dogs attended at 89 UK veterinary practices over a 2-year period (January 2010–December 2011).

3.2 Aetiology

Camacho *et al.* [40] reported 36% (21/58) dogs prevalence of azotemic with case fatality of 22% amongst UTI cases. Brown *et al.* [6] reported melamine and cyanuric acid pet food–associated renal failure affecting 16 animals in 2 different outbreaks. In a 5 year clinical study, Yhee *et al.* [41] reported prevalence of renal diseases such as glomerular disease (22.9%), tubulointerstitial disease (8.6%), neoplastic disease (8.6%), conditions secondary to urinary obstruction (24.3%) and other diseases (35.7%). Mshelbwala *et al.* [42] in a study between 2012 and 2015 reported 22.81% prevelance of glomerulonephritis. Out of these acute cases of glomerular and interstitial nephritis were mostly associated with leptospirosis (70%), colibacillosis (10%), other bacteria (15%) and unidentified causes (5%), whereas chronic cases were mostly associated with long standing cases of leptospirosis (70%), trypanosomosis (10%), babesiosis (10%) and unidentified causes (10%). Valentina *et al.* [43] reported 56% prevalence of Ochratoxin-toxicity in dogs leading to chronic renal failure.

4. Breed

Osborne *et al.* [44] documented congenital renal disease in more than 30 breeds of dogs such as German shepherd, Doberman, Great Dane, Lhasa apso and Boxer. Gabriel [45] recorded that Labradors were the most affected (46.42%) breed in renal failure, followed by German shepherd (32.14%), Spitz (14.28%), Cocker Spaniel (3.51%) and Saint Bernard (3.51%).

5. Age

Rubin [46] reported that CRF occurs in dogs and cats of all ages and is common disease in older animals as there was increase in incidence of CRF with age. The mean

age of CRF dogs was 7 years in dogs and it was 7.4 years age in cats. Paul *et al.* [47] concluded that the chronic kidney disease in dogs occurred at an average age of 9.9 years and 15 years in cats. Tarafder and Samad [48] in a case control study of 3670 sick pet dogs reported 48.12% prevalence of renal failure in age group above 36 months. Main causes were babesiosis (0.08%), sinusitis (0.08%), nephritis (0.19%), poisoning (0.33%), urinary tract infection (2.10%) and haematuria (2.34%).

Nabi et al. [49] observed higher prevalence of renal disease in dogs over ten years of age. Highest prevalence of 44.28 percent has been recorded in age range of 5–10 years followed by dogs older than 10 years (40.96%) and lowest prevalence in dogs aged 5 years (14.76%) [50].

6. Classification

6.1 IRIS staging of chronic kidney disease (CKD)

IRIS CKD staging is based on fasting blood creatinine concentration and blood SDMA concentration. SDMA is considered as more sensitive marker. The diagnosis of chronic kidney disease (CKD) is undertaken to promote adequate care and monitoring of canine or feline patients.

In stage 1, (non-azotemic) with normal blood creatinine (<125 µmol/l or < 1.4 mg/dl) or normal (<18 g/dl) or mild increase blood SDMA. Subsequently, increasing blood SDMA concentration (>14 µg/dl) may be used for early CKD diagnosis. The other renal abnormality must be checked such as decreased urinary concentrating ability without identifiable non-renal cause, abnormal renal palpation or renal imaging findings, proteinuria of renal origin, abnormal renal biopsy results or increasing blood creatinine or SDMA concentrations in preceding samples.

i. In stage 2, (mild renal azotemia) with normal or mildly elevated blood creatinine (125-150 µmol/l or 1.4–1.8 mg/dl) or mild elevated blood SDMA (18-35 g/dl). The clinical signs are usually mild or absent.

ii. In stage 3, with moderate renal azotemia and elevated blood creatinine (251-440 µmol/l or 2.9–5 mg/dl) or elevated blood SDMA (36–53 ug/dl). Many extra renal signs may be seen, but their extent and severity may vary. If signs are absent, the case could be considered as early Stage 3, while presence of marked systemic signs justifies classification as late Stage 3.

iii. The stage 4, by elevated blood creatinine (>440 µmol/l or > 5 mg/dl) or elevated blood SDMA (>54 µg/dl) with the increasing risk of systemic clinical signs and uremic conditions.

6.2 IRIS grading of UP:UC

The magnitude of protein loss in urine is interpreted by the quantity of protein excreted in urine in comparison to quantity of creatinine excreted in urine (UPC). The IRIS classification of proteinuria in CKD is divided in sub stages as proteinuric (UPC > 0.5), borderline (UPC 0.2–0.5) and non proteinuric (UPC <0.2). The proteinuric stage has worse prognosis with shorter survival time than other stages [51].

6.3 IRIS grading of blood pressure

The IRIS classification of systolic blood pressure (SBP) is based on the risk of future target organ damage i.e.: (i) Normotensive (<140 SBP) at minimal risk; (ii) Prehypertensive (140–159 SBP) at low risk; (iii) Hypertensive (160–179 SBP) at moderate risk; (iv) Severely hypertensive (>180 SBP) at high risk.

7. Aetiology

The cause of renal failure can be intrinsic or extrinsic. Extrinsic factors include cardiovascular disease, obesity, diabetes, sepsis and pulmonary & hepatic failure. Intrinsic causes include glomerular nephritis, polycystic renal disease, renal fibrosis, tubular cell death and stones [52].

Legatti *et al.* [3] reported 29.4% prevalence of infectious aetiology in ARF in dogs, which includes leptospirosis (43.6%), pyelonephritis (5.7%), pyometra (37.4%), sepsis (2.5%) and non-infectious aetiology (60.4%), which further included nephrotoxic (30.3%), obstructive (30.3%) and unknown aetiology (36.5%).

7.1 Bacteria

Dambach *et al.* [53] reported 18 positive cases of Lyme borelliosis in lyme endemic area leading to nephritis in dogs. Martinez *et al.* [54] reported 17 dogs with polypoid cystitis with clinical presentation of hematuria and recurrent urinary tract infection (UTI). Proteus species (23.1%) was the most common bacteria isolated on urine culture. Other isolated organisms were *Escherichia coli,* Staphylococcus and Enterococcus species. Hutton *et al.* [55] reported *Weissella viridescens, Shigella sonnei, Clostridium perfringens,* and *E. coli* in the renal tissue.

7.2 Leptospira

Urinalysis from dogs with leptospirosis is reported for isosthenuria and in rare cases hyposthenia while glycosuria and proteinuria were common observations [56]. Hepatic dysfunction along with azotemia characterised by increases in serum ALT, AST and ALKP and total bilirubin with electrolyte imbalance are indicative of suspicion of leptospirosis.

7.3 Viruses

Vright *et al.* [57] experimentally demonstrated proliferative glomerulonephritis with localization of IgG, C3 and viral antigen in mesangial in kidney after a trial of intravenous dose of canine adenovirus.

7.4 Hemoprotozoan and rickettsia

Poli *et al.* [58] in a prospective survey reported 413 dogs affected by naturally acquired *Leishmania infantum* infection out of which 34 dogs showed presence of glomerular lesions. Out of these, one group showed the mesangial-cell proliferation with focal features in 11 dogs and diffuse pattern in 10 dogs. The second group of 12 dogs

showed the typical findings of segmental membrano-proliferative glumeronephritis and one dog showed the amyloid deposits in the glomerular tuft and interstitial.

Chronic ehrlichiosis caused by *Ehrlichia canis* was suspected to be the cause of the dog's renal amyloidosis with development of proteinuria and renal failure, suggesting the presence of glomerulopathy [59]. Ferreira *et al.* [60] performed a comparative study between morphological and molecular tests for the diagnosis of *Anaplasma platys* infection in dogs in Brazil. The overall prevalence of *A. platysine* anaplasmosis in dogs was found to be 14.85% and 15.84% on basis of blood smear and PCR, respectively. Yabsley *et al.* [61] reported several tick-borne pathogens which were identified by serology and PCR. These included *E. canis* (24.7%), *A. platys* (19.2), *Babesia canis vogeli* (7%), *Hepatozoa canis* (7%) and *Bartonella sp*. (1.4%).

Tarafder and Samad [48] carried out a case control study to ascertain the prevalence of clinical diseases in 3670 sick pet dogs and reported 00.08% overall prevalence of babesiosis. Age-wise prevalence was higher in dogs above 36 months of age (00.05%) as compared to dogs between 7 to 36 months of age (00.03%). The haemogram showed mild anaemia and neutrophilic leucocytosis. Serum biochemical analysis showed a rise in ALP, ALT, globulin, BUN and creatinine and a reduction in total protein and albumin.

7.5 Urolithiasis

Urolithiasis is a frequent ailment that causes lower urinary tract disease in dogs and cats. The production of bladder stones is linked to the precipitation and crystallisation of a varied range of minerals like magnesium ammonium phosphate hexahydrate, calcium oxalate, urates, etc. Over the last 15 years, ureterolithiasis has emerged as a significant cause of acute and chronic renal illness in cats and dogs [62].

Calcium oxalate is the most prevalent component of upper urinary tract stones in dogs and cats with more than 90% of analysed nephrolith and urethrolith being CaO [63]. Because of a variety of anatomic factors, urethral blockage by uroliths is more common in male dogs than in female dogs. A smaller relative urethral diameter and longer urethral length, the curving path of the urethra around the ischium, and the existence of the os-penis, which limits urethral diameter expansion. Uroliths are most commonly found lodged at the ischial arch or immediately proximal to the os-penis in male dogs.

7.6 Neoplasms of urinary system

Transitional cell carcinoma (TCC) of the urinary bladder is one of the most prevalent neoplasms of the canine urinary system, accounting for 1.5–2.0 percent of all canine malignancies. TCC is typically an aggressive, and ultimately lethal cancer, with death due to post-renal blockage occurring within 3–12 months of diagnosis [64].

7.7 Fungal

Jin and Lin [65] retrospectively analysed 35 animals (23 dogs, 12 cats) affected by fungal urinary tract infections (UTIs) and identified 7 species of fungi in the affected animals. *Candida albicans* was the most common isolate. The common preceding diseases identified in affected animals were lower urinary tract diseases, diabetes mellitus, neoplasia and renal failure. Ahn *et al.* [66] reported renal failure related to ochratoxin A (OTA) and citrinin toxicity in 5 dogs referred to the Veterinary Medical Teaching Hospital at Kangwon National University with a common history of feeding pedigree dry dog food.

7.8 Role of diet

Dietary proteins of animal origin and proteins rich in sulphur-containing amino acids promote metabolic acidosis while vegetable proteins do not generally show this effect. Hence, marked restriction of dietary protein and decrease in phosphorus intake limits the renal ammoniagenesis [67].

Brown *et al.* [68] reported the supplementation with omega-6 polyunsaturated fatty acids (PUFA's) pace the decline of kidney function, and omega-3 polyunsaturated fatty acids (PUFA's) are Reno protective in nature.

The study on significance of clinical nutrition in geriatric dogs and cats suffering from chronic renal failure revealed that the renal diets used often have subtle protein, phosphorus and sodium content. The different dietary modifications such as subtle protein restriction, reduction in phosphorus and increase in the quantity of Omega 3 polyunsaturated fatty acids will aid in management and increasing the life span of the patient. The goal of nutritional treatment for dogs and cats affected by chronic renal disorders is to improve the quality and length of life, ensuring an adequate amount of energy and slow down the progression of renal failure [69]. Hyperkalaemia may be associated with commercial renal diets and it is a potential complication of CKD also. In CKD dogs, the formulated low potassium diets are effective for hyperkalaemia correction in renal failure.

8. Clinical signs

Mazzaferro *et al.* [70] reported oliguria or anuria and vomition after the ingestion of raisins or grapes in dogs. Jin and Lin [65] reported dysuria, haematuria, polyuria, anorexia, depression, and pyrexia as the most common clinical signs in dogs and cats affected with fungal urinary tract infections (UTI's). Grauer [29] stated that reduced erythropoietin production contributes to non-regenerative anaemia in CKD and decreased metabolism and excretion of parathyroid hormone and gastrin contributes to osteodystrophy and gastritis, respectively. Parathyroid gland hyperplasia and subsequent hyperparathyroidism may occur secondary to chronic renal failure in dog. Renal secondary hyperparathyroidism triggers changes in circulating levels of calcium, PTH, phosphorus and 1, 25-dihydroxycholecalciferol. The increased PTH level can have deleterious effects including soft tissue mineralisation, fibrous osteodystrophy, bone marrow suppression, urolithiasis and neuropathy.

Oburai *et al.* [7] noted anorexia, vomiting, weight loss, dullness, oral ulcers, polyuria/polydipsia, hypertension (SAP>150 mmHg), Malena, pallor mucous membrane, recumbency and blindness in 31 dogs suffering from chronic renal failure.

Sosnar et al. [38] stated that up to 67 percent loss of renal function, animal remains clinically asymptomatic and that with 67–75 percent loss of renal function there may polyuria and polydipsia and that loss of 75–95 percent of renal function would be manifested as vomiting, diarrhoea, apathy and when less than 10% of renal function is left, signs may be accompanied along with encephalopathy.

Grauer [31] claimed that acute renal failure in canines was accompanied with inflamed kidneys, hemconcentration, metabolic acidosis, increased urinary sedimentation, marked hyperkalemia and renal pathological.

Pugliese et al. [69] stated that severe polydipsia and polyuria occurs with a loss of 67–75 percent of the filtration rate, when renal failure further progress's (75–90%), the accumulation of blood nitrogen catabolic products determined the occurrence of

systemic signs such as anorexia, weight loss and specific signs such as vomiting and diarrhoea. When the residual renal function was found to be less than 10%, uremia was present along with neurological manifestations (uremic encephalopathy) indicating the terminal stage of illness. Other signs of deteriorating renal function include polyuria/polydipsia, dehydration, electrolyte imbalances, acidosis, anaemia, systemic hypertension and renal secondary hyperparathyroidism [2].

Klosterman et al. [71] reported that a history of prolonged anorexia, vomiting, diarrhoea, weight loss, or a combination of these factors, polyuria/polydipsia (PU/PD) and nocturia were more frequent in CRF. For whatever magnitude of azotemia, clinical symptoms were more severe in animals with ARF than in CRF. Emaciation, poor coat quality and mucous membrane pallor were more prevalent in CRF than in ARF.

9. Diagnosis

9.1 Haematological

Fiocchi *et al.* [72] reported different haematological parameters viz. PCV (20 ± 4.1%), MCV (67.8 ± 7.0 fL), MCHC (33.9 ± 1.6 g/dL), Absolute reticulocyte count ($20.7x10^6$/μL) and Platelet count ($440 \pm 242x10^3$/μL) in 33 dogs with renal disease. Torres *et al.* [73] reported normocytic normochromic anaemia in 84.1% of the dogs with CKD with no reduction in mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC), while other blood parameters declined.

Sumit *et al.* [74] in a study on 30 dogs with CKD observed lower mean values of haemoglobin (9.15 ± 0.67 g/dl), TEC ($4.47 \pm 0.30x10^6$/mm^3), PCV (29.22 ± 2.05%) and platelet counts ($196.23 \pm 18.31x10^3$/μL) in all affected dogs. The TLC and lymphocyte count are reportedly higher than reference values. Anaemia is a risk factor for mortality in CKD dogs. Anaemia is not only a consequence of CKD but also a risk to healthy patients to CKD progression and further to End Stage Renal Disease [75].

Erythropoietin is produced by the peritubular interstitial cells of the inner cortex and outer medullary cells of the kidney. As the kidney disease progresses, there are less erythropoietin-producing cells within the kidneys, hence anaemia is evident [76].

Dorgalaleh et al. [77] revealed RBC, Hb, HCT and MCHC levels were significantly lower in AKI affected patients along with anaemia and thrombocytopenia.

9.2 Biochemical parameters

In a study on renal failure due to Babesia infection, the azotemic dogs had showed significantly lower concentrations of total protein, albumin, β and γ globulins while significantly higher values of α-2 globulin. The azotemic dogs have comparatively higher concentrations of cholesterol and triglycerides which may be as a result of compensatory mechanism of liver to the loss of proteins [40].

CKD patients having hyperlipidaemia pathogenesis can represent significant risk factors for accelerated atherosclerosis. CKD has also been associated with insulin resistance and glucose uptake. Cortadellas *et al.* [78] reported that hyperphosphatemia leads to CKD progression. The detrimental effect of phosphorus retention leads to secondary renal hyperparathyroidism, which had adverse effects on bones, kidneys, brain, heart, pancreas, muscle tissue, lungs, erythrocytes, lymphocytes, adrenal glands and testicles. Phosphorus retention eased the formation of calcium

phosphorus (Ca-P) complexes that precipitated in the renal interstitial tissue and resulted in interstitial fibrosis and atrophy of the renal tubules, elevated urine protein to creatinine ratio (UP/UC ratio), increase excretion of ALP and GGT in urine, azotemia, hypercretenimia, hyperphosphatemia, hypernatremia with normal serum potassium and calcium level in renal failure dogs. Qurollo *et al.* [79] reported with IMHA, proteinuria, neutrophilia, abnormal lymphocytes and increased liver enzyme activity as common haemato-biochemical changes in renal failure dogs infected with *Ehrlichia sp.*

Adin and Cowgill [80] concluded that *Leptospira interrogans* in dogs often induces a hepatorenal syndrome defined by an acute onset of haemorrhagic diathesis, sub-acute icterus, or sub-acute uraemia followed by oliguria or anuria. Out of 37 dogs affected by leptospirosis, 17 of had neutrophilic leucocytosis.

Ross [81] stated that Na^+ retention is seen in animals with oliguric ARF, but urine Na^+ loss is higher in polyuric ARF. In renal failure, calcium levels are normally within range or slight lower, whereas phosphorus levels are generally on higher side as compared to CKD.

Cianciolo et al. [11] reported renal insufficiency in an English setter dog caused by ethylene glycol poisoning resulted in azotemia (BUN = 126 mg/dl and creatinine = 12 mg/dl) and marked hyperkalemic changes.

In the cases of renal failure caused by Babesiosis, azotemic dogs had significantly lower amounts of total proteins, albumin, beta and gamma globulins, but significantly higher quantities of alpha-2 globulin. As a result of the liver compensating for protein loss, azotemic dogs have comparatively higher serum cholesterol concentrations. Clinical findings in dogs with AKI includes increased BUN, Cr, hyperphosphatemia, hyper-or hypokalaemia and metabolic acidosis [82].

9.3 Serum renal biomarkers

Biomarkers are considered to be measurable indicators for normal or abnormal metabolic changes [8]. Commonly used biomarkers for renal insufficiency are SDMA, NGAL, Cystatin-C, RBP, Ig-G, UPC, etc., and are considered to be one of the efficient tools for early diagnosis of renal insult.

Creatinine is an indicator of renal function and is inversely correlated with GFR and its rise indicates 75% drop in GFR [83]. Almy *et al.* [84] reported the mean concentration of Cystatin C in healthy dogs and in dog's renal failure as 1.08 ± 0.16 mg/l and 4.37 ± 1.79 mg/l, respectively. Fliser *et al.* [85] reported that asymmetric dimethyl arginine (ADMA) is significantly associated with progression of nondiabetic kidney diseases. Lowering of plasma ADMA concentrations indicates response to therapeutic management of renal disease. Wehner *et al.* [86] reported high sensitivity and low specificity of Cystatin C as compared to creatinine for the diagnosis of renal failure in dogs. Serum cystatin C is better correlated than serum creatinine with exogenous plasma clearance of creatinine (ECPC), which is an indicator of GFR. Cobrin *et al.* [9] reported that the cystatin C was superior to creatinine in the assessment of GFR. The urinary biomarkers such as NGAL, KIM-1, IL-18 and NAG were diagnostic of AKI. Biomarkers such as cystatin C, RBP are good for assessing CKD. The biomarker RBP, the micro globulins and NAG A can detect the tubular dysfunction prior to proximal tubular injury. NGAL can detect ischaemic renal injury throughout the tubules and KIM-1 along with IL-18 can detect ischaemic AKI and acute tubular necrosis.

The definitive test to differentiate AKI from CKD is renal histopathology but despite that serum NGAL can differentiate AKI from CKD in dogs with renal

azotaemia with 65% sensitivity and 82% specificity [87]. Zhou *et al.* [88] reported high area under receiver operator characteristics (ROC) curve suggestive of high sensitivity of NGAL and clusterin for detection of gentamicin-induced renal proximal tubular toxicity. NAG is also recognised as potential biomarkers for the early detection of tissue injury in routine toxicity testing due to its high sensitivity.

Grauer [89] studied the assessment of serum NGAL levels in dogs with naturally occurring CKD and found as association between serum NGAL, creatinine and BUN, although NGAL was more related to creatinine. NGAL is reported as good diagnostic and prognostic marker for the diagnosis of stage III and IV CKD. SDMA being more sensitive than creatinine facilitates early diagnosis and treatment of CKD. Subsequent increase in SDMA above normal i.e. more than 14 μg/dL with isosthenuria and normal serum creatinine i.e. <1.4 mg/dl is an early indicator of impaired renal function.

Creatinine is regarded as the major biomarker in RIFLE renal failure staging. To determine AKI grades, a modified IRIS classification is used, which is based on serum creatinine, urine output and the need for renal replacement therapies [90].

Cystatin C permeates through glomerular pores and readily absorbed in proximal tubular cells, with negligible tubular secretion. Thus Cystatin C can be a promising marker for PCT injury [91].

Grauer [31] stated that SDMA is more sensitive than creatinine, aids in the early detection and thus treatment of renal illness. Increase in the levels of serum SDMA (more than 14 mcg/dL) with isosthenuric urine, normal renal echotexture and serum creatinine (more than 1.4 mg/dL) is an indication of kidney injury in dogs.

SDMA remains stable in healthy dogs, but rise with disease progression in sick dogs having renal impairment, associating substantially with an increase in serum creatinine and thus decrease in GFR values [92].

Kielstein et al. [93] indicated that ADMA and SDMA were specific markers of GFR and are good predictors of early renal failure compared to serum creatinine levels, and thus were considered promising biomarkers for the early identification of renal dysfunction in dogs.

NGAL is a potential biomarkers for the early detection of tissue injury associated with various toxicities due to its higher sensitivity in case of early renal injuries [88].

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Chapter 14

Evidence for Novel Pharmacotherapies in Diabetic Kidney Disease

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Abstract

Chronic kidney disease, defined as abnormal kidney function for more than 3 months, affects roughly 15% of the US, and approximately 40% of people with chronic kidney disease have type 2 diabetes. In the last decade, pharmacotherapies have been approved that may reduce chronic kidney disease progression and its complications. Sodium-glucose cotransporter-2 inhibitors (SGLT2Is) are recommended for diabetic kidney disease as they may reduce chronic kidney disease progression and cardiovascular events. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are recommended for those with diabetic kidney disease who have not achieved glycemic targets with metformin and SGLT2Is. Finerenone (a nonsteroidal mineralocorticoid receptor antagonist [MRA]) may reduce chronic kidney disease progression and cardiovascular events. This chapter will review the evidence for these pharmacotherapies for diabetic kidney disease.

Keywords: chronic kidney disease, diabetic kidney disease, SGLT-2 inhibitor, GLP-1 receptor agonist, mineralocorticoid receptor antagonist

1. Introduction

Chronic kidney disease (CKD) is defined as the presence of an abnormality in kidney structure or function persisting for more than 3 months [1]. This includes one or more of the following: (1) estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2; (2) urine albumin ≥30 mg per 24 h or urine albumin-to-creatinine ratio (UACR) ≥30 mg/g; (3) abnormalities in urine sediment, histology, or imaging suggestive of kidney damage; (4) renal tubular disorders; or (5) history of kidney transplantation [2]. Stages of CKD are based on UACR and eGFR and predict risk of progression to end-stage kidney disease (ESKD), defined as the requirement for renal replacement with chronic dialysis or kidney transplantation.

The prevalence of CKD in people with diabetes is approximately 20%, while it is 10% in those with prediabetes [1]. Because it is the leading cause of CKD, optimal screening and treatment of diabetes is essential in preventing CKD progression. This includes screening for proteinuria, optimizing glucose levels, and reducing cardiovascular morbidity and mortality [3].

Pharmacotherapy is a mainstay in the treatment of CKD for controlling blood pressure, glucose levels, and preventing CKD progression. Angiotensin converting

enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) demonstrated benefit for diabetic nephropathy decades ago. In 1993, The Collaborative Study Group Captopril Trial showed that in participants with insulin-dependent diabetes and proteinuria, captopril reduced the risk of serum creatinine doubling by 48%, and the composite risk of death, dialysis, and transplantation by 50% [4]. In 2001, The Irbesartan Diabetic Nephropathy Trial (IDNT) showed that irbesartan reduced disease progression in participants with diabetic nephropathy (32.6% vs. 39.0%; RR 0.8; p = 0.02), independent of its antihypertensive effects [5]. In 2001, The Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that losartan reduced progression to ESKD (19.6% vs. 25.5%; relative risk (RR) 0.72; p = 0.002) and serum creatinine doubling (21.6% vs. 26.0%; RR 0.75; p = 0.006) in participants with diabetic nephropathy [5].

Aside from ACEI/ARBs for CKD treatment, novel pharmacotherapies include sodium-glucose cotransporter-2 inhibitors (SGLT2Is), glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and finerenone. SGLT2Is are recommended for diabetic kidney disease to prevent CKD progression and cardiovascular events [6]. GLP-1 RAs are recommended for those with diabetic kidney disease who have not achieved glycemic targets with metformin and SGLT2Is [7]. Finerenone (a nonsteroidal mineralocorticoid receptor antagonist [MRA]) has been shown to reduce CKD progression and cardiovascular events [8].

2. Evidence

2.1 Sodium-glucose Cotransporter-2 Inhibitors

SGLT2Is reduce renal tubular glucose reabsorption, lowering blood glucose without stimulating insulin release. Several trials (CANVAS, CREDENCE, DAPA-CKD) have shown that SGLT2Is may reduce CKD progression (**Table 1**). The proposed mechanisms are: (1) reduction of glomerular hyperfiltration via increased delivery of sodium to the macula densa and afferent arteriolar constriction, which lowers intraglomerular pressure and reduces albuminuria, (2) reduction of tubular workload due to decreased SGLT2 co-transporter activity, and (3) reduced renal inflammation due to reduced albuminuria, tubular cell glucose, and induction of inflammatory cytokines and fibrotic mediators [9].

2.1.1 CANVAS

The CANagliflozin cardioVascular Assessment Study (CANVAS) involved two multicenter, randomized, placebo-controlled trials with 10,142 participants in 30 countries [10]. It was an intention-to-treat analysis that enrolled participants from 2009 to 2013 and followed participants for a median of 126 weeks, and it included those with type 2 diabetes with hemoglobin A1C (HbA1C) between 7% and 10.5% not currently on antihyperglycemic therapy. Progression of albuminuria, defined as >30% increase in UACR, and progression of CKD, defined as >40% reduction in eGFR, were lower in the canagliflozin group (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.67–0.79; and HR 0.60; 95% CI 0.47–0.77, respectively). Canagliflozin lowered the primary cardiovascular outcome, which included cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke (HR 0.86, 95% CI 0.75–0.97) [10]. Significant adverse events included: risk of amputation, genital infections, and osmotic diuresis.

	CANVAS	CREDENCE	DAPA-CKD
Study Design	Double-blind RCT	Double-blind RCT	Double-blind RCT
Participants	10,142	4401	4304
Inclusion Criteria	DM2, high CV risk	DM2, albuminuria	CKD, albuminuria, with or without DM2
Exclusion Criteria	DM1, DKA history	DM1, dialysis, transplant, non-DM kidney disease	DM1, PCKD, lupus nephritis, vasculitis, transplant history
Baseline Therapy	Antihyperglycemic agents or no therapy	ACEI/ARB therapy	Maximum ACEI/ARB therapy
Intervention	Canagliflozin (300 mg daily vs.100 mg daily) vs. placebo	Canagliflozin (100 mg daily) vs. placebo	Dapagliflozin (10 mg daily) vs. placebo
Outcomes	CV mortality, nonfatal MI, or nonfatal stroke: 26.9 vs. 31.5 participants per 1000 pt-yrs; HR 0.86; 95% CI 0.75–0.97	ESKD, Cr doubling, or renal/CV mortality: 43.2 vs. 61.2 events per 1000 pt-yrs; HR 0.70; 95% CI 0.59–0.82	Reduction in eGFR >50%, new ESKD, or renal/CV mortality: 9.2% vs. 14.5%; HR 0.61; 95% CI 0.51–0.72
	Albuminuria increase >30%: 89.4 vs. 128.7 participants per 1000 pt-yrs; HR 0.73; 95% CI 0.67–0.79	Cr doubling: 20.7 vs. 33.8 events per 1000 pt-yrs; HR 0.60; 95% CI 0.48–0.76	Reduction in eGFR >50%: 5.2% vs. 9.3%; HR 0–53; 95% CI 0.42–0.67
	Reduction in eGFR>40%, renal replacement or renal death: 5.5 vs. 9.0 participants per 1000 pt-yrs; HR 0.60; 95% CI 0.47–0.77	ESKD: 20.4 vs. 29.4 events per 1000 pt-yrs; HR 0.68; 95% CI 0.54–0.86	New ESKD: 5.1% vs. 7.5%; HR 0.64; 95% CI 0.50–0.82
Adverse Events	Mycotic genital infection, amputation risk (both higher in canagliflozin group)	Mycotic genital infection, DKA (higher in canagliflozin group).	Volume depletion (higher in dapagliflozin group)
Limitations	Few patients with baseline CKD	Statin use not controlled	Trial stopped early due to benefits; underpowering of less common endpoints

Abbreviations: SGLT2Is—sodium-glucose cotransporter-2 inhibitors; CANVAS—CANagliflozin cardioVascular Assessment Study; CREDENCE—Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD—Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; RCT—randomized controlled trial; DM2—type 2 diabetes mellitus; CV—cardiovascular; CKD—chronic kidney disease; DKA—diabetic ketoacidosis; DM1—type 1 diabetes mellitus; PCKD—polycystic kidney disease; ACEI—angiotensin converting enzyme inhibitor; ARB—angiotensin receptor blocker; mg—milligrams; MI—myocardial infarction; pt-yrs—patient-years; HR—hazard ratio; CI—confidence interval; eGFR—estimated glomerular filtration rate; ESKD—end-stage kidney disease; Cr—creatinine.

Table 1.
Clinical trials involving SGLT2Is.

CANVAS has been criticized for having too few participants with baseline CKD, and so these results may not be generalizable to the population with CKD. Overall, these were novel results because previous medications such as insulin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors had not been associated with improvements in cardiovascular outcomes or survival. This study was the first to show that SLGT2Is may reduce kidney disease progression.

2.1.2 CREDENCE

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was a prospective, double-blind randomized controlled trial with 4401 participants across 690 sites in 34 countries [11]. It was an intention-to-treat analysis that enrolled participants from 2014 to 2017, and followed them for a median of 2.6 years. The study included 4401 participants with type 2 diabetes (HbA1C 6.5–12.0%) and CKD stage G2-G3/A3 (baseline eGFR 30 to <90 mL/min/1.73m^2 and UACR>300 to 5000 mg/24 h) taking ACEI or ARB therapy. Those randomized to canagliflozin had a lower risk of developing the primary composite kidney outcome of doubling of serum creatinine, ESKD, or death from a kidney or cardiovascular cause, compared with those randomized to placebo (HR 0.70; 95% CI 0.59–0.82; $p < 0.01$). Significant adverse events included genital mycotic infection and diabetic ketoacidosis. A criticism of this study was that statin use was not universal in this trial and could have confounding effects since statins have been shown to prevent cardiovascular events [12].

2.1.3 DAPA-CKD

The Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial was a multicenter, double-blind, randomized placebo controlled trial with 4304 participants enrolled from 2017 to 2018 in 450 sites from 20 countries [13]. It was an intention-to-treat analysis with a mean follow-up of 2.4 years. Participants had eGFR between 25 and 75 mL/min/1.73 m^2, UACR between 200 and 5000 mg/g, and were already on maximum ACEI/ARB therapy. This study found reduced primary outcome of eGFR decline >50%, new ESKD, or kidney or CVD mortality in the dapagliflozin group (9.2% vs. 14.5%, HR 0.61, 95% CI 0.51–0.72). A subgroup analysis revealed that in participants without diabetes, dapagliflozin reduced the primary outcome (HR 0.50; CI 0.35–0.72).

2.1.4 EMPA-KIDNEY

The EMPAgliflozin Once Daily to Assess Cardiorenal Outcome in Patients with Chronic KIDNEY Disease (EMPA-KIDNEY) trial was designed to investigate the effect of empagliflozin on kidney outcomes and cardiovascular death in people with CKD [14]. It began in 2019 and is estimated to be completed near the end of 2022. This trial will shed light on whether SGLT2Is benefit people with proteinuria regardless of diabetes status.

2.2 Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) stimulate glucose-dependent insulin secretion. They are thought of as a "satiety peptide" that promotes release of insulin when glucose is elevated, while also decreasing prandial glucagon and delaying gastric emptying. GLP-1 RAs have the added benefit of promoting weight loss. Because they have shown to improve cardiovascular outcomes in the LEADER and REWIND trials among others, the American Diabetes Association (ADA) recommends GLP-1 RAs in people with type 2 diabetes with cardiovascular disease (**Table 2**) [7]. However, in a meta-analysis, GLP-1 RAs did not significantly decrease the risk of kidney events (RR 0.86 [0.72–1.03]) [15]. There has not been substantial evidence to date that GLP-1

	LEADER	REWIND
Study design	Double-blind RCT	Double-blind RCT
Participants	9340	9901
Inclusion Criteria	DM2	DM2, CV risk factors
Exclusion Criteria	DM1, previous use of GLP-1 RA, ESKD, prior transplant	eGFR<15 ml/min/1.73 m^2, life expectancy<1 yr, severe hypoglycemia in previous yr
Baseline Therapy	Antihyperglycemic agents or no therapy	Antihyperglycemic agents or no therapy
Intervention	Liraglutide (1.8 mg daily) vs. placebo	Dulaglutide (1.5 mg daily) vs. placebo
Outcomes	Nonfatal MI, nonfatal stroke, or CV mortality: 13.0% vs. 14.9%; HR 0.87; 95% CI 0.78–0.97	Nonfatal MI, nonfatal stroke, or CV mortality: 12.0% vs. 13.4%; HR 0.88; 95% CI 0.79–0.99
	All-cause mortality: 8.3% vs. 9.6%; HR 0.78; 95% CI 0.74–0.97	New albuminuria>300 mg/g, reduction in eGFR>30%, or need for renal replacement: 17.1% vs. 19.6%; HR 0.85; 95% CI 0.77–0.93
	New or persistent albuminuria, Cr doubling, CRRT need, or renal death: 5.7% vs. 7.2%; HR 0.78; 95% CI 0.67–0.92	
Adverse Events	Severe hypoglycemia (higher in placebo group), acute gallstone disease (higher in liraglutide group)	GI adverse events (higher in dulaglutide group)
Limitations	Unequal statin use between groups	>25% participants were not taking study drug at last visit

Abbreviations: GLP-1 RAs—Glucagon-like peptide-1 receptor agonists; LEADER—Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; REWIND—Researching Cardiovascular Outcomes with a Weekly Incretin in Diabetes; RCT—randomized controlled trial; DM2—type 2 diabetes mellitus; CV—cardiovascular; DM1—type 1 diabetes mellitus; ESKD—end-stage kidney disease; eGFR—estimated glomerular filtration rate; yr.—year; mg—milligrams; MI—myocardial infarction; HR—hazard ratio; CI—confidence interval; Cr—creatinine; CRRT—continuous renal replacement therapy; mg/g—milligrams per gram; GI—gastrointestinal.

Table 2.
Clinical trials involving GLP-1 RAs.

agonists slow CKD progression, as there has not been a published GLP-1 RA trial with primary endpoint of kidney events. Existing data on kidney outcomes have been provided by cardiovascular outcomes trials.

2.2.1 LEADER

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, liraglutide was found to reduce cardiovascular events compared to placebo in participants with diabetes at risk for cardiovascular disease [16]. This study was a multicenter, randomized, controlled trial that evaluated 9340 participants with type 2 diabetes at 410 sites in 32 countries. Participants had diabetes and cardiovascular diseases, including peripheral vascular disease, CKD, symptomatic congestive heart failure, or hypertension with left ventricular hypertrophy, among others. This intention-to-treat analysis enrolled participants from 2010 to 2012 and followed them up for a median of 3.8 years. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality.

Those who received liraglutide had a lower primary outcome compared to placebo (13.0% vs. 14.9%, HR 0.87, 95% CI 0.78–0.97). Those in the liraglutide group also had lower all-cause mortality (8.2% vs. 9.6%, HR 0.78, 95% CI 0.74–0.97, p = 0.02), and a lower rate of the kidney composite endpoint of new or persistent UACR>300 mg/g, doubling of serum creatinine and eGFR<45 ml/min/1.73m^2, need for continuous renal replacement therapy, or death due to kidney disease (5.7% vs. 7.2%, HR 0.78, 95% CI 0.67–0.92, p = 0.003).

2.2.2 REWIND

The Researching Cardiovascular Outcomes with a Weekly Incretin in Diabetes (REWIND) trial was a multicenter randomized, double-blind controlled trial spanning 371 sites in 24 countries [17, 18]. It examined participants with type 2 diabetes, cardiovascular risk factors, and eGFR>15. The primary composite outcome included non-fatal MI, non-fatal stroke, or death from cardiovascular causes. Compared to placebo, those in the dulaglutide group had fewer primary outcome events (12.0% vs. 13.4%, HR 0.88, 95% CI 0.79–0.99; p = 0.026). However, all-cause mortality was not significantly different between the groups (10.8% vs. 12.0%, HR 0.90, 95% CI 0.80–1.01; p = 0.067).

The kidney outcome evaluated was a composite of new albuminuria>300 mg/g, decline in eGFR 30% or more from baseline, or need for renal replacement therapy. Fewer in the dulaglutide group exhibited the composite kidney outcome (17.1% vs. 19.6%; HR 0.85; 95% CI 0.77–0.93; p = 0.0004). The most prominent effect was reduction of albuminuria (HR 0.77; 95% CI 0.68–0.87; p < 0.0001).

2.2.3 FLOW

The Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial was the first kidney outcome trial involving GLP-1 RAs, and it sought to determine the effects of semaglutide on kidney outcomes in people with type 2 diabetes [19, 20]. It began in 2019 and is estimated to be completed in 2024.

2.3 Finerenone

Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist. It has been studied recently in two trials (FIDELIO-DKD and FIGARO-DKD) to determine its effect on cardiovascular and kidney outcomes (**Table 3**). Its proposed mechanism is through decreased mineralocorticoid receptor activation, and subsequent reduction in inflammation, fibrosis, and reactive oxygen species [21].

2.3.1 FIDELIO-DKD

The FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) trial was a double-blinded randomized trial that showed in participants with CKD and type 2 diabetes, finerenone may lower risk of CKD progression and cardiovascular events [22]. The primary outcome was a composite of a sustained decrease of >40% in eGFR from baseline over a period of >4 weeks, or death from kidney causes. The secondary outcome event was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The primary and secondary outcomes

	FIDELIO-DKD	FIGARO-DKD
Study Design	Double-blind RCT	Double-blind RCT
Participants	5734	7437
Inclusion Criteria	DM2, CKD	DM2, CKD, albuminuria
Exclusion Criteria	Non-diabetic kidney disease, already on MRA, kidney transplant	Symptomatic chronic HFrEF, non-diabetic kidney disease, already on MRA, UACR>5000 mg/g
Baseline Therapy	Maximum ACEI/ARB therapy	Maximum ACEI/ARB therapy
Intervention	Finerenone (20 mg daily) vs. placebo	Finerenone (20 mg daily) vs. placebo
Outcomes	Reduction in eGFR > 40%, kidney failure, or death from kidney causes: 17.8 vs. 21.1%; HR 0.82; 95% CI 0.73–0.93	CV death, nonfatal MI, nonfatal stroke, or heart failure hospitalization: 12.4% vs. 14.2%; HR 0.87; 95% CI 0.76–0.98
	CV death, nonfatal myocardial infarction, nonfatal stroke, or heart failure hospitalization: 13.0% vs. 14.8%; HR 0.86; 95% CI 0.75–0.99	Reduction in eGFR>40%, kidney failure, or death from kidney causes: 9.5% vs. 10.8%; HR 0.87; 95% CI 0.76–1.01
Adverse Events	Hyperkalemia (higher in finerenone group)	Hyperkalemia (higher in finerenone group)
Limitations	Most patients had advanced CKD; only 4.7% Black patients	Only 3.5% Black patients

Abbreviations: FIDELIO-DKD—FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; FIGARO-DKD—Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; RCT—randomized controlled trial; DM2—type 2 diabetes mellitus; CKD—chronic kidney disease; MRA—mineralocorticoid receptor antagonist; HFrEF—heart failure with reduced ejection fraction; UACR—urine albumin-creatinine ratio; mg/g—milligrams per gram; ACEI—angiotensin converting enzyme inhibitor; ARB—angiotensin receptor blocker; mg—milligrams; eGFR—estimated glomerular filtration rate; HR—hazard ratio; CI—confidence interval; CV—cardiovascular; MI—myocardial infarction; CKD—chronic kidney disease.

Table 3.
Clinical trials involving Finerenone.

occurred less in the finerenone group (17.8% vs. 21.1%; HR 0.82; 95% CI 0.73–0.93 for the primary outcome; 13.0% vs. 14.8%; HR 0.86; 95% CI 0.75–0.99 for the secondary outcome). Hyperkalemia-related trial discontinuation was higher in the finerenone group vs. placebo (2.3% and 0.9%, respectively).

Finerenone may also reduce new-onset atrial fibrillation/flutter in people with CKD and type 2 diabetes [23]. In this study, new onset atrial fibrillation was lower in the finerenone group compared to placebo (3.2% vs. 4.5%, p = 0.016).

2.3.2 FIGARO-DKD

The Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) trial was a double-blind randomized trial that finerenone may reduce new onset heart failure and heart failure hospitalization rate among people with CKD and type 2 diabetes [8]. In this study of 7437 participants, 3686 were given finerenone, while there were 3666 in the placebo group. The primary outcome was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, or heart failure hospitalization. This primary outcome event occurred in 12.4% in the finerenone group, and in 14.2% of the placebo group (HR 0.87; 95% CI 0.76–0.98).

Most of the benefit of finerenone was found to be from heart failure hospitalization (HR 0.71). The secondary outcome was a composite of kidney failure, defined as a sustained decrease in eGFR from baseline of at least 40%, or death from kidney causes. This event occurred in 9.5% of the finerenone group and 10.8% of the placebo group (HR 0.87; 95% CI 0.76–1.01). Of note, hyperkalemia-related discontinuation of the trial regimen was higher in the finerenone group (1.2% vs. 0.4%).

3. Discussion

3.1 Summary of kidney outcomes

In people with type 2 diabetes, canagliflozin may reduce albuminuria progression, and the composite outcome of doubling of serum creatinine, ESKD, or kidney or cardiovascular mortality [10, 11]. In people with CKD, dapagliflozin may reduce the composite outcome of eGFR decline >50%, new ESKD, or kidney or CVD mortality, independent of diabetes status [13]. In people with diabetes at risk for cardiovascular disease, liraglutide may reduce all-cause mortality, and the composite outcome of new or persistent albuminuria, doubling of serum creatinine and eGFR<45 ml/min/1.73 m^2, need for continuous renal replacement therapy, or death due to kidney disease [16]. In people with diabetes and cardiovascular risk factors, dulaglutide may reduce the composite outcome of new albuminuria > 300 mg/g, decline in eGFR 30% or more from baseline, or need for renal replacement therapy [18]. In people with CKD and type 2 diabetes, finerenone may lower the composite outcome of sustained decrease of at least 40% in the eGFR, or death from kidney causes [8, 22].

3.2 Comparison of newer therapies to established therapies

It is important to note that the reduction in kidney events was higher in general for ACEI/ARBs compared to SGLT2Is or finerenone, although these therapies have not been directly compared [5, 10, 11, 22]. In the SGLT2I and finerenone trials, participants were also on ACEI/ARB therapies. Thus ACEI/ARB are still first line for treatment of kidney disease with albuminuria. Studies have not compared SGLT2Is to finerenone. The effects of combined SGLT2I and finerenone therapy on kidney outcomes are unknown. Both SGLT2Is and finerenone cause adverse events, which must also be considered along with their benefits [24].

3.3 Approach to therapy along the continuum of diabetic kidney disease

All people with CKD should follow lifestyle modifications (increased exercise, low sodium diet, protein restriction, and reduced dietary acid loads) to manage blood pressure and glucose levels, and to reduce cardiovascular risk (**Figure 1**).

ACEI/ARB therapy is recommended for treatment in people with CKD (diabetic or non-diabetic), with urine albumin excretion>30 mg/day. They can also be used as initial pharmacotherapy to treat hypertension. These medications should be held in the setting of acute kidney injury and should be discontinued if associated with hyperkalemia that cannot be controlled with dietary restriction or potassium binders [24].

SGLT2Is should be initiated in people with type 2 diabetes and CKD with eGFR≥30 mL/min/1.73 m^2. They have not been studied in people with eGFR <30 ml/min/1.73 m^2, thus they should not be initiated in people with CKD stages 4–5. Studies

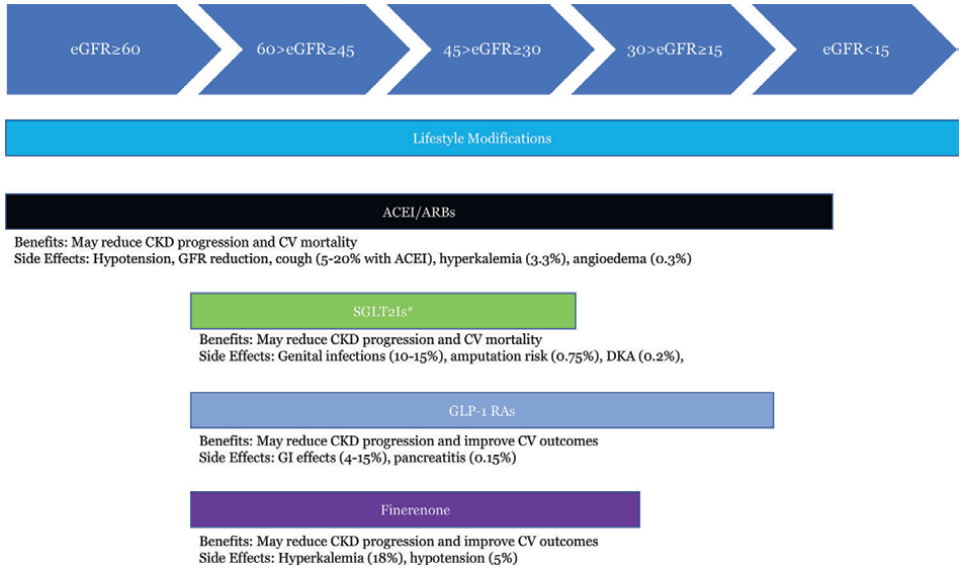

Figure 1.
*DKD treatment continuum. This illustrates therapeutic approaches that may reduce DKD progression, and the associated eGFRs for which they have been studied. Listed underneath each drug class are the benefits and side effects. Abbreviations: DKD—diabetic kidney disease; eGFR—estimated glomerular filtration rate; CKD—chronic kidney disease; ACEI—angiotensin converting enzyme inhibitor; ARB—angiotensin receptor blocker; CV—cardiovascular; GFR—glomerular filtration rate; SGLT2Is—sodium-glucose cotransporter-2 inhibitors; DKA—diabetic ketoacidosis; GLP-1 RAs—glucagon-like peptide-1 receptor agonists; GI—gastrointestinal. *SGLT2Is may be continued for eGFR < 30 mL/min/1.73 m^2 given that they were initiated when eGFR > 30 mL/min/1.73 m^2, and they may be continued until a person is on dialysis.*

have shown that if they are started when eGFR is above 30 mL/min/1.73 m^2, they can be continued until the individual is on dialysis and then stopped [25, 26]. However, they likely have benefit in people with eGFR<30 mL/min/1.73 m^2 based on a pooled analysis of phase 3 randomized controlled trials [27]. Dapagliflozin may benefit people who have albuminuria who do not have diabetes [13]. The DAPA-CKD study excluded patients with type 1 diabetes and specific kidney conditions including polycystic kidney disease, lupus nephritis, vasculitis, and history of organ transplantation [13]. Therefore, outcomes of SGLT2Is in these specific populations are unknown. SGLT2Is should be used with caution in people with a prior lower extremity amputation or threat of amputation. Adverse effects include polyuria, hyperkalemia, a higher risk for genital mycotic infections, diabetic ketoacidosis, bony fractures, and the need for lower limb amputations.

GLP-1 RAs may be used in people with type 2 diabetes and diabetic kidney disease, after metformin and SGLT2Is have not shown improved glycemic control. Studies have shown that liraglutide and dulaglutide improved kidney outcomes, although most of the trials involving GLP-agonists focused on improved cardiovascular outcomes as the primary endpoint. In REWIND, dulaglutide was studied in people with eGFR>15 mL/min/1.73 m^2, thus it may be used for Stage 4 CKD. Adverse effects include diarrhea, nausea, headache, and hypoglycemia.

Finerenone may be used in people with type 2 diabetes and diabetic kidney disease, with eGFR≥25 mL/min/1.73 m^2. It has not been studied among people with eGFR<25 mL/min/1.73 m^2. The risk of hyperkalemia may be higher among people on concurrent finerenone and ACEI/ARB therapy [28]. Caution is advised among people

with hepatic impairment and those taking strong CYP3A4 inhibitors, because finerenone is a sensitive CPY3A4 substrate and its effects may be increased through CYP3A4 inhibition [29].

3.4 Approaches to develop therapeutics for CKD progression

The rising global burden of CKD requires comprehensive educational campaigns, screening for early CKD, and novel therapeutics to mitigate progression to ESKD and the need for dialysis [30]. Coordination between scientists, policymakers, physicians, pharmaceutical companies, insurance companies, governments, and other key players is paramount in advancing therapies from bench to bedside. The relationship between CVD and CKD is complex—it is known that CVD is a common complication in people with CKD, yet there are limited evidence and therapies to prevent CVD in people with CKD [31]. Blood pressure control, statin use, and renin-angiotensin-aldosterone axis blockade have improved cardiovascular outcomes, however excess mortality remains in people with CKD compared with the general population [3]. There is also an increasing incidence of CKD resulting from unknown causes in certain "hotspots" that exacerbates this problem [32].

Pollock et al. outlined four major goals towards establishing and validating novel therapeutic targets to reduce CKD progression [33]. The first goal is to improve identification of therapeutic targets. This requires use of biomarkers, –omics data, and cross-disciplinary research to identify pathophysiologic mechanisms. For example, what we learn about the physiological mechanism of kidney fibrosis may be useful in informing drug mechanistic approaches to prevent fibrosis leading to CKD. Acute kidney injury (AKI) is associated with CKD development, and understanding the multifactorial relationship between the two is crucial [34].

The second goal is to enhance preclinical and early clinical development. This requires improving clinical networks for CKD populations to facilitate trial recruitment, developing infrastructure to study human tissue to better understand CKD progression, improving collaboration between academic research scientists and the biotechnology company researchers, and rewarding academic career development when involved with industry to develop therapeutics.

The third goal is to increase availability of novel therapeutic approaches. This entails evaluating opportunities for repurposing drugs to find treatments for CKD and its complications, as well as improving access to costly drugs and biologics in low- and middle-income countries.

The fourth goal—encouraging investment in CKD therapeutics—is crucial to the overall global mission to reduce CKD progression. This includes marketing economic opportunity and developing business cases, lobbying for funding from governments and industry, and documenting differences in CKD treatment practice patterns and the therapeutic needs of different countries. Therapeutics in development for CKD include those mentioned in this article as well as drugs that reduce inflammation and mitigate oxidative injury [35].

4. Conclusion

ACEI/ARBs have been the mainstay for preventing CKD progression for the last several decades [36]. SGLT2Is and finerenone are newer therapies that may prevent disease progression in those with diabetic kidney disease, while GLP-1 RAs are useful

in preventing cardiovascular disease in those with diabetes and cardiovascular risk factors. GLP-1 RAs have shown promise in preventing kidney outcomes through primary cardiovascular outcomes trials, but they have not directly been tested for kidney outcomes as a primary endpoint.

As the global burden of CKD rises, it is essential to improve the therapeutic development process from all perspectives, including academic research and industry. The scientific process of advancing basic and clinical biological research to identify therapeutic targets is just as critical as creating avenues for investment in CKD research, global collaboration in implementing clinical trials and information sharing, and improving access to costly drugs. To arrive at a comprehensive solution for CKD, many more advances in the basic science and genetics of kidney disease are essential. The increasing need to serve people with CKD will hopefully engender an era of evidence-based therapeutics that will revolutionize CKD care such that reaching ESKD will be a rarity.

Conflicts of interest and sources of funding

No conflicts of interest or funding sources are reported.

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Chapter 15

Renal Involvement in Glycogen Storage Diseases

Amel Ben Chehida, Mohamed Slim Abdelmoula and Neji Tebib

Abstract

Glycogen storage diseases (GSDs) are genetic diseases affecting the synthesis, degradation, or utilization of glycogen. Many GSDs comprise renal features: GSD Type I can be complicated by tubular anomalies, renal lithiasis, and chronic kidney disease similar to that of diabetes. Fanconi-Bickel syndrome (FBS) is characterized by hypophosphatemic rickets and a particular tubular dysfunction (Fanconi syndrome), the most constant element of which is glucosuria. Besides, Tarui disease (GSD-VII) and McArdle disease (GSD-V) may be present at the onset in the second decade as an acute renal failure (ARF) secondary to acute rhabdomyolysis or myoglobinuria. These particularities will be described here in more detail.

Keywords: kidney diseases, glycogen storage disease, inherited metabolic diseases, urolithiasis, angiotensin-converting enzyme inhibitors, Fanconi syndrome, microalbuminuria, proteinuria, renal failure, rhabdomyolysis

1. Introduction

Kidneys play three key roles in glucose homeostasis [1]. In the postprandial state, they take up the glucose from the circulation to satisfy the energy need of renal medulla, as it is an obligate consumer of glucose via glycolysis. In the postabsorptive state, the renal cortex produces glucose via gluconeogenesis; this pathway involves glucose-6-phosphatase in its final step. It is worth to note that the renal endogenous production of glucose (EPG) was previously underestimated and that it increases with the prolongation of fasting [2, 3]. Finally, to avoid glucose urine wasting, the renal proximal tubule cells ensure the reabsorption of glucose by three effectors: sodium-glucose cotransporters SGLT1 and SGLT2 at the apical membrane and the facilitative glucose transporter 2 (GLUT2) at the basolateral membrane. The maximal reabsorptive capacity, referred to as the renal threshold, is observed for plasma glucose around 11 mmol/L [1, 4].

Glycogen storage diseases (GSDs) are the inherited errors of carbohydrate metabolism, mostly transmitted in an autosomal recessive way, that alter glucose homeostasis and glycogen metabolism. They affect variably and mainly the liver and or the muscle. Some of them comprise a renal involvement at the presentation or as a complication of the disease (**Table 1**) [5–7].

Disease	GSD-Ia (Von- Gierke disease)	GSD-Ib	Fanconi-Bickel syndrome (GSD- XI)	GSD-V (McArdle's disease)	GSD-VII (Tarui's disease)
OMIM code	232200	232220 232240	227810	232600	232800
Etiology	Deficiency of glucose-6phosphatase complex		GLUT2 deficiency	Myophosphorylase deficiency	Muscle phosphofructokinase deficiency
	Catalytic subunit G6P-alpha	G6PT: G6P-translocase			
Gene (location)	G6PC (17q21)	SLC37A4 (11q23)	SLC2A2 (3q26.2-q27)	PYGM (11q13)	PFKM (12q13)
Age of onset	Infancy, neonatal			Infancy, childhood, adolescence, adulthood	
Mechanism	Defect in the release of glucose (gluconeogenesis)		Defect in reabsorption of glucose	Defect in utilization of glucose by muscle (anaerobic glycolysis)	
Transmission	Autosomal recessive				
Tubular dysfunction urolithiasis	(+) Proximal and distal tubular dysfunction		(+) Fanconi Syndrome (++) Glucosuria	(–)	
Chronic kidney disease	Nephromegaly, microalbuminuria, hyperfiltration, hypertension, renal failure		Nephromegaly, microalbuminuria, hyperfiltration?	(–)	
Acute renal failure (ARF)	Possible complicating urolithiasis		(–)	Rhabdomyoly sis induced ARF	Myoglobinuria induced ARF
Extra-renal manifestatio ns	Fasting hypoglycemia, Hepatomegaly Growth retardation, delayed puberty, osteopenia			Exercise intolerance (fatigue, myalgia, weakness)	
		Neutropenia neutrophil dysfunction infections inflammator y bowel disease	Post-feeding hyperglycemia Galactosemia Rickets	A second wind' phenomenon	Compensated hemolysis Hyperuricemia

Table 1.
Glycogen storage diseases associated to renal involvement.

In this chapter, we will describe renal disease associated with GSD type I (GSD-I) and Fanconi-Bickel syndrome (FBS) in more detail. They both are present in neonates or infants with renal and extra-renal features. On the other hand, we will briefly report Tarui disease (GSD type VII: GSD-VII) and McArdle disease (GSD type V: GSD-V), which are likely to present during the second decade as an acute renal failure (ARF) secondary to rhabdomyolysis or myoglobinuria, occurring after exercise [8–11]. Episodes of ARF and respiratory insufficiency were also described in patients with the adult form of Pompe disease (GSD-II) [12]. A Gitelman-like syndrome has also been reported in a patient with GSD-II [13].

2. Glycogen storage disease type I (GSD-I)

GSD-I is the more frequent GSD with an incidence of 1/100,000 to 1/400,000 births in Caucasian populations [5]. It seems to be more frequent in North Africa [14], in particular in Tunisia [15].

GSD-I is an inherited autosomal recessive deficit of glucose-6-phosphatase. This enzymatic complex, expressed in the liver, intestine, and kidneys, comprises a catalytic subunit located in the endoplasmic reticulum (ER) and a translocase (encoded by *G6PT* gene) allowing the entry of the substrate (glucose-6-phosphate: G6P) into the ER. The defect of the catalytic subunit encoded by *G6PC* gene leads to GSD-Ia and that of the translocase to GSD-Ib. In both the subtypes, glycogenolysis and gluconeogenesis are disrupted at their final step leading to the suppression of any EPG. This results in an accumulation of glycogen in the liver and kidneys and hypoglycemia occurring at a very short fasting (1.5–3 hours) [5, 6, 14]. GSD-Ia and GSD-Ib are present in the first weeks or months with the features of hypoglycemia (irritability, sweating, paleness, apnea, convulsions, and hyperventilation) associated with frequent feedings night and day, hepatomegaly, doll-rounded face, lactic acidosis, hyperuricemia, and hyperlipidemia [5, 6, 14]. Besides, GSD-Ib comprises neutropenia, severe and recurrent infections, and an inflammatory bowel disease (Crohn's-like colitis) [16]. The complications of both the subtypes include failure to thrive, pubertal delay, hepatic adenomas, and chronic kidney disease (CKD) [5, 6, 17, 18].

The frequency and severity of renal involvement in GSD-I was first described in 1988 [19]. This complication concerns both the proximal and distal tubular function [17, 20–29] and the glomerular function [17, 23–26, 28, 30, 31]. At first glance, it was explicated by hyperuricemia. However, optimal control did not eliminate renal involvement or lithiasis, and histological features were inconsistent with gout nephropathy. Indeed, kidney pathology revealed glycogen deposits in the proximal tubules and the glomerular apparatus, thickening and lamination of the glomerular basal membrane, focal or diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis [19, 26].

A personal retrospective cross-sectional study involving 38 Tunisian patients aged 8.6 ± 5 years (1.5–22 years) and followed for 7.4 ± 4.5 years found evidence of tubular involvement (62%), glomerular involvement (50%), and urolithiasis or nephrocalcinosis (18%). The age of the onset of tubular involvement was significantly earlier than that of glomerular involvement (6.3 years versus 11 years; $p = 0.003$) [17].

2.1 Tubular involvement, urolithiasis, and nephrocalcinosis

Proximal tubular involvement (Fanconi-like syndrome) was reported in young patients with GSD-I, often subclinical and causing little disturbances of plasma

electrolytes. It manifests as urinary loss of bicarbonates, hyperphosphaturia, generalized hyperaminoaciduria, and elevated urinary excretion of β2-microglobin. These abnormalities resolved under continuous glucose administration [1, 2].

Distal tubular acidosis associated with GSD-I remains rare [3]. It comprises the acidification defect of urine and a systemic acidosis that causes loss of bone calcium in the urine and hypocitraturia. This contributes to osteoporosis, kidney stones, and nephrocalcinosis. Hypercalciuria was reported in 33–60% of cases. The effect of diet on distal tubulopathy has not been studied in the literature [3–9].

In our series, hypercalciuria was more frequent (60%) than hyperphosphaturia (26%). Tubular anomalies were significantly related to acidosis ($p = 0.028$), higher lactate levels (5.9 ± 3.5 versus 3.7 ± 1.7 mmol/L; $p = 0.013$), and smaller height (−2.1 ± 1.5 SD versus −0.8 ± 1.5 SD; $p = 0.026$) [5].

Urolithiasis and nephrocalcinosis are a common complication of GSD-I (18–65%) [3, 5, 9, 10] and may lead to ARF [10]. Factors involved in lithogenesis in GSD-I are hyperuricemia, hyperuricuria, hypercalciuria, and/or hypocitraturia [3, 5–7]. Urine alkalinization with sodium bicarbonate, or better potassium citrate (10 mEq orally every 8 hours in adults, 5–10 mEq every 12 hours in children), is beneficial in preventing or ameliorating urolithiasis and nephrocalcinosis [11].

2.2 Glomerular involvement and chronic kidney disease (CKD)

Nephromegaly, secondary to the accumulation of glycogen, was observed on ultrasounds in 26–70% of cases [5, 10, 12] (**Table 2**). Glomerular hyperfiltration (GHF) indicates the beginning of CKD; it is isolated in younger patients. Microalbuminuria and proteinuria are detected in a later stage [5, 13, 14]. The European multicenter study of 288 cases of GSD-I aged 14 years on average (0.4–45.4 years) described microalbuminuria (31% of cases) detected at an average age of 13 years (0.5–22 years) and proteinuria (13% of cases) detected at an average age of 16 years (0.5–25 years). Beyond the age of 25 years, microalbuminuria was constant, and proteinuria was present in 50% of cases. Glomerular disease was more frequent in cases with severe hypertriglyceridemia ($p = 0.042$) and occurred at an older age ($p = 0.007$) [5]. Albuminuria was more important in subjects who started their diet later and those with poor metabolic balance [12].

References	**Wolfsdorf, 1997 [12]**	**Rake, 2002 [10]**	**Ben Chehida, 2015 [5]**
Type of study	Monocentric	Multicentric	Monocentric
Number of patients	23	288	38
Age of patients	13,9 years (5,9–26,9)	14 years (0,4–45,5)	8,6 years (1,5–22)
Nephromegaly	70%	Not available	26%
Glomerular Hyperfiltration	43%	Not available	29%
Microalbuminuria	35% (all cases > 10 years)	31% (average: 14 years)	48% (9/15 cases > 10 years)
Proteinuria	Not available	13% (average: 16 years)	9%
Hypertension	None	6% (average: 17 years)	None
Renal failure	None	2%	None

Table 2.
Glomerular involvement in glycogen storage disease type 1.

Thus, the natural history of CKD in GSD-I seems analogous to that in insulin-dependent diabetes starting with a phase of "silent" glomerular hyperfiltration (the first years of life). Microalbuminuria usually follows in the second decade, then proteinuria. Glomerular filtration decline and progressive end-stage renal failure start from the third decade [5, 10, 14] and can require hemodialysis or kidney transplantation [10].

The mechanisms of CKD in GSD-I are not completely elucidated, although similarities with diabetic nephropathy were noticed [15–18]. CKD in GSD-I seems to be related to accumulation of glycogen and lipids in kidneys [19], the activation of the renin-angiotensin system responsible for the development of renal fibrosis [18], enhanced ER oxidative stress, increased apoptosis [17, 20], and the enzymatic defect per se, as CKD phenotype was observed in a mouse model with a kidney-specific glucose-6-phosphatase deficiency (K.G6pc−/−mice) [32].

2.3 Renal preservation in GSD-I

Observational studies conclude to the benefit of metabolic imbalance on renal involvement [5, 12, 21–24]. It is achievable by a strict diet that ensures continuous carbohydrate needs by frequent meals with uncooked cornstarch (UCS) snacks or continuous nocturnal enteral nutrition during early childhood [10, 11]. No difference was found between the two types of diet regarding the frequency of kidney complications [5].

Angiotensin converter inhibitors reduce GHF and slow down the progression of CKD and the development of microalbuminuria and proteinuria. They should be started early, as soon as GHF is detected [11]. Lowering lipids levels by tight metabolic control and lipid-lowering drugs may improve renal prognosis, as it was demonstrated that severe hyperlipidemia is a factor in poor response to angiotensin converter inhibitors [21–23]. Combined liver-kidney transplantation has been proposed in cases with renal failure and hepatic adenomas with good long-term results [11, 25].

3. Fanconi-Bickel syndrome (FBS)

FBS is a rare autosomal recessive inborn error of monosaccharide transport [26, 27]. Recently, Sharari et al. [28] have reviewed 144 cases that have been described since the first reported in 1949 [29].

3.1 Pathophysiology: main features

FBS is related to pathogenic mutation(s) in the *SLC2A2* gene: at least 70 variants have been reported until 2020 [28]. *SLC1A2* gene encodes for GLUT2, a low-affinity facilitative glucose and galactose transporter, which is expressed in enterocytes, hepatocytes, pancreatic β-cells, renal tubular cells, neuronal cells, and astrocytes [27, 28].

The defect of glucose and galactose transport in intestine, liver, pancreas, and kidneys results in disturbances in glucose homeostasis and dysglycemia [28].

Indeed, the uptake of glucose and galactose is impaired leading to glucose and galactose intolerance manifesting as postprandial hyperglycemia and galactosemia, sometimes revealed at newborn screening. Animal models demonstrated that glucose intolerance may be aggravated by a decreased glucose-stimulated insulin secretion. Thus, GLUT2 might regulate the glucose-stimulated secretion of insulin in pancreatic β-cells [28, 30]. Rare cases of transient neonatal diabetes and later diabetes mellitus or gestational diabetes were reported in FBS [31, 33–35].

On the other hand, the defect in glucose release in FBS results in glucose and glycogen deposition in the liver and kidneys. In consequence, FBS patients present with hepatomegaly, nephromegaly, and a renal Fanconi syndrome. Glucosuria is mandatory; polyuria, phosphaturia, hypercalciuria, generalized aminoaciduria, bicarbonaturia, renal acidosis, hypokalemia, hypophosphatemic rickets, and osteoporosis are variably associated. Dwarfism is multifactorial and constant [26, 28, 29]. Besides, the impaired release of glucose in fasting state explains hypoglycemia tendency in FBS [28].

3.2 Renal involvement in FBS

Fanconi syndrome is the most frequent renal feature in inherited metabolic diseases. Differential diagnosis of FBS comprise cystinosis, tyrosinemia type 1, galactosemia, fructosemia, mitochondrial disorders, Lowe syndrome, Wilson disease, GSD-I, and growth retardation, aminoaciduria, cholestasis, iron overload, lactacidosis, and early death (GRACILE) [29, 36, 37]. Significant glucosuria, even in hypoglycemia, associated with galactosuria is typical of FBS [29, 36].

Glomerular involvement has also been reported and comprised nephromegaly, glomerular hyperfiltration, microalbuminuria (as early as 5 years of age) [36], and a reduction in glomerular filtration rate in some adults without renal insufficiency [29].

Pathologic examination of kidney biopsies showed moderate glomerular mesangial hypertrophy, discrete podocyte swelling, and moderate thickening of the glomerular basal membrane. Glycogen accumulation was detected at the tubular epithelium in FBS, while there was no accumulation of glycogen at the glomerular level [32, 38].

3.3 Management

The aim of the treatment is to avoid glycemic excursion and to correct electrolytic and mineral disturbances secondary to Fanconi syndrome. The restriction of galactose is warranted. Continuous nocturnal nasogastric drip feeding or UCS snacks ensure a slow release of glucose. The benefits of catch-up growth are not guaranteed. Liver transplantation is not indicated as long-term prognosis is preserved [29, 36, 39].

4. Glycogen storage disease type V (McArdle disease) and type VII (Tarui disease)

Muscular glycogen storage diseases (GSD-V and GSD-VII) present mainly in early childhood or in adolescence as a myopathy with a wide spectrum of phenotypes: hypotonia, fixed weakness associated with exercise intolerance (fatigue, weakness, and myalgias), isolated chronic elevation of creatine phosphokinase [40], or ARF induced by rhabdomyolysis or myoglobinuria [40–46].

4.1 Pathophysiology and diagnosis

McArdle disease (GSD-V) is an autosomal recessive GSD characterized by a complete disruption of glycogen breakdown in muscles related to the absence of myophosphorylase activity, a key enzyme of anaerobic glycogenolysis, which is crucial in brief and vigorous exercise. Exercise intolerance associated with a second

wind phenomenon (the relief of myalgia and fatigue after a few minutes of rest) is typical of GSD-V. Diagnosis is based on biological findings revealing an elevated creatine phosphokinase level, a decreased lactate production during ischemic forearm test but excessively increased ammonia upon exercise, an excess of glycogen content, and a deficient phosphorylase activity in the muscle biopsy. Several mutations were described in *PYGM* gene. The p.Arg50Ter mutation is particularly frequent in patients of European origin [47].

Tarui disease (GSD-VII) is the rarest GSD, transmitted in an autosomal recessive manner with a frank masculine predominance. The deficiency of phosphofructokinase-1, an enzyme of anaerobic glycolysis pathway, leads to insufficient fuel supply for muscle function and exercise intolerance that is more severe than that observed in GSD-V. Besides, hemolysis (hyperbilirubinemia and reticulocytosis) and hyperuricemia are frequent. Rarely, myoglobinuria can lead to ARF with oliguria or anuria. The diagnosis of GSD-VII is based on enzymatic assay in muscle or genetic testing (*PFKM* gene) [46].

4.2 Acute renal failure (ARF) in GSD-V and GSD-VII

Several case reports described rhabdomyolysis-induced ARF in GSD-V with a variable age at onset between 8 and 67 years [41, 43, 45]. The kidney biopsy, when done, showed evidence of acute tubular necrosis [42]. Many of these patients were previously healthy [45]. Others had vague symptoms or recurrent rhabdomyolysis with a long delay in diagnosis and management [42, 44].

Acute rhabdomyolysis episodes were triggered by intense exercise, infections, and drugs (lipid lowering drugs, anesthetics, and antidepressants). Prevention is based mainly on a moderate physical activity, a high-complex carbohydrate, and a low-fat diet. Vitamin B6, creatine, oral sucrose, ramipril, and high protein intake had variable results [48, 49].

Less frequently, acute liver failure secondary to myoglobinuria was reported in GSD-VII. Carbohydrates before exercise induce lower muscular performance in GSD-VII. The only treatment is to avoid intensive exercise [46].

The management of ARF in GSD-V and GSD-VII requires supportive treatment and can sometimes need intensive care, forced diuresis, or urgent renal dialysis. ARF is reversible in most cases [41–46].

5. Conclusion

GSDs are associated with different renal manifestations at variable onset ages. Mainly, Fanconi or Fanconi-like syndrome may reveal FBS and GSD-I. Rarely, acute severe renal onset is reported in muscular GSD (rhabdomyolysis- or myoglobinuria-induced ARF in GSD-V, GSD-VII, or GSD-II) and in GSD-I (related to obstructive urolithiasis). Progressive CKD, similar to diabetic nephropathy, should be monitored and prevented in GSD-I by an optimal diet and metabolic control, lipid-lowering drugs, and angiotensin convertor inhibitors. Long-term renal prognosis in FBS is still unknown.

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Conflict of interest

The authors declare no conflict of interest.

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This book provides a comprehensive overview of chronic kidney disease (CKD). It includes fifteen chapters over four sections on "Clinical Nephrology", "Biomarkers and Molecular Biology", "Hemodialysis and Transplantation", and "Basic Research and Innovation". Chapters address such topics as cardiovascular disease in CKD patients, diabetic kidney disease, palliative care in CKD, biochemical tests for evaluating CKD, renal replacement treatment options, artificial intelligence in CKD, and much more.

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