Maturitas 71 (2012) 94–103

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Chronic kidney disease and diabetes

Ronald Pyram[a,b], Abhishek Kansara[a,b,c], Mary Ann Banerji[a,c], Lisel Loney-Hutchinson[a,c,*]

[a] Division of Endocrinology SUNY Downstate Medical Center, 450 Clarkson Ave, Brooklyn, NY 11203, United States
[b] Division of Endocrinology Brooklyn VA Medical Center, Brooklyn, NY, United States
[c] Kings County Hospital Center, Department of Medicine, 451 Clarkson Ave, Brooklyn, NY 11203, United States

ARTICLE INFO

Article history:
Received 28 October 2011
Received in revised form 9 November 2011
Accepted 9 November 2011

Keywords:
Chronic renal disease
Diabetes
Glomerular filtration rate
Nephropathy
Renal failure

ABSTRACT

Chronic kidney disease has a significant worldwide prevalence affecting 7.2% of the global adult population with the number dramatically increasing in the elderly. Although the causes are various, diabetes is the most common cause of CKD in the United States and an increasing cause of the same worldwide. Therefore, we chose to focus on diabetic chronic kidney disease in this review.

The pathogenesis is multifactorial involving adaptive hyperfiltration, advanced glycosylated end-product synthesis (AGES), prorenin, cytokines, nephrin expression and impaired podocyte-specific insulin signaling. Treatments focus on lifestyle interventions including control of hyperglycemia, hypertension and hyperlipidemia as well treatment of complications and preparation for renal replacement therapy. This review examines the current literature on the epidemiology, pathogenesis, complications and treatment of CKD as well as possible areas of future disease intervention.

Published by Elsevier Ireland Ltd.

Contents

1. Introduction

Chronic kidney disease (CKD) affects a significant portion of the world population with a prevalence of 7.2% in adults over age 30 and dramatically increasing to 23.4–35.8% over age 65 [1]. Furthermore, population based studies in the United States reveals a CKD prevalence ranging from 1.4 to 43.3% [2]. The causes of CKD are

* Corresponding author at: Kings County Hospital Center, Department of Medicine, 451 Clarkson Ave, Brooklyn, NY 11203, United States.
Tel.: +1 718 270 6324.
E-mail address: lisel.loney-hutchinson@downstate.edu (L. Loney-Hutchinson).

0378-5122/$ – see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.maturitas.2011.11.009

various and include glomerular kidney disease, tubular and interstitial kidney disease, obstructive uropathy, pre renal and vascular disorders, diabetes and hypertension. Globally, diabetes is the most common cause of CKD.

There are multiple etiologies involved in the pathogenesis of diabetic CKD. The initial mechanism of damage involves adaptive hyperfiltration which leads to long term damage of functioning nephrons. Additional mechanisms of disease include advanced glycosylated end products (AGEs), vascular endothelial growth factor (VEGF), prorenin and the renin–angiotensin system, cytokines, nephrin expression and impaired podocyte signaling. Importantly, CKD is associated with an increased risk of cardiovascular disease, mortality and end stage renal disease. Most patients are likely to die than develop end stage renal disease. Treatments are limited but focus on treatment of associated causes including diabetes and hypertension, slowing progression of disease, treatment of complications and preparation for renal replacement therapy. This review examines the current literature on the epidemiology, pathogenesis, complications and treatment of CKD as well as possible areas of future disease intervention.

1.1. Epidemiology

Diabetes mellitus is a disease that affects over 23.5 million American adults [3] and type 2 diabetes accounts for over 90% [4,5]. Diabetes is the most common cause of CKD. The prevalence of some degree of CKD among adults with type 2 diabetes is 40% [3,6–11]. The 2009 annual report published by the United States Renal Data Systems, reports the prevalence rate of CKD in type 2 diabetes according to stage was 8.9% for stage I, 12.8% for stage II, 19.4% for stage III, and 2.7% for stages IV and V combined. The lifetime risk of developing CKD in type 1 diabetes is 25% [5,12–17].

The older population is especially affected by diabetic nephropathy. The incidence of end stage renal disease (ESRD) related to diabetes among the elderly markedly increased from the 1980s up until the late 1990s at which time there was slight decrease and leveling off to approximately 350–370/100,000 [4,18,19]. This more recent decline in CKD is likely due to earlier recognition and interventions.

In the 2010 Annual report published by the United States Renal Data Systems, the median age of incident ESRD population was 64.2 in 2008 which varied by race; the median age ranged from 59.2 among African Americans to 66.8 among whites. The rate of prevalence of CKD remains highest among the African American and Native American population, and lowest among the Caucasian and Asian population paralleling the rate of diabetes in these populations [20,21]. The trend of increasing prevalence is expected to continue to grow as the elderly population continues to rise with increased life expectancy.

CKD in diabetes causes significant disability and contributes greatly to health care costs; annually approaching $23 billion with ESRD in the US [22]. McFarlane et al. [23] evaluated the risk of hospitalization, cardiovascular risk and death in patients with chronic kidney disease and reported that the adjusted risk of hospitalization increased as the estimated glomerular filtration rate (eGFR) decreased ranging from an increase of 14% with an estimated GFR of 45 to 59 ml/min/1.73 m^2 to an increase of 315% with an estimated GFR of less than 15 ml/min/1.73 m^2.

2. Diabetic nephropathy

CKD is defined as progressive, irreversible loss in kidney function. The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) defined CKD as lasting three or more months with either kidney damage defined by structural or functional abnormalities of the kidney with or without decreased eGFR, or a GFR of less than 60 ml/min/1.73 m^2. These abnormalities include markers of kidney damage [1] such as albuminuria, abnormal urinary sediment (casts, epithelial cells), abnormal imaging (polycystic kidneys, hydronephrosis), blood and urine markers of 'tubular syndromes' and renal transplant recipients. In addition to the gold standard isotopic measures, several equations are used to estimate GFR. The Modification of Diet in Renal Disease (MDRD) equation [1], validated in patients with diabetic (type 2) and non-diabetic kidney disease and in transplant recipients is most commonly used. It is verified in US and European whites and African-Americans, but not with other racial/ethnic groups, extremes of age, pregnancy and certain other conditions [1]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is a new estimate of glomerular filtration and may be more accurate [24,25] at higher levels of eGFR.

Table 1
Stages of chronic kidney disease.

Stage	Description	eGFR (ml/min/1.73 m^2)
I	Normal or increased eGFR[a]	>90
II	Mildly decreases eGFR[a]	60–89
III	Moderately reduced eGFR	30–59
IV	Severely reduced eGFR	15–29
V	Kidney failure	<15 or dialysis

[a] With evidence of structural kidney damage such as albuminuria, abnormal urinary sediment (i.e. casts, tubular epithelial cells), abnormal imaging studies, renal transplant recipients [26].

Stages of chronic kidney disease: The stages of chronic kidney disease as described in Table 1 are defined on the basis of eGFR [26] *with* evidence of kidney damage.

2.1. Risk factors

- **Elevated blood pressure**: Elevated systolic blood pressure is well known to accelerate diabetic nephropathy [27–29]. The development of impaired renal function was associated with higher mean blood pressures even in patients who were normotensive with and without proteinuria [28] in long-term follow-up of type 2 diabetes patients.
- **Diabetes**: Strong evidence for the role of glycemia was provided by the DCCT (type 1 diabetes) and the UKPDS (type 2 diabetes) intervention trials where improved glycemia resulted in significantly lower progression rates for albuminuria [30]. The duration of diabetes is associated with progression of nephropathy in long-term follow-up in Saudis with duration of diabetes >10 years [31]. The odds of nephropathy were 4.6-fold higher in urban African-Americans with duration of diabetes greater than 5 years as compared to <1 year [32].
- **Cholesterol**: Elevated levels are associated with increased risk of nephropathy [26].
- **Microalbuminuria**: The prevalence of microalbuminuria in South Indian diabetics was 36%, similar to urban African-Americans with type 2 diabetes for <1 year [32,33]. Microalbuminuria predicts progression to clinical proteinuria and decreased renal function in patients with type 2 diabetes [34–36] as well as increased CVD and mortality [30,37,38]. The rate of progression in UKPDS, from diagnosis of diabetes without microalbuminuria to microalbuminuria is 2% per year; from microalbuminuria to macroalbuminuria is 2.8% per year; and macroalbuminuria to elevated creatinine or renal replacement therapy is about 2.3% per year. Patients without microalbuminuria at diagnosis remained free of nephropathy for a median period of about 19 years, while those who developed microalbuminuria progressed to macroalbuminuria (or worse) in 11 years [39]. Microalbuminuria is infrequently reversible to

normoalbuminuria in type 2 diabetes (21% over 2 years) [40]. In contrast, this occurs in up to 50% of type 1 diabetes with short duration microalbuminuria [41]. Thus, although microalbuminuria precedes proteinuria and decreased renal function, not all microalbiminuria will progress. The challenge is in identifying those with microalbuminuria who are likely to progress from those who will not. The GFR may also decline in the absence of any microalbuminuria [36,42].

- **Smoking**: In types 1 and 2 diabetes, albuminuria was greater in smokers [43].
- **Genetic factors:** An insertion /deletion polymorphism (specifically the deletion allele) of the ACE gene predicted severe structural kidney changes in patients with microalbuminuria [44]. Not all studies confirm this. Identifying the genetic risk of diabetic nephropathy [45] requires further study.
- **Age and BMI:** Advancing age and obesity are also risk factors [28].

2.2. Pathological disease progression

Classical hemodynamic and structural causes of diabetic nephropathy, best characterized in type 1 diabetes are summarized below [46–49]:

- **Glomerular hyperfiltration**: Vasodilatation and glomerular hyperfiltration, resulting in increased glomerular filtration rate, are known to occur *early* in type 1 diabetes, *but not always in type 2 diabetes* [46,49–52]. While hyperfiltration frequently predicts a decline in renal function, it is not invariable.
- **Glomerular lesions without clinical disease**: This stage is characterized by glomerular lesions-glomerular basement membrane thickening and mesangial expansion; without excess albumin excretion. Typical Kimmelstiel–Wilson lesions (nodular glomerulosclerosis) are found in only a small proportion early in nephropathy [49].
- **Incipient diabetic nephropathy**: This stage develops after about 10–15 years of type 1 diabetes characterized by microalbuminuria and structural lesions [53,54]; the GFR may be well preserved. It is of clinical interest because interventions, especially blood pressure control may prevent progression to overt nephropathy.
- **Overt diabetic nephropathy**: There is persistent and progressively worsening proteinuria, a decline in GFR, frequently leading to ESRD. This stage is characterized by advanced glomerular lesions-diffuse and nodular glomerulosclerosis, fibrinoid caps, capsular drops and arteriolar hyalinosis [49].

2.3. Mechanisms

The mechanisms by which diabetes induces renal damage are not adequate to formulate a cohesive model of nephropathy. Various physical and metabolic factors together result in mesangial hypertrophy, glomerular basement thickening, podocyte and endothelial dysfunction.

Glomerular hyperfiltration [55–57]: Various mediators include the renin–angiotensin system, vascular endothelial growth factor (VEGF), nitric oxide and transforming growth factor-beta (TGF-B).

Hyperglycemia: Hyperglycemia is linked to multiple metabolic perturbations (Fig. 1).

- **Advanced glycosylated end-products (AGEs)** are covalently glycosylated proteins [58] whose synthesis increases with hyperglycemia. These accumulate in the extracellular matrix and the glomerular basement membrane altering the elasticity, ionic charge and thickness [59]. AGEs bind with cell surface receptors (RAGE) and initiate cellular signaling cascades associated with increased VCAM expression causing vascular injury, mesangial cell growth, enhanced expression of growth factors, extracellular membrane proteins, ROS and activation of protein kinase C, releasing cytokines and growth factors.
- **Protein kinase C (PKC)**: Hyperglycemia activates isoforms of protein kinase C through diacylglycerol (DAG), which activates MAP kinase and vasotropic substances such as angiotensin II, endothelin and prostanoids causing glomerular hyperfiltration. PKC activation increases ROS and the actions of fibrotic factors such as TGF-beta and connective tissue growth factor (CGTF) resulting in glomerular hypertrophy and mesangial expansion. ROS increases cytokines and extracellular membrane proteins type IV collagen leading to glomerulosclerosis and renal failure [59].
- **Vascular endothelial growth factor (VEGF)** expression in podocytes is upregulated by hyperglycemia, increasing vascular permeability in the nephron [60].
- **Aldose reductase pathway**: Its role in CKD is unclear [61,62].

Table 2
Effects of RAAS in pathogenesis of diabetic nephropathy.

Prorenin	Angiotensin II	Aldosterone
Elevated in type 1 diabetics with microalbuminuria	↑ Production of reactive oxygen species ↓ Nitric oxide production ↑ Glomerular hypertension ↑ Vascular endothelial growth factor	Profibrotic Mitogenic

Nephrin: Nephrin, a protein found in podocytes is crucial in maintaining an intact filtration barrier. Lower renal expression of nephrin in kidney biopsies of patients with diabetes is reported [63].

mTOR (mammalian Target Of Rapamycin) is a serine/threonine protein kinase which integrates multiple signals including insulin, energy balance and oxidative stress and regulates cell growth and survival. In glomeruli from patients with diabetic nephropathy, mTOR activated target genes were increased including VEGF, SREBP, mitochondrial genes as well as mTOR mRNA [64]. mTOR may play a role in glomerular hypertrophy and podocyte enlargement.

Renin–Angiotensin System Aldosterone (RAAS) (see Table 2):

- **Prorenin**: Increased serum prorenin levels precede and predict the onset of microalbuminuria in normotensive type 1 diabetes [65]. Levels were also higher in non-diabetic siblings of these patients [66,67] and may be a marker for increased risk of nephropathy in non-diabetic patients at high risk for diabetes.
- **Angiotensin II** (Ang II) Ang II stimulates synthesis of matrix proteins, increases VEGF, oxidative stress, and decreases NO production and loss of endothelial integrity. Ang II causes efferent arteriolar vasoconstriction and increased intraglomerular pressure leading to renal hyperfusion [68,69].
- **Aldosterone** is known to be mitogenic and increases renal fibrosis through profibrotic TGF-beta [70,71].

Microalbuminuria: Elevated levels of inflammatory markers are proportional to the degree of albuminuria [68]. In patients with type 2 diabetes and persistent microalbuminuria, elevated levels of biomarkers of inflammation and endothelial dysfunction predicted development of nephropathy over a 2-year follow-up period [72]. Inflammatory factors lead to accumulation of macrophages in the tubular interstitium, producing free radicals, inflammatory cytokines and proteases that induce tubular damage [18,71].

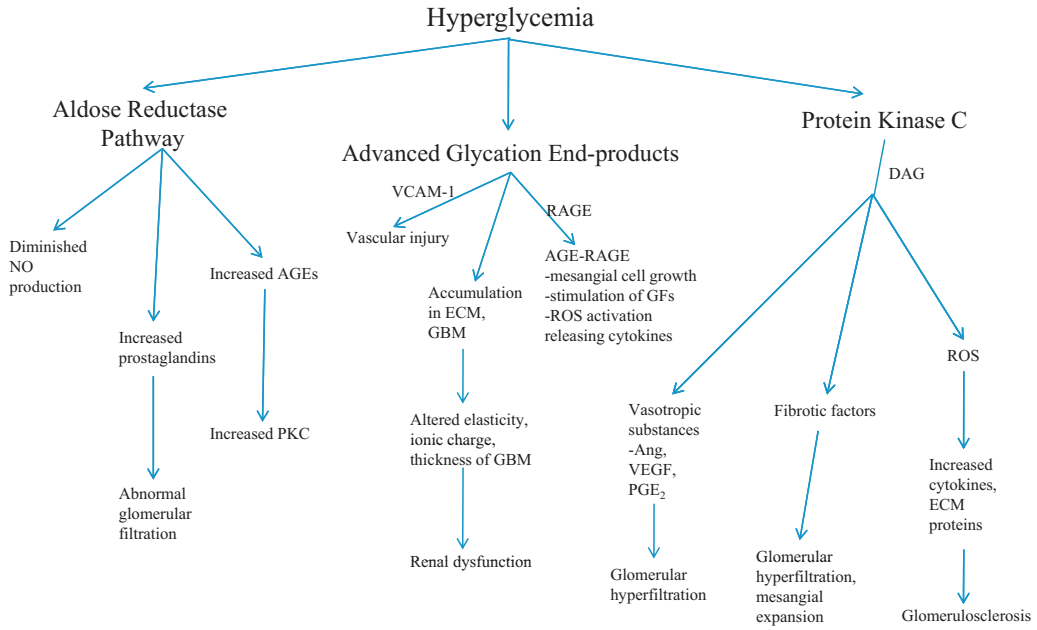

Fig. 1. Pathways of hyperglycemia causing renal damage. AR: aldose reductase; NO: nitric oxide; AGEs: advanced end-glycation products; PKC: protein kinase C; VCAM: 1-vascular cell adhesion molecule-1; RAGE: receptor for AGE; ECM: extracellular matrix; GBM: glomerular basement membrane; GFs: growth factors; ROS: reactive oxygen species; Ang: angiotensin; VEGF: vascular endothelial growth factor; PGE_2: prostaglandin E_2; DAG: diacylglycerol.

2.4. Complications

Anemia: Nearly 1 in 5 patients with stage III chronic kidney disease have anemia and likely due to decreased erythropoietin. Anemia is associated with a poor quality of life, increased fatigue, weakness, cognitive dysfunction, memory impairment and progression of renal disease (ESRD) and increased mortality from CVD [73–76].

Cardiovascular disease: As shown in Fig. 2, the prevalence of atherosclerotic vascular disease, congestive heart failure, renal replacement therapy and death was significantly higher in patients with both CKD and diabetes (49.1%, 52.3%, 3.4%, and 19.9%, respectively) compared with patients with neither underlying disease [77] in 1 million US elderly Medicare patients. The devastating CV consequences of CKD have been confirmed in numerous studies [78,79].

Bone disease: Renal osteodystrophy or chronic kidney disease-mineral and bone disorder (CKD-MBD) encompasses all disorders of bone and mineral metabolism that are associated with CKD.

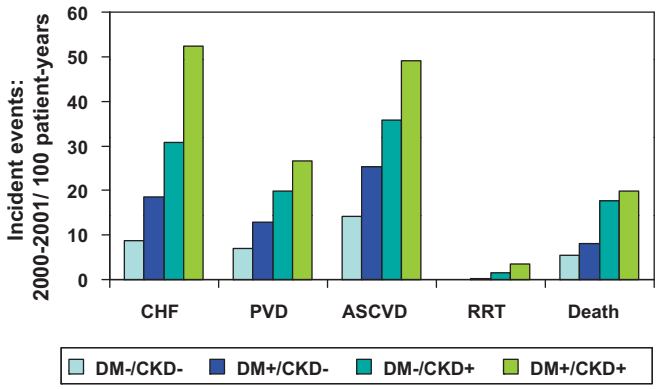

Fig. 2. Incident event rates in 2000–2001 in over 1 million elderly US Medicare beneficiaries (over age 67 years). CHF: congestive heart failure; PVD: peripheral vascular disease; ASCVD: atherosclerotic cardiovascular disease; RRT: renal replacement therapy; DM: diabetes mellitus; CKD: chronic kidney disease.

The spectrum ranges from high bone turnover secondary to elevated PTH levels (secondary hyperparathyroidism) to those with low bone turnover associated with normal-to-low PTH levels (adynamic bone disease, osteomalacia), including abnormal mineral metabolism, altered bone structure and composition, and extra-skeletal calcification.

Secondary hyperparathyroidism ensues with a decline in GFR, secondary phosphorus retention, hypocalcemia and impaired 1,25-dihydroxyvitamin-D production [80]. FGF-23 plays a key role in renal phosphate excretion and homeostasis; and suppresses $1,25(OH)_2$-vitamin D3. Persistent hyperphosphatemia and $1,25(OH)_2$-vitamin D3 are principal stimuli for its production. In patients with CKD, FGF-23 levels increase in response to phosphate retention which in turn suppresses 1-alpha-hydroxylase and renal synthesis of $1,25(OH)_2$-vitamin D3 which then leads to increased secretion of PTH. FGF-23 has been positively associated with left ventricular hypertrophy and CV mortality, especially in patients with low eGFR [81,82]. Recently, Klotho has been identified as a crucial cofactor essential for the biological effect of FGF-23 [80]. CKD may be a state of Klotho deficiency [83], with the lowest values in CKD stage V patients. Klotho protein may have anti-apoptotic and anti-senescent effects on endothelial cells including effects on vascular calcifications, endothelial dysfunction and kidney injury and repair. The ultimate role of FGF23 and its cofactor, Klotho protein, await further study.

The prevalence of adynamic bone disease or bone's resistance to the action of PTH ranges from 5% to 70% with a higher prevalence in advanced stages of CKD [84]. The CKD milieu promotes low bone formation. This milieu includes altered vitamin-D/calcium/phosphorus metabolism, acidosis, diabetes, age and AGEs (which increase circulating cytokines) [85–89].

3. Evidence of modifiable risk factors

3.1. Diet, weight reduction, exercise and smoking

Epidemiological studies reveal a relationship between lifestyle variables including diet, obesity, exercise and smoking and CKD.

However, evidence of benefit is limited as there are few robust intervention studies [90–98].

The diet recommended is low protein and low carbohydrate diet. In the early stages of CKD, protein intake should not exceed 0.8–1.0 g kg/wt d, while in later stages of CKD protein should be limited to 0.8 g kg/wt d. Dietary restriction can help improve renal function by decreasing urinary albumin excretion, presumably reducing the decline in eGFR [90,91]. In addition, a diet consisting of no more than 130 g of carbohydrates per day has also been advised [90], to decrease the toxic effects of hyperglycemia on the kidney.

3.2. Blood glucose control

Numerous studies have shown that hyperglycemia is strongly *associated* with the development and progression of CKD [99]. The ARIC study showed an increased hazard ratio for CKD with increasing of A1C: compared to an A1C of <6%, the HR was 1.37, 2.49 and 3.67 at A1Cs of 6–7%, 7–8% and >8% HR respectively. Furthermore, each 1% increase in A1C was associated with a 31% higher risk of CKD. Those who developed either albuminuria or retinopathy early in the study were at much higher risk of CKD than those with neither. Surprisingly, of individuals who developed CKD, only 1/4 had established retinopathy, 13% had albuminuria, 29% had both and 33% had neither with higher A1C. The large ADVANCE trial in type 2 diabetes patients showed a 21% relative risk reduction in nephropathy with intensive glycemic regulation (target A1C $\leq$ 6.5%) versus conventional treatment (mean A1C 7.3%) [100]. When intensive glucose control was coupled with good blood pressure control there was an additive benefit in overall clinical outcomes, including renal events, with a risk reduction of 33% in new or worsening nephropathy; specifically a 54% reduction in new onset macroalbuminuria (>300 mg/24 h) and 26% reduction in new onset microalbuminuria [101] (30–300 mg/24 h). The ACCORD [102] trial demonstrated a 21% reduction in microalbuminuria in the intensively treated study arm and a decrease in macroalbuminuria. Due to an increased overall mortality in the intensive group with A1C of <6% as compared to the standard glycemia group (A1C 7–8%), the study was stopped early. The STENO-2 study demonstrated the importance of multiple risk factor control with a 61% reduction of progression to diabetic nephropathy in type 2 diabetes with baseline micro-albuminuria [103,104].

Considering the benefits and risks, the diabetes and nephrology professional organizations recommend an overall A1C goal of 7.0% [90,91], in order to optimally preserve renal function. The readers refer to a recent and comprehensive review detailing management strategies for type two diabetes and glycemia in the elderly [105].

3.3. Blood pressure control

Guidelines for blood pressure goals in diabetes, based on expert opinion, is <130/80 [90]. One of the earliest trials which demonstrated the benefit of maintaining lower blood pressures in diabetics with no or early nephropathy was the Normotensive ABCD study. It involved 480 normotensive participants, were randomized into intensive control (mean BP of 128/75 mm Hg, using nisoldipine or enalapril to achieve 10 mm Hg reduction of BP from baseline) and moderate control (mean 137/81, with placebo given) groups. After 5 years, there was a significant increase in the rate of urinary albumin excretion in the moderate compared to the intensive group. Overall renal function, assessed using 24 h urine creatinine clearance, remained stable in both normoalbuminuric and microalbuminuric groups. Possibly even more interesting, the progression from normoalbuminuria to microalbuminuria, or microalbuminuria to macroalbuminuria was clearly demonstrated to be slower in the intensive group compared to those in the moderate blood pressure group. This was not the case in patients who had already displayed overt macroalbuminuria at baseline, as their renal function continued to decline regardless of which blood pressure group they were enrolled in [106].

Further data from the ABCD study using hypertensive patients, treated also with Nisoldipine or Enalapril (switched to solely Enalapril during course of trial due to its cardiovascular benefit). After 5-year follow up, the intensive (mean BP 133/78) and moderate (mean BP 139/86) groups' results were similar to the prior mentioned normotensive study arm. Renal function remained stable for those who had normoalbuminuria or microalbuminuria at baseline, independent of initial therapy (Nisoldipine or Enalapril). Once again, those with overt macroalbuminuria continued to show decline in renal function, with the rate of decline of about 5 ml/min/year. This decline was still markedly less than untreated hypertensives (10–12 ml/min/year), hence, very much suggestive of a significant benefit even in more advance CKD [106].

Ravid et al. conducted a 5-year randomized study of 94 type 2 diabetes with normal blood pressure and renal function but with microalbuminuria. Even in these normotensive patients there was a benefit of tighter blood pressure control with enalapril on renal function. In the enalapril group, the initial 24 h urine microalbumin of 143 mg/24 h initially decreased to a mean of 123 mg/24 h, but rose to 140 mg/24 h after 5 years of treatment. In contrast, the placebo group began with a mean microalbumin level of 123 mg/24 h with an astonishing increase in microalbuminuria to a mean of 310 mg/24 h [107]. Additionally, there were significant differences in kidney function which decreased by 13% in the placebo group over the course of 5 years, while remaining stable in the enalapril group. These findings lead to the conclusion that intensive blood pressure control is beneficial for renal protection, especially when started early and may be less valuable in advanced CKD. Currently, the recommendations from the American Society of Hypertension [3], patients with hypertension with eGFR > 50 ml/min/1.73 m^2 or greater, should be started on anti-hypertensive medications. The medication regimen for patients with systolic blood pressures >20 mm Hg above goal should include an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) plus a thiazide diuretic or a calcium channel blocker. Patients with a systolic blood pressures <20 mm Hg above goal can be started just on an ACE inhibitor or ARB.

3.4. Management of complications

Management is focused on correcting or stabilizing the following complications.

Treatment for **hyperkalemia** includes potassium restriction <60 mmol/d, and kayexalate, a potassium binder that lowers serum potassium levels via GI loss. Additional interventions include the re-evaluation and/or adjustment of medications with the potential to induce or exacerbate hyperkalemia (i.e. ACEi, potassium sparing diuretics, beta-blockers) [108].

Volume overload can best be managed with fluid restriction and diuretic therapy [108,109].

Although still somewhat controversial, many studies have shown the potential benefit of aggressive treatment of **metabolic acidosis**. Sodium bicarbonate supplementation resulted in a significant decrease in progression to dialysis at the end of 2 years [96,97]. Therefore, sodium bicarbonate may be a safe and effective treatment for metabolic acidosis, with the possible added benefit of reducing the rate of decline in renal function.

Controlling **hyperphosphatemia** is important because of the increased risk development of secondary hyperparathyroidism, renal osteodystrophy and cardiovascular mortality, mostly seen in the hemodialysis population [109,110]. This can be achieved with

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.