Abstract

Since the 1930s when Kimmelstiel and Wilson first described the classic nodular glomerulosclerosis lesions in diabetic kidneys, nephropathy has been recognized as a major and common complication of diabetes. Nearly 40% of diabetics around the world have microalbuminuria, a marker of progression to chronic kidney disease (CKD). Diabetic kidney disease (DKD) is also considered a leading cause of CKD worldwide. Given the significant morbidity, mortality, and health-care burden, several clinical and scientific societies continue to seek a better understanding of this disease. Screening for microalbuminuria and controlling hyperglycemia remain the pillars for the prevention of diabetic nephropathy. However, evidence from multiple studies suggests that controlling DKD is more challenging. Some studies suggest that there is variability in the incidence of renal complications among patients despite comparable hyperglycemic control. Therefore, there has been great interest in studying the inherent, renal protective role of the different antihyperglycemic agents. This review will shed light on the pathophysiology, screening, and diagnosis of DKD. It will also discuss the treatment and prevention of diabetic nephropathy, with a specific focus on comparing the mechanisms, safety profiles, and efficacy of the different antihyperglycemic medications.

Keywords: chronic kidney disease; diabetes; diabetic complications; diabetic nephropathy; microalbuminuria

Introduction

Diabetes and chronic kidney disease (CKD) are worldwide public health problems that affect millions of people. A study speculates that the global prevalence of diabetes mellitus would grow from 2.8% in 2000 to nearly 4.4% in 2030, equivalent to nearly 366 million people. The greatest increases in prevalence are anticipated to occur in the Middle East, sub-Saharan Africa, and India (1). Another global epidemiologic study estimated that 382 million people had diabetes in 2013, a number that is expected to rise to 592 million by 2035 (2). This pattern is even more pronounced in the United States with anticipated 165% increase in the prevalence of diabetes between 2000 and 2050 (3). Diabetes is a leading cause of CKD worldwide. Nearly 43% of diabetics in the United States have microalbuminuria, a marker of progression to CKD. According to data from National Health and Nutrition Examination Survey (NHANES), diabetic kidney disease (DKD) accounts for 39% of prevalent kidney failure (4). With the increasing prevalence of CKD, the costs of management are becoming a public health issue. In 2013, more than
Diabetic nephropathy: From pathophysiology to treatment

30 billion dollars from Medicare expenditure were spent on management of end-stage renal disease (ESRD), 14 billion of which were due to DKD (4). Given these factors, clinical societies continue to offer strategies to diagnose and manage DKD to improve outcomes.

Pathophysiology

Diabetes leads to progressive structural alterations of the kidneys including extracellular matrix (ECM) accumulation in the mesangium, glomerular basement membrane, and tubulointerstitial tissue. The pathophysiology of diabetic nephropathy is complex and multifactorial. Poor glycemic control was previously considered the sole driving factor that drives diabetic nephropathy. However, some studies demonstrated variability in the development of renal complications despite comparable hyperglycemic control. For example, the Diabetes Control and Complications Trial (DCCT) showed that nearly 30% of type I diabetics and 25–40% of type II diabetics develop nephropathy despite intensive glycemic control (5). Variations between ethnic groups also point to the significant role of genetic background. Relatives of African Americans on renal replacement therapy secondary to diabetic nephropathy are at fivefold risk of developing ESRD (6). Additionally, the incidence of ESRD per capita in African Americans, Hispanics, and Native Americans is significantly higher than the white population (7). The incidence of proteinuria among Pima Indians has also been increasing over the past 36 years. However, the incidence of progression to ESRD declined after 1990, possibly due to improved control of risk factors (8). A multicenter study in 10 Asian countries on type II diabetic patients of different ethnic groups showed nearly 40% prevalence rate of microalbuminuria, a worrisome marker for developing ESRD (9). Familial aggregation further supports the role of genetics in development of ESRD. A large population-based study showed that nearly 23% of incident dialysis patients had relatives with ESRD, with greater prevalence in African Americans compared to European Americans (10). Individuals with family history of ESRD were also more likely to have diabetes and obesity (11).

AGEs, RAGE, and oxidative stress

Advanced glycosylation end products (AGEs) are the result of nonenzymatic interaction of sugars like glucose with amino acid groups of proteins, lipoproteins, and nucleic acids. Alteration of these cellular components leads to the formation of various reactive intermediate products like α-dicarbonyls or oxoaldehydes. These intermediate products react with intracellular and extracellular proteins to form irreversibly covalent products, known as AGEs. Circulating AGEs have been implicated in the pathophysiology of diabetic nephropathy through mechanisms that are either receptor-dependent or receptor-independent. AGEs modify basement membrane proteins, cross-link ECM components, and increase expression of type IV collagen. These changes lead to structural alterations of the surface charge, membrane permeability, proteolytic digestion, and membrane stability. These changes disrupt intercellular interaction, and hence cause impairment of tissue function and maintenance (12).

As for the receptor-dependent mechanisms, AGEs interact with a wide array of receptors on various cell types such as macrophages, monocytes, endothelial cells, podocytes, tubular epithelial cells, and smooth muscle cells.

Examples of these receptors are the macrophage scavenger receptor type I and II, AGE-R1, AGE-R2, AGE-R3, receptor for AGE (RAGE), and CD36. RAGE is a multi-ligand receptor that mediates intracellular and extracellular signaling pathways leading to immune response initiation. This receptor exists in full-length, surface-bound form or as a soluble, truncated form known as soluble RAGE (sRAGE). It is hypothesized that sRAGE competes with full-length RAGE over ligand binding. The off-balance between the synthesizes of these two forms is one of the AGE-induced nephropathy mechanisms (13). RAGE activation by AGEs leads to activation of several signal transduction pathways that lead to the generation of reactive oxygen species (ROS) and activation of transcription factors, such as NF-kappaB. Consequently, NF-kappaB leads to the release of cytokines and growth factors, including transforming growth factor-β1 (TGF-β1), interleukin-1β and interleukin-6, insulin-like growth factor-1, tumor necrosis factor (TNF-α), and platelet-derived growth factor. These proinflammatory growth factors play a key role in the development of diabetic complications (14). For example, TGF-β1 leads to the overexpression of mRNA of glucose transporter 1 (GLUT-1) in mesangial cells, eventually leading to increased glucose uptake by cells and accelerated metabolic abnormalities (15). Human studies support the proposed AGE-driven mechanism of diabetic nephropathy. A study in type I diabetic patients showed that significantly elevated levels of fluorescent non-carboxymethyllysine AGEs correlate with the deterioration of renal function (16). Similarly, levels of AGEs concentrations were increased in type II diabetic patients with nephropathy (17). As for other AGE receptors, AGE-R1 and AGE-R3 are considered clearance receptors. AGE-R1 expression is suppressed in diabetic human beings and mice, suggesting possible protective role against AGEs. Whereas, AGE-R3 is involved in AGE turnover, tissue integrity, and macrophage endocytosis. These are important compensatory mechanisms that counteract AGE-induced injury. AGE-R2, like RAGE, is involved in fibroblast growth factor signaling and the inflammatory response propagation (14).

Metabolic reactions result in the formation of active byproducts and free radicals known as ROS and reactive nitrogen species. Inadequate removal of these active molecules leads to detrimental effects on the cellular level, a process known as oxidative stress. Examples of these radicals are superoxide, peroxyl, hydroxyl, and hydroperoxyl molecules. Superoxide (O2·−) is a common radical implicated in diabetic complications.
It is produced by mitochondrial electron transport chain, oxidative phosphorylation, NAD(P)H oxidase, cytochrome P-450, nitric oxide synthase, and other enzymatic processes (14). Normally, superoxide radicals are eliminated by mitochondrial and cytosolic antioxidant defense mechanisms. Impaired clearance, as in diabetes, leads to the oxidation of membrane lipids, DNA, proteins, and carbohydrates. These alterations lead to impaired structure and function of several cellular components.

There is evidence that diabetic complications arise from interplay between pathways of AGEs and oxidative stress. A study showed that diabetic glomerular lesions might undergo autoxidation by ROS and could be converted to reactive carbonyl compounds, a subgroup of AGEs (18).

**Sodium glucose cotransporter (SGL-2)**

A new target for pharmacotherapy of diabetic nephropathy is sodium–glucose cotransporter-2 (SGLT-2), a major determinant of glucose reabsorption in kidneys. Hyperglycemia and hyperinsulinemia in early diabetes may lead to increased expression of SGLT-2, and hence, glucose reabsorption. This in turn is believed to lead to worsening of hypertension and maintain hyperglycemia (19). With emergence of SGLT-2 inhibitors, studies started to examine the possible protective role of these medications on the kidneys. Increasing tubuloglomerular feedback, weight loss, lowering blood pressure by osmotic diuresis, and decreasing inflammation through activation of ACE2 and angiotensin 1-7/1-9 upregulation are all possible mechanisms of renal protection by SGLT-2 inhibition (20, 21).

**Glucagon-like peptide-1**

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that stimulates insulin secretion from β-islet cells. In addition to its antihyperglycemic function, GLP-1 has antioxidative protective role in various tissues. GLP-1 receptor (GLP-1R) is expressed in pancreas, brain, gut, heart, lung, and kidneys. Activation of this receptor leads to the stimulation of adenylylate cyclase which in turn increases the production of cyclic adenosine monophosphate (cAMP). Increased levels of cAMP lead to the activation of protein kinase A or guanine nucleotide exchange factor II (Epac2). This pathway mediates insulin secretion and inhibits renal NAD(P)H oxidase, a major source of oxidative stress. A study showed that treatment with GLP-1R agonist reduced albuminuria and mesangial expansion, and reduced expression of glomerular superoxide. These findings highlight the protective role of GLP-1 pathway and its potential as a target for pharmacotherapy (22).

**Screening and diagnosis**

Historically, the term “diabetic nephropathy” has been used loosely to describe the pathologic effect of diabetes on renal function. However, there are key definitions and stages of this process to assist with diagnosis and management. DKD is the finding of proteinuria in a person with diabetes, regardless of the presence of pathologic changes or a decreased glomerular filtration rate (GFR). Diabetic glomerulopathy on the other hand, is a term reserved for biopsy-proven renal disease caused by diabetes. Measuring serum albumin on spot urine tests is the first step in screening and diagnosis of diabetic nephropathy as recommended by most professional medical societies concerned with diabetes and kidney disease (23).

**Albuminuria**

Over the years, the threshold for detection of albuminuria has changed with the introduction of more sensitive assays. Albuminuria is reported as albumin excretion rate (AER), albumin-to-creatinine ratio (ACR), or urinary albumin concentration (UAC). Estimation of AER is obtained from timed collections (expressed in µg/min) or 24-h collection (expressed in mg/24 h). Urine spot test on the other hand provides information about ACR (expressed in mg/g creatinine) and UAC (mg/L). Patients with ACR between 30 and 300 mg/g creatinine on spot urine test (AER 20–200 µg/min or 30–300 mg/24 h) are considered to have microalbuminuria. Greater degrees of albumin excretion are referred to as macroalbuminuria. Variations in ACR with gender are expected, given lower urine creatinine levels in females, which make diagnostic thresholds higher in females compared with males. Sensitivity and specificity of ACR is between 92% and 94%, whereas sensitivity and specificity of UAC is between 89% and 90%, at discriminator value of 15 mg/L. Although ACR performs better than UAC statistically, gender variations and cost make UAC a feasible and accurate option (24). Other studies suggest that using 17 mg/L of UAC as cutoff for detecting microalbuminuria yields 100% sensitivity and 80% specificity when 24-h urine collection was used as reference (25).

Although patients with microalbuminuria have stable kidney function, they are at risk of progressing to macroalbuminuria and kidney failure (26). Physicians must be cognizant of the variability in urine albumin excretion. Levels can vary with exercise, time of day, fever, infection, heart disease, degree of hyperglycemia at time of collection, pregnancy, hypertension, and other physiologic processes (27). Therefore, at least two specimens within 3 to 6 months should be obtained to confirm staging. Twenty-four-hour and timed collections are cumbersome and prone to collection errors.

**Glomerular filtration rate**

GFR should be measured routinely when screening for diabetic nephropathy. Data from NHANES III (Third National Health and Nutrition Examination Survey) showed that nearly 30% of type 2 diabetic patients had worsening GFR despite absence of albuminuria and retinopathy (28). This might suggest that albuminuria may not truly reflect
underlying DKD and raises the question of the inevitability of the disease progression (29). American Diabetes Association, National Kidney Foundation, and other medical societies support annual screening for microalbuminuria, but they recognize the need for further studies to outline benefits of this approach. There is still lack of strong evidence about benefit of screening on major outcomes like ESRD, cardiovascular risk, morbidity, and mortality. GFR can be measured by clearance of endogenous creatinine, insulin clearance, 51Cr-EDTA, 125I-iothalamate, or iohexol techniques. Equations for estimation of GFR are commonly used in clinical practice. National Kidney Foundation recommends using the Modified Diet in Renal Disease (MDRD) equation, which is more accurate than the Cockcroft–Gault equation (30).

**Retinopathy**

Concomitant presence of retinopathy has been considered a helpful finding in screening for diabetic nephropathy. However, careful interpretation of the presence or lack of retinopathy must be done. Type I diabetics with nephropathy almost always have signs of other microvascular complications like retinopathy or neuropathy (31). This correlation is not as clear with type II diabetes. For example, in type II diabetic patients with macroalbuminuria, the positive predictive value (PPV) of retinopathy for diabetic glomerulopathy ranges between 67% and 100%. However, the negative predictive value (NPV) is lower, ranging between 20% and 84%. On the contrary, type II diabetic patients with microalbuminuria had NPV close to 100% and PPV as low as 45%. Hence, the presence of retinopathy is strongly suggestive of DKD in type II diabetics with macroalbuminuria, whereas its absence is highly indicative of non-DKD pathology in type II diabetics with microalbuminuria (32). Given shared determinants like poor glycemic control, hypertension, and hyperlipidemia between diabetic retinopathy and nephropathy, retinopathy should be considered a marker of microvascular involvement rather than a risk factor or diagnostic finding for DKD.

**Atypical features**

Presence of albuminuria and reduced GFR in patients in the absence of other identifiable causes of kidney disease are enough for establishing diagnosis of DKD. Because diabetes is a highly prevalent problem, coincidence with other nondiabetic pathologies is somewhat frequent. Therefore, atypical features such as refractory hypertension, presence of urine sediments, nephrotic syndrome, rapid disease progression despite proper glycemic control, and renin–angiotensin system blockade should prompt further evaluation for nondiabetic kidney disease. Workup for concomitant nondiabetic kidney disease should be tailored based on the patient’s medical history and risk factors. Kidney biopsy can be very valuable in evaluating the underlying disease, but bleeding complications should be considered. Diabetes causes several pathologic changes to the mesangium, tubules, and vasculature in the kidneys. These changes can be classified into four progressive groups according to the Renal Pathology Society classification. Class I is characterized by isolated glomerular basement membrane thickening and mild, nonspecific changes in the mesangium. Mesangial expansion without diffuse glomerulosclerosis or nodular sclerosis (Kimmelstiel–Wilson lesions) is seen in class II diabetic nephropathy. Nodular sclerosis is noted in class II, whereas more severe mesangial matrix changes are noted in class III. Global glomerulosclerosis involving more than 50% of glomeruli is the hallmark of class IV diabetic nephropathy (33).

**Glycemic control: glycemic goals and measurements**

**Standard versus intensive control**

Diabetic complications including nephropathy are mainly driven by hyperglycemia-induced vascular injury. Therefore, glycemic control is in the center of management of DKD which may slowly progress to ESRD. Major medical societies like the National Kidney Foundation and the American Diabetes Association recommend intensive glucose control to goal hemoglobin A1C (HbA1C) levels <7%. The DCCT study closely examined the effect of intensive glycemic control compared with conventional treatment on the development of diabetic complications in 1441 subjects with type I diabetes. Intensive treatment led to about 2% more reduction in HbA1C in comparison to conventional treatment. After 6.5 years of intensive treatment, the incidence of microalbuminuria was reduced by nearly 34% in primary prevention group (patients with no retinopathy or albuminuria at baseline) and by 43% in secondary prevention group (patients with retinopathy and with or without albuminuria but normal GFR at baseline) (5). In 1993, The Epidemiology of Diabetes Interventions and Complications (EDIC) observational study examined 1349 of the original subjects from the DCCT study. Persistent benefits of intensive glycemic control on albuminuria were noted at 7–8 years after DCCT study closeout (34). The DCCT/EDIC research group further confirmed the persistence of these results after median follow-up period of 22 years (35). These results affirmed that intensive glycemic control should be pursued early in type I diabetic while keeping patient’s safety in mind and avoiding hypoglycemia.

Similar association between poor glycemic control and development of albuminuria is noted with type II diabetes. The Kumamoto study was designed similar to DCCT, with 110 Japanese subjects with type II diabetes. Mean HbA1C was 7.1% in intensive glycemic control group compared to 9.4% in conventional treatment group. During 6 years, only 7.7% of subjects in the primary prevention group receiving intensive treatment developed albuminuria compared to 28% in the conventional treatment group. However, subjects of this trial were relatively young with normal body mass...
index, features that are not necessarily typical or generalizable to type II diabetes population (36). In 1998, a larger trial that examined glycemic control effect on nephropathy was the United Kingdom Prospective Diabetes Study (UKPDS) that examined 3867 newly-diagnosed type II diabetics. This study randomized patients to conventional treatment with diet only versus intensive treatment, which was defined by goal fasting glucose of 108 mg/dL. Diet, metformin, sulfonylurea, insulin, or a combination of agents, were used to achieve intensive control. Over 10 years, mean HbA1C in intensive group was 7.0% compared to 7.9% in the conventional group, with no significant differences in HbA1C among agents in the intensive group. Relative risk reduction for the development of microalbuminuria after the duration of the study was 24%. No differences in risk reduction were noted between agents in the intensive group (37). Effect of intensive glycemic control on diabetic complications in a population of 153 veterans was examined by Veterans Affairs Cooperative Study of Diabetes Mellitus (VACSDM). After 2 years, the incidence of microalbuminuria in the intensive treatment group (mean HbA1C of 7.1%) was 17% compared to 35% in the conventional treatment group (mean HbA1C of 9.2%). Veterans who had microalbuminuria at baseline, and received intensive treatment, had retardation of the progression of albuminuria, but still had deterioration of creatinine clearance at 2 years nonetheless (38). The Veterans Affairs Diabetes Trail (VADT) was a large study with mean follow-up of 5.6 years that examined the effects of intensive glycemic control on vascular complications, mainly cardiovascular events. The study included nearly 1791 veterans with suboptimal diabetes type II control. Although the study showed no significant improvement in cardiovascular events, death, neuropathy, or retinopathy with intensive control (mean HbA1C 6.9%) compared to the conventional treatment group (mean HbA1C 8.4%), there was modest improvement in the progression of albuminuria. However, this improvement in albuminuria did not translate into prevention of creatinine and GFR worsening (39). Lack of benefit of intensive control in VADT and VACSDM might be secondary to shorter follow-up duration (possible delayed effect of glycemic control) or longer duration of diabetes in the included veterans compared with the newly-diagnosed subjects in UKPDS.

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, approximately 11,000 patients were randomized to intensive therapy (mean HbA1C 6.5%) compared with standard-control group (mean HbA1C 7.3%) and were followed up for median of 5 years. There was no significant improvement in retinopathy or macrovascular outcomes; however, intensive control was associated with 21% relative risk reduction in new or worsening nephropathy (defined as macroalbuminuria, doubling of creatinine, the need for renal replacement therapy, or death secondary to renal disease) (40). A follow-up study of the ADVANCE trial participants showed persistence of these results with no improvement in retinopathy or macrovascular outcomes but reduction in the progression to ESRD after median total follow-up of 9.9 years (41). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, 10,250 patients with type II diabetes were assigned to intensive (median HbA1C 6.4%) versus standard glycemic control (median HbA1C 7.5%) and followed up for median 3.7 years. Because of higher cardiovascular deaths in the intensive treatment group, patients were switched to standard treatment and microvascular outcomes were followed for the remaining duration of the study (5 years). There was 29% reduction in developing macroalbuminuria at transition and study end with the intensive treatment. There was 19% reduction in development of microalbuminuria at time of transition only with the intensive treatment (42). Worsening or lack of improvement in the cardiovascular outcomes from the ACCORD and ADVANCE trials despite the improvement of nephropathy markers raises concerns about glycemic control. Intensive glucose control should be pursued in low-risk groups to avoid harm from hypoglycemia. As GFR deteriorates, patients become more prone to hypoglycemia, secondary to factors such as prolonged action of insulin, deficiency of gluconeogenic precursors, and malnutrition. Hence, caution with glycemic control is warranted especially in advanced kidney disease.

**Limitations of glycemia measurements**

Intensive treatment is not the only area of uncertainty in management of DKD. The reliability of several glycemic measurement tests has been questioned. HbA1C estimates time-averaged exposure to glucose for a red blood cell with 120-day life cycle. However, as kidney function deteriorates, the life cycle of red blood cells becomes much shorter, resulting in falsely lower HbA1C readings (43). Other comorbidities noted in DKD like acid–base disturbances, anemia, and erythropoietin deficiency may further lower HbA1C (43). Although imprecise, HbA1C should still be performed to assist with therapy decisions while being cognizant of its limitations. Serum fructosamine, a test reflecting glycemic levels over 2–3 weeks period, is a possible alternative to HbA1C. It also reflects levels of total glycated serum proteins (43). Therefore, it might be falsely decreased in DKD secondary to hypoalbuminemia. Serum concentration of 1,5-anhydroglucitol, a monosaccharide that is present in nearly all foods, can be utilized to assess glycemic control. Renal reabsorption of this sugar is dependent on glucose concentration and will be lost in the urine when blood glucose level is higher than 180 mg/dL (43). Since many diabetics usually have higher levels of hyperglycemia, the utility of this test is very limited. In particular, it is not recommended in advanced kidney disease. Glycated albumin is a new marker that reflects average glucose levels over 2–3 weeks. Unlike HbA1C, this test is not affected by low GFR or anemia. However, there is lack of data regarding clinical outcomes and correlation of levels with diabetic
complications. Given the limitations of the aforementioned tests, self-monitoring of blood glucose remains the most valuable tool to guide treatment (43).

**Glycemic control: antihyperglycemic agents**

Like all diabetic complications, hyperglycemia is the major contributing factor to vascular injury and renal disease. Therefore, antihyperglycemic agents are expected to exhibit their renal protective properties by controlling glucose levels. However, there is variability in incidence of renal complications with different antihyperglycemic agents despite comparable glycemic control. This observation led to interest in the inherent renal protective role of these agents that is independent of their antihyperglycemic effect (Figure 1). Our current understanding of these mechanisms is discussed in detail in the following sections.

**Metformin**

Metformin, a drug that was first used in 1958, is widely prescribed for its hypoglycemic and pleiotropic effects (e.g., endothelium protection, polycystic ovarian syndrome, hepatic steatosis, and obesity) (44). Although it is considered the first line of treatment of diabetes, there is controversy about its safety in patients with kidney disease. For many years, the fear of developing lactic acidosis in patients with elevated creatinine deterred a lot of physicians from prescribing the medication. Previous U.S Food and Drug Administration (FDA) guideline advised against using metformin in men with serum creatinine greater than or equal to 1.5 mg/dL and in women with serum creatinine greater than or equal to 1.4 mg/dL. Several proposed mechanisms link metformin to lactate accumulation (45). Several mechanisms were proposed for metformin-associated lactic acidosis including inhibition of lactate conversion through gluconeogenesis in the liver, increased production by glycolysis augmentation, and activation of anaerobic metabolism of glucose in the intestine (46). These mechanisms do not lead to significant accumulation of lactate at usual metformin therapeutic doses because of the conversion of lactate back to glucose in the liver via the Cori cycle (46). Nevertheless, high levels of metformin reduce lactate clearance by the liver, which might ultimately lead to metformin-induced lactic acidosis. On the contrary, several studies questioned whether lactic acidosis in diabetic patients can solely be attributed to metformin use (46). Diabetic patients are predisposed to hyperlactemia with lactate levels being double than those in healthy individuals. Ketoacidosis, heart failure, impaired circulation, liver dysfunction, and physical exercise are all factors contributing to elevated lactate regardless of metformin use (46). Although reported in literature, the risk of metformin-induced lactic acidosis is low and not strongly supported by epidemiologic evidence. A Cochrane analysis of pooled data from 347 studies examined approximately 70,000 patient-years of metformin use. The study revealed no increased risk of fatal or nonfatal lactic acidosis compared to other antihyperglycemic treatments (47). Given mounting evidence against the significance of “pure” metformin-induced lactic acidosis, the FDA announced early in 2016 that metformin can be used safely in patients with stable mild-to-moderate renal impairment. Metformin use is still contraindicated in patients with GFR < 30 mL/min/1.73 m², but no dosage adjustments are needed.

![Figure 1](image-url). The different antihyperglycemic agents exhibit their renal protective properties through hyperglycemia-dependent and independent mechanisms. This figure attempts to map out our understanding of some of these mechanisms.
for GFR > 45 mL/min/1.73m². Initiation of metformin is not recommended or 50% dosage reduction is advised for GFR between 30 and 45 mL/min/1.73m². Frequent monitoring of renal functions is encouraged and discontinuation of treatment is necessary in the presence of concurrent conditions that further increase the risk of lactate accumulation (e.g., sepsis, acute kidney injury, shock, use of radiographic contrast, or myocardial infarction).

Second-generation sulfonylureas

Sulfonylureas are medications that bind to ATP-sensitive K⁺ (Kₐ₅p) channels on the membranes of pancreatic beta cells (48). This leads to trapping of potassium intracellularly, causing cell depolarization and opening of voltage-gated calcium channels (48). The influx of intracellular calcium causes increased secretion of insulin. First-generation sulfonylureas (e.g., chlorpropamide, tolbutamide, acetohexamide) are not commonly used, given the risk of hypoglycemia owing to their long duration of action, risk of hyponatremia, and possible increased cardiovascular risk. Second-generation sulfonylureas (e.g., glipizide, glyburide, glimepiride) are more commonly used for diabetes control (49). Glyburide is almost entirely metabolized by the liver, with elimination of active metabolites in the urine (49). Impaired renal function may lead to higher levels of active metabolites and increased risk of hypoglycemia. Therefore, its use in CKD is not recommended. Interestingly, although metabolized by the liver, glyburide levels were lower than expected in patients with CKD while metabolites remained elevated. This was attributed to possible decreased protein binding leading to rapid metabolism and elimination of parent drug (49). Rapid metabolism of glyburide might contribute to risk of hypoglycemia in CKD. Glipizide on the other hand is metabolized by the liver into inactive metabolites whose clearance is not affected by renal impairment. Hence, dose adjustments for glipizide are not necessary. Nonetheless, cautious use of sulfonylureas is necessary, given their inherent hypoglycemic effect (43).

Thiazolidinediones

Thiazolidinediones (TZDs) (e.g., rosiglitazone, pioglitazone) are medications that act through the activation of peroxisome proliferator–activated receptors, a group of nuclear receptors (50). This process leads to the activation of an intranuclear pathway that leads to increased transcription of specific genes, and consequently, increased storage of fatty acids in the adipose tissue and increased cellular utilization of glucose and carbohydrates. Eventually, these changes result in lower circulating fatty acids and glucose, and improved insulin sensitivity (50). Like sulfonylureas, TZDs are metabolized by the liver and no dosage adjustments are needed. Relatively small studies evaluated whether TZDs were more efficacious than metformin, sulfonylureas, or diet in decreasing albuminuria in type II diabetics. In a 52-week cardiac safety study, rosiglitazone was associated with a decrease in microalbuminuria compared to glyburide (51). Similar outcomes were noted when comparing troglitazone with metformin. It is not clear if TZDs truly have a renal protective role or if these changes were because of better control of glycemia and hypertension in the involved subjects. However, side effects such as hypertension, fluid retention, increased fracture risk in women, bladder cancer, and anemia make its use in CKD unfavorable (43, 49).

Alpha-glucosidase inhibitors

Acarbose and miglitol are saccharides that bind to key enzymes in the small intestine that are required for carbohydrate absorption (48). Competitive inhibition of these enzymes leads to reduced glucose absorption from food which leads to improved serum glucose levels. High frequency of gastrointestinal side effects, like flatulence, and modest HbA1C-lowering effect (0.5%–1.0%) limit the use of those medications. There is no need for dose adjustments in mild or moderate CKD, but they should be avoided when GFR is less than 30 mL/min/1.73m² due to increased plasma levels. There is lack of clinical data comparing alpha-glucosidase inhibitors (AGIs) to other antidiabetic agents in context of renal outcomes (49, 52).

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors or gliptins (e.g., sitagliptin, saxagliptin, and linagliptin) are relatively new hypoglycemic medications that were first approved by the FDA for diabetes treatment in 2006. These medications inhibit dipeptidyl peptidase whose function is to inactivate incretins, GLP-1, and gastric inhibitory polypeptide (53). Subsequently, elevated levels of incretins lead to stimulation of insulin release and inhibition of glucagon release. These changes lead to lowering of blood glucose. With the exception of linagliptin, these medications require dosing adjustments in renal impairment. Given lower risk of hypoglycemia, DPP-4 inhibitors are potentially useful in CKD patients, a population more prone to hypoglycemia (49). The effect of DPP-4 inhibitors on inflammation and microvascular complications was examined by several experimental studies. DPP-4 (also known as CD26) is expressed in the epithelial cells, renal tubules, endothelial cells, and as well as leukocytes. It can bind adenosine deaminase, the deficiency of which can lead to impaired cellular and humoral immunity (54). Therefore, DPP-4 has been considered a possible culprit of renal injury and interest in its inhibition became a focus of many studies. However, the results were conflicting. Tofovic et al. (55) showed that sitagliptin enhanced renovascular response to angiotensin II in hypertensive rats, an effect that may cause a decline in renal function. In contrast, a study by Mega et al. (56) found that chronic low-dose sitagliptin in diabetic rats led to improvement of glomerular, tubulointerstitial, and vascular lesions. A Japanese study of 36 type II diabetic patients with inadequate control despite diet, exercise, and medical
management showed that treatment with sitagliptin led to lowering of postprandial glucose, HbA1C, glycated albumin, blood pressure, and ACR after 6 months of sitagliptin. However, it is not clear if these findings were independent of improved glycemic control (57). A pooled analysis of four studies with 217 subjects with type II diabetes and albuminuria despite RAAS blockade (ACR of 30–3000 mg/g creatinine) examined the effect of linagliptin on renal outcomes. This study concluded that the use of linagliptin in addition to stable RAAS inhibitors led to significant albuminuria reduction, independent of changes in glucose level or blood pressure (58). However, none of these studies were designed to specifically evaluate the effect of linagliptin on microalbuminuria. The Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin (MARLINA–T2D™) trial is a recent multicenter, multinational, randomized, double-blind, placebo-controlled trial that specifically evaluated the effects of linagliptin on glycemic control and renal function compared to placebo in total 350 patients. In 2016, the trial concluded and linagliptin was found to significantly reduce HbA1C by 0.6% over 24 weeks. However, no significant changes in albuminuria were noted compared to placebo group (59, 60). Interestingly, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial, patients receiving saxagliptin had better renal outcomes at the end of trial compared to placebo group. Approximately 13% of saxagliptin group had worse ACR compared to 15.9% of those in placebo group. Also, more people in saxagliptin group had improvement in ACR ratio compared to placebo group, 10.7% and 8.7%, respectively. Although the difference in HbA1C was relatively small, it is unclear whether this desirable effect is secondary to glycemic control or inherent property of saxagliptin (61). The data from SAVOR-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial did report improvement in ACR that is not accounted for by changes in HbA1C (62).

GLP-1R agonists

GLP-1 is an incretin and neuropeptide that is secreted in the intestine and hypothalamus in response to the presence of nutrients. It has potent antihyperglycemic effects such as enhancement of glucose-dependent insulin secretion, proliferation of β-cells, and inhibition of β-cell apoptosis. It also slows gastric emptying, increases satiety, and results in body weight loss (63). GLP-1R agonists also have antioxidative and pleiotropic properties (64). Liraglutide has been shown to inhibit NADPH oxidase, NF-κB, and TNFα-induced oxidative stress pathways in endothelial cells (65). In an experimental study, Fujita et al. (23) showed that GLP-1 receptors are present in glomerular capillary wall, but not tubules, in mice. Their study also showed that GLP-1R-deficient mice had higher urinary albumin levels, increased oxidative stress markers, and more advanced mesangial expansion than mice in the control group despite comparable hyperglycemia levels. On the contrary, liraglutide treatment in nephropathy-prone mice showed reduced albuminuria, mesangial expansion, and superoxide levels. These findings are suggestive of direct protective role against oxidative stress (22). Another experimental study in streptozotocin-induced diabetic rats showed inhibition of oxidative stress and normalization of urinary albumin with liraglutide treatment (66). Clinically, liraglutide has been shown to reduce albuminuria. The SCALE Diabetes Randomized Trial showed nearly 18% reduction in ACR in patients receiving 3.0 mg/day dosing of liraglutide for 56 weeks compared to placebo (67). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial examined the effect of liraglutide treatment and safety in more than 9000 patients. This trial demonstrated better renal outcomes in liraglutide treatment group compared to placebo, defined as composite outcome of reduction in incident macroalbuminuria, doubling of the serum creatinine level, and eGFR ≤ 45 ml/min/1.73m², need for continuous renal replacement therapy, or death from renal disease (68). Exenatide is a synthetic version of the salivary hormone exendin-4, which was first identified in Gila monster in 1992. Exendin-4 has similar properties to human GLP-1. Similarly, exenatide has been shown to have renoprotective potential. In a randomized controlled trial, exenatide was shown to significantly reduce urinary TGF-β1, type IV collagen excretion, and 24-h urinary albumin after 16 weeks compared to glimepiride (69).

In terms of safety, there are some concerns about the use of GLP-1R agonists in moderate and severe CKD. There are few case reports about acute renal injury with exenatide use. However, these patients had other possible contributory factors like gastrointestinal fluid loss and concomitant use of diuretics and angiotensin-converting enzyme (ACE) inhibitors (70, 71). The consensus among most medical societies such as the American College of Endocrinology/American Association of Clinical Endocrinologists, the National Kidney Foundation, the Canadian Diabetes Association, and the European Association for the Study of Diabetes is that no dosing adjustments are necessary with mild impairment, cautious use is needed in moderate kidney, and avoidance is necessary with severe CKD (49). Although there is lack of a large clinical study to assess the safety of GLP-1 receptor agonists in CKD, the emerging evidence (67–69) for their possible renal protective role might change their future use.

Insulin

Assessing inherent role of insulin in prevention of diabetic nephropathy is difficult. There are no head-to-head comparative studies to evaluate for inherent, renoprotective role of insulin compared to other hypoglycemic agents. Improved renal outcomes with insulin are likely driven by better glycemic control. The metabolism of insulin in kidney disease is another important focus which affects dosage requirements (49).
Nearly 60% of renal insulin clearance occurs by glomerular filtrations and 40% by peritubular vessels. Once filtrated, it undergoes extensive reabsorption by the proximal tubule. As the renal function deteriorates, renal insulin clearance declines as well due to reduced renal blood flow (72). Patients with renal failure also have worsening insulin sensitivity, the mechanism of which is not yet clear. Endogenous insulin secretion also worsens with renal impairment (72). Metabolic acidosis and excess parathyroid hormone have been implicated as possible causes of suppressed insulin production from pancreatic β cells (72). Subsequently, these changes in metabolism of insulin reflect on daily requirements. In early kidney disease, insulin resistance leads to worsening of hyperglycemia and escalation of treatment might be necessary. However, impaired renal insulin clearance in advanced kidney disease can lead to higher serum insulin concentration, which in turn can cause hypoglycemia. This may warrant lowering of insulin doses or even cessation of insulin therapy (73).

**Sodium-coupled glucose transporter type 2 (SGLT2) inhibitors**

SGLT2 inhibitors (e.g., canagliflozin, dapagliflozin, and empagliflozin) are new medications that inhibit filtered glucose reabsorption in the renal proximal tubule. This results in significant glycosuria which subsequently leads to low blood glucose levels, weight loss, lower lipid and uric acid levels, decreased oxidative stress, and sodium loss (74). Reduced proximal tubular sodium reabsorption leads to increased sodium delivery to the macula densa, which activates tubuloglomerular feedback which in turn causesafferent vasomodulation and decreased hyperfiltration. These effects can be theoretically beneficial in preserving renal function (75). The increased glycosuria puts patients at increased incidence of dehydration, and genitourinary tract infections, especially candida infection. Experimental studies also suggest that SGLT2 inhibitors induce glucagon secretion from alpha cells, which is counter regulatory mechanism to the medication-induced hypoglycemia. This increase in glucagon secretion could mean that drops in serum glucose levels are less than anticipated with the degree of urinary glucose loss. Another important consideration with the use of SGLT2 inhibitors is that although they improve glycemic control, the increased glycosuria results in worsening of the typical diabetes symptoms such as polyuria, polydipsia, and genitourinary infections (76). Recent clinical trials have shown possible protective role of SGLT2 inhibitor against macrovascular and microvascular complications, nephropathy included. In 2015, the EMPA-REG OUTCOME trial concluded that empagliflozin was associated with better cardiovascular and mortality outcomes compared with placebo (77). The trial also examined renal outcomes that were defined as progression to macroalbuminuria, doubling of serum creatinine level, eGFR ≤ 45 mL/min/1.73m², initiation of renal replacement therapy, or death from renal disease. Approximately 12.7% of the 4124 patients in empagliflozin group had composite incident or worsening of nephropathy, compared with 18.8% of 2061 patients in placebo group. This corresponds to a significant 39% relative risk reduction. Of note, there was no difference between the two groups in rates of incident albuminuria in patients with normal albumin levels at baseline. Some of the limitations of this study are that it was conducted in patients with high cardiovascular risk. Generalization of results to diabetic patients with lower cardiovascular risk or to African–American patients might not reflect the same outcomes (75). Although results of this study are encouraging, more comparative trials with other hypoglycemic agents are needed to shed light on effectiveness of SGLT2 inhibitors.

In terms of safety, SGLT2 inhibitors can safely be used in mild kidney disease, but are contraindicated in severe and ESRD (49). Dosing adjustments and caution are recommended when using these medications in moderate kidney disease. Safety aside, these medications are also not ideal with advanced renal disease because they lose their efficacy, given their tubular-based mechanism of action (49). Studies examining cardiovascular outcomes of other SGLT2 inhibitors like canagliflozin (Canagliflozin Cardiovascular Assessment Study [CANVAS]; ClinicalTrials.gov number: NCT01032629) and dapagliflozin (DECLARE–TIMI58, ClinicalTrials.gov number: NCT01730534) are still ongoing. Renal and safety outcomes from those studies will provide more information about the role of SGLT2 inhibitors in DKD.

**Hypertension management**

Along with increasing albuminuria and decreasing GFR, worsening of hypertension is part of the natural process of DKD. It is one of the most common comorbidities in diabetic nephropathy, with prevalence of approximately 65% in patients with macroalbuminuria and insulin-dependent diabetes (78). Even in the absence of albuminuria, the prevalence of hypertension is high at 58% in type II diabetics. These numbers increase with progression of albuminuria and CKD and approach 90% (79). Based on most recent Joint National Committee (JNC) 8 and KDIGO (Kidney Disease: Improving Global Outcomes) practice guideline, the goal blood pressure in patients with diabetes should be below 140/90 mmHg to reduce cardiovascular mortality and progression to CKD. This recommendation is based on trials that were designed to examine cardiovascular events and not CKD specifically. Also, the trials that supported the goal BP of less than 140/90 mmHg in preventing CKD were in non-DKD patients and included African Americans predominantly. Therefore, the relevance of this recommendation was questioned by experts, and many physicians continue to aim for goal blood pressure of 130/80 mmHg in diabetics with moderate or severe albuminuria (80). The consensus is that more studies are needed to identify blood pressure targets in management of DKD.
As for the choice of antihypertensive medications, ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown by several studies to decrease urine albumin excretion and delay progression of kidney disease in diabetes type I and II. The Irbesartan in Diabetic Nephropathy Trial (IDNT) was a randomized controlled trial that evaluated the effect of irbesartan on progression of DKD. Approximately 1700 patients were randomized to irbesartan, amlopidine, or placebo groups. Although rates of ESRD and death were not significantly different between the groups, irbesartan led to significant slowing of rate of creatinine doubling (81). Another landmark study is the Reduction in Endpoints in NIDDM with the Angiotensin Antagonist Losartan (RENAAL), which randomized 1513 patients with type II diabetes to losartan and placebo groups. The study showed that losartan was associated with reduction of doubling of creatinine but had no effect on death (82). Unlike IDNT, there was reduction in occurrence of ESRD with losartan treatment. The Irbesartan in MicroAlbuminuria (IRMA) showed significant reduction in rates of progression from microalbuminuria to macroalbuminuria with 300 mg irbesartan compared to placebo, further supporting the protective role of ARBs (83). As for primary prevention of albuminuria, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) compared trandolapril, verapamil, combination therapy, and placebo. The study concluded that trandolapril monotherapy and combination therapy were associated with lower incidence of microalbuminuria compared to verapamil alone and placebo (79). This suggests that treatment with ACE inhibitors could delay onset of microalbuminuria in type II diabetics. The Randomized Olmesartan and Diabetics MicroAlbuminuria Protection (ROADMAP) study showed similar findings to BENEDICT (84). The Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial demonstrated non-inferiority of ARBs to ACE inhibitors in preventing GFR decline in type II diabetics. Given the protective role of these medications individually, several studies were interested in assessing combination therapy of ARBs and ACE inhibitors (85). The Candesartan and Lisinopril Microalbuminuria (CALM II) study showed that combination therapy was not different from maximization of initial monotherapy in terms of blood pressure control and albuminuria after 1 year (86). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed higher rates of hyperkalemia, decline in GFR, and incidence of acute kidney failure requiring dialysis with combination therapy (87). The VA NEPHRON-D study examined the rates of acute kidney injury with combined losartan and lisinopril therapy in nearly 1400 veterans. Higher rates of acute renal injury were noted with combination therapy than monotherapy (88). Based on these results, combination of ACE inhibitors and ARBs should not be offered to patients, given lack of strong evidence that shows benefit and potential harm.

Direct renin inhibitors like aliskiren can lower blood pressure and albuminuria in diabetic patients. A study showed that combination therapy with aliskiren and irbesartan achieved lower rates of albuminuria than monotherapy or placebo despite comparable blood pressure control (79). However, the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular Endpoints (ALTITUDE) trial showed increased risk of adverse events and no preservation of renal function. The trial included 8561 diabetic patients with either preexisting cardiac or renal condition. Patients were randomized to 300 mg/day of aliskiren or placebo. All patients were receiving an ACE inhibitor or ARB at baseline as well. After 32 months, 18.3% of patients in aliskiren group reached primary endpoint of cardiovascular event, death from renal or cardiac cause, doubling of creatinine, or onset of ESRD, compared to only 17.1% in placebo group. Adverse effects like hyperkalemia were significantly higher in aliskiren group (15.2% vs. 10.2%). Based on these results, the trial was stopped early (89).

Nondihydropyridine calcium channel blockers, diltiazem and verapamil, appear to have antiproteinuric effects. A small study of 30 type 2 diabetes patients showed that addition of verapamil to lisinopril led to much greater reductions in rates of albuminuria (90). Although promising, there is still no strong evidence about the role of nondihydropyridine calcium channel blockers in management of DKD. Dihydropyridine calcium channel blockers have an even more obscure role in DKD, with studies showing variable effects ranging from worsening proteinuria to no effect to improved albuminuria.

Another area of interest in hypertension management in DKD is the role of mineralocorticoid receptor antagonists. In some patients on ACE inhibitors and ARBs, plasma aldosterone levels increase to pretreatment level which may lead to detrimental changes in the kidneys like worsening of albuminuria and hypertension. This phenomenon is referred to as “aldosterone escape.” Using mineralocorticoid receptor antagonists like spironolactone as an add-on therapy to ACE inhibitor or ARB has been shown to reduce albuminuria in several small, randomized controlled trials. However, increased risk of hyperkalemia raises concerns about combining ACE inhibitors/ARBs with mineralocorticoid receptor antagonists (79).

Bardoxolone methyl was an experimental antioxidant medication that was shown to have benefits in animal models with kidney injury. There was interest in the possible protective role of this medication in DKD. In the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial, nearly 220 patients with type 2 diabetes and low GFR were randomized to bardoxolone methyl treatment or placebo. GFR improved in patients receiving bardoxolone methyl treatment, an effect that was not observed in placebo group (91). However, the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus (BEACON) trial showed that bardoxolone methyl
not only did not improve ESRD or cardiovascular death outcomes but also increased the rate of cardiovascular events (a composite of cardiovascular death, heart failure hospitalization, nonfatal stroke, and nonfatal myocardial infarction). Bardoxolone methyl was also associated with higher blood pressure and albuminuria in the BEACON trial (92).

Despite the continuous interest in finding newer antihyper- tensive medications that could slow the progression of DKD, ACE inhibitors and ARBs remain the most important tools in our arsenal at this time in controlling blood pressure and albuminuria in diabetic nephropathy.

Hyperlipidemia management

Hyperlipidemia is common in patients with diabetes, a condition that is exacerbated with impaired renal function. Elevated cholesterol not only promotes atherosclerosis but also accelerates glomerulosclerosis in CKD. The clinical impact of this process on diabetic nephropathy is not clear. A study in type I diabetics showed that total cholesterol concentration above 220 mg/dL and diastolic pressure above 85 mmHg were the strongest predictors for progressive renal disease (93). Statins remain the most frequently used lipid-lowering medications in managing hyperlipidemia in diabetic patients. According to the 2013 ACC/AHA guidelines for assessment of cardiovascular risk and management of atherosclerotic cardiovascular disease, diabetic patients would benefit from lipid-lowering medications. Different intensities of statins are used in diabetics based on the 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate. Patients with DKD have comparable magnitude of low-density lipoprotein cholesterol reduction with statin therapy to those with normal kidney function. Cardiovascular events and mortality in patients with CKD are reduced with lipid-lowering treatment, statins or statin/ezetimibe, compared to placebo (94). Although statin therapy improves cardiovascular outcomes, it has no beneficial effect on the progression of preexisting kidney disease (95). KDIGO guidelines recommend initiating statin therapy in patients with nondialysis-dependent CKD; however, clinical trials showed no benefits in prevention of cardiovascular death in patients on dialysis. Although there is no strong evidence to support initiating statin therapy in dialysis patients, it is clinically sound to continue statin therapy in patients with CKD who progress to ESRD. A large meta-analysis also showed that statins have a reasonable safety profile in CKD with no significant adverse events (94). Fenofibrate has been shown to slow down progression of albuminuria in type II diabetics. Possible mechanisms for their renoprotective role are suppression of inflammation, decreased production of type I collagen in mesangial cells, and increased activity of peroxisome proliferator-activated receptor-alpha (96–98).

Conclusion

DKD remains the leading cause of CKD despite considerable progress in our understanding of its pathophysiology and risk factors. The focus remains on early screening and prevention of microalbuminuria through the adoption of multiple interventions and strategies targeting control of hyperglycemia, hypertension, and hyperlipidemia. There is promising evidence that some antihyperglycemic agents, like SGLT-2 inhibitors, have inherent renal protective properties that could add to the arsenal of diabetes control. However, more studies that are specifically designed to examine the renal outcomes of the different antihyperglycemic agents are necessary.

Conflict of interest

The authors report no conflicts of interest with respect to research, authorship, and/or publication of this article.

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