Diabetes and Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- Diabetic nephropathy remains the most common cause for CKD in those with type 1, type 2, and other secondary forms of diabetes mellitus.
- Lifetime risk of developing nephropathy is similar for type 1 and type 2 diabetes.
- Predisposing factors for diabetic kidney disease include positive family history; race, particularly if African American, Hispanic, or Pima Indian; obesity; poor blood glucose control; and poor blood pressure control.
- Urinary albumin excretion is a clinical hallmark for the presence of diabetic nephropathy.
- Expansion of mesangium, glomerular basement membrane thickening, and glomerular sclerosis are the major histologic changes of diabetic nephropathy.

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4.1 Epidemiology

Worldwide prevalence of diabetes is expected to increase from an estimated 285 million in 2010 to approximately 439 million by 2030 for ages between 20 and 79 years with estimated health expenditures approximated at 561 billion dollars. Diabetic kidney disease is the leading cause of end-stage renal disease (ESRD) in developed countries with 20–30 % of those with diabetes expected to develop chronic kidney disease (CKD). While the development and progression of diabetic kidney disease has been most studied in those with type 1 DM, clinical and pathologic progression and changes appear to be similar for those with type 2 DM. *Factors predisposing* to the development of nephropathy include a *positive family history* of diabetic kidney disease and

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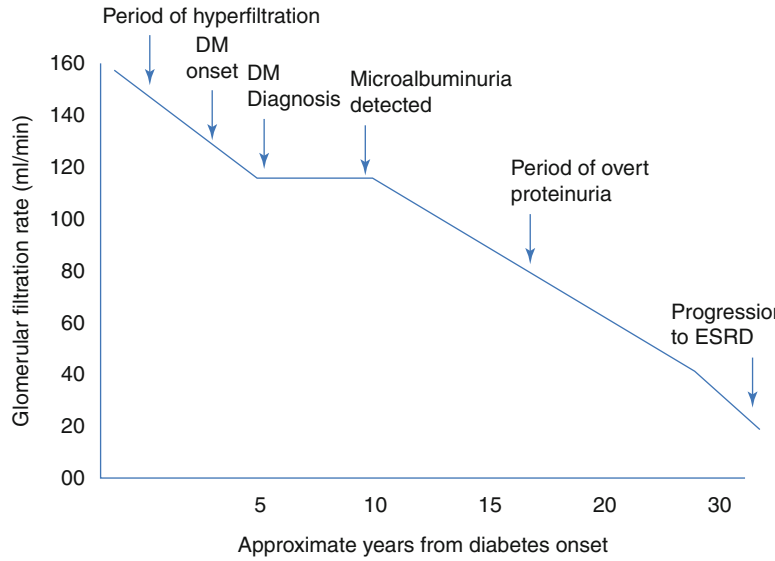

Fig. 4.1 Proposed clinical progression of diabetic kidney disease

ethnicity with particular high prevalence seen in those of African American origin and Hispanic origin and in Pima Indians. In addition, obese individuals seem to be more predisposed to the development of diabetic kidney disease as well as those that have or develop high blood pressure and/or have poor control of their diabetes. Of the modifiable risk factors, smoking and the use of oral contraceptives are noted to have added risk for the development of diabetic nephropathy. Diabetic nephropathy (DN) is clinically characterized by hyperfiltration early on with subsequent occurrence of microalbuminuria, progression to macroalbuminuria over the course of 10–20 years, and then progression to ESRD (Fig. 4.1).

4.2 Clinical Presentation of Diabetic Kidney Disease

Kidney disease develops in approximately 30 % of patients with either type 1 DM or type 2 DM. Diabetic nephropathy is generally a *pathologic diagnosis of diabetic kidney disease* in diabetic patients who have undergone renal biopsy. Diabetic kidney disease is more generally used for the presumed *clinical diagnosis* given to patients with long-standing diabetes with proteinuria in the presence of other diabetic microvascular complications, particularly diabetic retinopathy. Patients with this clinical diagnosis generally undergo clinical evaluation to rule out other secondary glomerular or renal pathology. In patients with long-standing diabetes and CKD without proteinuria or other evidence of microvascular complications such as retinopathy, the presumption of diabetic kidney disease is less certain, and renal biopsy may need to be considered particularly if progression of CKD is rapid (Box 4.1).

Mogensen best characterized the *presentation and progression of diabetic nephropathy* into *5 stages* (Table 4.1): (1) *hyperfiltration* (increased renal plasma flow and increased glomerular filtration) with renal hypertrophy, (2) *normoalbuminuria with pathologic changes* of basement membrane thickening and mesangial expansion, (3) microalbuminuria with early hypertension, (4) *overt urine protein excretion*, and (5) advanced kidney failure with *end-stage renal disease*.

Glomerular hyperfiltration may be noted early in patients with DM and in some patients preceding the diagnosis of diabetes [1]. Several factors can lead to hyperfiltration in the diabetic patient including renal vasodilation induced by elevated blood glucose levels and glycosylated proteins, insulin-like growth factor, atrial natriuretic peptide, as well as increased proximal tubular NaCl reabsorption. Blood glucose control and

Box 4.1. Criteria for Renal Biopsy in Patients with Diabetes and Kidney Disease to Rule Out Other Glomerular Pathologies

1. Rapid deterioration of renal function
2. Diabetes duration <10 years
3. No evidence of microalbuminuria or gross proteinuria despite long-standing diabetes
4. No evidence of other microvascular complications such as retinopathy in the presence of diabetes
5. Signs and symptoms of other systemic diseases
6. Sudden onset or rapidly increasing levels of proteinuria or nephrotic syndrome
7. Active urine sediment

Source: Recommendations based on authors' clinical practice. See also NKF Clinical Practice Guidelines [21]

Table 4.1 Clinical stages of presentation and progression of diabetic kidney disease

Stage 1	Hyperfiltration with renal hypertrophy	Increased renal plasma flow and increased glomerular filtration
Stage 2	Normoalbuminuria	Pathologic changes of basement membrane thickening and mesangial expansion
Stage 3	Microalbuminuria (30–300 mg albumin/g creatinine)	Early hypertension
Stage 4	Overt proteinuria >300 mg albumin/g creatinine	Increased urine protein excretion
Stage 5	Advanced kidney failure	Progression to end-stage renal disease

blood pressure control are noted to decrease hyperfiltration.

Microalbuminuria *defined* as urine albumin excretion of 20–200 ug/min (or 30–299 mg/24 h or 30–300 mg albumin/g creatinine in a random urine sample) hallmarks the early onset of diabetic kidney disease with overt proteinuria noted within 10 years of persistent microalbuminuria. Though regression to normoalbuminuria can be seen in some patients with good metabolic control, progression to macroalbuminuria frequently occurs with intermittent and gradual increase of urine protein. Persistent and increasing overt proteinuria over 5–10 years frequently results in gradual loss of renal function, fluid retention and edema, and eventual need for renal replacement therapy. Urine sediment is often bland for patients with diabetic kidney disease; however, microhematuria may also occur. An active urine sediment with dysmorphic red cells, red or white cell casts, or persistent significant hematuria should be investigated to rule out other glomerular or genitourinary pathologies. In addition, glomerulopathy other than diabetic nephropathy should also be entertained in patients that have onset of diabetes less than 10 years or have no evidence of other microvascular disease, microalbuminuria, or proteinuria or in those with diabetes who appear to have a rapid deterioration in their kidney function.

Screening for microalbuminuria should be at least yearly from the time of diabetes diagnosis with a positive result confirmed for persistence of proteinuria over the next 3–6 months. Microvascular disease including retinopathy and neuropathy is often evident in those with both type 1 and type 2 diabetes even prior to the diagnosis of diabetic nephropathy. These findings are less reliable in those with type 2 DM with 60–70 % presenting with concurrent microvascular disease. Therefore, careful screening and follow-up for microvascular disease in patients with diabetes is also important (Box 4.2).

Box 4.2. What the Guidelines Say You Should Do: Screening Recommendations for Diabetic Kidney Disease

1. Urine albumin creatinine ratio (ACR) in spot urine, serum creatinine with calculated estimated GFR at 5 years after type 1 DM diagnosis, or at diagnosis of type 2 DM, then yearly.
2. Follow up confirmation of microalbuminuria and proteinuria within 3–6 months if noted on initial screening.

Source: Data from KDOQI [21]

4.3 Pathologic Manifestations and Proposed Mechanisms of Diabetic Nephropathy

Changes in *renal histology* associated with diabetes can usually be seen within 3–5 years of diabetes onset, although glomerular and tubular basement membrane thickening has been noted as early as 1.5–2.5 years after the onset of type 1 DM. Glomerular basement membrane thickening with proteinuria may also precede the clinical diagnosis of diabetes in some patients. Changes in glomerular hemodynamics may not necessarily parallel these early changes in histology. Glomerular filtration rate by inulin clearance and effective renal plasma flow by para-aminohippurate clearance did not change significantly when compared to renal biopsy changes at 1 year and 6 years in type 1 DM patients with mean diabetes duration of 10 years at initial biopsy. Further changes in the mesangium with matrix expansion may be seen within 5–7 years of diabetes onset although interstitial expansion occurs [2] and progresses in a variable manner over 15–20 years in both type 1 and type 2 DM. These *changes* have been recently *classified* by expert renal pathologists and summarized as presented in Table 4.2. Figures 4.2, 4.3, and 4.4 represent classic pathologic changes in diabetic nephropathy.

Increased blood glucose affects various pathways leading to podocyte injury and cell apoptosis. Hyperglycemia is associated with oxidative stress-induced production of reactive oxygen species, proinflammatory transcription of nuclear factors, increased flux of polyol and hexosamine pathways with increased protein kinase C, transforming growth factor-β, renin-angiotensin-aldosterone, and advanced glycation end products. These effects result in extracellular matrix protein deposition in the glomerulus and tubulointerstitium. Laboratory studies have also noted *abnormal insulin signaling as contributing to changes in podocyte structure and function*. Both mitogen-activated protein kinase (MAPK) and phosphoinositide-3 kinase (PI3K) pathways work via the insulin receptor to remodel the actin cytoskeleton of podocytes with abnormal signaling leading to altered actin dynamics and podocytopathy. The concept of *metabolic memory* has also been suggested to *play a role* in the continued *pathogen-*

Table 4.2 Classification of diabetic glomerular changes

Class 1	Glomerular basement membrane thickening	Isolated glomerular basement membrane thickening and only mild, nonspecific changes by light microscopy that do not meet the criteria of classes II through IV
Class II	Mesangial expansion, mild (IIa) or severe (IIb)	Glomeruli classified as having mild (<25 %) or severe (>25 %) mesangial expansion but without nodular sclerosis (Kimmelstiel-Wilson lesions) or global glomerulosclerosis in more than 50 % of glomeruli
Class III	Nodular sclerosis (Kimmelstiel-Wilson lesions)	At least one glomerulus with nodular sclerosis but does not meet criteria for class IV
Class IV	Advanced diabetic glomerulosclerosis	Lesions from class I–III plus >50 % glomeruli with global glomerulosclerosis

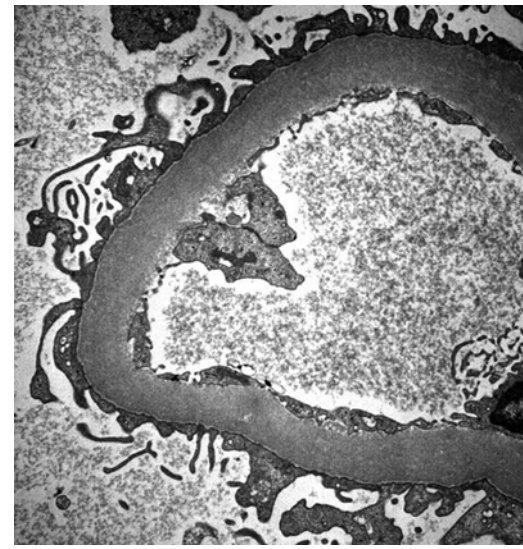

Fig. 4.2 Electron microscopy of thickened glomerular basement membrane in diabetic nephropathy (Courtesy of Irfan Warraich, MD)

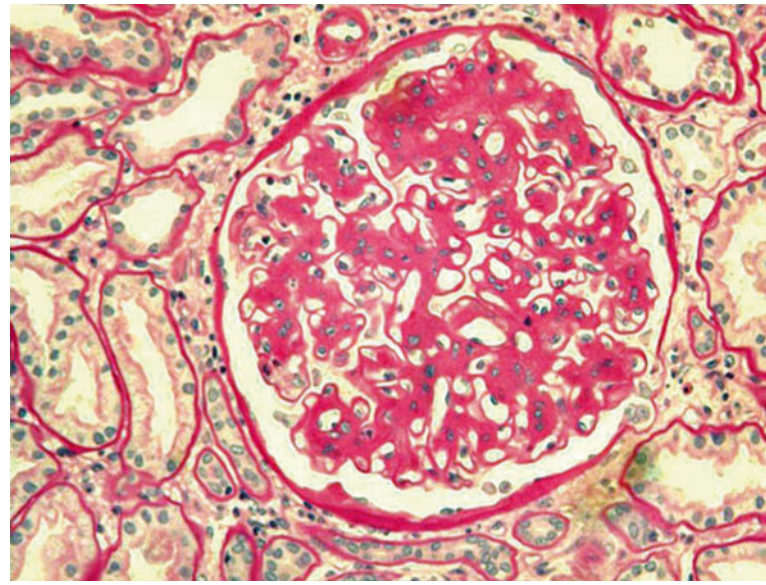

Fig. 4.3 Mesangial expansion and thickened basement membrane in diabetic nephropathy on light microscopy with PAS staining (Courtesy of Irfan Warraich, MD)

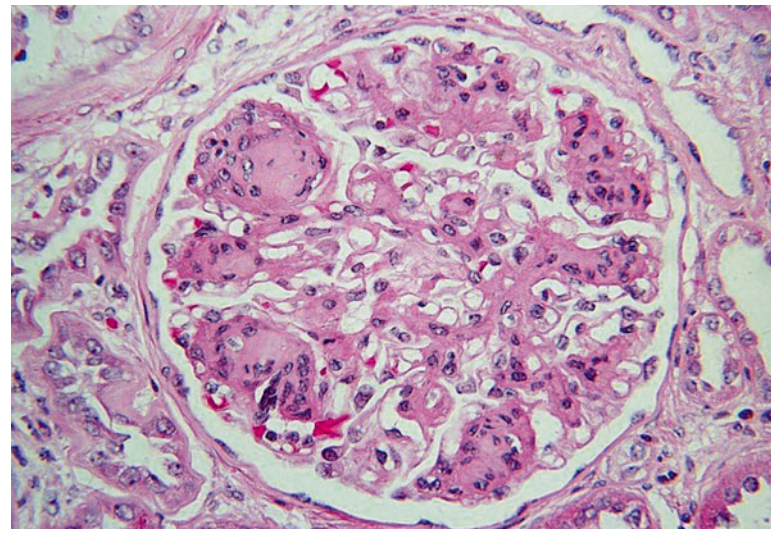

Fig. 4.4 Classic changes of diabetic Kimmelstiel-Wilson nodules in addition to mesangial expansion and basement membrane thickening on light microscopy with H&E stain (Courtesy of Irfan Warraich, MD)

esis of diabetic nephropathy despite achievement of blood glucose control. Epigenetic mechanisms such as hyperglycemia-mediated post-transcriptional histone acetylation, deacetylation, methylation, demethylation, phosphorylation, ubiquitination, and activation of microRNAs may serve as metabolic memory that leads to gene regulation when transient hyperglycemia occurs despite good blood glucose control. These important biologic associations are important for further understanding of pathologic changes in diabetic nephropathy with hopes of treatment that can prevent these irreversible processes.

4.4 Prevention and Treatment of Diabetic Nephropathy

A multi-targeted approach in *treating the risk factors leading to diabetic kidney disease* as well as avoidance of nephrotoxins that can affect

Table 4.3 Medications associated with poor glycemic control

Medication or class of medication	Mechanism of poor glycemic control
Steroid agents	Weight gain, increased hepatic glucose production, decreasing peripheral insulin sensitivity
Calcineurin inhibitors Tacrolimus > cyclosporine	Impaired insulin secretion, possible islet cell damage
Sirolimus	Decreased insulin sensitivity and insulin content and decreasing islet cell mass
Antidepressants (Doxepin, imipramine, mirtazapine, phenelzine, tranylcypromine)	Weight gain
Antipsychotics (Fluphenazine, haloperidol, paliperadone, perphenazine < quetiapine, risperidone, thioridazine < clozapine, olanzapine)	Weight gain (clozapine and olanzapine dysregulate insulin and carbohydrate metabolism)
Mood stabilizers (Carbamazepine < gabapentin < lithium, valproate)	Weight gain

renal function appears to be best for those with diabetes. Treatment in the progression of DN should start with *strict control of hyperglycemia* (glycosylated hemoglobin A1C <7.0 %), *normalizing elevated blood pressure*, and avoidance of hyperfiltration [3, 4]. With dyslipidemia adding to microvascular damage and progression of DN, *lipid lowering* becomes an important part of the treatment. An *LDL goal of <100 mg/dl* (<70 mg/dl for those at high risk) is advocated in DM patients [5]. Since tobacco users are at increased risk of micro- and macrovascular complications, *smoking cessation* must also be advocated early on in patients with DM. Careful use and follow-up are necessary with various medications associated with poor glycemic control including steroids, calcineurin inhibitors, sirolimus, as well as several antipsychotic agents, particularly in those with diabetes or predisposed to diabetes (Table 4.3). Similarly the presence of hepatitis C virus (HCV) infection is associated with insulin resistance, decreased glucose uptake, glycogenesis, as well as pancreatic β cell toxicity. In addition, poor glycemic control often results with various bacterial infections. Therefore, treatment of acute and chronic infections in those with underlying diabetes can improve glycemic control. *Weight control* becomes important as increased weight and obesity are associated with an increase in protein excretion in patients with diabetes. Furthermore, vigilance in *avoiding or minimizing exposure* of patients with diabetic kidney disease or high risk for diabetic kidney disease *to common nephrotoxins* including intravenous radiocontrast agents, nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, or herbal and/or oral supplements of unclear sources should be practiced.

4.4.1 Glycemic Control

Hyperglycemia exacerbates microvascular complications of retinopathy, nephropathy, and neuropathy in DM; therefore, *strict glycemic control* to reach near-normal blood glucose levels *delays development and progression of diabetic nephropathy* [4, 6]. The Diabetes Control and Complications Trial (DCCT), a prospective study of 1441 type 1 DM patients randomly assigned to either intensive or conventional therapy, demonstrated that intensive therapy targeted at maintaining near-normal blood glucose levels markedly reduced the risks of development or progression of microvascular complications over an average of 6.5 years' follow-up period [6]. In a smaller study of Japanese individuals, intensive blood glucose control using insulin in type 2 DM patients with target fasting blood glucose of 110 mg/dl, hemoglobin A1C 6.5 %, and 2 h postprandial blood glucose of 180 mg/dl also confirmed delay in the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with type 2 DM [8]. Reversal of established DN lesions with more than 5 years of normoglycemia with pancreas transplantation further underscores the importance of glycemic control [9].

However, *glycemic targets should be individualized* for each *patient and weighed against the*

increased risk for hypoglycemia. Microvascular benefits of intensive glycemic control (target HbA1c of <6.0 %) need also be considered in light of a greater risk for cardiovascular mortality as well as overall mortality in addition to increased risk for weight gain and high risk for hypoglycemia. Cautious monitoring of hemoglobin A1C is essential with a glycosylated hemoglobin A1C value of ≤7.0 % appropriate for most patients; however, glycemic targets are generally higher for children (given hypoglycemia unawareness), adolescents, and older patients (given life expectancy) (Box 4.3).

Exogenous insulin agents are usually necessary to achieve optimal glycemic control for type 1 DM. Lispro, aspart, and glulisine are fast-acting insulin analogs and quickly absorbed. A short duration of action makes these agents useful for blood glucose control during a meal compared to regular insulins. Glargine and detemir are long-acting analogs to mimic basal insulin release with lower peak action in order to decrease the number of hypoglycemic events [10].

Pancreas or islet transplantation provides excellent glycemic control and freedom from insulin use, making these treatments attractive. Insulin independence at 1 year is approximately 80 % with either treatment. However, the morbidity of major surgery for pancreas transplantation, with requirements for long-term immunosuppression with either pancreas or islet transplantation, is an important factor that needs to be considered with these treatment options [11]. Adult stem cells that can induce islet and beta cell function are under current investigation and may provide other treatment options for glycemic control in the prevention of diabetic nephropathy in patients with type 1 DM [12].

Box 4.3. What the Guidelines Say You Should Do: Recommendations of Diabetes Care in CKD

1. HbA1c at or near 7 % is currently recommended for those with diabetes to prevent microvascular complications.
2. Avoid strict HbA1C <7 for those with risk for hypoglycemia.
3. HbA1c targets above 7 % are acceptable for those with repeated hypoglycemic events or decreased life expectations.

Source: Data from KDOQI [21] and American Diabetes Association [22]

A number of *oral agents* are available for patients with type 2 diabetes for blood glucose control prior to using insulin therapy. The use and choice of oral agents should be made on the basis of patient tolerability as well as renal clearance. Oral hypoglycemic classes of *insulin sensitizers* biguanides and thiazolidinediones (TZDs) directly improve insulin action. The biguanide metformin is often not used in patients with decreased GFR given the risk for lactic acidosis. US Food and Drug Administration (US FDA) recommends avoidance in patients with serum creatinine over 1.4 mg/dl for women and 1.5 mg/dl for men, whereas the British National Formulary and Japanese Society of Nephrology recommends avoidance in diabetic patients with renal clearance less than 30 ml/min. TZDs act by stimulating the nuclear hormone receptor PPARγ to decrease insulin resistance with favorable effects of decreasing urinary albumin excretion [13]. However lower doses of TZDs are recommended when used for patients with serum creatinine >2.0 mg/dl and not recommended for use in those with concurrent New York Heart Association class III or IV heart failure as these agents lead to increased fluid retention. In addition, TZDs have potential for hepatotoxicity, decreasing bone density with increased risk for fracture, particularly in women.

Of the *oral insulin secretagogues*, first-generation sulfonylureas are not recommended for use in patients with CKD beyond stage 2 given an increased risk of hypoglycemia. Of the second-generation sulfonylureas, glipizide and gliclazide require no dose adjustment in patients with reduced renal clearance. Of the glinides, dose adjustment is usually not necessary; however, initiation with lower doses of repaglinide is suggested with cautious monitoring given reported cases of hypoglycemia in those with impaired kidney function. Oral dipeptidyl peptidase IV (DPP-IV) inhibitors (sitagliptin and saxagliptin) may be used at reduced doses with renal clearances less than 50 ml/min.

Of the *non-oral insulin secretagogues*, glucagon-like peptide 1 (GLP1) agonists exenatide and liraglutide have increased risk of hypoglycemia when used with insulin, and their use is not recommended in patients with renal clearances <30 ml/min. Of other non-oral agents, amylin analog pramlintide should also be avoided in those with renal clearances <20 ml/min. Any specific effects of these agents on diabetic nephropathy are yet to be determined.

Other oral agents that decrease blood glucose by decreasing intestinal carbohydrate and fat absorption are alpha-glucosidase inhibitors. Alpha-glucosidase inhibitors acarbose and miglitol are not recommended for use in patients with serum creatinine >2.0 mg/dl (177 mmol/l) (Table 4.4).

Another potential target to control blood glucose is selective inhibition of the proximal renal tubule glucose transporter, SGLT2. Found primarily in the S1 segment of the proximal renal tubule, these inhibitors lead to glucosuria and may have beneficial effects on glucose regulation in individuals with type 2 diabetes [14]. Canagliflozin has recently been approved for use in the USA, while dapagliflozin is available outside of the

Table 4.4 Dose adjustment for insulin and oral medications for diabetes and CKD

Medication class and agents	CKD stages 3, 4, and 5 (not on dialysis)
Insulin	
Glargine, detemir, neutral protamine Hagedorn (NPH), Regular, aspart, lispro, Glulisine	Adjust dose based on patient response
First-generation sulfonylureas	
Acetohexamide	Avoid use
Chlorpropamide	Decrease dose 50 % for GFR between 50 and 80 ml/min/1.73 m^2
Tolazamide, tolbutamide	Avoid use for GFR <50 ml/min/1.73 m^2 Avoid use
Second-generation sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start 1 mg daily
Glyburide	Avoid use
Gliclazide	No dose adjustment
Meglitinides	
Repaglinide	Start 0.5 mg with meals if GFR <30 ml/min/1.73 m^2
Nateglinide	Start 60 mg with meals if GFR <30 ml/min/1.73 m^2
Biguanides	
Metformin	US FDA recommends not to use for SCr ≥1.5 mg/dl for men and 1.4 mg/dl for women British National Formulary and Japanese Society of Nephrology recommends discontinuation for GFR <30 ml/min/1.73 m^2
Thiazolidinediones	
Pioglitazone, rosiglitazone	No dose adjustment necessary
Alpha-glucosidase Inhibitors	
Acarbose	Avoid if GFR<30 ml/min/1.73 m^2
Miglitol	Avoid if GFR <25 ml/min/1.73 m^2
DPP-4 inhibitor	
Sitagliptin	100 mg daily for GFR >50 ml/min/1.73 m^2; 50 mg daily for GFR 30–50 ml/min/1.73 m^2; 25 mg daily for GFR <30 ml/min/1.73 m^2
Saxagliptin	5 mg daily for GFR >50 ml/min/1.73 m^2; 2.5 mg daily for GFR ≤50 ml/min/1.73 m^2
Linagliptin	No dose adjustment
Vildagliptin	50 mg twice daily for GFR ≥50 ml/min/1.73 m^2 50 mg daily for GFR <50 ml/min/1.73 m^2
Incretin mimetic	
Exenatide	Not recommended for GFR <30 ml/min/1.73 m^2
Liraglutide	Not recommended for GFR <60 ml/min/1.73 m^2
Amylin analog	
Pramlintide	No dose adjustment, however not recommended for patients with CKD 4 or greater
Dopamine receptor agonist	
Bromocriptine mesylate	Not studied in patients with reduced GFR

Source: Data from KDOQI [21]

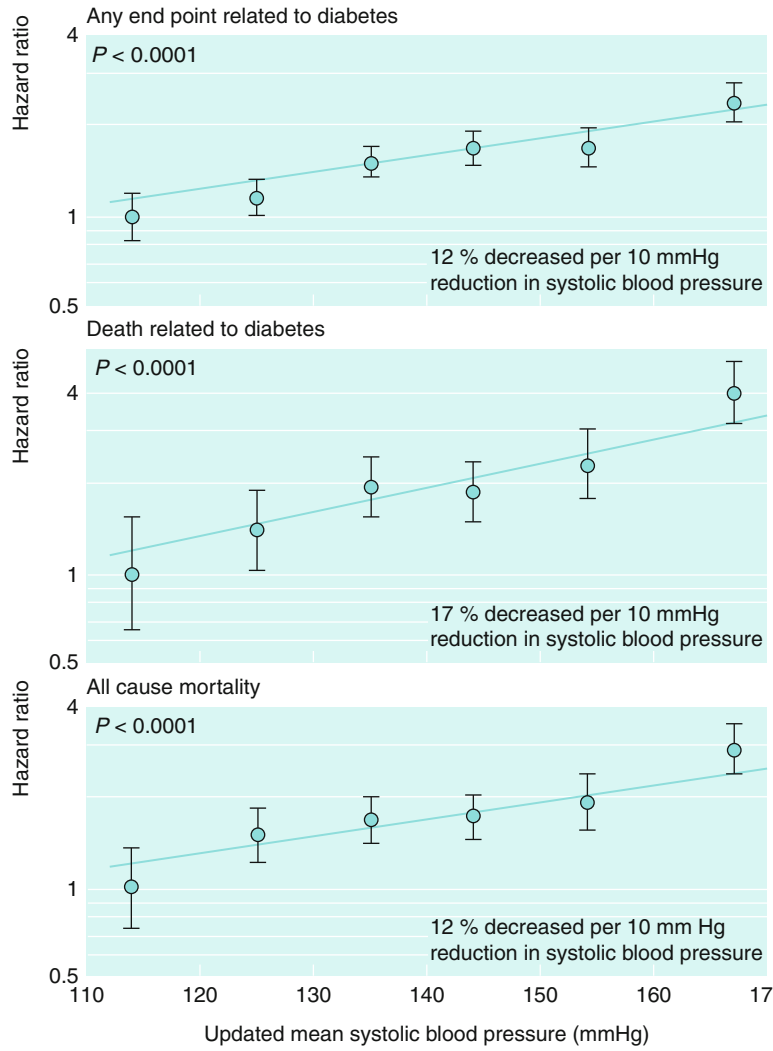

Fig. 4.5 Hazard rates (95 % confidence intervals as floating absolute risks) as estimate of association between category of updated mean systolic blood pressure and any end point related to diabetes, death related to diabetes, and all-cause mortality with log-linear scales (Reproduced from Adler et al. [23], with permission from BMJ Publishing Group Ltd.)

USA. Currently canagliflozin use is not recommended for renal clearance below 45 ml/min with dose adjustment to 100 mg daily for those with GFR between 45 and 60 ml/min. Other potential agents are currently being evaluated for use with their use in those with decreased renal clearances and/or specific effects on diabetic kidney disease being currently investigated.

4.4.2 Blood Pressure Control

Strict blood pressure control in patients with DM reduces onset of both microalbuminuria and macroalbuminuria and improves retinopathy when systolic blood pressure is targeted <130 mmHg. In addition, there is graded and continuous increase in mortality with increasing blood pressure in patients with diabetes across the entire range of levels of systolic blood pressure, including prehypertensive levels (Fig. 4.5). The United Kingdom Prospective Diabetes Study (UKPDS) including 4,801 patients with type 2 DM showed that every 10 mmHg decrease in systolic pressure was associated with a 12 % decrease in risk of diabetic complications [7]. The lowest risk was at a systolic pressure below 120 mmHg. While these data prompted the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and

Treatment of High Blood Pressure (JNC 7) to recommend starting antihypertensive agents in patients with diabetes who have systolic blood pressures of 130 mmHg or higher with a targeted systolic blood pressure below 130 mmHg, more recent trials examining blood pressure in diabetics have provided less clear evidence for a lower limit of systolic blood pressure.

The impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial suggested that BP ≤120/85 mmHg may be associated with an increase in CV events. Similarly the ACCORD BP trial assessed the effect of targeting a systolic blood pressure of 120 mmHg, as compared with a goal of 140 mmHg, in type 2 diabetics at high risk for cardiovascular events. Study results failed to show a decrease in rate of composite cardiovascular events with rigorous blood pressure control [15]. Given these data, individualizing blood pressure control to avoid symptomatic hypotension while achieving systolic targets close to 130 mmHg may be appropriate (Box 4.4).

Blood pressure control with RAAS-*blocking agents are particularly favorable in patients with type 1 and type 2 diabetes* given their additional benefits of decreasing intraglomerular pressure and hyperfiltration to reduce urine protein excretion beyond effects on BP. The use of angiotensin converting enzyme inhibitor (ACEI), captopril, in type 1 DM patients decreased urine protein excretion and doubling of serum creatinine independent of the effects of blood pressure. Two major clinical trials, Irbesartan Diabetic Nephropathy Trial (IDNT) and Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy (REENAL), demonstrated renoprotective effects of angiotensin receptor blockers (ARBs) in type 2 diabetic patients with diabetic nephropathy. However, combination therapy with ACEI and ARBs does not seem to add further benefit to use of ACEI or ARB alone and in fact was associated with increased hypotension, syncope, and renal dysfunction. Similarly combination use of a direct renin inhibitor (aliskiren) with either an ACEI or ARB did not preserve kidney function and was associated with increased events of hypotension and hyperkalemia [16]. Thus careful monitoring of blood pressure to avoid hypotension, thereby decreasing kidney perfusion, and hyperkalemia is of paramount importance with the use of RAAS agents particularly for diabetic patients with baseline kidney dysfunction. In addition, the use of ACEI and ARBs is contraindicated during pregnancy because of teratogenicity.

Box 4.4. What the Guidelines Say You Should Do: Blood Pressure Recommendations in DKD

1. Recommended target blood pressure for those with CKD 1–4 is <130/80 mmHg.
2. RAAS blockers with a diuretic are recommended as the first choice if tolerated by the patient.

Source: Data from KDOQI [21]

4.4.3 RAAS Blockers Not for Primary Prevention

While RAAS-blocking agents have shown benefit in decreasing urinary protein excretion, current evidence does not support the use of ACEI and ARB for the primary prevention of microalbuminuria in diabetic patients. With a lack of clinical trial data showing benefit of RAAS in preventing development of microalbuminuria in normoalbuminuric, normotensive patients with either type 1 or type 2 DM, these drugs cannot be recommended for primary prevention for this purpose [17, 18].

4.4.4 Lipid Control

Elevated triglycerides and LDL cholesterol are a common pattern of hyperlipidemia in diabetic patients. Moreover, the tendency for dyslipidemia is further increased by the development of CKD. Since diabetes is considered a coronary artery disease equivalent, *aggressive lipid lowering* becomes *important* in the intensive medical

management of all patients with diabetes. Hyperlipidemia is also thought to play a role in the development of glomerulosclerosis in CKD patients (Box 4.5).

Hydroxymethylglutaryl-coenzyme A (*HMG-CoA*) *reductase inhibitors* (statins) remain *first-line agents* in achieving target low-density lipoprotein (LDL) levels in diabetic patients. In addition, statins have anti-inflammatory effects by decreasing inflammatory chemokines, such as MCP-1, VCAM1, and ICAM1, and cytokines TNF and IL1β. Antioxidant effects of statins on mesangial and tubular cells in diabetic rodent models have suggested a decrease in diabetic nephropathy with their use. Studies in diabetic patients suggest a decrease in microalbuminuria with statin use. Secondary analysis of the randomized placebo-controlled Collaborative Atorvastatin Diabetes Study (CARDS Trial) however did not find differences in either the incidence of albuminuria or regression of albuminuria in diabetics though there was a modest benefit in estimated GFR in those treated with statins. Statin-treated group showed a modest benefit in estimated GFR [19].

Box 4.5. What the Guidelines Say You Should Do: Recommended Lipid Lowering in Diabetic Patients with Renal Disease (CKD 1–4)

1. LDL cholesterol (LDLc) <100 mg/dl; <70 mg/dl is a therapeutic option.
   (a) Statin is recommended for those with LDLc >100 mg/dl.
2. ADA recommends HDL levels in men and women older than 50 years of age. No specific recommendations have been made for those with chronic kidney disease.
3. ADA recommends triglyceride levels <150 mg/dl in general. No specific recommendations for triglyceride levels have been made for those with chronic kidney disease.

Sources: Data from KDOQI [21] and American Diabetes Association [22]

The use of fenofibrate in type 2 DM patients is associated with an improvement in lipid profiles in addition to a decrease in the rate of progression from normoalbuminuria to microalbuminuria. Fenofibrates in part mediate clinical effects via PPAR-α activation resulting in a 35–50 % decrease in triglyceride levels and a 5–20 %increase in high-density lipoprotein (HDL) cholesterol. These agents also moderately decrease total and LDL cholesterol. The use of fenofibrates, however, requires dose adjustment for creatinine clearance of <50 ml/min.

The use of statins in combination with fibric acid derivatives does increase risk for myopathy and/or rhabdomyolysis with incidence reported in the literature of 0.12%, particularly in those with comorbidities including diabetes and kidney disease, as well as increased age, female gender, increased exercise habits, alcoholism, thyroid disease, liver disease, or those undergoing surgery. Therefore, caution in weighing benefits with risks, as well as careful follow-up of patients, is required in those with underlying predisposition and specific need for combined therapy.

4.4.5 Weight Control

Weight control remains a crucial part in the management of diabetic patients as an increase in waist circumference is associated with progression of albuminuria in type 2 diabetics [20]. *A reduction in weight has been shown to improve kidney function and decrease urine protein excretion in obese patients with diabetic nephropathy* (Fig. 4.6).

Since the use of anti-glycemic agents such as sulfonylureas, thiazolidinediones, and insulin is often associated with modest weight gain, control of weight in diabetic patients becomes challenging. Therefore, the effect of weight gain and weight control, in addition to blood glucose control with use of anti-glycemic agents, must be carefully balanced in order to optimize the effect of weight in its contribution to diabetic kidney disease.

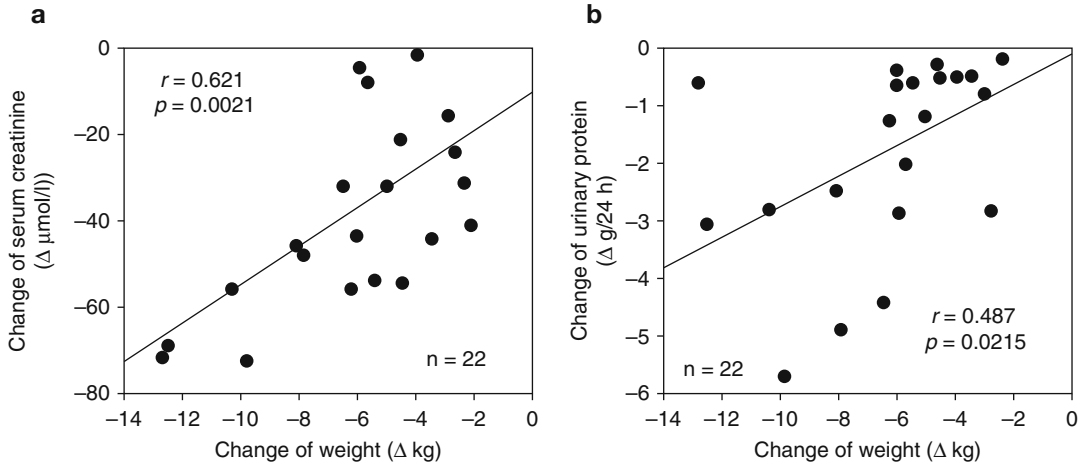

Fig. 4.6 (**a**) Correlation between change of the body weight and change of serum creatinine. Decrease in serum creatinine and weight loss show a significant correlation ($r=0.62$, $P<0.005$). (**b**) Correlation between change of the body weight and change of urinary protein. Decrease in proteinuria correlates with weight loss ($r=0.49$, $P<0.05$) (Reprinted by permission of Macmillan Publishers Ltd: Saiki et al. [24], copyright 2005)

4.4.6 Protein Restriction

Whether dietary protein restriction slows the long-term decline in GFR in diabetic nephropathy is unclear. In addition to the problem of a lack of patient adherence to treatment, protein malnutrition becomes a problem particularly for type 1 diabetics who are at increased risk for protein breakdown from insulin deficiency. A dietary protein intake of 0.8–1.0 g/kg of body weight per day is reasonable though it remains unclear at this time whether careful protein intake adds further in the management of nephropathy given aggressive blood pressure and blood glucose control as well as RAAS inhibition.

Before You Finish: Practice Pearls for the Clinicians

- Early diagnosis of DN is crucial in preventing long-term devastating consequences of kidney failure, and screening for urine albumin excretion should be routine for those with diabetes, particularly for those at high risk.
- Microvascular disease including retinopathy and neuropathy frequently coexists with diabetic kidney disease although the absence of other microvascular diseases does not rule out the presence of diabetic kidney disease.
- As chronic kidney disease from diabetes progresses over decades, a rapid loss of kidney function in those with diabetes or diabetics with active urine sediment suggestive of other glomerular pathologies require further investigation including kidney biopsy if indicated.
- Optimizing blood glucose control, blood pressure, serum lipids, and weight in patients with diabetes is crucial early on to prevent progression to nephropathy and improve cardiovascular mortality.
- Avoidance or minimizing nephrotoxins in those with diabetic kidney disease is necessary.
- The use of RAAS-blocking agents if tolerated has proven particularly beneficial in patients with diabetes in decreasing progression of their diabetic kidney disease.

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