BMJ Best Practice

Diabetic kidney disease

The right clinical information, right where it's needed

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Summary

- Symptoms, which may be absent until the disease is advanced, include fatigue, anorexia, and swelling of the extremities. Symptoms of retinopathy (impaired vision) and neuropathy (decreased or abnormal sensation in lower extremities) are common.
- Signs include hypertension, oedema, and findings of diabetic retinopathy and neuropathy. In clinical uraemia, nausea and vomiting, dysgeusia (altered taste), and hiccoughs supervene.
- Proteinuria is the characteristic laboratory finding. Azotaemia may develop as the disease advances.
- Treatment includes intensive control of hyperglycaemia and hypertension with ACE inhibitors, angiotensin-receptor blockers (ARBs), or other antihypertensives. Lipid reduction, low-protein diets, and smoking cessation may be beneficial.
- Complications include hypoglycaemia due to intensive treatment of hyperglycaemia, hyperkalaemia as an adverse effect of ACE inhibitors or ARBs, volume depletion due to diuresis, and inadequate protein/caloric intake leading to malnutrition. Some patients may reach end-stage renal failure, requiring dialysis.

BASICS

Definition

Diabetic kidney disease (DKD) is defined as macroalbuminuria (albumin to creatinine ratio [ACR] >34 mg/mmol [300 mg/g]), or microalbuminuria (ACR 3.4-34.0 mg/mmol [30-300 mg/g]) associated with retinopathy (type 1 or type 2 diabetes) and/or >10 years' duration of type 1 diabetes mellitus.[1] The terms 'moderately increased albuminuria' and 'severely increased albuminuria' are now frequently used instead of microalbuminuria and macroalbuminuria. In most patients with diabetes, chronic kidney disease (CKD) can be attributable to diabetes if these criteria are met. Other cause(s) of CKD should be considered in the presence of any of the following circumstances: absence of diabetic retinopathy, rapidly decreasing GFR, presence of active urinary sediment (e.g., cellular casts in urine), or signs or symptoms of other systemic disease. The characteristic clinical presentation is progressive albuminuria, hypertension, and decline in GFR in a long-standing (duration >10 years) diabetic patient. The diagnosis is most conclusively made by kidney biopsy, though it is rarely necessary.

Epidemiology

The epidemiology of DKD has been best studied in patients with type 1 disease, since the time of clinical onset is usually known. Approximately 20% to 30% will have microalbuminuria after a mean duration of diabetes mellitus of 15 years.[2] However, approximately half of these patients will not progress to overt proteinuria.[3] Although in the past it was stated that the risk of nephropathy was less in type 2 diabetes than in type 1 diabetes, data suggest that the renal risk is equivalent.[4] Diabetes mellitus is the most common cause of chronic kidney disease (CKD) worldwide.

Aetiology

The aetiology of DKD is multifactorial, with the most important factors being extent and duration of hyperglycaemia,[5] and hypertension.[6] Other factors that are thought to increase likelihood of DKD, or to increase its progression, are glomerular hyperfiltration, smoking, obesity, physical inactivity, dyslipidaemia,[7] proteinuria, and high dietary content of protein and fat. Genetic susceptibility appears to be a prerequisite to development of DKD.[8]

Pathophysiology

DKD is caused by both metabolic alterations (hyperglycaemia and possibly hyperlipidaemia) and haemodynamic alterations (systemic and glomerular hypertension). Other factors that are the subject of intensive research include inflammation,[9] endothelial dysfunction,[10] and oxidative stress.[11] Oxidative stress consumes nitric oxide, which prevents flow-mediated dilation (FMD) of blood vessels (endothelial dysfunction), subjecting the endothelium to injury. This leads to production of cytokines, acceleration of inflammation, worsening of blood vessel rigidity due to atherosclerosis, and further impairment of FMD and susceptibility to oxidative stress. From a unified perspective, inflammation, endothelial dysfunction, and oxidative stress are intertwined in a vicious cycle that leads to significant kidney damage and cardiovascular events. One study demonstrated that endothelial dysfunction and inflammation were predictors of progression of diabetic kidney disease in patients with type 2 diabetes and microalbuminuria.[12]

Diabetes mellitus is characterised by high glucose levels and increased glomerular pressure, both of which can cause glomerular mesangium expansion via increased mesangial stretch. Platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-beta) mediate mesangial expansion and fibrosis via the stimulation of matrix protein (collagen and fibronectin) synthesis and decreased matrix degradation. Glucose forms advanced glycosylation end products (AGEs) by binding irreversibly to proteins. Over years, AGEs form crosslinks, stimulate the release of growth factors such as

TGF-beta, and cause fibrosis. Angiotensin II (ATII), elevated in DKD, constricts the efferent arteriole in the glomerulus, causing high glomerular capillary pressures, and also stimulates fibrosis and glomerular inflammation. Mesangial expansion is characteristic of early diabetic glomerulosclerosis and is followed by fibrosis in the late stages. **[Fig-3] [Fig-4]** Kimmelstiel-Wilson nodules, **[Fig-1] [Fig-2]** areas of mesangial expansion on biopsy, are the hallmark of diabetic glomerulosclerosis and are seen in half of the cases of DKD. Increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis, microaneurysm, and hyaline arteriosclerosis are present in addition to tubular and interstitial changes.**[13]** Hypertension, via mesangial stretch, can aggravate progression of diabetic kidney disease.

Glomerular filtration rate (GFR) may be increased at the onset of diabetes mellitus (both in those destined to develop nephropathy and in those who will not develop nephropathy), but once microalbuminuria is present the GFR is usually normal. According to the natural history of the disease, macroalbuminuria occurs before a decline in GFR. However, interventions, especially BP control with drugs that block the renin-angiotensin system, can alter the natural history, and some patients have a decline in GFR in the absence of macroalbuminuria.

Primary prevention

Intensive treatment of hyperglycaemia and hypertension prevents development of microalbuminuria, as well as progression to macroalbuminuria, and may slow progression of chronic kidney disease.[5] [6] One systematic review found that ACE inhibitors prevented new-onset DKD and death in normoalbuminuric people with diabetes; however, the review concluded that more data were needed with regard to angiotensin receptor blockers (ARBs).[17]

Screening

Chronic kidney disease (CKD) screening is reported to be cost-effective in patients with diabetes and hypertension.[21]

Reason for screening for DKD:

- Detecting microalbuminuria is important because interventions such as renin-angiotensin system (RAS) inhibition can prevent progression to macroalbuminuria, which is associated with significantly greater morbidity, mortality, and progression to ESRD.[22] [23]
- Advanced DKD is more resistant to treatment, is associated with greater cardiovascular morbidity and mortality, and is more likely to progress to ESRD and dialysis. However, patients with DKD are likely to die of cardiovascular causes before they progress to kidney failure.[22] [23]

Populations to screen for DKD:[1]

- Type 1 diabetics - 5 years after diagnosis.
- Type 2 diabetics - at the time of diagnosis.

Screening tests for DKD:

- Albumin to creatinine ratio (ACR) annually.[1] [24]
- Advanced DKD is often associated with diabetic retinopathy because of microvascular disease. In the US, screening for diabetic retinopathy is recommended within 5 years of initial diagnosis of diabetes for adults with type 1 diabetes, and at diagnosis for adults with type 2 diabetes, and then 2 years thereafter if no evidence of retinopathy. More frequent follow-up may be required (e.g., annually) if findings are abnormal.[25] In the UK, screening for retinopathy is offered at the time of diagnosis and annually to all type 1 diabetes patients over the age of 12.[26]

Screening for diabetes mellitus:[25]

- Risk factors for diabetes include:
  - Age ≥45 years
  - Overweight (body mass index [BMI] ≥25 kg/m2)
  - Diabetes mellitus in a first-degree relative
  - Sedentary lifestyle
  - High-risk ethnic or racial group (e.g., African-American, Hispanic, Native American, Asian-American, and Pacific Islander)

- History of delivering a baby weighing >4.1 kg (9 lb) or of gestational diabetes mellitus
- Hypertension (blood pressure ≥140/90 mmHg)
- Dyslipidaemia (serum high-density lipoprotein cholesterol concentration ≤35 mg/dL [0.9 mmol/L] and/or serum triglyceride concentration ≥250 mg/dL [2.8 mmol/L])
- A1C ≥5.7%, impaired glucose tolerance or impaired fasting glucose
- Polycystic ovary syndrome
- History of vascular disease.

The American Diabetes Association (ADA) recommends testing at 3-year intervals for diabetes or pre-diabetes in all adults with BMI ≥25 kg/m2 and one or more additional risk factors for diabetes using either A1C, fasting plasma glucose, or 2-hour oral glucose tolerance test. In individuals without risk factors, the ADA recommends that testing begin at age 45 years.[27]

The United States Preventive Services Task Force (USPSTF) recommends screening for abnormal glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. The optimal interval for screening is unknown. The USPSTF suggests screening every 3 years based on limited evidence.[28]

The Canadian Task Force on Preventive Health Care (CTFPHC) recommends using a validated risk calculator to identify people at high risk for diabetes. They recommend screening individuals at increased risk with HbA1c, to be repeated every 3 to 5 years for those at high risk, and yearly for those at very high risk.[29]

The UK National Institute for Health and Care Excellence (NICE) recommends risk assessment using a self-assessment questionnaire or risk-assessment tool for diabetes for adults aged 40 and above, younger adults in high-risk ethnic groups, those with a body mass index >30, or those with comorbidities including hypertension or cardiovascular disease.[30]

Secondary prevention

ACE inhibitors and angiotensin receptor blockers (ARBs) reduce the incidence of microalbuminuria in diabetic patients with hypertension. In addition, the use of ACE inhibitors or ARBs in patients with normal blood pressure (<130/80 mmHg) who have microalbuminuria or macroalbuminuria stabilises albuminuria and may reduce progression of DKD, ESRD, and death.[106] [134]

Aspirin (81 mg) is given in absence of contraindication.

Avoidance of NSAIDs, radiocontrast media, or other nephrotoxic drugs is warranted. For patients with elevated serum creatinine still <177 micromol/L (<2 mg/dL), low-molecular-weight non-ionic contrast media are associated with decreased risk for contrast nephropathy. Gadolinium-based MRI contrast agents should be avoided because of a risk of systemic sclerosis in patients with DKD, especially when GFR is below 30 mL/min/1.73 m^2.

Lipid reducing agents (e.g., statins) to reduce LDL-cholesterol to <2.59 mmol/L (<100 mg/dL) are also indicated.

In a randomised trial, hydration with sodium bicarbonate was not superior to hydration with sodium chloride in preventing contrast-induced nephropathy in patients with diabetic kidney disease undergoing coronary or endovascular angiography or intervention.[135] In another randomised trial, rosuvastatin significantly reduced the risk of nephrotoxicity in patients with DM and chronic kidney disease (CKD) undergoing arterial contrast medium injection.[136]

Case history

Case history #1

A 25-year-old woman with a 12-year history of poorly controlled type 1 diabetes presents with anasarca (severe generalised oedema) and impaired vision. She is found to have nephrotic syndrome and proliferative diabetic retinopathy.

Case history #2

A 50-year-old man with a 15-year history of type 2 diabetes presents with oedema, fatigue, and impaired sensation in the lower extremities. He is found to have proteinuria, azotaemia, anaemia, background diabetic retinopathy, and peripheral neuropathy.

Other presentations

DKD can present with macroalbuminuria, and even nephrotic syndrome (massive proteinuria, hyperlipidaemia, oedema and hypoalbuminaemia), in patients with type 2 diabetes without other microvascular complications (e.g., retinopathy).

Step-by-step diagnostic approach

History

Patients destined to develop DKD usually have poorly controlled diabetes and a family history of hypertension and/or kidney disease. They may also have hypertension and in particular nocturnal hypertension (non-dippers). Patients who do develop DKD may have no symptoms of kidney disease until the disease is quite far advanced. In advanced stages, patients may develop constitutional symptoms such as fatigue and anorexia. As patients become clinically uraemic, symptoms such as nausea and vomiting, dysgeusia (altered taste), and hiccoughs supervene.

Symptoms of numbness in the legs (suggestive of peripheral neuropathy), poor vision (suggestive of retinopathy or cataracts), and pain in the legs (suggestive of neuropathy, or peripheral vascular disease) are typical of advanced diabetes mellitus and should prompt further evaluation for DKD.

Physical examination

In the early stages of the disease, physical examination may be normal. Physical examination should assess for findings of diabetic kidney disease, including hypertension and peripheral oedema, as well as for other microvascular complications of diabetes mellitus, such as:

- Retinopathy: decreased vision, retinal findings including dot and blot haemorrhages, microaneurysms (background retinopathy), and/or neovascularisation (proliferative retinopathy)
- Neuropathy: decreased sensation in lower extremities in 'stocking' pattern, foot ulcers, Charcot joints (peripheral neuropathy), and/or orthostatic hypotension without increase in heart rate (autonomic neuropathy).

Physical examination should also assess for macrovascular complications, including hypertension, vascular bruits, decreased pulses in extremities, and ischaemic ulcers. Other findings of long-standing and/or poorly controlled diabetes may be evident, including:

- Skin changes, such as xerosis (abnormal dryness of the skin), hyperpigmentation, necrobiosis lipoidica, and acanthosis nigricans
- Costovertebral tenderness or a positive kidney punch, which is a sign of pyelonephritis (a not uncommon complication in diabetes)
- Muscular atrophy
- Pallor, which may signify anaemia.

In overtly uraemic patients, pericardial and/or pleuritic friction rubs, asterixis, and/or myoclonus may be evident. There may be platelet dysfunction, which manifests as bleeding tendency. Metabolic acidosis may be accompanied by Kussmaul's respirations.

Tests

Tests performed in the assessment of DKD include:

1. Urinalysis

- This may show proteinuria. Increased specific gravity may point to pre-renal causes of azotaemia.
- Urinary leukocytes, bacteria, and nitrites indicate urinary tract infection.
- An active urinary sediment with RBC casts should prompt evaluation for non-diabetic causes of glomerular disease (glomerulonephritis). Other aetiologies of chronic kidney disease (CKD) need to be excluded if there is active urine sediment (i.e., cellular casts), rapid progression of nephrosis and/or renal failure, absence of retinopathy, short duration of diabetes mellitus, or manifestations of another systemic disease.**[1]**
- After the initial screen, urinalysis is not needed unless there is a specific indication (e.g., unexpected rapid decline in renal function, symptoms of urinary tract infection).

2. Quantification of albuminuria

- Albuminuria may be quantified by the urinary albumin:creatinine ratio (ACR) in a spot sample, or quantified in a timed (e.g., 24-hour) urine collection.
- If no urinary tract infection is present and the first ACR is increased, the test should be repeated with 2 subsequent collections of first-void urine specimens during the next 3 to 6 months, to confirm diagnosis.**[1]**
- Detecting microalbuminuria is important because early intervention can prevent progression to macroalbuminuria.
- ACR on a first-void spot urine specimen is the preferred test; a random spot urine specimen is an acceptable alternative.**[18]**

3. Blood biochemistry

- Serum creatinine should be measured and the estimated glomerular filtration rate (GFR) calculated.**[1]** [National Kidney Foundation: MDRD GFR Calculator]

4. Imaging

- Initial imaging should include ultrasound, which is useful to demonstrate kidney size and rule out differentials such as hydronephrosis, pyelonephritis, and stones. Kidney size may initially be large if diabetes is uncontrolled, but is usually normal once DKD supervenes. Doppler ultrasound may demonstrate renal artery stenosis.
- CT scan is useful to demonstrate hydronephrosis and kidney size and may also help to clarify a possible differential diagnosis.
- Magnetic resonance angiography (MRA) is useful in diagnosing renal artery stenosis or vasculopathies.

5. Kidney biopsy:

- The most sensitive and specific test for diagnosing DKD is a kidney biopsy. Although rarely necessary, it may be indicated under certain circumstances. Such circumstances include: people with type 1 diabetes who have had diabetes mellitus for a short period of time; people with type 2 diabetes who do not have retinopathy; a rapid decline in renal function associated with an active urine sediment; or evidence of another systemic disease.

Risk factors

Strong

sustained hyperglycaemia

- An elevated HbA1c increases the risk of developing DKD. Duration of diabetes is usually >10 years.[5]

hypertension (HTN)

- Uncontrolled HTN causes more rapid decline in glomerular filtration rate (GFR).
- Aggressive treatment of HTN reduces the rate of progression of chronic kidney disease, including the incidence of microalbuminuria and the progression of microalbuminuria to macroalbuminuria.

FHx of HTN and/or kidney disease

- DKD is typically seen in patients with a FHx of HTN and/or kidney disease.
- The genetic predisposition is complex and is the subject of much current research.
- The importance of genetic factors is highlighted by the observation that only a minority of diabetic patients develop DKD.

obesity

- Obesity can predict the development of type 2 diabetes as well as reduce GFR and increase proteinuria. Obese patients have elevated leptins that stimulate the inflammatory process; although leptins should cause weight loss, hypothalamic resistance in obese diabetic people creates a vicious cycle of leptin production, inflammation, and weight gain.[14]

smoking

- Studies document a relation between smoking and loss of GFR. The mechanisms underlying the adverse renal effects of smoking are still incompletely understood.

Weak

physical inactivity

- Physical inactivity is a known risk factor for the development of type 2 diabetes. Exercise may reduce proteinuria and stabilise GFR decline in chronic kidney disease (CKD), but studies specifically in patients with DKD are needed.[15]

dyslipidaemia

- There are insufficient data on whether statins prevent decline in GFR or whether they decrease proteinuria.

high protein, fat and sodium intake

- Diets with high protein, high saturated fat, high cholesterol and high sodium are associated with progression of DKD. There are weak data to support the claim that low-protein diets prevent decline in GFR and reduce progression of proteinuria.[16]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include sustained hyperglycaemia; hypertension (HTN), in particular nocturnal hypertension; FHx of HTN/kidney disease; obesity; and smoking.

hypertension (HTN) (common)

- Characteristic of DKD.

signs of retinopathy (common)

- Chronic kidney disease (CKD) with microalbuminuria in diabetic people with retinopathy fulfils the criteria for diagnosis of DKD.
- Retinal findings include dot and blot haemorrhages, microaneurysms (background retinopathy), and/or neovascularisation (proliferative retinopathy).

oedema (common)

- May be present in advancing DKD, which can also present with nephrotic syndrome.

Other diagnostic factors

poor vision (common)

- Retinopathy is usually present in patients with DKD.

numbness of the lower extremities (common)

- Peripheral neuropathy is a sign of advanced diabetes mellitus and may be present in a patient with DKD. Its presence should prompt further evaluation of kidney function to establish if DKD is also present.
- It presents with impaired sensation in the feet, and loss of vibration, pain, temperature, and position sense in the lower extremities. Carpal tunnel syndrome may cause symptoms in the hands in patients with DKD. Charcot joints may also be present.

pain of the lower extremities (common)

- Claudication in a patient with diabetes mellitus and CKD should prompt evaluation for prevention, screening, and diagnosis of DKD.
- Reduced pulses may be detected on palpation.
- May also signify painful neuropathy.

constitutional symptoms (advanced disease) (common)

- Fatigue and anorexia may be present in advanced disease. As patients become clinically uraemic, symptoms such as nausea and vomiting, dysgeusia (altered taste), and hiccoughs supervene.

foot changes (common)

- Foot ulcers and Charcot joints may be present in DKD.

orthostatic hypotension (uncommon)

- Can occur if autonomic neuropathy is present.

skin changes (uncommon)

- Xerosis (abnormal dryness of the skin) is due to atrophy of eccrine and sebaceous sweat glands. Hyperpigmentation due to melanin deposition and sallow or yellow skin due to urochrome deposition is common in CKD. Necrobiosis lipoidica and acanthosis nigricans may be found in DKD.

muscular atrophy (uncommon)

- Muscular atrophy may be present in DKD.

pallor (as GFR declines) (uncommon)

- Anaemia due to lack of erythropoietin or anaemia of chronic disease may cause pallor.

bleeding tendency (advanced disease) (uncommon)

- Platelet dysfunction manifests as easy bruising, bleeding gums, or epistaxis.

Kussmaul's respirations (advanced disease) (uncommon)

- Metabolic acidosis (due to either ketoacidosis or end-stage renal disease) may be accompanied by Kussmaul's respirations, characterised by deep inspiratory efforts without tachypnoea.

Diagnostic tests

1st test to order

Test	Result
urinalysis • Proteinuria indicates nephropathy is present. • Increased specific gravity may point to pre-renal causes of azotaemia. • Urinary leukocytes, bacteria and nitrites indicate urinary tract infection. • An active urinary sediment with RBC casts should prompt evaluation for glomerulonephritis. Other aetiologies of chronic kidney disease (CKD) need to be excluded if there is active urine sediment (i.e., cellular casts), rapid progression of nephrosis and/or renal failure, absence of retinopathy, short duration of diabetes mellitus, or manifestations of another systemic disease.[1] • After the initial screen, urinalysis is not needed unless there is a specific indication (e.g., unexpected rapid decline in renal function, symptoms of urinary tract infection).	**proteinuria**
urinary albumin to creatinine ratio (ACR) • Performed on spot urine collection. • If no urinary tract infection is present and the first ACR is raised, the test should be repeated with 2 subsequent collections of first-void urine specimens during the next 3 to 6 months, to confirm diagnosis.[1]	**may be elevated**
blood biochemistry • Important baseline test.	**elevated creatinine**
serum creatinine with GFR estimation • GFR may be calculated using the patient's serum creatinine, age, race, and sex.[1] [National Kidney Foundation: MDRD GFR Calculator]	**Glomerular filtration rate (GFR) may be raised in CKD stage 1, normal in CKD stage 2, and reduced in CKD stages 3 to 5**
kidney ultrasound • Kidney size may initially be large if diabetes uncontrolled, but usually normal once DKD supervenes. • Ultrasound is important to exclude other causes of renal impairment in diabetic patients, such as obstruction, infection, cysts, or mass. Pyelonephritis may show as swelling of the parenchyma.	**normal-to-large kidneys with increased echogenicity; may show hydronephrosis if vesiculopathy and/or obstruction is superimposed**

Other tests to consider

Test	Result
24-hour urine collection • Allows quantification of albuminuria.	**microalbuminuria: albumin 30 to 300 mg/24 hours; macroalbuminuria: albumin >300 mg/24 hours**
CT abdomen • CT scan is rarely warranted but may be useful if ultrasound is of poor quality in obese patients or if follow-up imaging is required to clarify pathology seen on ultrasound. • Can exclude hydronephrosis, pyelonephritis, kidney stones, cysts, masses, renal cell carcinoma, and abnormal kidney ureter or bladder architecture.	**may show hydronephrosis; wedge-shaped areas of low attenuation; loss of the ability to distinguish the corticomedullary border; perinephric stranding; cysts; masses; stones**

Test	Result
magnetic resonance angiography • Magnetic resonance angiography (MRA) should be considered in patients who develop renal failure shortly after an ACE inhibitor has been started, or in patients with refractory HTN who have failed to respond to 3 of 4 antihypertensives. Gadolinium should not be given if the estimated GFR is <30 mL/min/1.73 m^2.	**to rule out renal artery stenosis**
Doppler ultrasound • Provides haemodynamic information about renal artery flow.	**may show renal artery stenosis**
kidney biopsy • Considered in the following circumstances: in patients with type 1 diabetes who have had diabetes mellitus for a short period of time; in patients with type 2 diabetes who do not have retinopathy; if there is a rapid decline in renal function associated with an active urine sediment; or if there is evidence of another systemic disease.	**mesangial expansion, fibrosis, Kimmelstiel-Wilson nodules**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Non-diabetic kidney disease	• Since both diabetes mellitus and chronic kidney disease (CKD) are common disorders, patients with both conditions may or may not have DKD. • A diagnosis other than DKD should be considered if there is a rapid progression of renal failure, evidence of another systemic disease, or short duration of diabetes (although onset is insidious in type 2, and DKD may occasionally be the presenting manifestation of type 2 diabetes mellitus).	• Minimal proteinuria may indicate non-diabetic kidney disease. • Other specific diagnostic tests for other systemic disorders associated with non-diabetic kidney disease may be positive (e.g., serum protein electrophoresis or serum free light chains in myeloma, ANA in SLE, ANCA in vasculitis, hypocomplementaemia in SLE, cryoglobulinaemia).

Condition	Differentiating signs / symptoms	Differentiating tests
Multiple myeloma	• Multiple myeloma (MM) patients also may present with renal failure and proteinuria. • Symptoms of bone pain and anaemia are the most common presenting features, affecting 80% of patients with MM.	• The characteristic test results that differ from DKD are: the presence of paraproteinaemia/paraproteinuria; hypercalcaemia; impaired production of normal immunoglobulin; and lytic bone lesions.[19] • Urinalysis with sulfosalicylic acid (SSA) was classically utilised to evaluate for discrepancy between albumin and total protein, as standard urinalysis dipstick detects albumin only. SSA causes precipitation of all of the urinary proteins, including paraproteins (Bence Jones proteins). • Serum protein electrophoresis (PEP), urine protein electrophoresis (UPEP): paraprotein spike. • Serum and urine free light chains: increased concentrations of free light chain in serum. • Skull x-rays, CT, or MRI bone: lytic lesions. • Bone marrow biopsy: plasma cell proliferation.
Renal tract obstruction	• Can be caused by stones, cancer, fibrosis, prostate hypertrophy/cancer, neurogenic bladder, or pelviureteric junction obstruction. • Obstruction to urine flow can result in post-renal failure. Symptoms include trouble passing urine, anuria, oliguria, haematuria, pain (with kidney stones), and urinary leakage/incontinence. • Physical examination findings include enlarged prostate on rectal examination, costovertebral angle tenderness, suprapubic tenderness, and bladder fullness.	• Passage of Foley catheter may result in flow of urine and relief of obstruction. • Kidney ultrasound: hydronephrosis, stones. • Prostate ultrasound: hypertrophy, cancer. • CT abdomen: hydronephrosis, stones, mass, congenital abnormalities, fibrosis. • PSA: elevated in BPH, prostate cancer. • MRI: not routine but may show hydronephrosis, stones, mass, congenital abnormalities, fibrosis.

Condition	Differentiating signs / symptoms	Differentiating tests
Glomerulonephritis	• Glomerulonephritis, such as lupus nephritis and cryoglobulinaemia, is in the differential for DKD. • Patient presentation and physical examination may be similar to that of DKD. However, there may be symptoms and signs of other systemic disease, such as rashes or joint involvement.	• Urinalysis: haematuria, proteinuria, RBC casts, dysmorphic red cells. • Albuminuria. • Positive serology (e.g., ANA, ANCA, hepatitis serology). • Complement: decreased in immune glomerulonephritis (e.g., lupus). • Kidney biopsy: glomerulonephritis.
Renal artery stenosis	• Renal artery stenosis presents either as HTN refractory to multiple maximised antihypertensives or as renal failure shortly after the initiation of an ACE inhibitor or angiotensin-receptor blockers (ARBs). • Physical examination is significant for an abdominal bruit.[20]	• Ultrasound, CT scan, MRI: shrunken kidney, decreased flow through the renal artery. • Magnetic resonance angiography (MRA): renal artery stenosis. • Renal angiogram: renal artery stenosis.

Diagnostic criteria

Staging of diabetic nephropathy[1]

DKD is classified according to presence of microalbuminuria (30-300 mg albumin/24 hours or albumin to creatinine ratio [ACR] of 3.4-34.0 mg/mmol [30-300 mg/g]) or macroalbuminuria (>300 mg albumin/24 hours or ACR >34 mg/mmol [300 mg/g]).

Step-by-step treatment approach

General approach

In order to minimise the progression of DKD, treatment should be comprehensive and should involve simultaneous evaluation and intervention of hyperglycaemia, hypertension, dyslipidaemia, nutrition, and behaviour. Patient behaviour and self-management significantly improves diabetic outcomes and diabetic kidney disease outcomes.[31] [32] Proper nutrition, with decreased intake of saturated fat, cholesterol, and salt, is beneficial. Treatment guidelines for US practice have been published in 2012.[33] [34]

Treatment of hyperglycaemia

Treatments for hyperglycaemia include insulin and oral hypoglycaemic agents (e.g. sulfonylureas, meglitinides, and dipeptidyl peptidase-4 [DPP-4] inhibitors). Regardless of which treatment is used, caution must be taken when administering to patients with chronic kidney disease (CKD) as there is a risk for hypoglycaemia because of impaired kidney clearance of medications such as insulin (two-thirds of insulin is degraded by the kidney) or sulfonylureas, and because of impaired kidney gluconeogenesis.

Type 1 diabetes patients require treatment with insulin regardless of whether they are on dialysis or not. Type 2 diabetes patients with CKD who are not on dialysis may begin with an oral hypoglycaemic agent (e.g., metformin if eGFR adequate; or else glipizide, repaglinide, or sitagliptin), and then insulin can be added or substituted as needed. Metformin, generally the first choice oral hypoglycaemic agent for type 2 diabetes, is contraindicated when eGFR is <30 mL/min/1.73 m^2 and should be used only with caution when 30-45 mL/min/1.73 m^2.[35] Glipizide is the sulfonylurea agent of choice due to its metabolite having little or no hypoglycaemic activity.[34] Repaglinide is a meglitinide and is considered within its drug class to be safest for CKD for similar reasons.[36] Sitagliptin, a DPP-4 inhibitor, can also be used, but the dose must be adjusted depending on the degree of renal dysfunction.[37] Other DPP-4 inhibitors, such as saxagliptin and linagliptin, can also be used in patients with CKD, including ESRD, though there is limited experience with their use. Saxagliptin requires a dose adjustment in renal impairment. Linagliptin has the advantage that it is not renally cleared and thus a dose adjustment is not necessary. Type 2 diabetes patients who are on dialysis (e.g., due to end-stage renal disease) are preferentially treated with insulin. However, low-dose oral hypoglycaemic agents (e.g. glipizide or sitagliptin) can be used either instead of insulin or added to insulin. There is no evidence to support the use of repaglinide in dialysis patients.

Although there is evidence showing that thiazolidinediones reduce hyperglycaemia, albuminuria, and proteinuria in people with diabetes, the clinical significance of this finding is unclear.[38] Thiazolidinediones are associated with fluid retention, and rosiglitazone has been withdrawn in Europe due to associated cardiovascular risk, though previous restrictions applied to rosiglitazone have since been lifted in the US. Studies with sodium glucose co-transporter 2 (SGLT2) inhibitors suggest that they may be effective in mild to moderate CKD, though data are conflicting.[39] [40] They are not effective in patients with eGFR <30 mL/min/1.73 m^2, including patients with ESRD who are on dialysis.

A number of studies have investigated the benefits of intensive glycaemic control for nephropathy, but this approach remains under scrutiny. Intensive treatment may prevent DKD, including development of microalbuminuria, but there is little evidence that it slows the progression of established CKD.[5] [41] In addition, it has not been shown to reduce cardiovascular risk, which is the major cause of mortality in people with diabetes.

In type 1 diabetes, the Diabetes Control and Complications (DCCT) Research Group trial demonstrated that intensive treatment was associated with decreased incidence of microalbuminuria and reduced progression to macroalbuminuria compared with conventional treatment.[42] The Stockholm study showed similar findings.[43]

In type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) Group trial demonstrated a reduced incidence of microalbuminuria in the intensively treated group compared with conventional treatment, but a parallel finding in macroalbuminuria was not significant.[44] In another study, intensive management of patients with type 2 diabetes detected by screening (including glucose control) was not associated with significant reductions in the frequency of microvascular events at 5 years when compared with routine care.[45] The Kumamoto study[46] and the Veterans Affairs Cooperative study[47] have both shown intensive treatment to be effective for primary prevention (decreased incidence of microalbuminuria) and secondary prevention (reduced progression to macroalbuminuria).

The Epidemiology of Diabetes Interventions and Complications (EDIC)/DCCT follow-up study[5] and the UKPDS study[44] also found that lowering HbA1c reduced decline in GFR in type 1 and type 2 diabetes, respectively. However, it is not clear whether this is the case for long-standing type 2 diabetes, as shown in the Veterans Affairs Cooperative study.[47]

The ADVANCE study treated hyperglycaemia with gliclazide and BP with perindopril/indapamide. The findings demonstrated that intensive glucose control and BP lowering were independently beneficial and their combination produced synergistic benefits in nephropathy, new-onset microalbuminuria, and new-onset macroalbuminuria.[48] In fact, the combination of BP lowering and intensive glucose control reduced cardiovascular mortality and all-cause mortality, and improved renal outcomes.[49] [50] Intensive glucose control was not associated with a significant reduction in macrovascular events.[51] However, one analysis of ADVANCE found that the number of individuals needed to treat with intensive glucose control to prevent one case of ESRD ranged from 410 individuals overall, to 41 individuals with overt albuminuria.[52]

The benefits of intensive glucose control have been re-demonstrated in a more recent review.[53] However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, assignment of the treatment group to an HbA1c goal of <42 mmol/mol (6%) led to increased mortality and cessation of the trial.[54] In contrast to findings of the ADVANCE study, in one analysis of data from the ACCORD study, combined intensive BP and glycaemic control did not produce an additive benefit on microvascular outcomes in type 2 diabetic patients.[55]

In one study in patients with type 2 diabetes, intensive glycaemic control had no significant effect on the progression of renal disease. However, it was associated with some protection against increasing albuminuria in those with more advanced microvascular disease, lower baseline DBP, or higher baseline BMI, and with worsening of eGFR in those with high baseline ACR.[56]

UK guidelines recommend a target HbA1c in type 2 diabetes of 48 mmol/mol (6.5%) (although this may be set at a slightly higher target depending on the individual).[57] Current American Diabetes Association guidelines recommend keeping HbA1c at ≤53 mmol/mol (7%), except for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetic complications and comorbidity, or long-standing diabetes, where a less stringent goal may be appropriate (e.g., <8%).[25] These guidelines have been adopted for patients with CKD by the National Kidney Foundation, who also stress that less intensive control is warranted in individuals at risk for hypoglycaemia, substantial comorbidities, or limited life expectancy.[33] A Cochrane review has concluded that intensive glucose control reduces the risk of developing microvascular diabetes complications, but the evidence of benefit is mainly from studies in younger patients at early stages of the disease. Benefits need to be weighed against risks including severe hypoglycaemia in older patients and in those with diabetic complications. Treatment goals need to be individualised, taking into account age, disease progression, and macrovascular risk, as well as the patient's lifestyle and disease management capabilities.[58]

Treatment of hypertension

Treatment of hypertension reduces progression of DKD.[6] Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly

among those with proteinuria.[60] A BP goal of <140/90 mmHg is currently recommended by the Joint National Committee 8 (JNC 8) for patients aged 18 to 59 years without major comorbidities (e.g., diabetes or CKD), and for patients of all ages who have diabetes or CKD, or both.[61] The American Diabetes Association also recommend a BP goal of <140/90 mmHg for patients with diabetes and hypertension.[25] This recommendation is based primarily on the findings of the ACCORD BP trial, which found no significant cardiovascular benefit and more drug side effects at a mean attained systolic pressure of 119.3 compared with 133.5 mmHg, with the exception of a reduction in stroke.[62]Patients with DKD may, however, benefit from lower BP targets as recommended by Kidney Disease: Improving Global Outcomes.[63] For adults with diabetes and CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a BP goal of ≤140/90 mmHg if urinary albumin excretion is less than 30 mg/24 hours, or a BP goal of ≤130/80 mmHg if urinary albumin excretion is 30 mg/24 hours or more. The American Diabetes Association (ADA) states that systolic blood pressure <130/80 mmHg may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if this can be achieved without undue treatment burden. A recent analysis of the VA-NEPHRON D trial supports a BP goal of <140/80 mmHg.[64]

First-line treatment should include ACE inhibitors or angiotensin receptor blockers (ARBs). The ONTARGET study demonstrated that ARBs and ACE inhibitors are equal in prevention of cardiovascular morbidity and mortality, MI, and stroke.[65] [66] Moreover, renoprotective effects are also similar.[67] ACE inhibitors slow progression of DKD in type 1[68] and type 2[69] diabetic patients with microalbuminuria. One study could not demonstrate prevention of nephropathy with renin-angiotensin system (RAS) blockade in normoalbuminuric patients, but did demonstrate slowed progression of retinopathy.[70] Losartan, independent of its effect on BP, has been shown also to reduce proteinuria in people with normotensive type 2 diabetes.[71] The ADVANCE trial demonstrated renoprotection with perindopril/indapamide in normotensive individuals.[72] There is some research to suggest that drugs that block the renin-angiotensin system (ACE inhibitors and ARBs) reduce the risk of ESRD and worsening creatinine but may not have an effect on all-cause mortality.[73]

Dual therapy with ACE inhibitor and ARB has been extensively studied in patients with albuminuria, including DKD.[74] Meta-analyses have found that dual blockade reduced proteinuria to a greater extent than monotherapy, and was associated with a decrease in BP, but also a small decline in GFR and increase in serum potassium.[75] [76] However, the Canadian Hypertension Education Program (CHEP) recommends against combining ACE inhibitors and ARBs in people with uncomplicated hypertension, CKD without proteinuria, or coronary artery disease without co-existing systolic heart failure.[77] The ONTARGET study also demonstrated that combined renin-angiotensin system inhibition achieved no further benefits and was associated with more adverse events.[65] [66] In patients with vascular risk, dual therapy reduced proteinuria but worsened renal outcomes (dialysis, doubling of creatinine, and death). The patient population in ONTARGET was at low renal risk, and thus this study is possibly not applicable to patients with overt proteinuria. However, two large clinical trials in diabetic patients with overt proteinuria (ALTITUDE,[78] NEPHRON-D [79]) have been stopped due to adverse safety events. On the basis of this evidence, dual blockade should not be employed in patients with overt DKD.[79]

Diuretics in conjunction with ACE inhibitors and ARBs provide the clinician with a greater ability to achieve recommended BP levels in DKD patients with hypertension, most of whom will require 3 to 4 agents to reach BP goals.[80] Diuretics are generally ineffective for BP management in dialysis patients due to markedly impaired renal function. In selected patients with residual renal function, loop diuretics may still be efficacious in preventing fluid overload and hypertension as adjunctive therapy to ultrafiltration during dialysis. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers.[81]

Carvedilol has a beneficial effect on glycaemic control as well as insulin resistance and is a valuable agent as part of antihypertensive regimens in patients with diabetes mellitus and CKD.[82]

Non-dihydropyridine calcium-channel blockers are also protective against proteinuria. Dihydropyridine calcium-channel blockers such as amlodipine are not recommended as lone therapy because they worsen proteinuria and have not been shown to improve outcomes.[83] However, they are acceptable if the patient is already on an ACE inhibitor or an ARB.[84] One study found that trandolapril/verapamil was not superior to benazepril/amlodipine.[85] Another study showed that benazepril/hydrochlorothiazide resulted in greater reduction in proteinuria than benazepril/amlodipine.[86]

Finally, in a recent large meta-analysis examining efficacy and safety of antihypertensive agents in diabetic patients with CKD, no blood pressure-lowering strategy prolonged survival. ACE inhibitors and ARBs, alone or in combination, were the most effective strategies to prevent end-stage kidney disease. However, the authors confirmed that combined ACE inhibitor and ARB treatment risks potential harms of hyperkalaemia and acute kidney injury.[87]

Treatment of dyslipidaemia

People with diabetes mellitus and CKD have a high risk of cardiovascular events. Owing to the high risk of cardiovascular disease (CVD) in diabetic people, management of cardiovascular risk must be a strong consideration in people with DKD in order to reduce mortality from CVD.[33] Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA),[88] ADA,[25] and KDIGO[89] recommend that lipid treatment (e.g., with statins) should be guided by CVD risk. Diabetic patients with atherosclerotic cardiovascular disease should be treated with high-intensity statin therapy. The addition of ezetimibe to moderate-intensity statin therapy should be considered for patients with a recent acute coronary syndrome or for those patients who cannot tolerate high intensity statin therapy. One systematic review and meta-analysis of fibrate therapy concluded that these agents also prevented cardiovascular events and decreased proteinuria in mild to moderate CKD; however, their effects on long-term kidney outcomes are unknown.[90] Fibrates are not generally recommended in CKD patients, especially those with eGFR <30 mL/min/1.73 m^2.

KDIGO considers non-dialysis CKD to be a CVD risk equivalent, and it recommends statin therapy (e.g., with atorvastatin or rosuvastatin) for all non-dialysis CKD patients ages 50 years or older; no specific treatment target is given.[89] Patients with diabetes and CKD may derive great cardiovascular benefit from statins,[7] and there is some evidence that statins may have a beneficial effect on kidney function.[91]

In patients on dialysis, KDIGO recommends continuation of statin therapy if the patient is already receiving these agents, but not to start statin therapy due to lack of evidence of benefit in ESRD. This is because the 4D study failed to show any benefit of statins on cardiovascular outcomes in such patients.[92] Moreover, in the SHARP study, a reduction of LDL-cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events in non-dialysis CKD, though there was no significant benefit in ESRD.[93]

Nutrition

According to the American Dietetic Association, medical nutrition therapy by a registered dietician is recommended for patients with type 1 or type 2 diabetes.[94] An initial series of 3 to 4 encounters results in positive outcomes, including reductions in HbA1c, lipids, and weight, a positive adjustment in medications, and a decrease in comorbidities. In addition, patients should have a follow-up visit annually.[94] There are some data to support the claim that low-protein diets prevent decline in GFR and reduce progression of proteinuria.[16] Dietary protein restriction of 0.8 g/kg of ideal body weight per day is suggested.[16] High-protein diets should be avoided. However, other research has suggested that a low-protein diet does not improve renal function in type 1 or type 2 diabetic kidney disease.[95] In addition, a systematic review was unable to show a benefit of protein restriction on renal failure.[96] Limited intake of saturated fat, cholesterol, and sodium (2.3 g/day) is beneficial.[97] Salt restriction may prevent the onset of diabetic kidney disease in diabetes.[98] Although a multivitamin is recommended, high doses of B vitamins have been found to result in increased vascular events.[99]

Smoking cessation

Smoking cessation is strongly recommended, as studies document a relation between smoking and loss of GFR. The mechanisms underlying the adverse renal effects of smoking are still incompletely understood. Beyond its effect on progression of renal failure, smoking is also an important cardiovascular risk factor in CKD patients.[100]

Due to the increasing use of e-cigarettes, the American Diabetes Association guidelines make it clear that e-cigarettes are not supported either as an alternative to smoking or to facilitate smoking cessation.[25]

Pancreas kidney transplantation

Diabetes is the most common cause of ESRD requiring renal replacement therapy (RRT). RRT is not only time consuming and fraught with uncomfortable side effects such as cramps, fatigue, and central venous stenosis, but it is also associated with significant morbidity and mortality. Pancreas kidney transplantation not only frees patients from the need for RRT but also has a significant survival benefit. With modern surgical and immunosuppressive protocols, 5-year patient survival is 95%, kidney survival is 90%, and pancreas survival is greater than 80%.[101] In the US, in 2013, 760 simultaneous pancreas kidney (SPK) transplants, 127 pancreas transplants alone (PTA), and 107 pancreas after kidney (PAK) transplants were performed.[102]

SPK recipients are generally younger (60 years or less) than kidney transplant recipients (70 years or less). They are usually patients with type 1 diabetes who have hypoglycaemia unawareness or markedly uncontrolled diabetes; they usually are on insulin therapy (typically <1 unit/kg/day) and their C-peptide is less than 2 nanograms/mL. Patients with type 2 diabetes may be considered if they do not have significant insulin resistance (C-peptide >2 and BMI <30), In addition, recipients must have a GFR <20 mL/min/1.73 m^2 or be dialysis dependent. They must go through strict cardiovascular, psychosocial, and anatomical (CT angiogram) clearance.[101]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Ongoing (summary)

Patient group	Tx line	Treatment
type 1 diabetes with nephropathy: not on dialysis	**1st**	**glycaemic control**
	plus	**ACE inhibitor or angiotensin receptor blocker (ARB)**
	plus	**nutrition**
	plus	**smoking cessation**
	adjunct	**statin**
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB	**plus**	**added diuretic**
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic	**plus**	**added beta-blocker**
with BP not controlled below 130/80 to 140/90 by ACE	**plus**	**added calcium-channel blocker**

Ongoing (summary)

inhibitor/ARB + diuretic + beta-blocker		
type 2 diabetes with nephropathy: not on dialysis	1st	glycaemic control
	plus	ACE inhibitor or angiotensin receptor blocker (ARB)
	plus	nutrition
	plus	smoking cessation
	adjunct	statin
▪ with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB	plus	added diuretic
▪ with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic	plus	added beta-blocker
▪ with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic + beta-blocker	plus	added calcium-channel blocker
on peritoneal dialysis or haemodialysis	1st	glycaemic control
	plus	ACE inhibitor or angiotensin receptor blocker (ARB)
	plus	nutrition
	plus	smoking cessation
	adjunct	statin
▪ with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB	plus	added beta-blocker
▪ with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + beta-blocker	plus	added calcium-channel blocker
	2nd	consideration for pancreas-kidney transplantation

TREATMENT

Treatment options

Ongoing

Patient group	Tx line	Treatment
type 1 diabetes with nephropathy: not on dialysis	**1st**	**glycaemic control**

» In all type 1 diabetic patients, regardless of whether they are on dialysis or not, treatment with insulin is needed. Insulin is usually given subcutaneously.

» Diabetes patients with chronic kidney disease (CKD) are at risk for hypoglycaemia because of impaired clearance of insulin, and because of impaired kidney gluconeogenesis.

» Current guidelines recommend keeping HbA1c at ≤7%, except for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetic complications and comorbidity, or long-standing diabetes, where a less stringent goal may be appropriate (e.g., <8%).[25] [33] Treatment goals need to be individualised, taking into account age, disease progression, and macrovascular risk, as well as the patient's lifestyle and disease management capabilities.[58]

» Intensive treatment of hyperglycaemia may prevent the development of microalbuminuria as well as progression to macroalbuminuria, though there is little evidence that it slows the progression of established CKD.[5]

Primary options

» insulin lispro: injected subcutaneously three times daily before meals
-and-
» insulin glargine: injected subcutaneously once daily

plus **ACE inhibitor or angiotensin receptor blocker (ARB)**

» Treatment of hypertension reduces progression of DKD.[6] BP should probably be maintained at ≤130/80 mmHg in patients with overt proteinuria.[59] [61] [63] However, some guidelines recommend a less stringent BP goal of <140/90 mmHg,[25] [61] which is based on findings from the ACCORD BP trial.[62] One analysis of the VA-NEPHRON D trial supports a BP goal of <140/80 mmHg.[64]

» ACE inhibitors have been shown to slow progression of DKD in type 1 diabetic patients with microalbuminuria.[68] In type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to slow progression of DKD.[69] [104]

Ongoing

Patient group	Tx line	Treatment

» ACE inhibitors and ARBs have been shown to be equally protective against DKD progression in type 2 diabetes with microalbuminuria.[105] There are similar findings in patients with macroalbuminuria for ACE inhibitors in type 1 diabetes[106] and ARBs in type 2 diabetes.[107] However, there are few data on the effectiveness of ACE inhibition in type 2 diabetic patients with macroalbuminuria and on the effectiveness of ARBs in type 1 diabetic patients with macroalbuminuria.

» The combination of ACE inhibitors and ARBs can further reduce proteinuria in people with type 1 diabetes[108] and type 2 diabetes.[109] However, the combination is not commonly used in practice because of the risk of hyperkalaemia. Moreover, several studies involving diabetes patients with overt proteinuria have been stopped early due to safety concerns with this combination therapy.[78] [79]

Primary options

» captopril: 25-50 mg orally three times daily; dose should be adjusted according to level of renal impairment

OR

» enalapril: 2.5 to 20 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» lisinopril: 2.5 to 40 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» ramipril: 2.5 to 20 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» trandolapril: 0.5 to 8 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» losartan: 25-100 mg orally once daily

OR

» valsartan: 80-320 mg orally once daily

Ongoing

Patient group	Tx line	Treatment
		OR » candesartan: 4-32 mg orally once daily; dose should be adjusted according to level of renal impairment
	plus	**nutrition** » According to the American Dietetic Association, medical nutrition therapy by a registered dietician is recommended for people with type 1 or type 2 diabetes.[94] An initial series of 3 to 4 encounters results in positive outcomes, including reductions in HbA1c, lipids, and weight, a positive adjustment in medications, and a decrease in comorbidities. In addition, patients should have a follow-up visit annually.[94] » There are some data to support the claim that low-protein diets prevent decline in GFR and reduce progression of proteinuria.[16] Dietary protein restriction of 0.8 g/kg of ideal body weight per day is suggested.[16] High-protein diets should be avoided. However, other research has suggested that a low-protein diet does not improve renal function in type 1 or type 2 diabetic kidney disease.[95] The 2016 American Diabetes Association guidelines do not recommend protein restriction.[25] In addition, a systematic review was unable to show a benefit of protein restriction on renal failure.[96] Limited intake of saturated fat, cholesterol, and sodium (2.3 g/day) is beneficial.[97] Salt restriction may prevent the onset of diabetic kidney disease in diabetes,[98] and potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers (ARBs).[81] Although a multivitamin is recommended, high doses of B vitamins resulted in increased vascular events.[99] **Primary options** » low-protein diet: 0.8 g/kg/day maximum May cause malnutrition; it should be ensured that caloric intake is adequate. **-and-** » low-sodium diet: 2.3 g/day maximum Reduces blood pressure and prevents oedema. **-and-** » low saturated fat diet Prevents atherosclerosis.
	plus	**smoking cessation** » Smoking cessation is strongly recommended, as studies document a relation between smoking and loss of GFR. The mechanisms underlying the adverse renal effects of smoking are still incompletely understood.

Ongoing

Patient group	Tx line	Treatment
		Beyond its effect on progression of renal failure, smoking is also an important cardiovascular risk factor in chronic kidney disease patients.[100] » E-cigarettes are not recommended either as an alternative to smoking or to facilitate smoking cessation.[25]
	adjunct	**statin** » Patients with DKD are 5 to 10 times more likely to die of cardiovascular causes than reach ESRD requiring renal replacement therapy (dialysis and/or transplantation).[110] » Statins are likely to be beneficial because of their anti-inflammatory properties and the correlation of inflammation in chronic kidney disease (CKD) with associated cardiovascular morbidity. » A study involving non-dialysis patients with diabetic CKD showed that atorvastatin has a beneficial effect on both GFR and CVD.[91] However, a study involving haemodialysis patients failed to show any benefit of statins on cardiovascular outcomes.[92] In the SHARP study, a reduction of LDL-cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.[93] » There is current debate about whether there is a recommended lower limit for LDL-cholesterol. Studies have shown that the lower the LDL-cholesterol, the greater the cardiovascular benefit. Previous guidelines recommend that LDL should be maintained at least <2.59 mmol/L (<100 mg/dL) and probably <1.81 mmol/L (<70 mg/dL).[111] However, many guidelines now recommend that lipid treatment (e.g., with statins) should be driven by cardiovascular risk rather than by LDL levels.[25] [88] [89]For example, Kidney Disease: Improving Global Outcomes (KDIGO) recommend statin therapy (e.g., with atorvastatin or rosuvastatin) for all non-dialysis CKD patients aged 50 years or older; no specific treatment target is given.[89] In patients on dialysis, KDIGO recommend continuation of statin therapy if the patient is already receiving these agents, but not to start statin therapy due to lack of evidence of benefit in ESRD. **Primary options** » atorvastatin: 20 mg orally once daily **OR** » rosuvastatin: 5-10 mg orally once daily

TREATMENT

Ongoing

Patient group	Tx line	Treatment
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB	**plus**	**added diuretic**

» Diuretics are considered second-line therapy for hypertension in DKD.

» In conjunction with ACE inhibitors and ARBs, they provide a greater ability to achieve recommended BP levels. Loop diuretics are generally needed when the GFR falls to <30 mL/min/1.73 m^2.[103] Renal failure is a complication of aggressive loop diuretic use.

» Beta-blockers or calcium-channel blockers may then be added, if needed.

» Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61]

Primary options

» hydrochlorothiazide: 12.5 to 50 mg orally once daily
Not considered effective when CrCl is <30 mL/min/1.73 m^2.

OR

» chlortalidone: 12.5 to 50 mg orally once daily
Not considered effective when CrCl is <30 mL/min/1.73 m^2.

Secondary options

» metolazone: 2.5 to 10 mg orally once daily or once on alternate days; dose should be adjusted according to level of renal impairment

OR

» furosemide: 20-160 mg orally twice daily; dose should be adjusted according to level of renal impairment
Used in setting of oedema.

OR

» spironolactone: 25-50 mg orally once daily; dose should be adjusted according to level of renal impairment
Risk of hyperkalaemia when renal function is impaired.

Ongoing

Patient group	Tx line	Treatment
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic	**plus**	**added beta-blocker** » Beta-blockers may be added if BP is not controlled with a diuretic in combination with an ACE inhibitor or ARB. » Carvedilol is better than metoprolol at stabilising glycaemic control and decreasing insulin resistance. It is generally used with co-existing CHF.[82] » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] **Primary options** » carvedilol: 3.125 to 50 mg orally twice daily **Secondary options** » propranolol: 40-240 mg orally twice daily **OR** » metoprolol: 25-200 mg orally (immediate-release) twice daily **OR** » atenolol: 25-100 mg orally once daily; dose should be adjusted according to level of renal impairment
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic + beta-blocker	**plus**	**added calcium-channel blocker** » Non-dihydropyridine calcium-channel blockers are preferred, if heart rate allows. Dihydropyridine calcium-channel blockers should not be used as sole therapy as they may worsen proteinuria and renal injury, but can be used in conjunction with ACE inhibitors or ARBs. » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] **Primary options**

Ongoing

Patient group	Tx line	Treatment
		» verapamil: 40-120 mg orally (immediate-release) three times daily; 120-360 mg orally (extended-release) once daily **OR** » diltiazem: 30-90 mg orally (immediate-release) four times daily; 120-360 mg orally (extended-release) once daily
type 2 diabetes with nephropathy: not on dialysis	**1st**	**glycaemic control** » Type 2 diabetes patients with CKD who are not on dialysis may begin with an oral hypoglycaemic agent (e.g., metformin if estimated GFR [eGFR] adequate; or else glipizide, repaglinide, or sitagliptin), and then insulin can be added or substituted as needed. Metformin, generally the first choice oral hypoglycaemic agent for type 2 diabetes, is contraindicated when when eGFR is <30 mL/min/1.73 m^2 and should be used only with caution when 30-45 mL/min/1.73 m^2.[35] » Glipizide is the sulfonylurea agent of choice due to its metabolite having little or no hypoglycaemic activity.[112] Repaglinide is a meglitinide and is considered within its drug class to be safest for CKD for similar reasons.[36] Sitagliptin, a DPP-4 inhibitor, can also be used, but this is based on limited evidence.[37] » Diabetes patients with CKD are at risk for hypoglycaemia because of impaired clearance of medications such as insulin and many oral hypoglycaemic agents, and because of impaired kidney gluconeogenesis. » Current guidelines recommend keeping HbA1c at ≤7%, except for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetic complications and comorbidity, or long-standing diabetes, where a less stringent goal may be appropriate (e.g., <8%).[25] [33] Treatment goals need to be individualised, taking into account age, disease progression, and macrovascular risk, as well as the patient's lifestyle and disease management capabilities.[58] » The benefit of intensive glycaemic control for nephropathy remains under scrutiny. In one study, compared with routine care, intensive management of patients with type 2 diabetes detected by screening (including glucose control) was not associated with significant reductions in the frequency of microvascular events at 5 years.[45] Intensive treatment of

Ongoing

Patient group	Tx line	Treatment

hyperglycaemia may prevent the development of microalbuminuria as well as progression to macroalbuminuria, though there is little evidence that it slows the progression of established CKD.[5] [41]

Primary options

» metformin: eGFR >45 mL/min/1.73 m^2: 500 mg orally (regular-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day
Use is contraindicated in patients with eGFR <30 mL/min/1.73 m^2. Should not be started in patients with eGFR 30-45 mL/min/1.73 m^2. In patients who are started on metformin, if their eGFR falls below 45 mL/min/1.73 m^2, assess benefits/risks of continuing treatment and reduce dose. Obtain eGFR at least annually.

OR

» glipizide: 2.5 to 5 mg orally (immediate-release) once daily initially, increase by 2.5 to 5 mg/day increments every 1-2 weeks according to response, maximum 20 mg/day; 5 mg orally (extended-release) once daily initially, increase according to response, maximum 10 mg/day
Dose applies to patients with CKD (eGFR <50 mL/min/1.73 m^2) and those on dialysis.

OR

» repaglinide: 0.5 to 4 mg orally before each meal up to three times daily
Dose should be started low and titrated carefully to desired clinical response.

OR

» sitagliptin: 25-100 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» metformin: eGFR >45 mL/min/1.73 m^2: 500 mg orally (regular-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day
Use is contraindicated in patients with eGFR <30 mL/min/1.73 m^2. Should not be started in patients with eGFR 30-45 mL/min/1.73 m^2. In patients who are started on metformin, if their eGFR falls below 45 mL/min/1.73 m^2, assess benefits/risks of continuing treatment and reduce dose. Obtain eGFR at least annually.
-and-

Ongoing

Patient group	Tx line	Treatment
		» insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily
		OR
		» glipizide: 2.5 to 5 mg orally (immediate-release) once daily initially, increase by 2.5 to 5 mg/day increments every 1-2 weeks according to response, maximum 20 mg/day; 5 mg orally (extended-release) once daily initially, increase according to response, maximum 10 mg/day Dose applies to patients with CKD (eGFR <50 mL/min/1.73 m^2) and those on dialysis. **-and-** » insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily
		OR
		» repaglinide: 0.5 to 4 mg orally before each meal up to three times daily Dose should be started low and titrated carefully to desired clinical response. **-and-** » insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily
		OR
		» sitagliptin: 25-100 mg orally once daily; dose should be adjusted according to level of renal impairment **-and-** » insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily
		OR
		» insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily

Ongoing

Patient group	Tx line	Treatment
	plus	**ACE inhibitor or angiotensin receptor blocker (ARB)**

» Treatment of hypertension reduces progression of DKD.[6] BP should probably be maintained at ≤130/80 mmHg in patients with overt proteinuria.[59] [61] [63] However, some guidelines recommend a less stringent BP goal of <140/90 mmHg,[25] [61] which is based on findings from the ACCORD BP trial.[62] One analysis of the VA-NEPHRON D trial supports a BP goal of <140/80 mmHg.[64]

» ACE inhibitors have been shown to slow progression of DKD in type 1 diabetic patients with microalbuminuria.[68] In type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to slow progression of DKD.[69] [104]

» ACE inhibitors and ARBs have been shown to be equally protective against DKD progression in type 2 diabetes with microalbuminuria.[105] There are similar findings in patients with macroalbuminuria for ACE inhibitors in type 1 diabetes[106] and ARBs in type 2 diabetes.[107] However, there are few data on the effectiveness of ACE inhibition in type 2 diabetic patients with macroalbuminuria and on the effectiveness of ARBs in type 1 diabetic patients with macroalbuminuria.

» The combination of ACE inhibitors and ARBs can further reduce proteinuria in people with type 1 diabetes[108] and type 2 diabetes.[109] However, the combination is not commonly used in practice because of the risk of hyperkalaemia. Moreover, several studies involving diabetes patients with overt proteinuria have been stopped early due to safety concerns with this combination therapy.[78] [79]

Primary options

» captopril: 25-50 mg orally three times daily; dose should be adjusted according to level of renal impairment

OR

» enalapril: 2.5 to 20 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» lisinopril: 2.5 to 40 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

Ongoing

Patient group	Tx line	Treatment
		» ramipril: 2.5 to 20 mg orally once daily; dose should be adjusted according to level of renal impairment
		OR
		» trandolapril: 0.5 to 8 mg orally once daily; dose should be adjusted according to level of renal impairment
		OR
		» losartan: 25-100 mg orally once daily
		OR
		» valsartan: 80-320 mg orally once daily
		OR
		» candesartan: 4-32 mg orally once daily; dose should be adjusted according to level of renal impairment
	plus	**nutrition**
		» According to the American Dietetic Association, medical nutrition therapy by a registered dietician is recommended for people with type 1 or type 2 diabetes.[94] An initial series of 3 to 4 encounters results in positive outcomes, including reductions in HbA1c, lipids, and weight, a positive adjustment in medications, and a decrease in comorbidities. In addition, patients should have a follow-up visit annually.[94]
		» There are some data to support the claim that low-protein diets prevent decline in GFR and reduce progression of proteinuria.[16] Dietary protein restriction of 0.8 g/kg of ideal body weight per day is suggested.[16] High-protein diets should be avoided. However, other research has suggested that a low-protein diet does not improve renal function in type 1 or type 2 diabetic kidney disease.[95] The 2016 American Diabetes Association guidelines do not recommend protein restriction.[25] In addition, a systematic review was unable to show a benefit of protein restriction on renal failure.[96] Limited intake of saturated fat, cholesterol, and sodium (2.3 g/day) is beneficial.[97] Salt restriction may prevent the onset of diabetic kidney disease in diabetes,[98] and potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers (ARBs).[81] Although a multivitamin is recommended, high doses of B vitamins resulted in increased vascular events.[99]

Primary options

Ongoing

Patient group	Tx line	Treatment
		» low-protein diet: 0.8 g/kg/day maximum May cause malnutrition; it should be ensured that caloric intake is adequate. **-and-** » low-sodium diet: 2.3 g/day maximum Reduces blood pressure and prevents oedema. **-and-** » low saturated fat diet Prevents atherosclerosis.
	plus	**smoking cessation** » Smoking cessation is strongly recommended, as studies document a relation between smoking and loss of GFR. The mechanisms underlying the adverse renal effects of smoking are still incompletely understood. Beyond its effect on progression of renal failure, smoking is also an important cardiovascular risk factor in chronic kidney disease patients.[100] » E-cigarettes are not recommended either as an alternative to smoking or to facilitate smoking cessation.[25]
	adjunct	**statin** » Patients with DKD are 5 to 10 times more likely to die of cardiovascular causes than reach ESRD requiring renal replacement therapy (dialysis and/or transplantation).[110] » Statins are likely to be beneficial because of their anti-inflammatory properties and the correlation of inflammation in chronic kidney disease (CKD) with associated cardiovascular morbidity. » A study involving non-dialysis patients with diabetic CKD showed that atorvastatin has a beneficial effect on both GFR and CVD.[91] However, a study involving haemodialysis patients failed to show any benefit of statins on cardiovascular outcomes.[92] In the SHARP study, a reduction of LDL-cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.[93] » There is current debate about whether there is a recommended lower limit for LDL-cholesterol. Studies have shown that the lower the LDL-cholesterol, the greater the cardiovascular benefit. Previous guidelines recommend that LDL should be maintained at least <2.59 mmol/L (<100 mg/dL) and probably <1.81 mmol/L (<70 mg/dL).[111] However, many guidelines now recommend that lipid treatment (e.g., with statins) should be driven by cardiovascular risk rather than by LDL levels.[25] [88] [89] For example, Kidney Disease:

Ongoing

Patient group	Tx line	Treatment
		Improving Global Outcomes (KDIGO) recommend statin therapy (e.g., with atorvastatin or rosuvastatin) for all non-dialysis CKD patients aged 50 years or older; no specific treatment target is given.[89] In patients on dialysis, KDIGO recommend continuation of statin therapy if the patient is already receiving these agents, but not to start statin therapy due to lack of evidence of benefit in ESRD. **Primary options** » atorvastatin: 20 mg orally once daily **OR** » rosuvastatin: 5-10 mg orally once daily
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB	**plus**	**added diuretic** » Diuretics are considered second-line therapy for hypertension in DKD. » In conjunction with ACE inhibitors and ARBs, they provide a greater ability to achieve recommended BP levels. Loop diuretics are generally needed when the GFR falls to <30 mL/min/1.73 m^2.[103] Renal failure is a complication of aggressive loop diuretic use. » Beta-blockers or calcium-channel blockers may then be added, if needed. » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] **Primary options** » hydrochlorothiazide: 12.5 to 50 mg orally once daily Not considered effective when CrCl is <30 mL/min/1.73 m^2. **OR** » chlortalidone: 12.5 to 50 mg orally once daily Not considered effective when CrCl is <30 mL/min/1.73 m^2. **Secondary options**

Ongoing

Patient group	Tx line	Treatment
		» metolazone: 2.5 to 10 mg orally once daily or once on alternate days; dose should be adjusted according to level of renal impairment **OR** » furosemide: 20-160 mg orally twice daily; dose should be adjusted according to level of renal impairment Used in setting of oedema. **OR** » spironolactone: 25-50 mg orally once daily; dose should be adjusted according to level of renal impairment Risk of hyperkalaemia when renal function is impaired.
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic	**plus**	**added beta-blocker** » Beta-blockers may be added if BP is not controlled with a diuretic in combination with an ACE inhibitor or ARB. » Carvedilol is better than metoprolol at stabilising glycaemic control and decreasing insulin resistance. It is generally used with co-existing CHF.[82] » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] **Primary options** » carvedilol: 3.125 to 50 mg orally twice daily **Secondary options** » propranolol: 40-240 mg orally twice daily **OR** » metoprolol: 25-200 mg orally (immediate-release) twice daily **OR** » atenolol: 25-100 mg orally once daily; dose should be adjusted according to level of renal impairment

Ongoing

Patient group	Tx line	Treatment
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + diuretic + beta-blocker	**plus**	**added calcium-channel blocker** » Non-dihydropyridine calcium-channel blockers are preferred, if heart rate allows. Dihydropyridine calcium-channel blockers should not be used as sole therapy as they may worsen proteinuria and renal injury, but can be used in conjunction with ACE inhibitors or ARBs. » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] **Primary options** » verapamil: 40-120 mg orally (immediate-release) three times daily; 120-360 mg orally (extended-release) once daily **OR** » diltiazem: 30-90 mg orally (immediate-release) four times daily; 120-360 mg orally (extended-release) once daily
on peritoneal dialysis or haemodialysis	**1st**	**glycaemic control** » In all type 1 diabetic patients, regardless of whether they are on dialysis or not, treatment with insulin is needed. Patients with type 2 diabetes who are on dialysis (e.g., due to ESRD) are preferentially treated with insulin. Insulin is usually given subcutaneously. » There is evidence to suggest that either low-dose glipizide or sitagliptin can be used in dialysis patients with type 2 diabetes. These oral hypoglycaemic agents can be used either instead of insulin or added to insulin. There is no evidence to support the use of repaglinide in dialysis patients. » Diabetes patients with chronic kidney disease (CKD) are at risk for hypoglycaemia because of impaired clearance of medications such as insulin and many oral hypoglycaemic agents, and because of impaired kidney gluconeogenesis. » Current guidelines recommend keeping HbA1c at ≤7%, except for patients with a history of severe hypoglycaemia, limited life expectancy, advanced diabetic complications and comorbidity, or

Ongoing

Patient group	Tx line	Treatment

long-standing diabetes, where a less stringent goal may be appropriate (e.g., <8%).[25] [33] Treatment goals need to be individualised, taking into account age, disease progression, and macrovascular risk, as well as the patient's lifestyle and disease management capabilities. [58]

» The benefit of intensive glycaemic control for nephropathy remains under scrutiny. In one study, compared with routine care, intensive management of patients with type 2 diabetes detected by screening (including glucose control) was not associated with significant reductions in the frequency of microvascular events at 5 years.[45] Intensive treatment of hyperglycaemia may prevent the development of microalbuminuria as well as progression to macroalbuminuria, though there is little evidence that it slows the progression of established CKD.[5] [41]

Primary options

» insulin lispro: injected subcutaneously three times daily before meals
-and-
» insulin glargine: injected subcutaneously once daily

Secondary options

» glipizide: (type 2 diabetes) 2.5 to 5 mg orally (immediate-release) once daily initially, increase by 2.5 to 5 mg/day increments every 1-2 weeks according to response, maximum 20 mg/day; 5 mg orally (extended-release) once daily initially, increase according to response, maximum 10 mg/day
Dose applies to patients with CKD (eGFR <50 mL/min/1.73 m^2) and those on dialysis.

OR

» sitagliptin: (type 2 diabetes) 25 mg orally once daily; dose should be adjusted according to level of renal impairment

OR

» glipizide: (type 2 diabetes) 2.5 to 5 mg orally (immediate-release) once daily initially, increase by 2.5 to 5 mg/day increments every 1-2 weeks according to response, maximum 20 mg/day; 5 mg orally (extended-release) once daily initially, increase according to response, maximum 10 mg/day
Dose applies to patients with CKD (eGFR <50 mL/min/1.73 m^2) and those on dialysis.
-and-

Ongoing

Patient group	Tx line	Treatment
		» insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily
		OR
		» sitagliptin: (type 2 diabetes) 25 mg orally once daily; dose should be adjusted for renal impairment **-and-** » insulin lispro: injected subcutaneously three times daily before meals **-and-** » insulin glargine: injected subcutaneously once daily
	plus	**ACE inhibitor or angiotensin receptor blocker (ARB)**

» Treatment of hypertension reduces progression of DKD.[6] BP should probably be maintained at ≤130/80 mmHg in patients with overt proteinuria.[59] [61] [63] However, some guidelines recommend a less stringent BP goal of <140/90 mmHg,[25] [61] which is based on findings from the ACCORD BP trial.[62] One analysis of the VA-NEPHRON D trial supports a BP goal of <140/80 mmHg.[64]

» ACE inhibitors have been shown to slow progression of DKD in type 1 diabetic patients with microalbuminuria.[68] In type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to slow progression of DKD.[69] [104]

» ACE inhibitors and ARBs have been shown to be equally protective against DKD progression in type 2 diabetes with microalbuminuria.[105] There are similar findings in patients with macroalbuminuria for ACE inhibitors in type 1 diabetes[106] and ARBs in type 2 diabetes.[107] However, there are few data on the effectiveness of ACE inhibition in type 2 diabetic patients with macroalbuminuria and on the effectiveness of ARBs in type 1 diabetic patients with macroalbuminuria.

» The combination of ACE inhibitors and ARBs can further reduce proteinuria in people with type 1 diabetes[108] and type 2 diabetes.[109] However, the combination is not commonly used in practice because of the risk of hyperkalaemia. Moreover, several studies involving diabetes patients with overt proteinuria have been stopped early due to safety concerns with this combination therapy.[78] [79]

Primary options

Ongoing

Patient group	Tx line	Treatment
		» captopril: 25-50 mg orally three times daily; dose should be adjusted according to level of renal impairment **OR** » enalapril: 2.5 to 20 mg orally once daily; dose should be adjusted according to level of renal impairment **OR** » lisinopril: 2.5 to 40 mg orally once daily; dose should be adjusted according to level of renal impairment **OR** » ramipril: 2.5 to 20 mg orally once daily; dose should be adjusted according to level of renal impairment **OR** » trandolapril: 0.5 to 8 mg orally once daily; dose should be adjusted according to level of renal impairment **OR** » losartan: 25-100 mg orally once daily **OR** » valsartan: 80-320 mg orally once daily **OR** » candesartan: 4-32 mg orally once daily; dose should be adjusted according to level of renal impairment
	plus	**nutrition** » According to the American Dietetic Association, medical nutrition therapy by a registered dietician is recommended for people with type 1 or type 2 diabetes.[94] An initial series of 3 to 4 encounters results in positive outcomes, including reductions in HbA1c, lipids, and weight, a positive adjustment in medications, and a decrease in comorbidities. In addition, patients should have a follow-up visit annually.[94] » There are some data to support the claim that low-protein diets prevent decline in GFR and reduce progression of proteinuria.[16] Dietary protein restriction of 0.8 g/kg of ideal body weight per day is suggested.[16] High-protein diets should be avoided.

Ongoing

Patient group	Tx line	Treatment
		However, other research has suggested that a low-protein diet does not improve renal function in type 1 or type 2 diabetic kidney disease.[95] The 2016 American Diabetes Association guidelines do not recommend protein restriction.[25] In addition, a systematic review was unable to show a benefit of protein restriction on renal failure.[96] Limited intake of saturated fat, cholesterol, and sodium (2.3 g/day) is beneficial.[97] Salt restriction may prevent the onset of diabetic kidney disease in diabetes,[98] and potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers (ARBs).[81] Although a multivitamin is recommended, high doses of B vitamins resulted in increased vascular events.[99]
		Primary options
		» low-protein diet: 0.8 g/kg/day maximum May cause malnutrition; it should be ensured that caloric intake is adequate. **-and-** » low-sodium diet: 2.3 g/day maximum Reduces blood pressure and prevents oedema. **-and-** » low saturated fat diet: Prevents atherosclerosis.
	plus	**smoking cessation**
		» Smoking cessation is strongly recommended, as studies document a relation between smoking and loss of GFR. The mechanisms underlying the adverse renal effects of smoking are still incompletely understood. Beyond its effect on progression of renal failure, smoking is also an important cardiovascular risk factor in chronic kidney disease patients.[100]
		» E-cigarettes are not recommended either as an alternative to smoking or to facilitate smoking cessation.[25]
	adjunct	**statin**
		» Patients with DKD are 5 to 10 times more likely to die of cardiovascular causes than reach ESRD requiring renal replacement therapy (dialysis and/or transplantation).[110]
		» Statins are likely to be beneficial because of their anti-inflammatory properties and the correlation of inflammation in chronic kidney disease (CKD) with associated cardiovascular morbidity.
		» A study involving non-dialysis patients with diabetic CKD showed that atorvastatin has a beneficial effect on both GFR and CVD.[91] However, a study involving

Ongoing

Patient group	Tx line	Treatment
		haemodialysis patients failed to show any benefit of statins on cardiovascular outcomes.[92] In the SHARP study, a reduction of LDL-cholesterol with simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD.[93] » There is current debate about whether there is a recommended lower limit for LDL-cholesterol. Studies have shown that the lower the LDL-cholesterol, the greater the cardiovascular benefit. Previous guidelines recommend that LDL should be maintained at least <2.59 mmol/L (<100 mg/dL) and probably <1.81 mmol/L (<70 mg/dL).[111] However, many guidelines now recommend that lipid treatment (e.g., with statins) should be driven by cardiovascular risk rather than by LDL levels.[25] [88] [89] For example, Kidney Disease: Improving Global Outcomes (KDIGO) recommend statin therapy (e.g., with atorvastatin or rosuvastatin) for all non-dialysis CKD patients aged 50 years or older; no specific treatment target is given.[89] In patients on dialysis, KDIGO recommend continuation of statin therapy if the patient is already receiving these agents, but not to start statin therapy due to lack of evidence of benefit in ESRD. **Primary options** » atorvastatin: 20 mg orally once daily **OR** » rosuvastatin: 5-10 mg orally once daily
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB	**plus**	**added beta-blocker** » Beta-blockers may be added if BP is not controlled with an ACE inhibitor or ARB. » Carvedilol is better than metoprolol at stabilising glycaemic control and decreasing insulin resistance. It is generally used with co-existing CHF.[82] » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] In dialysis patients, BP goal should generally be <140/90 pre-dialysis with a post-dialysis value of <130/80. If home BPs are measured, a mean BP of <135/85 is reasonable.

Ongoing

Patient group	Tx line	Treatment
		Primary options » carvedilol: 3.125 to 50 mg orally twice daily **Secondary options** » propranolol: 40-240 mg orally twice daily **OR** » metoprolol: 25-200 mg orally (immediate-release) twice daily **OR** » atenolol: 25-100 mg orally once daily; dose should be adjusted according to level of renal impairment
with BP not controlled below 130/80 to 140/90 by ACE inhibitor/ARB + beta-blocker	**plus**	**added calcium-channel blocker** » Non-dihydropyridine calcium-channel blockers are preferred, if heart rate allows. Dihydropyridine calcium-channel blockers should not be used as sole therapy as they may worsen proteinuria and renal injury, but can be used in conjunction with ACE inhibitors or ARBs. » Home BP monitoring may be beneficial in monitoring response to treatment. Past recommendations were that BP should be maintained at ≤130/80 mmHg.[59] Intensive blood pressure lowering provides protection against kidney failure, particularly among those with proteinuria,[60] although in the absence of overt proteinuria it is now thought that the BP goal may be more liberal (i.e., 140/90 or below).[61] In dialysis patients, BP goal should generally be <140/90 pre-dialysis with a post-dialysis value of <130/80. If home BPs are measured, a mean BP of <135/85 is reasonable. **Primary options** » verapamil: 40-120 mg orally (immediate-release) three times daily; 120-360 mg orally (extended-release) once daily **OR** » diltiazem: 30-90 mg orally (immediate-release) four times daily; 120-360 mg orally (extended-release) once daily
	2nd	**consideration for pancreas-kidney transplantation** » Diabetes is the most common cause of ESRD requiring renal replacement therapy (RRT). RRT is not

Ongoing

Patient group	Tx line	Treatment
		only time consuming and fraught with uncomfortable side effects such as cramps, fatigue, and central venous stenosis, but it is also associated with significant morbidity and mortality. Pancreas-kidney transplantation not only frees patients from the need for RRT, but it also has a significant survival benefit. With modern surgical and immunosuppressive protocols, 5-year patient survival is 95%, kidney survival is 90%, and pancreas survival is greater than 80%.[101] In the US, in 2013, 760 simultaneous pancreas-kidney (SPK) transplants, 127 pancreas transplants alone (PTA), and 107 pancreas after kidney (PAK) transplants were performed.[102] » SPK recipients are generally younger (60 years or less) than kidney transplant recipients (70 years or less). Patients with type 2 diabetes may be considered if they do not have significant insulin resistance (C-peptide >2 and BMI <30), In addition, recipients must have a GFR <20 or be dialysis-dependent. They must go through strict cardiovascular, psychosocial, and anatomical (CT angiogram) clearance.[101] » Other management strategies should be continued as necessary.

Emerging

Endothelin antagonists

Avosentan, an endothelin-A antagonist, in combination with ACE inhibitor/angiotensin receptor blocker (ARB), improves proteinuria in patients with diabetic kidney disease and macroalbuminuria.[113] However, in larger doses, there have been reports of a high incidence of serious, sometimes life-threatening adverse effects, including pulmonary oedema and congestive heart failure.[114] Whether avosentan is safe in lower doses in diabetic kidney disease is not yet known. More selective endothelin antagonists, such as atrasentan, are being studied.[115]

Aldosterone antagonists

Spironolactone, being an aldosterone antagonist, should theoretically be promising in the treatment of DKD. However, data are lacking and there are concerns about hyperkalaemia in the presence of decreased renal function.[116] ACE inhibitors or ARBs should be considered first-line agents; spironolactone may be used as a second- or third-line drug, especially in the presence of heart failure, providing the serum potassium is normal and closely followed. In a study in which some subjects had substantial renal dysfunction, serum potassium >6 mmol/L (>6mEq/L) was noted in 52% of patients treated with combined high-dose ACE inhibitors plus low-dose spironolactone.[117] In a large study of microalbuminuric patients with generally preserved renal function, eplerenone in combination with the ACE inhibitor lisinopril decreased albuminuria by about 40%, but 8% of patients treated with the higher dose of eplerenone had to be withdrawn from the study due to hyperkalaemia.[118] There are no long-term data demonstrating any beneficial effect of combining an ACE inhibitor or ARB with aldosterone blockade in slowing the rate of loss of GFR.

Aliskiren

Recent research focused on the use of aliskiren in conjunction with an ACE inhibitor or ARB; however, in December 2011 the manufacturer recommended that physicians should no longer prescribe aliskiren-containing products with these two classes of drugs based on the results, and subsequent early termination, of the ALTITUDE trial.[78] The trial was testing the effect of aliskiren (in combination with ACE inhibitors or ARBs) in people with type 2 diabetes at high risk for cardiovascular and renal events, and found an increased risk for non-fatal stroke, renal complications, hyperkalaemia, and hypotension in patients taking the drug for 18-24 months. The US FDA now recommends that the combination of aliskiren with ACE inhibitors or ARBs is contra-indicated in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalaemia. It also recommends that this combination of drugs be avoided in patients with moderate to severe renal impairment (i.e., GFR <60 mL/min/1.73 m^2). Further research is required into its use as monotherapy as it has been shown to reduce urinary albumin to creatinine ratio (ACR) independently of its BP-lowering effect.[119] [120] One study has shown no effects on hard renal outcomes (defined as a sustained doubling of serum creatinine, ESRD, or renal death). Delayed progression to microalbuminuria and macroalbuminuria and improved regression to microalbuminuria and normoalbuminuria have been demonstrated.[121]

Pentoxifylline

A number of small studies have suggested that pentoxifylline may decrease proteinuria and possibly slow decline of renal function in DKD. A Cochrane review meta-analysis on pentoxifylline in DKD concluded that there was insufficient evidence to support the use of pentoxifylline, but the authors of the review did stress the need for large-scale, rigorously designed, multi-centre randomised trials to further assess its use in DKD.[122] The PREDIAN study reported that treatment with pentoxifylline slowed the progression of diabetic kidney disease in type 2 diabetes patients with stage 3 to 4 chronic kidney disease (CKD) who were receiving standard medical care, which included maximum RAS blockade.[123] Pentoxifylline decreased proteinuria and urinary concentration of TNF-alpha, and slowed the decline in eGFR by 4.3 mL/min/1.73 m^2 when compared with standard medical care (P = 0.001). No serious adverse events were reported. Adverse events that were more common in the treatment arm compared with placebo were mainly digestive symptoms (e.g., abdominal discomfort, flatus, dyspepsia, nausea, and vomiting). The favourable safety profile of pentoxifylline is supported by its extensive clinical experience and use in treating peripheral vascular disease.

Paricalcitol

An active vitamin D analogue, paricalcitol has been reported to reduce albuminuria in patients with diabetes and could be renoprotective.[124] However, further clinical trials using hard end points are needed before this therapy can be widely recommended.[125]

Sevelamer

Increased inflammation and oxidative stress may be caused by proteins and lipids modified by cytotoxic advanced glycation end products (AGEs) in food. Sevelamer carbonate, a phosphate-binding agent used in CKD and end-stage kidney disease (ESKD) patients, sequesters cytotoxic AGEs in the gut, preventing their uptake and thereby reducing AGE-induced abnormalities. In a single-centre, randomised, 2-month, open-label, intention-to-treat, crossover study which compared sevelamer carbonate with calcium carbonate treatment in stage 2 to 4 diabetic CKD, sevelamer carbonate significantly reduced HbA1c, fibroblast growth factor 23, lipids, and markers of inflammation and oxidative stress; it also markedly increased anti-oxidant markers, independently of phosphorus in patients with diabetes and early kidney disease. Whether or not these changes affect progression of early diabetic CKD requires further study.[126]

Genomics/proteomics/metabonomics

With the development of mass spectroscopy, liquid chromatography, and microarray protocols, evaluation of DNA, RNA, or protein is increasingly being applied to all disease states. Genomics has, for example, been touted as a potential replacement for kidney biopsies in the diagnosis of acute cellular rejection in kidney transplant patients. Similarly, microRNAs in diabetic kidney disease will pave the way for development of future biomarkers and therapeutic options.[127]

Recommendations

Monitoring

HbA1c should be checked twice per year. Blood pressure should be checked at each primary care visit. Lipids should be checked every 3 to 6 months. Albumin to creatinine ratio (ACR) should be checked annually.

Patient instructions

Blood glucose and blood pressure are monitored at home. The patient should be encouraged to adhere to a low-protein, low-saturated fat, low-sodium diet; stop smoking (including e-cigarettes); exercise regularly; and adhere to prescribed medicines. Use of OTC drugs or complementary medicines should be avoided until they have been discussed with physician.

Complications

Complications	Timeframe	Likelihood
chronic renal failure requiring dialysis	**long term**	**high**
DKD frequently progresses to dialysis, but patients with macroalbuminuria usually die due to cardiovascular causes before reaching ESRD.[110]		
hyperkalaemia	**long term**	**high**
The failing kidney fails to excrete potassium. Hyporeninaemic hypoaldosteronism due to diabetes may be present and increases the risk of hyperkalaemia. In advanced chronic kidney disease (CKD), uncontrolled hyperkalaemia indicates need for dialysis.		
cardiovascular events	**long term**	**high**
DKD is complicated by a triad of inflammation, endothelial dysfunction, and oxidative stress and is associated with marked cardiovascular morbidity and mortality. Cardiovascular events should be treated as in any other patient population: with stenting and/or coronary artery bypass graft (CABG). Angina pectoris and cardiovascular disease are common in DKD, and are reasons to aggressively treat coronary artery disease with stent/CABG and to intensify treatment of DKD.[128] Aspirin 81 mg/day is beneficial and has an acceptable risk:benefit ratio in CKD.[129] Aspirin has cardiovascular benefits and is also anti-inflammatory. Bleeding has not been shown to be a concern.		
blindness	**long term**	**high**
Advanced DKD is frequently associated with diabetic retinopathy because of microvascular disease.		
peripheral vascular disease	**long term**	**high**
DKD is associated with progressive peripheral vascular disease because of microvascular and macrovascular disease. Amputation may be necessary.		

FOLLOW UP

Complications	Timeframe	Likelihood
refractory hypertension	**long term**	**high**
With progressive loss of kidney function, hypertension becomes very difficult to control.		
bone disease	**long term**	**high**
As in all patients with CKD, diabetic patients with CKD often develop secondary hyperparathyroidism due to hyperphosphataemia and vitamin D deficiency. Treatment includes phosphorus (and protein) restriction, phosphate binders (including calcium carbonate, calcium acetate, sevelamer, lanthanum carbonate), and vitamin D replacement, generally with ergocalciferol in early stages of CKD and calcitriol or an active analogue (such as paricalcitol) in later stages. Compared with non-diabetic people, patients with diabetes mellitus are more likely to have adynamic bone disease.[130]		
anaemia	**long term**	**high**
As CKD progresses, there is a progressive increase in the prevalence and severity of anaemia. Iron indices should be obtained and iron deficiency treated. Erythropoietic stimulating agents (ESAs) (e.g., epoetin alfa, darbepoetin) are indicated to reduce the need for blood transfusions. Although there is some variability in results among studies, the CHOIR and CREATE trials indicate better outcomes in CKD patients with Hb values between 110 and 120 g/L, or between 11 and 12 g/dL (i.e., Hct between 33% and 36%) compared with values above this range.[131] [132] Thus, normalisation of Hb values is not recommended. However, in another study, improvement in quality of life has been noted with near-normal Hb in diabetic patients with CKD, so the issue is not completely settled.[133] Treatment includes iron compounds (ferrous sulfate, iron dextran, ferric gluconate, iron sucrose) and ESAs. ESAs should be avoided in a Hb >130 g/L (13 g/dL) due to increased risk of cardiovascular events.		
hypoglycaemia	**variable**	**high**
Intensive treatment of hyperglycaemia may result in hypoglycaemia because of impaired gluconeogenesis and because insulin and other oral hypoglycaemics are poorly cleared by the kidney. Reduction in antidiabetic treatment is warranted.		

Prognosis

DKD, compared with other types of chronic kidney diseases (CKD), is associated with continued worsening of proteinuria, earlier appearance of complications, and worse performance on dialysis. However, morbidity and mortality can be avoided or delayed with intensive treatment of hyperglycaemia, hypertension, and dyslipidaemia and with careful attention to diet and avoidance of nephrotoxic agents. Diabetes mellitus itself is responsible for significant morbidity and mortality, including blindness, myocardial infarctions, cerebrovascular accidents, amputations, and death.

Diagnostic guidelines

Europe

Management of diabetes: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2010

Systematic review on urine albumin testing for early detection of diabetic complications

Published by: Health Technology Assessment NHS R&D HTA Programme **Last published:** 2005

North America

Standards of medical care in diabetes - 2016

Published by: American Diabetes Association **Last published:** 2016

Summary: Updated annually by the American Diabetes Association.

Abnormal blood glucose and type 2 diabetes mellitus: screening

Published by: US Preventive Services Task Force **Last published:** 2015

Summary: Recommends screening for abnormal glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. The optimal interval for screening is unknown.

KDOQI clinical practice guideline for diabetes and CKD: update 2012

Published by: National Kidney Foundation **Last published:** 2012

Summary: Provides updates of some guidelines from the 2007 KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease that address haemoglobin A1c (HbA1c) targets, treatments to lower low-density lipoprotein cholesterol (LDL-C) levels, and use of angiotensin converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) treatment in diabetic patients with and without albuminuria.

North America

KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease

Published by: National Kidney Foundation **Last published:** 2007

Summary: In patients with type 1 diabetes of 5 years' duration, screening is done with albumin to creatinine ratio (ACR). In patients with type 2 diabetes, screening for microalbuminuria is started from the onset of diagnosis. In diabetic patients with microalbuminuria and retinopathy, the diagnosis of DKD is highly likely. In patients with type 1 diabetes of 10 years' duration and microalbuminuria, the diagnosis of DKD is highly likely. In patients with diabetes mellitus and macroalbuminuria, the diagnosis of DKD is highly likely. The differential diagnosis of DKD must be explored in type 1 diabetic patients who have had diabetes mellitus for a short period of time, in type 2 diabetic patients who do not have retinopathy, in patients who have a rapid decline in renal function, and in patients in whom decline in GFR is not accompanied by albuminuria. DKD is classified according to presence of microalbuminuria (30 to 300 mg albumin/24 hours or ACR of 3.4 to 34.0 mg/mmol [30-300 mg/g]) and macroalbuminuria (>300 mg albumin/24 hours or ACR >34 mg/mmol [300 mg/g]). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest the use of chronic kidney disease (CKD) staging to determine the likelihood that CKD in diabetic patients is due to DKD. Using the CKD staging likelihood of DKD can be determined as follows: - Normoalbuminuria in CKD stages 3 to 5 (GFR <60 mL/min/1.73 m^2) is unlikely to be DKD. - Microalbuminuria in CKD stages 1 to 3 (GFR >30 mL/min/1.73 m^2) is possible DKD. - Microalbuminuria in CKD stages 4 to 5 (GFR <30 mL/min/1.73 m^2) is unlikely to be DKD. - Macroalbuminuria at all stages of CKD is highly likely to be DKD.

Treatment guidelines

Europe

Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Management of diabetes: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2010

Type 2 diabetes in adults: management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Diagnosis and management of chronic kidney disease: a national guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2008

Summary: All patients with DM should have their renal function monitored regularly. Albumin/creatinine ratio is recommended for detecting and monitoring diabetic kidney disease, and may also be used to exclude diabetic kidney disease in patients with diabetes. Patients with type 2 DM with CKD and microalbuminuria should be treated with an ACE inhibitor or ARB, irrespective of their BP. Statins and low-dose antiplatelet therapy should both be considered in all patients who have stage 1 to 3 CKD and a predicted 10-year cardiovascular risk of 20% or greater. Restricting dietary protein (< 0.8 g/kg/day) is not recommended in patients with stage 1 to 3 CKD. A high protein intake (>1 g/kg/day) is not recommended in stage 4 CKD. Reducing sodium intake to <2.4 g/day is recommended for patients with CKD and hypertension.

Europe

Diabetes commissioning toolkit

Published by: National Diabetes Support Team; Diabetes UK; Primary Care Diabetes Society; Department of Health; Association of British Clinical Diabetologists; Yorkshire and Humber Public Health Observatory **Last published:** 2006

North America

Standards of medical care in diabetes - 2016

Published by: American Diabetes Association **Last published:** 2016

Summary: Updated annually by the American Diabetes Association.

2015 Canadian Hypertension Education Program recommendations

Published by: Canadian Hypertension Education Program **Last published:** 2015

Summary: Annually updated standardised recommendations and practice guidelines for healthcare professionals in clinical and community settings to detect, treat, and control hypertension.

2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee

Published by: Eighth Joint National Committee (JNC 8) **Last published:** 2014

Summary: Evidence-based recommendations regarding the management of high blood pressure. The guideline provides analysis of treatment thresholds, treatment goals, and strategies to achieve those goals.

KDOQI clinical practice guideline for diabetes and CKD: update 2012

Published by: National Kidney Foundation **Last published:** 2012

Summary: Provides updates of some guidelines from the 2007 KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease that address haemoglobin A1c (HbA1c) targets, treatments to lower low-density lipoprotein cholesterol (LDL-C) levels, and use of angiotensin converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) treatment in diabetic patients with and without albuminuria.

KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease

Published by: Kidney Disease: Improving Global Outcomes **Last published:** 2012

Summary: Provides evidence-based guidance on blood pressure management and treatment for chronic kidney disease (CKD) nondialysis patients with diabetes mellitus.

GUIDELINES

North America

Diabetes mellitus type 1 and 2 evidence-based nutrition practice guideline

Published by: Academy of Nutrition and Dietetics (American Dietetic Association)**Last published:** 2015

Summary: The registered dietician plays an integral role on the inter-disciplinary healthcare team by making the optimal nutrition prescription, and by developing the nutrition intervention plan for patients undergoing diabetes therapy. Based on the treatment plan and comorbid conditions, other nutrition practice guidelines, such as adult weight management, hypertension, disorders of lipid metabolism, critical illness, and nutrition care in bariatric surgery may be needed in order to provide optimal treatment.

KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease

Published by: National Kidney Foundation **Last published:** 2007

Summary: Treatment is multi-factorial. Intensive treatment of hyperglycaemia is essential. Goal HbA1c is <53 mmol/mol (7%). Intensive treatment of hypertension is also important. ACE inhibitors and ARBs are first-line antihypertensives, followed by diuretics, beta-blockers and non-dihydropyridine calcium-channel blockers. Aggressive treatment of dyslipidaemia is important. LDL goal is <2.59 mmol/L (<100 mg/dL), but <1.81 mmol/L (<70 mg/dL) is likely to be better. Dietary restriction of protein to 0.8 g/kg is beneficial. Diet low in saturated fats, cholesterol, and sodium (2 to 3 g/day) is recommended. Aspirin has a beneficial risk:benefit profile and should be utilised. Nephrotoxic agents such as NSAIDs and radiocontrast media should be avoided.

Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Published by: National Heart, Lung, and Blood Institute **Last published:** 2004

Summary: Intensive treatment of hypertension is also important. ACE inhibitors and ARBs are first-line antihypertensives, followed by diuretics, beta blockers and non-dihydropyridine calcium-channel blockers.

Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines

Published by: National Heart, Lung, and Blood Institute **Last published:** 2004

Summary: Aggressive treatment of dyslipidaemia is important. LDL goal is <2.59 mmol/L (<100 mg/dL), but <1.81 mmol/L (<70 mg/dL) is likely to be better.

Online resources

1. National Kidney Foundation: MDRD GFR Calculator *(external link)*

REFERENCES

Key articles

- Lv J, Perkovic V, Foote CV, et al. Antihypertensive agents for preventing diabetic kidney disease.Cochrane Database Syst Rev. 2012;(12):CD004136. Full text Abstract
- American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39(suppl 1):S1-112. Full text
- National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60:850-886. Full text Abstract
- Coca SG, Ismail-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med. 2012;172:761-769. Abstract
- Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23(Suppl 2):B21-B29. Abstract
- Zoungas S, de Galan BE, Ninomiya T, et al; ADVANCE Collaborative Group. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care. 2009;32:2068-2074. Full text Abstract
- Ismail-Beigi F, Craven TE, O'Connor PJ, et al. Combined intensive blood pressure and glycemic control does not produce an additive benefit on microvascular outcomes in type 2 diabetic patients. Kidney Int. 2012;81:586-594. Abstract
- Fullerton B, Jeitler K, Seitz M, et al. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014;(2):CD009122. Full text Abstract
- Maione A, Navaneethan SD, Graziano G, et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrol Dial Transplant. 2011;26:2827-2847. Full text
- Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-1903. Full text Abstract
- Suckling RJ, He FJ, Macgregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. Cochrane Database Syst Rev. 2010;(12):CD006763. Full text Abstract
- National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S1-S290. Full text Abstract
- Grundy SM, Cleeman JI, Mertz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-239. Full text Abstract
- Lee SW, Kim WJ, Kim YH, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT Trial). Am J Cardiol. 2011;107:1447-1452. Abstract

References

1. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49(suppl 2):S1-S179. Full text

2. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes. 1990;39:1116-1124. Abstract

3. Perkins BA, Ficociello LH, Silva KH, et al. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003;348:2285-2293. Abstract

4. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med. 1999;341:1127-1133. Abstract

5. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type I diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. JAMA. 2003;290:2159-2167. Full text Abstract

6. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36:646-661. Abstract

7. Tonelli M, Keech A, Shepherd J, et al. Effect of pravastatin in people with diabetes and chronic kidney disease. J Am Soc Nephrol. 2005;16:3748-3754. Full text Abstract

8. Freedman BI, Bostrom M, Daeihagh P, et al. Genetic factors in diabetic nephropathy. Clin J Am Soc Nephrol. 2007;2:1306-1316. Full text Abstract

9. Stenvinkel P, Heimburger O, Paultre F, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55:1899-1911. Abstract

10. Antolini F, Valente F, Ricciardi D, et al. Normalization of oxidative stress parameters after kidney transplant is secondary to full recovery of renal function. Clin Nephrol. 2004;62:131-137. Abstract

11. Ghiadoni L, Cupisti A, Huang Y, et al. Endothelial dysfunction and oxidative stress in chronic renal failure. J Nephrol. 2004;17:512-519. Abstract

12. Persson F, Rossing P, Hovind P, et al. Endothelial dysfunction and inflammation predict development of diabetic nephropathy in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA 2) study. Scand J Clin Lab Invest. 2008;68:731-738. Abstract

13. Shumway JT, Gambert SR. Diabetic nephropathy - pathophysiology and management. Int Urol Nephrol. 2002;34:257-264. Abstract

14. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol. 2004;15:2792-2800. Full text Abstract

REFERENCES

15. Howden EJ, Coombes JS, Strand H, et al. Exercise training in CKD: efficacy, adherence, and safety. Am J Kidney Dis. 2015;65:583-591. Abstract

16. Hansen HP, Tauber-Lassen E, Jensen BR, et al. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int. 2002;62:220-228. Abstract

17. Lv J, Perkovic V, Foote CV, et al. Antihypertensive agents for preventing diabetic kidney disease.Cochrane Database Syst Rev. 2012;(12):CD004136. Full text Abstract

18. Johnson DW, Jones GR, Mathew TH, et al; Australasian Proteinuria Consensus Working Group. Chronic kidney disease and measurement of albuminuria or proteinuria: a position statement. Med J Aust. 2012;197:224-225. Full text Abstract

19. Bataille R, Harousseau JL. Multiple myeloma. N Engl J Med. 1997;336:1657-1664. Abstract

20. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431-442. Abstract

21. Komenda P, Ferguson TW, Macdonald K, et al. Cost-effectiveness of primary screening for CKD: a systematic review. Am J Kidney Dis. 2014;63:789-797. Abstract

22. Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in type I (insulin-dependent) diabetes mellitus. Diabetologia. 1985;28:590-596. Abstract

23. Nelson RG, Pettitt DJ, Carraher MJ, et al. Effect of proteinuria on mortality in NIDDM. Diabetes. 1988;37:1499-1504. Abstract

24. Farmer AJ, Stevens R, Hirst J, et al. Optimal strategies for identifying kidney disease in diabetes: properties of screening tests, progression of renal dysfunction and impact of treatment - systematic review and modelling of progression and cost-effectiveness. Health Technol Assess. 2014;18:1-128. Full text Abstract

25. American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39(suppl 1):S1-112. Full text

26. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. August 2015. https://www.nice.org.uk/ (last accessed 3 May 2016). Full text

27. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2016;39(suppl 1):S13-22. Full text Abstract

28. Siu AL; US Preventive Services Task Force. Screening for abnormal blood glucose and type 2 diabetes mellitus: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:861-868. Full text Abstract

29. Canadian Task Force on Preventive Health Care, Pottie K, Jaramillo A, et al. Recommendations on screening for type 2 diabetes in adults. CMAJ. 2012;184:1687-1696. Full text Abstract

30. National Institute for Health and Care Excellence. Type 2 diabetes: prevention in people at high risk. July 2012. https://www.nice.org.uk/guidance/ph38 (last accessed 3 May 2016). Full text

31. American Association of Diabetes Educators (AADE). AADE guidelines for the practice of diabetes self-management education and training (DSME/T). Chicago, IL: American Association of Diabetes Educators; 2010.

32. Diabetes Australia, Royal Australian College of General Practitioners, Australian Diabetes Society, et al. National evidence based guideline for patient education in type 2 diabetes. June 2009. https://www.diabetesaustralia.com.au/ (last accessed 3 May 2016). Full text

33. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60:850-886. Full text Abstract

34. Slinin Y, Ishani A, Rector T, et al. Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline. Am J Kidney Dis. 2012;60:747-769. Abstract

35. US Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. April 2016. http://www.fda.gov/ (last accessed 3 May 2016). Full text

36. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide. Clin Pharmacokinet. 2002;41:471-483. Abstract

37. Bergman AJ, Cote J, Yi B, et al. Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-4 inhibitor. Diabetes Care. 2007;30:1862-1864. Full text Abstract

38. Sarafidis PA, Stafylas PC, Georgianos PI, et al. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. Am J Kidney Dis. 2010;55:835-847. Abstract

39. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab. 2014;16:1016-1027. Abstract

40. Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int. 2014;85:962-971. Full text Abstract

41. Coca SG, Ismail-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med. 2012;172:761-769. Abstract

42. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int. 1995;47:1703-1720. Abstract

43. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329:304-309. Abstract

44. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-853. Abstract

REFERENCES

45. Sandbæk A, Griffin SJ, Sharp SJ, et al. Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes: a randomized controlled trial: the ADDITION-Europe Study. Diabetes Care. 2014;37:2015-2023. Abstract

46. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23(Suppl 2):B21-B29. Abstract

47. Levin SR, Coburn JW, Abraira C, et al; Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. Diabetes Care. 2000;23:1478-1485. Full text Abstract

48. Zoungas S, de Galan BE, Ninomiya T, et al; ADVANCE Collaborative Group. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care. 2009;32:2068-2074. Full text Abstract

49. Patel A, MacMahon S, Chalmers J, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-2572. Full text Abstract

50. Poulter NR. Blood pressure and glucose control in subjects with diabetes: new analyses from ADVANCE. J Hypertens Suppl. 2009;27:S3-S8. Abstract

51. Joshi R, de Galan BE, Chalmers J, et al. Routine blood pressure lowering and intensive glucose control in patients with type 2 diabetes: the ADVANCE trial. Expert Rev Endocrinol Metab. 2009;4:111-118.

52. Perkovic V, Heerspink HL, Chalmers J, et al; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int. 2013;83:517-523. Full text Abstract

53. Mattila TK, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. Drugs. 2010;70:2229-2245. Abstract

54. Ismail-Beigi F, Craven T, Banerji MA, et al; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376:419-430. [Erratum in: Lancet. 2010;376:1466.] Abstract

55. Ismail-Beigi F, Craven TE, O'Connor PJ, et al. Combined intensive blood pressure and glycemic control does not produce an additive benefit on microvascular outcomes in type 2 diabetic patients. Kidney Int. 2012;81:586-594. Abstract

56. Agrawal L, Azad N, Emanuele NV, et al. Observation on renal outcomes in the Veterans Affairs Diabetes Trial. Diabetes Care. 2011;34:2090-2094. Full text Abstract

57. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. December 2015. http://www.nice.org.uk/ (last accessed 3 May 2016). Full text

58. Fullerton B, Jeitler K, Seitz M, et al. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014;(2):CD009122. Full text Abstract

59. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-1252. Full text Abstract

60. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185:949-957. Full text Abstract

61. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507-520. Full text Abstract

62. Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-1585. Full text Abstract

63. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012;2:337-414. Full text

64. Leehey DJ, Zhang JH, Emanuele NV, et al. BP and renal outcomes in diabetic kidney disease: The Veterans Affairs Nephropathy in Diabetes Trial. Clin J Am Soc Nephrol. 2015;10:2159-2169. Abstract

65. Yusuf S, Teo KK, Pogue J, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547-1559. Full text Abstract

66. Mann JF, Schmieder RE, McQueen M, et al; ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372:547-553. Abstract

67. Wu HY, Peng YS, Chiang CK, et al. Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis. JAMA Intern Med. 2014;174:1108-1115. Abstract

68. Viberti G, Mogensen CE, Groop LC, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA. 1994;271:275-279. Abstract

69. Ravid M, Lang R, Rachmani R, et al. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med. 1996;156:286-289. Abstract

70. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med. 2009;361:40-51. Full text Abstract

71. Agha A, Amer W, Anwar E, et al. Reduction of microalbuminuria by using losartan in normotensive patients with type 2 diabetes mellitus: a randomized controlled trial. Saudi J Kidney Dis Transpl. 2009;20:429-435. Abstract

72. de Galan BE, Perkovic V, Ninomiya T, et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol. 2009;20:883-892. Full text Abstract

REFERENCES

73. Sarafidis PA, Stafylas PC, Kanaki AI, et al. Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis. Am J Hypertens. 2008;21:922-929. Abstract

74. Maione A, Navaneethan SD, Graziano G, et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrol Dial Transplant. 2011;26:2827-2847. Full text

75. Jennings DL, Kalus JS, Coleman CI, et al. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. Diabet Med. 2007;24:486-493. Abstract

76. Pham JT, Schmitt BP, Leehey DJ. Effects of dual blockade of the renin angiotensin system in diabetic kidney disease: a systematic review and meta-analysis. J Nephrol Therapeut. 2012;(suppl 2):003. Full text

77. Canadian Hypertension Education Program. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2015;31:549-568. Full text Abstract

78. Parving HH, Brenner BM, McMurray JJ, et al; ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367:2204-2213. Full text Abstract

79. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-1903. Full text Abstract

80. Hart PD, Bakris GL. Managing hypertension in the diabetic patient. In: Egan BM, Basile JN, Lackland DT, eds. Hot topics in hypertension. Philadelphia, PA: Hanley and Belfus; 2004:249-252.

81. Lambers Heerspink HJ, Holtkamp FA, Parving HH, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. Kidney Int. 2012;82:330-337. Full text Abstract

82. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA. 2004;292:2227-2236. Full text Abstract

83. Lewis JB, Berl T, Bain RP, et al. Effect of intensive blood pressure control on the course of type I diabetic nephropathy. Collaborative Study Group. Am J Kidney Dis. 1999;34:809-817. Abstract

84. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL Study. Arch Intern Med. 2003;163:1555-1565. Full text Abstract

85. Toto RD, Tian M, Fakouhi K, et al. Effects of calcium channel blockers on proteinuria in patients with diabetic nephropathy. J Clin Hypertens (Greenwich). 2008;10:761-769. Abstract

86. Bakris GL, Toto RD, McCullough PA, et al. Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study. Kidney Int. 2008;73:1303-1309. Abstract

87. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet. 2015;385:2047-2056. Abstract

88. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. J Am Coll Cardiol. 2014;63(25_PA):2889-2934. Full text Abstract

89. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:259-305. Full text

90. Jun M, Zhu B, Tonelli M, et al. Effects of fibrates in kidney disease: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;60:2061-2071. Abstract

91. Colhoun HM, Betteridge DJ, Durrington PN; CARDS Investigators. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009;54:810-819. Abstract

92. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238-248. Abstract

93. Baigent C, Landray MJ, Reith C, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181-2192. Abstract

94. Academy of Nutrition and Dietetics (American Dietetic Association). 2015 Diabetes Types 1 and 2 Evidence-Based Nutrition Practice Guideline. 2015. http://www.andeal.org/ (last accessed 3 May 2016). Full text

95. Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2008;88:660-666. Full text Abstract

96. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev. 2007;(4):CD002181. Abstract

97. Sacks FM, Svetkey LP, Vollmer WM, et al; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344:3-10. Full text Abstract

98. Suckling RJ, He FJ, Macgregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. Cochrane Database Syst Rev. 2010;(12):CD006763. Full text Abstract

99. House AA, Eliasziw M, Cattran DC, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. JAMA. 2010;303:1603-1609. Full text Abstract

100. Orth SR, Ritz E. The renal risks of smoking: an update. Curr Opin Nephrol Hypertens. 2002;11:483-488. Abstract

101. Ollinger R, Margreiter C, Bösmüller C, et al. Evolution of pancreas transplantation: long-term results and perspectives from a high-volume center. Ann Surg. 2012;256:780-786; discussion 786-787. Abstract

102. Kandaswamy R, Skeans MA, Gustafson SK, et al. OPTN/SRTR 2013 annual data report: pancreas. Am J Transplant. 2015;15(suppl 2):1-20. Full text Abstract

REFERENCES

103. National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S1-S290. Full text Abstract

104. Parving HH, Lehnert H, Bröchner-Mortensen J, et al; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345:870-878. Full text Abstract

105. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004;351:1952-1961. Abstract

106. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456-1462. Full text Abstract

107. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851-860. Full text Abstract

108. Jacobsen P, Andersen S, Jensen BR, et al. Additive effect of ACE inhibition and angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy. J Am Soc Nephrol. 2003;14:992-999. Full text Abstract

109. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ. 2000;321:1440-1444. Full text Abstract

110. MacLeod JM, Lutale J, Marshall SM. Albumin excretion and vascular deaths in NIDDM. Diabetologia. 1995;38:610-616. Abstract

111. Grundy SM, Cleeman JI, Mertz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-239. Full text Abstract

112. Spiller HA, Sawyer TS. Toxicology of oral antidiabetic medications. Am J Health Syst Pharm. 2006;63:929-938. Abstract

113. Wenzel RR, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. J Am Soc Nephrol. 2009;20:655-664. Full text Abstract

114. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol. 2010;21:527-535. Abstract

115. Andress DL, Coll B, Pritchett Y, et al. Clinical efficacy of the selective endothelin A receptor antagonist, atrasentan, in patients with diabetes and chronic kidney disease (CKD). Life Sci. 2012;91:739-742. Full text Abstract

116. Wang H, Zhang GL, Zhang QB, et al. Spironolactone for diabetic nephropathy: a systematic review. Chin J Evid Based Med. 2009;9:71-75.

117. Mehdi UF, Adams-Huet B, Raskin P, et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol. 2009;20:2641-2650. Full text Abstract

118. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2006;1:940-951. Full text Abstract

119. Parving HH, Persson F, Lewis JB, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med. 2008;358:2433-2446. Full text Abstract

120. Rizos EC, Agouridis AP, Elisaf MS. Aliskiren in patients with diabetes: a systematic review. Curr Vasc Pharmacol. 2012;10:140-146. Abstract

121. Heerspink HJ, Persson F, Brenner BM, et al. Renal outcomes with aliskiren in patients with type 2 diabetes: a prespecified secondary analysis of the ALTITUDE randomised controlled trial. Lancet Diabetes Endocrinol. 2016;4:309-317. Full text Abstract

122. Shan D, Wu HM, Yuan QY, et al. Pentoxifylline for diabetic kidney disease. Cochrane Database Syst Rev. 2012;(2):CD006800. Full text Abstract

123. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, et al. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. J Am Soc Nephrol. 2015;26:220-229. Abstract

124. Shepler B, Nash C, Smith C, et al. Update on potential drugs for the treatment of diabetic kidney disease. Clin Ther. 2012;34:1237-1246. Abstract

125. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet. 2010;376:1543-1551. Abstract

126. Vlassara H, Uribarri J, Cai W, et al. Effects of sevelamer on HbA1c, inflammation, and advanced glycation end products in diabetic kidney disease. Clin J Am Soc Nephrol. 2012;7:934-942. Full text Abstract

127. Simpson K, Wonnacott A, Fraser DJ, et al. MicroRNAs in diabetic nephropathy: from biomarkers to therapy. Curr Diab Rep. 2016;16:35. Full text Abstract

128. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med. 1997;157:1413-1418. Abstract

129. Baigent C, Landray M, Leaper C, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis. 2005;45:473-484. Abstract

130. Pei Y, Hercz G, Greenwood C, et al. Renal osteodystrophy in diabetic patients. Kidney Int. 1993;44:159-164. Abstract

131. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355:2071-2084. Abstract

132. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098. Abstract

REFERENCES

133. Ritz E, Laville M, Bilous RW, et al. Target level for hemoglobin correction in patients with diabetes and CKD: primary results of the Anemia Correction in Diabetes (ACORD) study. Am J Kidney Dis. 2007;49:194-207. Abstract

134. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861-869. Full text Abstract

135. Lee SW, Kim WJ, Kim YH, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT Trial). Am J Cardiol. 2011;107:1447-1452. Abstract

136. Han Y, Zhu G, Han L, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. J Am Coll Cardiol. 2014;63:62-70. Full text Abstract

Images

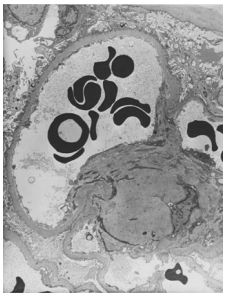

Figure 1: Diabetic kidney disease: at 5 o'clock - early Kimmelstiel-Wilson nodule, a rounded increase in mesangial matrix that probably originated in relation to a microaneurysm

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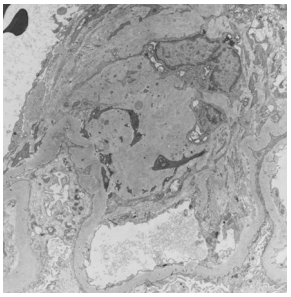

Figure 2: Diabetic kidney disease: at 12 o'clock - early Kimmelstiel-Wilson nodule, a rounded form of mesangial expansion

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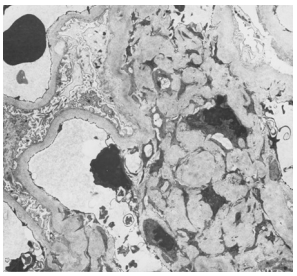

Figure 3: Diabetic kidney disease: mesangial expansion due to increased mesangial matrix and decreased degradation of glycosylated collagen

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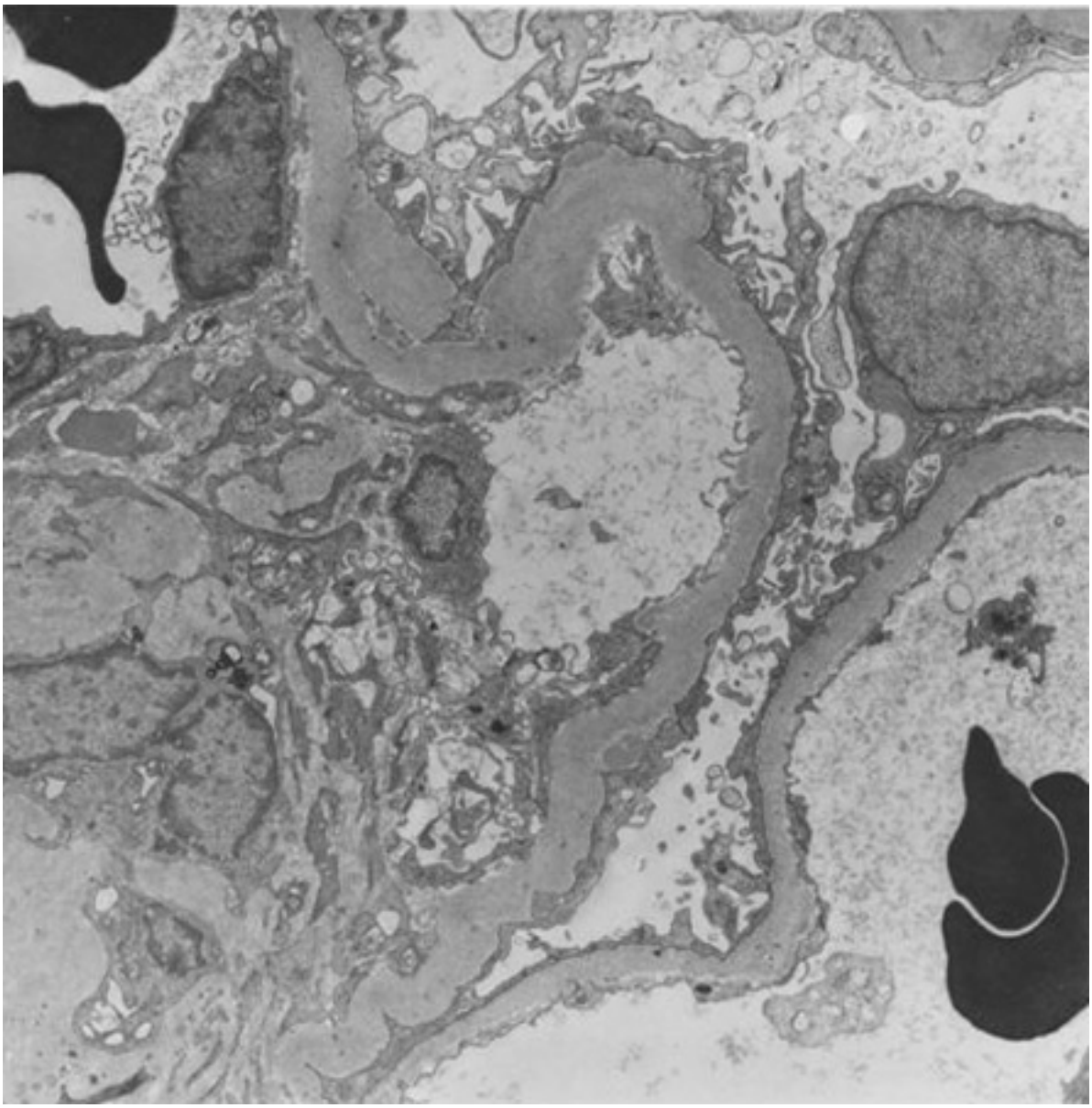

Figure 4: Diabetic kidney disease: mesangial expansion is usually recognised when it has exceeded 1.5 times the normal mesangial matrix

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Contributors:

// Authors:

David J. Leehey, MD, FACP

Professor of Medicine
Division of Nephrology, Loyola University Medical Center, Maywood, IL, Associate Chief of Staff for Clinical Affairs and Education, Veterans Affairs Hospital, Hines, IL
DISCLOSURES: DJL declares that he has no competing interests.

Irfan Moinuddin, MD

Assistant Professor of Medicine
Southern Illinois University School of Medicine, Springfield, IL
DISCLOSURES: IM declares that he has no competing interests.

// Peer Reviewers:

Rajiv Agarwal, MD

Professor of Medicine
Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN
DISCLOSURES: RA declares that he has no competing interests.

Merlin C. Thomas, PhD

Associate Professor
Baker IDI Heart and Diabetes Institute, Melbourne, Australia
DISCLOSURES: MCT has received honoraria for speaking and educational sessions conducted by Sanofi-Aventis, Servier, Boehringer-Ingleheim, Abbott, Amgen, and Jansen-Cilag.

Damian Fogarty, BSc, MD, FRCP

Consultant/Senior Lecturer in Renal Medicine
Belfast City Hospital and Queen's University Belfast, Belfast City Hospital, Belfast, Northern Ireland, UK
DISCLOSURES: DF has no share options, research support, or employment with pharmaceutical companies. He has received one-time speaking fees to cover his time preparing educational talks in the broad areas of diabetic nephropathy and chronic kidney disease, promoting early recognition and evidence-based or best practice management.