Diabetes and CKD

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Clinical Scenario

A 60 year old woman presents to your nephrology clinic. She has a history of hypertension and type 2 diabetes mellitus for 12 years, which are managed with amlodipine 5 mg OD and metformin 1 g OD. Her blood pressure was 146/80 mmHg, and her body mass index is 32 kg/m^2. She recently presented to her general practitioner with new-onset ankle oedema. Her albumin–creatinine ratio (ACR) was measured as 254.9 mg/g (25.5 mg/mmol) on an early-morning urine sample, her HbA1c was recently measured as 79 mmol/mol (9.4%), and creatinine 110 mmol/L (1.24 mg/dL). She was referred to you for clinical advice regarding (1) changes to her diabetic therapy and (2) initiation of renal-protective therapy.

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Introduction

The global prevalence of diabetes mellitus is increasing. This is largely driven by an increase in prevalence of type 2 diabetes (T2DM) and its associated metabolic syndrome. However, there has also been a smaller but significant increase in prevalence of type 1 diabetes (T1DM).

T1DM is caused by autoimmune destruction of insulin-producing pancreatic β cells. T2DM is associated with peripheral insulin resistance and a decrease in insulin secretion. Solid-organ transplantation may result in post-transplant diabetes mellitus (PTDM). This is associated with immunosuppression, as well as risk factors for T2DM.

Hyperglycaemia caused by diabetes leads to microvascular changes within the kidney, which cause diabetic kidney disease (DKD/diabetic nephropathy). Combined DM and CKD (DM-CKD) increases cardiovascular morbidity and mortality, and is a leading cause of death in CKD patients.

The aim of the clinician in treating DKD should be primary prevention of progression to end-stage kidney disease (ESKD). This may be achieved via control of blood glucose, blood pressure, and body weight, and avoidance of nephrotoxic medications.

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Epidemiology and Causes

Prevalence of diabetes is closely linked to obesity and varies from <6% to >12% according to obesity rates. The prevalence of diabetes varies by country and by region (Table 10.1). Estimates are limited by diagnosis rates: more than half of individuals suffering from diabetes in Sub-Saharan Africa are thought to be undiagnosed. 537 million adults are living with diabetes and it is predicted that global rates of diabetes will increase to 734 million by 2045 [1].

T1DM accounts for <15% of the global diabetes burden and is more common amongst Northern European genetic groups. T2DM accounts for around 85% of cases, and its incidence is higher amongst South Asian, Afro-Caribbean, Polynesian, Middle Eastern, and Native American groups.

Studies in the USA have shown that 40% of individuals with CKD G1–5 have concurrent DM; there is little data available for other parts of the world. The incidence of PTDM following kidney transplantation has been estimated at 10–30%, with rates increasing with time after transplantation. It is important to note, however, that the prevalence of non-diabetic kidney disease (NDKD) in patients with diabetes ranges from 33 to 73% according to centres with high rates of kidney biopsy (although the predominance of atypical presentations amongst individuals who receive a kidney biopsy may lead to an over-estimation of this figure). Hence, a diabetic individual presenting with signs of kidney disease should not be assumed to have isolated DKD.

T1DM and T2DM cause DKD in the same way. Hyperglycaemia leads to a greater prevalence of glycated compounds in the blood and a greater oxidative stress load, leading to microvascular damage, increased glomerular capillary pressures, podocyte damage, and endothelial dysfunction. Other causes of kidney disease, such as hypertension or other primary kidney diseases, will accelerate the disease course.

Table 10.1 Prevalence of diabetes in adults aged 20–79 years according to IDF region (from IDF Diabetes Atlas 9th Edition)

IDF region	Prevalence of diabetes (age 20–79 years)
Africa	3.9%
Europe	8.9%
Middle East and North Africa	12.9%
North America and Caribbean	13.3%
South and Central America	9.4%
South-East Asia	8.8%
Western Pacific	9.6%

Table 10.2 Definitions of diabetes and associated conditions [2]

Condition	Definition
Diabetes mellitus	WHO criteria—any of: 1. Symptoms of hypoglycaemia **AND** raised venous glucose levels detected once (fasting glucose ≥ 7.0 mmol/L **OR** random glucose ≥ 11.1 mmol/L) 2. Raised plasma glucose (fasting ≥ 7.0 mmol/L **OR** random ≥ 11.1 mmol/L) on two occasions **OR** OGTT 2-hour glucose ≥ 11.1 mmol/L. 3. HbA1c ≥ 48.0 mmol/mol (i.e. ≥ 6.5%).
Impaired glucose tolerance	WHO criteria— • OGTT 2-hour plasma glucose 7.8–11.0 mmol/L • Fasting plasma glucose may be normal or elevated
Impaired fasting glucose	WHO criteria— • Fasting plasma glucose 6.1–6.9 mmol/L
Metabolic syndrome	International Diabetes Foundation (IDF) criteria— • Central obesity (BMI > 30 kg/m^2 or increased waist circumference according to ethnic groups • Plus two of: 1. Plasma triglyceride level > 1.7 mmol/L **OR** on treatment for hypertriglyceridaemia 2. Plasma HDL cholesterol < 1.0 mmol/L **OR** on treatment for cholesterol derangement 3. Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, **OR** on treatment for hypertension 4. Fasting plasma glucose ≥ 5.6 mmol/L **OR** previously-diagnosed T2DM
Post-transplant diabetes mellitus	Diagnosis can be made by the above WHO criteria once a patient is stable on post-transplant immunosuppression.

BP blood pressure, *BMI* body mass index, *OGTT* oral glucose tolerance test, *T2DM* type 2 diabetes mellitus, *WHO* World Health Organization

Clinical Presentation

The vast majority of T1DM cases present during adolescence, but presentation may be at any age. Classic presenting features of T1DM are polyuria, polydipsia, and weight loss despite adequate nutritional intake, classically described as "starvation in the face of plenty". Patients may present for the first time in an acute setting with diabetic ketoacidosis.

Individuals with T2DM generally present >30 years of age, but it is increasingly being diagnosed in adolescents. It is associated with progression from a stage of impaired glucose tolerance and/or metabolic syndrome to frank diabetes (Table 10.2).

A patient may present completely asymptomatic or with severe complications of diabetes, depending on the length and severity of their disease. Complications to look for in the history and examination include diabetic retinopathy, neuropathy, signs or symptoms of macrovascular disease (e.g. stroke, myocardial infarction).

Diabetic nephropathy presents with a typically picture of proteinuric kidney disease. Oedema is a classical symptom and may be generalised, in gravity-dependent areas such as the ankles, or in areas of low tissue resistance such as the periorbital tissue. Patients may also present with frothy or bubbling urine, recurrent or resistant urinary tract infections, and other signs or symptoms of hypoalbuminaemia. The peak of presentation is in individuals who have had diabetes for 10–20 years.

Investigations

Standard investigations for diabetes include plasma glucose, capillary glucose, and HbA1c levels. These should be interpreted in the context of a patient's most recent glucose load (see Table 10.2). Blood glucose levels are particularly useful diagnostically following an oral glucose tolerance test, and acutely for diagnosing hypoglycaemia. Blood ketone levels should be taken to diagnose potential diabetic ketoacidosis when suspected.

The HbA1c is a useful marker of chronic hyperglycaemic load. HbA1c measurements are unreliable in certain patient groups: CKD G4–5; dialysis patients; those with any disease affecting lifespan of red blood cells (e.g. iron-deficiency anaemia, thalassaemia, recent acute blood loss, spherocytosis); those receiving HIV antiretroviral therapy; chronic liver disease; hypertriglyceridaemia. See annex Table 10.3 below for conversion of HbA1c units.

Renal biopsy is the only true way to confirm whether CKD in a diabetic patient is a direct result of the diabetes disease process. However in practice, a long history (>10 years) of diabetes, proteinuria, and signs of retinopathy are typically taken as sufficient criteria for a diagnosis of DKD. Any individual with a shorter history of diabetes should undergo a full CKD assessment looking for other causes. If a patient exhibits proteinuria with a diabetic history of <5 years, with no signs of microvascular complications, and the suspicion of systemic disease, a diagnostic kidney biopsy is recommended. Individuals with T2DM often have multiple renal pathologies, including primary glomerulopathies, age-related nephropathy, or damage from previous acute kidney injury. CKD in these individuals may therefore be a combination of DKD and NDKD.

Table 10.3 HbA1c values are variously reported worldwide as a measurement in mmol/mol or as a percentage; these units can be approximately compared using the table below

% HbA1c	HbA1c mmol/mol	% HbA1c	HbA1c mmol/mol	% HbA1c	HbA1c mmol/mol	% HbA1c	HbA1c mmol/mol
4	20	6.1	43	8.2	66	10.3	89
4.1	21	6.2	44	8.3	67	10.4	90
4.2	22	6.3	45	8.4	68	10.5	91
4.3	23	6.4	46	8.5	69	10.6	92
4.4	25	6.5	48	8.6	70	10.7	93
4.5	26	6.6	49	8.7	72	10.8	95
4.6	27	6.7	50	8.8	73	10.9	96
4.7	28	6.8	51	8.9	74	11	97
4.8	29	6.9	52	9	75	11.1	98
4.9	30	7	53	9.1	76	11.2	99
5	31	7.1	54	9.2	77	11.3	100
5.1	32	7.2	55	9.3	78	11.4	101
5.2	33	7.3	56	9.4	79	11.5	102
5.3	34	7.4	57	9.5	80	11.6	103
5.4	36	7.5	58	9.6	81	11.7	104
5.5	37	7.6	60	9.7	83	11.8	105
5.6	38	7.7	61	9.8	84	11.9	107
5.7	39	7.8	62	9.9	85	12	108
5.8	40	7.9	63	10	86		
5.9	41	8	64	10.1	87		
6	42	8.1	65	10.2	88		

Table 10.4 Differential diagnosis for diabetic nephropathy [2]

Primary nephropathy	Systemic conditions causing secondary nephropathy
Minimal change disease	Systemic lupus erythametosus
Membranous nephropathy	Rheumatoid disease
Focal segmental glomerusclerosis	Myeloma
Menbranoproliferative glomerulonephritis	Amyloidosis
	Infection (e.g. HIV, hepatitis B/C, malaria)

Differential Diagnosis

Differential diagnoses of diabetic kidney disease will include any proteinuric kidney disease. This may be primary renal disease (e.g. minimal change disease, membranous nephropathy) or renal disease secondary to a systemic condition (Table 10.4).

Diabetes Management

Glycaemic Control

Glycaemic control is the cornerstone of primary prevention in DM-CKD patients, and is monitored using HbA1c. Patients should be encouraged to meet an individual HbA1c "target" (see Table 10.5), which should be as close to normal as sustainably possible in order to reduce the risk of kidney disease progression. HbA1c targets <53 mmol/mol (7.0%) have been shown to reduce risk of progressive micro- and macroalbuminaemia compared with targets ≥53 mmol/mol (7.0%).

Routine monitoring of HbA1c should be twice-yearly. The frequency of monitoring can be increased in patients whose glycaemic targets are not met, or for patients undergoing changes in antihyperglycaemic therapy.

Self-monitoring of blood glucose levels is less useful as a marker of long-term glycaemic control. However, it is useful practise to prevent hypoglycaemic episodes. Patients taking antihyperglycaemic therapies that predispose to hypoglycaemia should be trained to self-monitor.

Due to the limitations of HbA1c, direct glucose monitoring is useful more accurate indicator of sugar control. The glucose can be monitored by repeated finger prick testing using a traditional glucometer or newer flash glucose monitoring system like "free style libra" device. Glycated albumin and serum fructosamine have been prosed as better indicators but further studies are needed for establishing the role of these two agents.

Table 10.5 Glycaemic targets in people with DKD [2]

Condition	Glycaemic target	CKD stage and albuminuria	Age
Type 1 diabetes	48-58 mmol/mol (6.5–7.5%)*	CKD stage G2 with variable albuminuria	Younger people with < 10 years diabetes duration
	58-62 mmol/mol (7.5–7.8%)	CKD stage G3–4 and/or albuminuria	Majority of age groups
	58-69 mmol/mol (7.5–8.5%)	CKD stage G5 to dialysis	Any age
Type 2 diabetes	48-58 mmol/mol (6.5–7.5%)*	CKD stage G1–2	Age < 40 ** diet-controlled at any age
	52-58 mmol/mol (6.9–7.5%)	CKD stage G3–4 May be appropriate with GLP-1 and/or SGLT-2 inhibitor treatment regime without insulin	Any age
	58-69 mmol/mol (7.5–8.5%)	CKD stage G3–4 and CKD stage G5 on dialysis People with albuminuria on insulin-based regime	Any age

* perform confirmatory blood glucose monitoring in cases of concern of hypoglycaemia or anaemia.
** over 20% of people with dietary-controlled diabetes and CKD can have an HbA1c 42-48 mmol/mol (6.0–6.5%) without hypoglycaemia.

Antihyperglycaemic Therapy

Lifestyle Changes

Holistic lifestyle changes are a cornerstone of management in DM-CKD, and include nutritional, exercise, smoking, and weight loss guidance. The range of lifestyle issues affecting DM-CKD patients highlights the need for management by and effective multi-disciplinary team comprising nutritionists/dieticians, physiotherapists, occupational therapists, specialist nurses, and podiatrists.

Individuals with DM-CKD are recommended to take a diet high in fruits, vegetables, wholegrains, and unsaturated fats, and to eat less processed food, sugar, and refined carbohydrates. Current guidance suggests ensuring a daily protein intake of 0.8 g/kg body weight for individuals not on dialysis, and 1.0–1.2 g/kg body weight for patients receiving dialysis. In addition, patients with DM-CKD should restrict their sodium intake to <2 g/day (equivalent to 90 mmol of sodium or 5 g sodium chloride per day). Reduced sodium intake reduces systolic and diastolic BP, and evidence suggests concurrent reductions in risk for CVD and stroke.

Exercise for physical conditioning and weight loss should be encouraged, and exercise plans should be tailored to individuals' current levels of physical activity. It is recommended that patients with DM-CKD undertake 150 min of moderate intensity physical exercise (e.g. brisk walking,

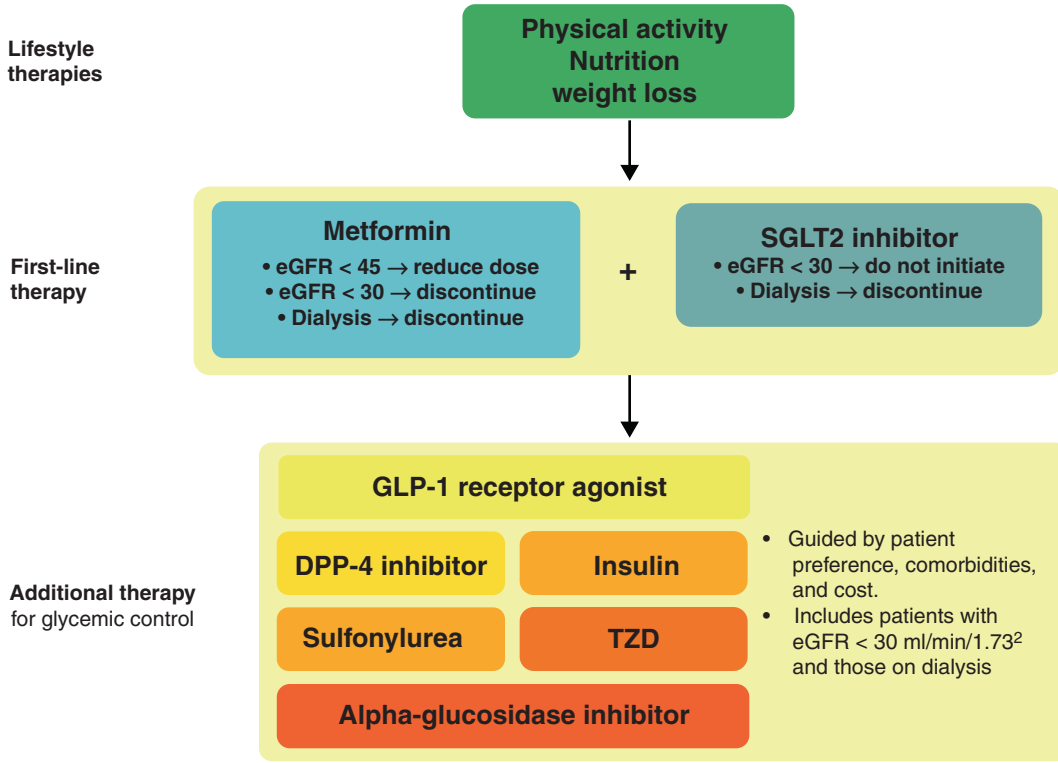

Fig. 10.1 Choice of antihyperglycaemic therapy in DM-CKD. (From KDIGO 2020 [2])

cycling, yoga, swimming) per week. If an individual is unable to achieve this due to poor cardiovascular or physical tolerance, they should begin with less intense exercise such as slow walking for short distances until their conditioning improves. If an individual's conditioning is too low for even light exercise, the involvement of exercise specialists and physiotherapists may be necessary.

Individuals with DM-CKD should have a target body mass index (BMI) of 20–25 kg/m^2. Alcohol intake should be limited to one standard drink per day for women and two for men. Smoking should be discouraged and cessation advice should be given.

First-Line Therapy

Along with lifestyle interventions, first-line treatment for individuals with DM-CKD should include metformin and an SGLT2 inhibitor if eGFR ≥30 mL/min/1.73 m^2 (Fig. 10.1). Individuals on metformin should have their eGFR monitored regularly, with increased monitoring frequency if eGFR <60 mL/min/1.73 m^2, and should have metformin stopped if eGFR falls below 30 mL/min/1.73 m^2. Dosing should then be titrated according to eGFR and renal function should be monitored regularly (see Fig. 10.2).

Patients on metformin for more than 4 years should have their vitamin B12 levels monitored due to increased frequency of vitamin B12 deficiency in these individuals. Metformin is associated with the rare complication of type B (non-hypoxic) lactic acidosis in around 5 in 100,000 individuals. The mortality of this condition is estimated at 30–50%. Due to this potential severe complication of metformin use, patients should be given sick day guidance and metformin should be withheld in periods of acute illness.

Metformin should be combined with an SGLT-2 inhibitor for optimal glycaemic control. The sodium/glucose co-transporter 2 protein is located in the proximal renal tubule and is responsible for 80–90% of renal glucose

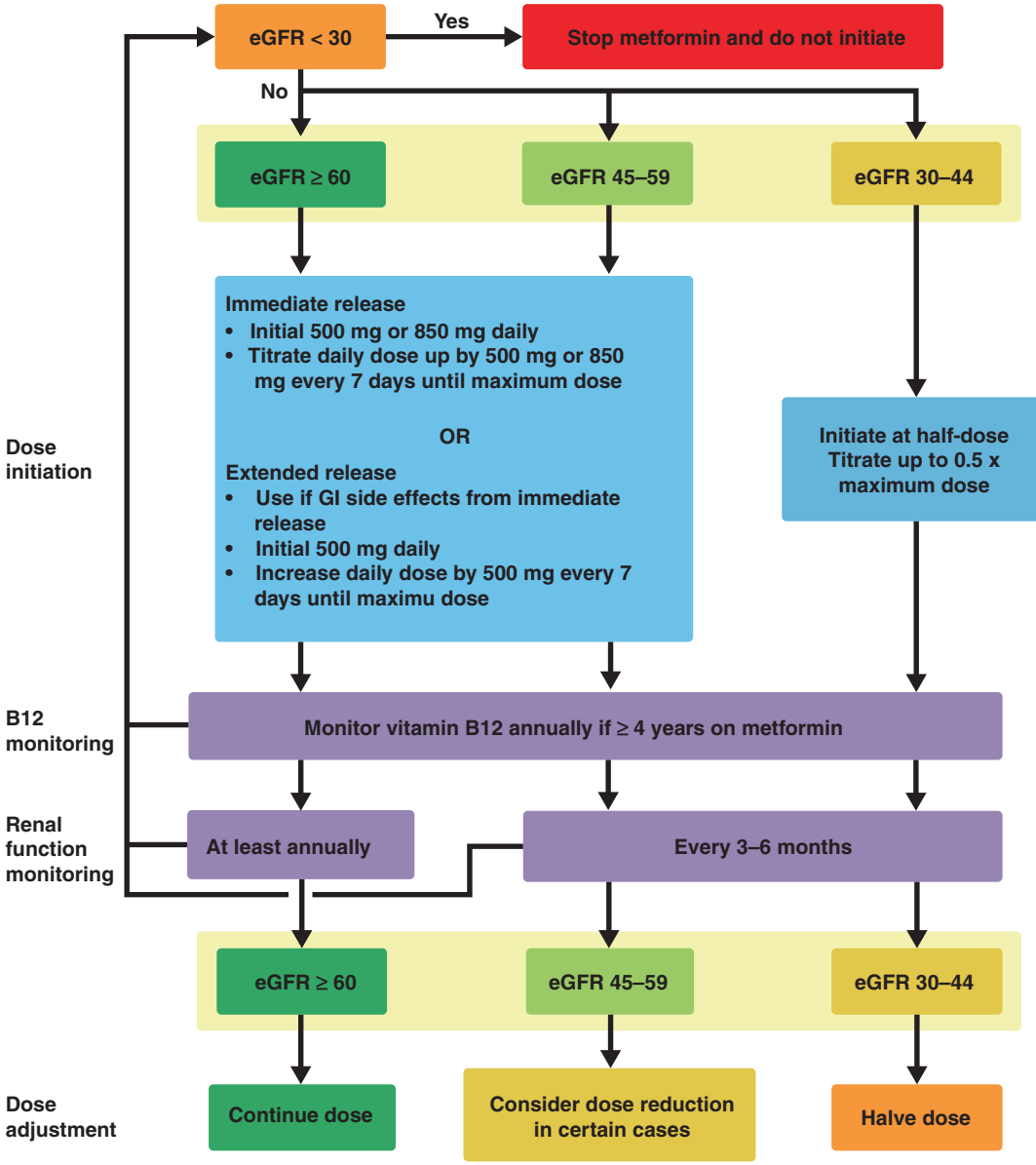

Fig. 10.2 Metformin dosing algorithm in CKD. (From KDIGO 2020 [2])

reabsorption. Inhibition of the co-transporter prevents glucose reabsorption and promotes urinary glucose excretion. There is strong evidence that SGLT-2 inhibitors prevent progression of DKD down to an eGFR of 30 mL/min/1.73 m^2. It is not recommended to initiate SGLT2 therapy in patients with eGFR <30 mL/min/1.73 m^2, however it may be continued if already begun.[2, 3]

There is strong evidence that SGLT-2 inhibitors reduce risk of (1) major adverse cardiac events, and (2) development and progression of heart failure in patients with T2DM with CVD risk factors.

Individuals taking SGLT2 inhibitors should be monitored for hypotension (especially if they also take diuretic medication) due to the drugs' diuretic effects, and for hypoglycaemia during at-risk peri-

Table 10.6 Choice of second-line antihyperglycaemic medication by clinical situation (adapted KDIGO 2020 [2])

Clinical situation	Suitable medications	Less-suitable medications
eGFR < 15 mL/min/1.73 m^2 or concurrent with dialysis	• DPP4 inhibitors • Thiazolidinedione • Insulin	• Thiazolidinedione
Co-morbid heart failure	• SGLT2i • GLP1 receptor agonists	• Thiazolidinedione
High-risk for atherosclerotic cardiovascular disease	• SGLT2i • GLP1 receptor agonists	
Higher-potency for glucose-lowering	• GLP1 receptor agonists • Insulin	• DPP4 inhibitors • Thiazolidinedione • -glucosidase inhibitors
To aid weight loss	• GLP1 receptor agonists	• Sulfonylureas • Insulin • Thiazolidinedione
To avoid hypoglycaemia	• GLP1 receptor agonists • DPP4 inhibitors • Thiazolidinedione • -glucosidase inhibitors	• Sulfonylureas • Insulin
To avoid injections	• DPP4 inhibitors • Thiazolidinedione • Sulfonylureas • -glucosidase inhibitors • Oral GLP1 receptor agonists	• GLP1 receptor agonists • Insulin
Low cost	• Sulfonylureas • Thiazolidinedione • -glucosidase inhibitors	• GLP1 receptor agonists • DPP4 inhibitors • Insulin

ods (e.g. illness, fasting, surgery) or if they take other medications which increase risk of hypoglycaemia (e.g. insulin, sulfonylureas). There has been evidence of increased risk of diabetic ketoacidosis associated with SGLT-2 inhibitor use.[2, 3]

Augmenting Therapy

There are several therapeutic options for individuals who do not meet their glycaemic targets on metformin and SGLT2 inhibitors (see Table 10.6). An overview of agents and doses to be utilised in different stages of CKD is provided in Table 10.7. Contraindications for glycaemic control medications are listed in Table 10.8.

GLP-1 Receptor Antagonists

GLP-1 receptor agonists (GLP-1 RAs) are often the first-choice second-line therapy. They are associated with gastrointestinal side-effects, so should be started at a low dose and titrated upwards as tolerated by the patient (see Table 10.9). Combination therapy using GLP-1 RAs with DPP4 inhibitors (DPP4i) is not recommended. These medications both act via the incretin pathway to stimulate insulin and inhibit glucagon release. Randomised controlled trials have not demonstrated benefits of combined therapy for glycaemic control [3].

GLP-1 RAs confer an increased risk of hypoglycaemia if used in conjunction with some other

Table 10.7 Antihyperglycaemic dosing in DKD. CrCl measured by Cockroft–Gault equation [2]

Class of drug	Drug	Stage 1 eGFR > 90	Stage 2 eGFR 60–90	Stage 3a eGFR 45–59	Stage 3b eGFR 30–44	Stage 4 eGFR 15–29	Stage 5 eGFR < 15
Biguanide	Metformin				Reduce dose to 500 mg BD	Potential role for 500 mg BD	
Sulphonylurea	Gliclazide	Monitor capillary blood glucose (CBG	CBG	CBG	Dose reduction advised, CBG	Off-licence. High risk of hypoglycaemia	
Meglitinide	Repaglinide	CBG	CBG	CBG	CBG	Dose reduction advised, CBG	
DPP-4 inhibitor	Sitagliptin			eGFR < 50 reduce dose to 50 mg	Reduce dose to 50 mg	Reduce dose to 25 mg	
	Saxagliptin			EGFR < 50 reduce dose to 2.5 mg	Reduce dose to 2.5 mg		
	Linagliptin						
Thiazolidinedione	Pioglitazone						
GLP-1 agonist	Lixisenatide			Caution if CrCl < 50 mL/min			
	Exenatide			Caution if CrCl < 50 mL/min	Conservative dosing advised		
	Exenatide MR			Stop if CrCl < 50 mL/min			
	Liraglutide					Dose reduction may be required	Off-licence
	Dulaglutide						
SGLT-2 inhibitor	Dapagliflozin			Reduce dose to 5 mg			
	Canagliflozin			Reduce dose to 100 mg			
	Empagliflozin			Reduce dose to 10 mg			
Insulin					Dose reduction may be required	Dose reduction required	

Table 10.8 Contraindications to antihyperglycaemic medications in diabetic complications [2]

Condition	Drug	Note
Biliary conditions	GLP-1 analogues	• Relative contraindication in active gallbladder disease
Bladder conditions	SGLT-2 inhibitors	• Relative contraindication of all medications in this class for individuals with (1) documented neuropathic bladder or (2) recurrent urinary tract infections • Relative contraindication / caution to initiation in individuals with (1) active bladder cancer or (2) unexplained and uninvestigated haematuria
	Pioglitazone	• Relative contraindication / caution to initiation in individuals with (1) active bladder cancer or (2) unexplained and uninvestigated haematuria.
Bone conditions	Pioglitazone	• Absolute contraindication in individuals with previous osteoporotic fractures • Relative contraindication in osteoporosis with neuropathy
	SGLT-2 inhibitors	• Relative contraindication in those with established osteoporotic fractures
Foot conditions	SGLT-2 inhibitors	• Absolute contraindication in diabetic foot disease with vascular complications or sepsis
Heart failure	Pioglitazone	• Absolute contraindication in established heart failure and when at-risk individuals have raised BNP
	Saxagliptin	• Absolute contraindication in established heart failure
Pancreatic conditions	GLP-1 analogues	• Absolute contraindication with previously-documented pancreatitis • Relative contraindication in those at risk of pancreatitis or with: (1) raised triglycerides; (2) on steroid therapy; (3) documented alcoholism; or (4) using other drugs associated with pancreatitis
Retinopathy	Pioglitazone	• Absolute contraindication in diabetic maculopathy
	Semaglutide	• Relative contraindication in marked hyperglycaemia (≥ 10.5%) who have diabetic retinopathy requiring ophthalmology input

Table 10.9 Dosing of GLP-1 RAs in CKD[2]

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use if eGFR >15 mL/min/1.73 m^2
Exenatide	10 μg twice daily	Use with CrCl >30 mL/min/1.73 m^2
Exenatide extended release	2 mg once weekly	Use with CrCl >30 mL/min/1.73 m^2
Liraglutide	0.6 mg, 1.2 mg, and 1.8 mg once daily	No dosage adjustments Limited data for severe CKD
Lixisenatide	10 μg and 20 μg once daily	No dosage adjustments Limited data for severe CKD
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustments Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg once daily	No dosage adjustments Limited data for severe CKD

medications (e.g. sulfonylureas, insulin). If combined therapy using these agents is to be considered, patients should be started on low doses which should be titrated carefully and with close monitoring of blood glucose levels.

DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors selectively bind to the DPP-4 enzyme and prevent breakdown of glucagon-like peptide 1 (GLP-1), leading

to a moderate reduction in blood glucose levels. An advantage of their use lies in their favourable safety and tolerability profiles, as well as a low risk of hypoglycaemia. Because of this profile, DPP-4 inhibitors may be used in all CKD stages, including individuals on maintenance haemodialysis. Doses should be adjusted according to the stage of CKD.

Several trials have been conducted to understand the safety of DPP-4 inhibitor use in individuals with CVD. Large trials investigating sitagliptin (TECOS trial) and linagliptin (CARMELINA trial) have found no evidence of increased CVD risk in patients taking these medications compared with placebo. Retrospective analysis has also emphasised the safety of vildagliptin.

The EXAMINE trial found a mild increase in prevalence of heart failure in patients taking alogliptin, but no increase in hospital admissions due to heart failure. In contrast, the SAVOR-TIMI trial found that individuals taking saxagliptin with pre-existing risk factors for CVD were more likely to develop and be hospitalised for heart failure in the first 12 months after starting the medication. There was no increase in incidence of major adverse cardiac events.

Sulfonylureas

Sulfonylurea compounds act to decrease blood glucose levels in two principal ways. They act to close ATP-sensitive potassium channels in pancreatic β-cells, triggering insulin release via an intracellular cascade. Also, they stimulate activity of glucose receptors in muscle and adipose cells, increasing sensitivity to insulin. The sulfonylureas gliclazide and glipizide are metabolised by the liver into inactive metabolites, and are recommended as adjunct therapy for T2DM while eGFR >30 mL/min/1.73 m^2. Gliclazide has a more favourable cardiovascular safety profile. Dose reduction is advised with decreasing eGFR (see Table 10.6) and sulfonylureas are not licensed in individuals with eGFR <30 mL/min/1.73 m^2.

Other sulfonylureas such as glibenclamide, glimepiride, and tolbutamide are not recommended in CKD.

Key side effects of sulfonylureas are weight gain and hypoglycaemia. The risk of hypoglycaemia is greater in CKD than non-CKD individuals due to renal excretion of active and non-active metabolites. Due to this increased risk, co-prescribing with insulin is not recommended, and sulfonylureas should not be used in T1DM. Regular blood glucose monitoring should be considered.

Thiazolidinediones

Pioglitazone is licensed for use in T2DM. It acts to lower peripheral insulin resistance. Its advantages include a low risk of hypoglycaemia and its hepatic metabolism, due to which dose reduction is not required as renal function declines. Hence pioglitazone can be considered for individuals with any stage of CKD.

Disadvantages of pioglitazone include its association with increased fluid retention, and it should be avoided in heart failure and macular oedema and used with caution in known fluid-retainers. Pioglitazone is also associated with an increased risk of bladder cancer; it should be avoided in known cases and also in anyone with haematuria until cancer is excluded.

Meglitinides

Meglitinides (nateglinide, repaglinide) are compounds which act to increase insulin secretion in a similar manner to sulfonylureas. They act rapidly, and have the advantage of dosage flexibility with the concurrent drawback of multiple administrations. Repaglinide may be considered as monotherapy, while both compounds may be considered as adjuncts to metformin.

Both nateglinide and repaglinide have the potential to cause hypoglycaemia and doses should be reduced as eGFR declines. While repaglinide is secreted by the biliary system, nateglinide is excreted renally and hence carries increased risk of hypoglycaemia in CKD. For this reason, repaglinide is recommended at lower

eGFRs. Both are partially metabolised by the cytochrome P450 system.

Post-transplant Diabetes Mellitus

In the immediate post-transplant period, patients should be actively monitored for hyperglycaemia while in hospital. Mild hyperglycaemia (<14 mmol/L) may be treated using oral therapy, while higher blood glucose levels should be managed via intravenous or subcutaneous insulin therapy. Following discharge and entering the maintenance phase of immunosuppressive therapy, post-transplant patients should be screened for PTDM yearly.

Recommended first-line therapy for patients with PTDM and eGFR ≥30 mL/min/1.73 m^2 is metformin (see Fig. 10.3). This may be augmented using sulfonylureas, DPP4 inhibitors, GLP1 RAs, and pioglitazone. SGLT2 inhibitors should be used with caution due to the risk of urinary tract infection in the immunocompromised patient. There is a low threshold for utilising insulin therapy in post-transplant patients if they display poor glucose management or symptomatic hyperglycaemia.

Management of Hypertension in DKD *[for details see* Chap. 8*]*

Type 1 Diabetes

Hypertension (HTN) is the greatest risk factor for the progression of CKD. Blood pressure targets for individuals with T1DM vary between 130/80 and 140/90 mmHg. Stricter targets are recom-

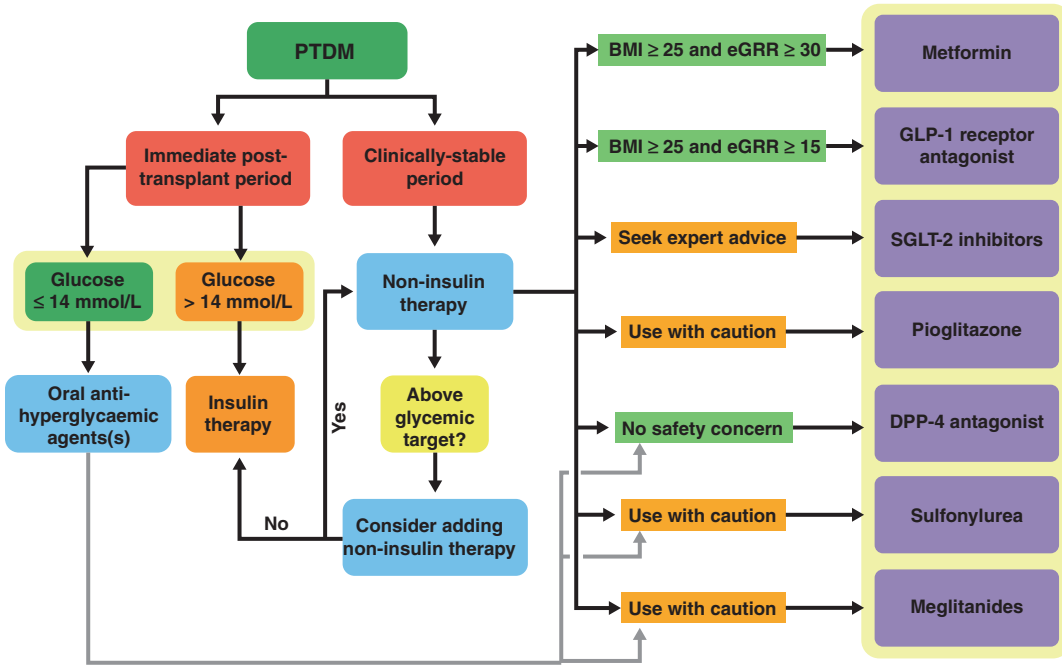

Fig. 10.3 Flow chart for glycaemic management of post-transplant diabetes mellitus (PTDM) [4]. On an individual basis, it should be considered whether immunosuppression represents a significant risk factor for the development of PTDM. It is currently recommended that the primary factor in deciding on immunosuppressive therapy should be to reduce the risk of allograft rejection, and there is no evidence to suggest that alterations to a patient's immunosuppressive regime will help to manage PTDM. However, in a patient starting immunosuppressive therapy for the first time who is at high risk of PTDM, a regime with lower risk of hyperglycaemia should be considered

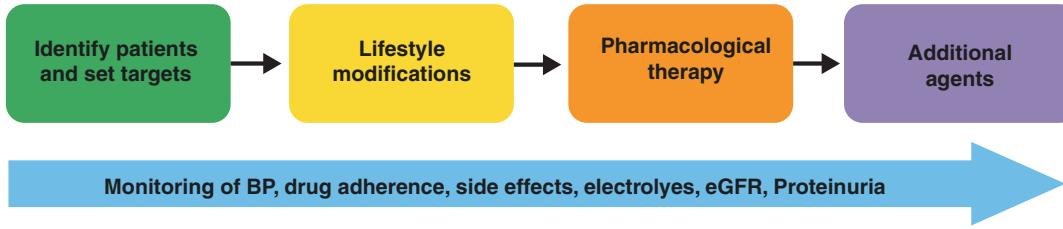

Fig. 10.4 Management principles of HTN in CKD. *BP* blood pressure, *eGFR* estimated glomerular filtration rate [from ABCD-RA guidelines on management of hypertension in diabetes 2021 [5]]

Table 10.10 Lifestyle factors and hypertension in T1DM[2]

Lifestyle factor	Impact
Salt intake	• KDIGO guidance recommends a sodium intake of <90 mmol/day (equal to 2 g/day, or 5 g of sodium chloride) • Salt intake has greater impact on HTN risk in combined DM-CKD due to reduced renal excretion
Weight and Body Mass Index	• Abdominal obesity and high BMI are associated with HTN in T1DM • KDIGO guidance recommends maintaining a BMI of 20–25 kg/m^2
Exercise	• There is evidence that regular exercise reduces BP in individuals with T1DM • KGIDO guidance recommends 30 min of exercise five times per week, with intensity determined by tolerance
Alcohol intake	• KDIGO guidance recommends limiting intake to two standard drinks for men and one for women per day

mended in younger individuals due to the increased number of years at risk. The management paradigm for HTN in T1DM similar to that in the non-diabetic population: lifestyle modifications should be trialled first, followed by antihypertensive medications, with augmentation if required (Fig. 10.4).

Lifestyle factors and their impact on HTN in T1DM are outlined in Table 10.10.

Antihypertensive Medication in T1DM

ACE inhibitors are the recommended first-line antihypertensive therapy in individuals with CKD and T1DM. If ACEi medication cannot be tolerated, ARBs should be considered as a second-line alternative. Doses should be titrated upwards as tolerated. Spironolactone may be considered as a third-line agent, but carries a significant risk of severe, even fatal, hyperkalaemia. There is little evidence pertaining to the use of beta-blockade in CKD and T1DM, but some studies suggest a benefit to HTN.

The threshold for starting antihypertensive therapy will vary according to age and albumin-creatinine ratio (ACR), as outlined in Fig. 10.5.

There is no evidence that multiple antihypertensive therapy is of benefit in CKD-T1DM, and trials have shown significant increases in risk of hyperkalaemia and acute kidney injury (AKI).

RAASi medication is associated with fetal cardiovascular, neurological, and renal abnormalities in pregnancy, and so should be

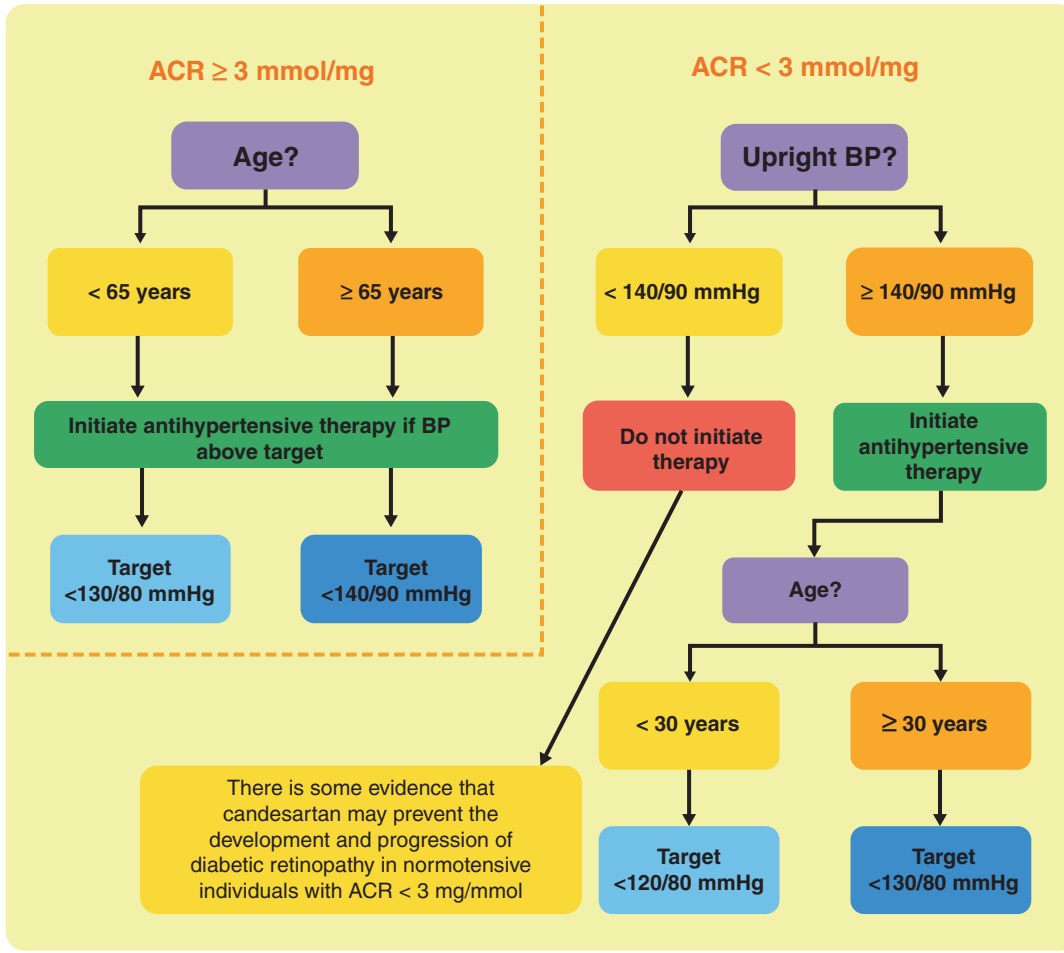

Fig. 10.5 Guidance on initiating antihypertensive therapy in patients with CKD and T1DM (adapted from ABCD-RA guidance [5])

stopped if an individual is pregnant or planning a pregnancy.

Type 2 Diabetes Mellitus

Lifestyle modifications recommended for HTN in T2DM are similar to those in T1DM (Table 10.8). Also similarly to T1DM, thresholds initiation of pharmacological therapy will depend on age and ACR (Fig. 10.6). In individuals with an ACR < 3 mg/mmol, there is no specific recommended first-line agent in DKD. If ACR ≥ 3 mg/mmol, ACEi medication—or ARB if ACEi is not tolerated—is recommended. The target blood pressures are summarised below (Table 10.11):

Practice Points

- Insulin resistance increases in early CKD, which worsens sugar control
- Insulin clearance decreases in advanced CKD, eGFR <20 mL/min/1.73 m^2, which makes patients prone to hypoglycaemia
- Blood sugars may fall during haemodialysis due to relatively low dialysate glucose and removal of glucagon
- Fluid assessment and therapy in DKA can be challenging in patients on dialysis
- Blood glucose rises during peritoneal dialysis and reduces ultrafiltration
- HbA1c may not be accurate due to altered red cell life span

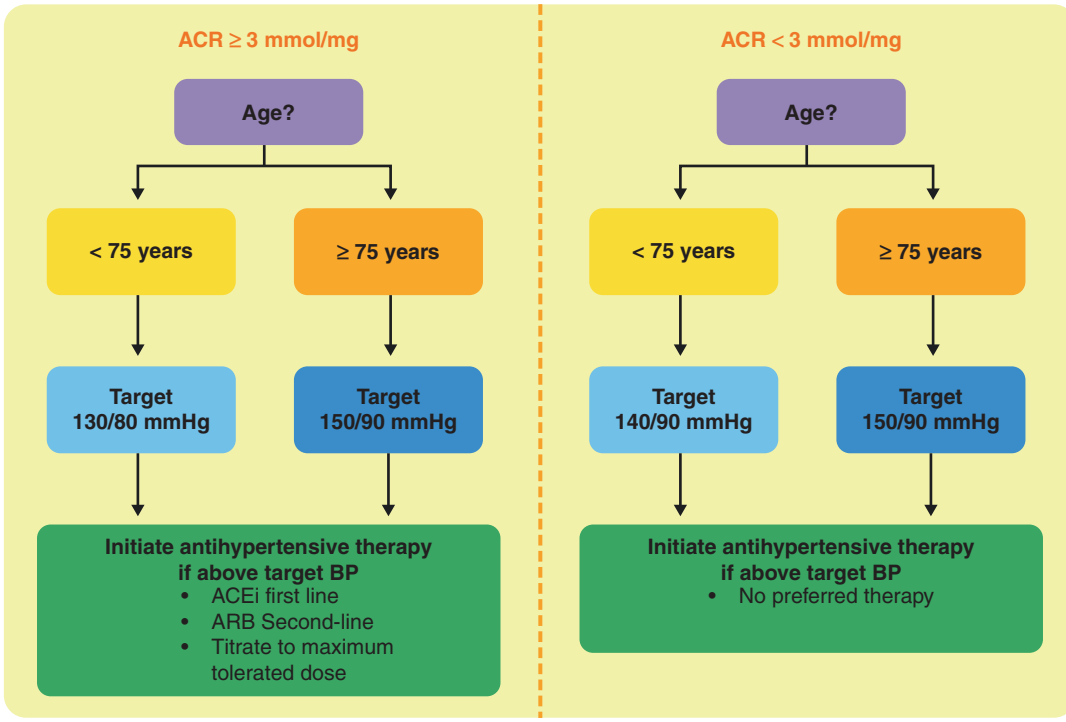

Fig. 10.6 Antihypertensive guidance in T2DM and CKD

Table 10.11 Blood pressure targets in Type 2 diabetes (adapted from ABCD-Renal Association Guidelines [5])

	CKD stages 1-3	CKD stages 4-5	Dialysis
ACR<3mg/g (> 30 mg/mmol)	<140/90 mmHg	<140/90 mmHg	<140/90 mmHg
ACR>3 mg/g (> 30 mg/mmol)	<130/80 mmHg	<130/80 mmHg	

Conclusions

Returning to our case from the beginning of the chapter—the patient has a long history of diabetes mellitus, with a likely clinical diagnosis of diabetic kidney disease. She has comorbidities, including clinical obesity, suboptimal blood sugar control, and suboptimal blood pressure control. The next steps in her management in clinic should include:

- Establishing her diagnosis from her long history of diabetes mellitus, and the presence of diabetic retinopathy
- Starting an ACE inhibitor (or angiotensin receptor blocker)
- Achieve more optimal blood pressure control <130/80 mmHg
- Achieve better blood sugar control (target HbA1c 52–58 mmol/mol for Type 2 DM associated CKD stage G3A3)
- Start dapagliflozin
- Monitor creatinine, potassium, Blood pressure and HBA1c

Questions

1. A 57 year-old woman presents to nephrology clinic for the first time following referral for new-onset significant proteinuria. She has a three-year history of type 2 diabetes which has so far been controlled with lifestyle modifications. Her BMI is 31.1 kg/m^2 and she has no other past medical history. Her eGFR is measured as 54 mL/min/1.73 m^2. Which of the following is the most appropriate initial action?
   A. As her diabetes has been controlled by lifestyle modifications, it would be appropriate to monitor her HbA1c and initiate pharmacological therapy when it is >48 mmol/mol (6.5%)
   B. Initiate metformin and an SGLT2 inhibitor as first-line therapy as eGFR ≥30 mL/min/1.73 m^2 and discharge to her general practitioner for follow-up.
   C. Refer to ophthalmology to examine for diabetic retinopathy before starting glucose lowering therapy.
   D. Perform a full CKD assessment looking for causes other than diabetes.
   E. Initiate GLP1 receptor agonist therapy as this is recommended to aid weight loss.

   Answer: D

   A. **Incorrect**: in all cases of diabetic kidney disease with an eGFR of ≥30 mL/min/1.73 m^2, dual therapy with metformin and an SGLT2 inhibitor is recommended.
   B. **Incorrect**: as this patient has a short (<10 years) history of diabetes and no known evidence of microvascular complications, she should undergo a full assessment for other potential causes of CKD.
   C. **Incorrect**: While she should have annual screening for retinopathy this would not necessarily need to precedent the commencement of glucose-lowering treatment.
   D. **Correct**: as mentioned, due to the short and relatively well-controlled history of diabetes, this patient requires a full workup to look for other causes.
   E. **Incorrect**: in all cases of diabetic kidney disease with an eGFR of ≥30 mL/min/1.73 m^2, recommended first-line therapy is with metformin and an SGLT2 inhibitor.
2. A 65 year-old man with G3aA2 CKD and T2DM presents to clinic for a follow-up appointment. He currently takes metformin with dapagliflozin and pioglitazone for diabetes management. He was recently had an echocardiogram demonstrating a left ventricular ejection fraction of 35–40% and blood tests returning a NT-proBNP level of 1200 pg/mL. Which of the below is the most appropriate immediate action?
   A. Stop metformin with dapaglifozin as dapaglifozin is contraindicated in G3a CKD.
   B. Stop pioglitazone and replace with another agent as thiazolidinedione medications are contraindicated in heart failure.
   C. Continue current antihyperglycaemic therapy and add an ACE inhibitor .
   D. Continue current antihyperglycaemic therapy and add a beta blocker.
   E. Continue current antihyperglycaemic therapy and add a GLP-1 agonist to control hyperglycaemia and reduce cardiovascular risk.

   Answer: B

   A. **Incorrect**: dapaglifozin is contraindicated in G3b CKD. In G3a CKD dose reduction is advised.
   B. **Correct**: thiazolidinediones can cause fluid retention and are contraindicated in heart failure.
   C. **Incorrect**: while an ACE inhibitor may be beneficial for patients with combined CKD-HF, current antihyperglycaemic therapy should not be continued as thiazolidinediones are contraindicated in heart failure.
   D. **Incorrect**: as above, thiazolidinediones are contraindicated in heart failure.

E. **Incorrect**: as above, thiazolidinediones are contraindicated in heart failure.

3. A 59 year-old woman with G2 CKD and recently-diagnosed T2DM is referred to the renal clinic by her GP for advice on medications. She has started metformin immediate-release 500 mg with dapagliflozin 10 mg daily for glycaemic control, and her latest HbA1c is 65 mmol/mol (8.1%). She has a history of hypertension and gastro-oesophageal reflux disease, and her blood pressure in clinic is 153/91 mmHg. She currently takes nifedipine 30 mg daily. Which of the below is the most appropriate option?
   A. Increase metformin to 1000 mg and send urine sample for ACR testing.
   B. Add a GLP-1 agonist and send urine sample for ACR testing.
   C. Increase metformin to 1000 mg and increase nifedipine to 60 mg daily.
   D. Add a GLP-1 agonist and increase nifedipine to 60 mg daily.
   E. Add a DPP-4 inhibitor and change nifedipine to ramipril.

   Answer: A

   A. **Correct**: since the patient is only taking a low dose of metformin, it is appropriate to titrate the dose upwards. In addition, it is important to know her ACR as if it is ≥3 mmol/mg, she should be taking an ACE inhibitor as first-line antihypertensive therapy.
   B. **Incorrect**: the patient is only taking a small dose of metformin; it would be more appropriate to up-titrate the dose before switching drug classes.
   C. **Incorrect**: while it is appropriate to up-titrate the dose of metformin, we must check the patient's ACR to determine what her ideal antihypertensive therapy should be.
   D. **Incorrect**: we should first up-titrate the metformin dose and also must send a urine sample for ACR to determine optimal antihypertensive therapy.
   E. **Incorrect**: We should first up-titrate the metformin dose and also must send a urine sample for ACR to determine optimal antihypertensive therapy. There is no one preferred therapy for those with an ACR < 3 mmol/mg.

4. A 52 year-old man is an inpatient on the renal ward having been admitted via the Emergency Department with abdominal pain, nausea and vomiting. He received a kidney transplant 6 months ago. Nursing staff are routinely monitoring his blood glucose levels and call you to report that the latest measurement is 16.4 mmol/L. His latest eGFR is 35 mL/min/1.73 m^2. What is the most appropriate management?
   A. Start metformin 500 mg and continue monitoring blood glucose.
   B. Start a variable-rate insulin infusion.
   C. On discharge, request his GP to begin antihyperglycaemic therapy.
   D. Start dapagliflozin 10 mg and continue monitoring blood glucose.
   E. Start subcutaneous long-acting insulin injections.

   Answer: B

   A. **Incorrect**: oral therapy is an option for inpatient management of post-transplant diabetes, but as this patient's blood glucose level is >14 mmol/L, insulin therapy is a more appropriate option.
   B. **Correct**: the patient is not "clinically stable" and his blood glucose is >14 mmol/L, therefore oral antihyperglycemic therapy would not be appropriate.
   C. **Incorrect**: the patient's blood glucose is high enough to warrant inpatient management and it would be inappropriate to ask the GP to begin therapy after this admission.

D. **Incorrect**: not only is insulin therapy is more appropriate in this situation, but SGLT-2 inhibitors should not be used in immunocompromised patients due to an increased risk of urinary infection.
E. **Incorrect**: long-acting insulin would not be appropriate as initial management alone in the context of acute illness and vomiting

5. Which of the following statements is false with regard to contraindications of antihyperglycemic medications in CKD?
   A. All SGLT-2 inhibitors are contraindicated in patients with unexplained haematuria.
   B. All pioglitazones are contraindicated in patients with heart failure.
   C. All DPP-4 inhibitors are contraindicated in patients with heart failure.
   D. Metformin is contraindicated in patients with eGFR <30 mL/min/1.73 m^2.
   E. All GLP-1 agonists are contraindicated in patients with a history of pancreatitis.

   Answer: C

   A. **Incorrect**: this statement is true.
   B. **Incorrect**: this statement is true.
   C. **Correct**: only saxagliptin is contraindicated in heart failure.
   D. **Incorrect**: this statement is true.
   E. **Incorrect**: this statement is true.

6. A 65 year old man with heart failure (EF 30%) was seen in diabetes clinic. His HBA1c was 54. He was on metformin 2000 mg and ramipril 10 mg daily. What is the next best medication to control his blood sugar?
   A. Acarbose
   B. Dapagliflozin
   C. Gliclazide
   D. Insulin
   E. Pioglitazone

   Correct answer is B dapagliflozin

7. His eGFR declines from 65 to 60 mL/min/1.73 m^2 after 2 weeks. His dapagliflozin should be stopped.
   A. True
   B. False

   Correct answer B False: this drop in eGFR is seen acutely and does not have any long-term side effects

8. What is the cause of the acute decline in eGFR?
   A. Efferent arteriolar vasodilatation
   B. Tubuloglomerular feedback

   Correct answer is B: tubuloglomerular feedback

9. The dapagliflozin will continue provide benefit even if the eGFR<30 mL/min/1.73 m^2
   A. True
   B. False

   Correct answer is True: it reduces the chance of ESKD (End Stage Kidney Disease)

10. The dapagliflozin is unlikely to reduce the chance of hospitalisation
    A. True
    B. False

    Correct answer is false: Dapagliflozin reduces heart failure hospitalisations

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